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ORIGINAL RESEARCH

Efficacy, Safety and Pharmacokinetics of IL-17 Monoclonal Antibody Injection (AK111) in Patients with Moderate-to-Severe Plaque Psoriasis: A Randomized, Double-Blinded, Placebo-Controlled Phase Ib Multidose Escalation Clinical Study

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ABSTRACT

Objectives: To evaluate the safety, tolerability, immunogenicity, and induced expression of skin biomarkers of AK111 injection after multiple administrations in subjects with moderate-to-severe plaque psoriasis.

Methods: This study is a randomized, double-blinded, placebo-parallel-controlled study using a dose escalation mode of multiple doses. A total of 48 subjects were sequentially randomized to receive each AK111 dose regimen (75 mg, 150 mg, 300 mg, 450 mg) or the corresponding placebo. All subjects were treated with the study drug at weeks 0, 1, 4, and 8 and were unblinded at week 12, with the placebo group ending and the AK111 group being followed up to 20 weeks.

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Results: At week 12, compared with placebo, the percentage of subjects achieving Psoriasis Area and Severity Index 75 (PASI75) and static Physician Global Assessment (sPGA) 0/1 in the AK111 75 mg–450 mg dose groups was significantly increased, and higher PASI90 was achieved in the 150 mg, 300 mg, and 450 mg dose groups than in the 75 mg group. All efficacy indicators were maintained at week 20. The incidence of treatment-emergent anti-drug antibodies (ADAs) was 0% (0/48). Neutralizing antibodies (NAbs) were not detected in any subject. The proportion of subjects who reported any treatment-emergent adverse event (TEAE) was 75.0% in the AK111 group, similar to the 66.7% in the placebo group. The most commonly reported adverse events were hyperglycemia, elevated blood pressure, and hypokalemia. The AK111 pharmacokinetics showed approximate dose proportionality with regard to the maximum observed concentration (C_{max}) and area under the curve from 0 to the time of the last quantifiable concentration ($AUC_{0–t}$) following subcutaneous injection doses of 150–450 mg.
Conclusions: After moderate-to-severe plaque psoriasis subjects received multiple subcutaneous AK111 injections of 150–450 mg, AK111 exposure increased in a roughly dose-proportional relationship. AK111 was safe and tolerable. In subjects with moderate-to-severe plaque psoriasis, AK111 demonstrated encouraging preliminary efficacy, which was sustained for a relatively long time after the last dose administration.
Clinical trial registration: The clinical trial identification number is NCT05504317.

Keywords: AK111; Interleukin-17; Safety; Phase Ib; Psoriasis

Key Summary Points

AK111 is a biologic monoclonal antibody targeting interleukin-17 (IL-17) that was tested for its safety at different doses in a phase I clinical study in healthy subjects in New Zealand. This phase Ib clinical study was conducted to evaluate the efficacy and safety of AK111 in patients with moderate-to-severe plaque psoriasis.

AK111 demonstrated that the clinical response rate continued to increase during the first few weeks of treatment, and there was no significant difference in the safety or tolerability of AK111 in patients with moderate-to-severe plaque psoriasis compared with the reports of similar drugs on the market.

This study provides preliminary data on the treatment of patients by AK111, and it can be used as a reference for later phase II clinical trials.

INTRODUCTION

Psoriasis is a common chronic, recurrent, inflammatory skin disease that mainly affects young and middle-aged people [1]. There are more than 125 million patients with psoriasis worldwide, with a morbidity rate of 0.1–3%. The incidence rate in China rose from 0.12% in 1987 to 0.47% in 2012 [2], and the incidence is as high as 2–3% in European and American countries [3, 4]. The impact of psoriasis on patients is multifaceted. Skin surface red papules and silvery white scales can affect the patient's appearance, mood, social communication, and even employment. The itching and tingling of skin lesions, scalp scales, pain, and

inflammation and deformation of joints can affect the quality of life, normal activities, and ability to work and can even lead to death [5]. Psoriasis is associated with a lipid metabolism disorder and an increased cardiovascular risk [6]. A survey showed that the direct and indirect economic burden of patients with psoriasis was more serious than that of eczema patients, and that of patients with severe psoriasis was more than twice that of patients with moderate psoriasis. The disease cost was shown to be higher than their monthly family income for 64% of patients [7]. It places a heavy economic burden on individual patients, their families, and society.

There is no radical cure for psoriasis [8]. Traditional local and systemic treatments have limited effects, or long-term treatment has significant side effects: phototherapy has limited efficacy and a high recurrence rate; methotrexate and cyclosporine A have low efficiency and serious side effects and increase immune system involvement [9, 10]. In recent years, biologic agents targeting inflammatory cytokines have been used in the treatment of patients with moderate-to-severe psoriasis who have had a poor response to traditional systemic drugs, showing good efficacy and safety [11]. Current biological agents used in the clinical treatment of psoriasis include the tumor necrosis factor (TNF) antagonist infliximab [12]. TNF inhibitors, although superior to conventional immunosuppressants, have high immunogenicity due to the clinical risk of infection and malignancy [13]. At present, secukinumab, ixekizumab, and brodalumab, which target IL-17, have been approved to treat psoriasis [14–16]. Its good efficacy and safety make IL-17 a popular target for the treatment of psoriasis [17]. Since the current treatment of psoriasis mAb drugs is expensive, there is still no IL-17 monoclonal antibody produced in China with definite efficacy, safe effects, and acceptable price. Finding one is an urgent clinical need for patients with moderate and severe psoriasis in China and other developing countries.

As a proinflammatory cytokine, IL-17A plays a key role in the pathogenesis of psoriasis. AK111 is a humanized IgG1 monoclonal antibody targeted to human IL-17A that binds it with specificity and high affinity, preventing its binding to T cells, natural killer cells, and IL-17 receptor A (IL-17RA) expressed on the surface of antigen-presenting cells, thus blocking its downstream cellular immune response. Compared with other commercially available IL-17 antibodies, AK111 showed similar activity and safety in antigen binding tests, cytological tests, and animal models. A phase I trial of AK111 single subcutaneous dose escalation in healthy subjects was completed in New Zealand and demonstrated good safety and tolerability (NCT04172233).

This study evaluated the safety, tolerability, immunogenicity, and pharmacokinetic (PK) properties of multiple doses of AK111, as well as preliminary efficacy, and explored biomarkers as surrogate endpoints of clinical efficacy to provide a basis for future clinical trials.

METHODS

Study Design

This study is a randomized, double-blinded, placebo-parallel-controlled, phase Ib clinical study with multiple doses of AK111 given in a dose–escalation manner. Subjects were assigned to the subcutaneous AK111 injection group and placebo group at a 3:1 ratio for each dose injection group to the corresponding placebo group. Dose escalation was performed at 75 mg, 150 mg, 300 mg, and 450 mg successively. The interval between the first two subjects in the same dose group (one patient in each test group and the placebo group) and the rest of the subjects should not be less than 24 h (for the observation period of drug acute anaphylaxis). The study was designed, implemented, and reported by the guidelines Good Clinical Practice (GCP), the current Declaration of Helsinki, and National Medical Products Administration (NMPA), and approved by the Ethics Committee of the First Affiliated Hospital of Bengbu Medical College. All participants signed informed consent to participate in the trials.

Participants

Adults aged 18–60 years, with a body mass index (BMI) 18–28 kg/m^2, with moderate-to-severe plaque psoriasis [defined as body surface area (BSA) $\geq$ 10%, PASI $\geq$ 12 and sPGA score $\geq$ 3] diagnosed no less than 6 months earlier were selected. Subjects were able to understand and voluntarily sign a written informed consent form (ICF). Subjects with any of the following could not be enrolled in this study: having been treated with uchizumab (secukinumab), echizumab (ixekizumab), or other IL-17 antibodies; having psoriasis other than the chronic plaque type (such as pustules, erythroderma, etc.) or having drug-induced psoriasis; other active skin diseases or skin infections (bacteria, fungi, or viruses) that may affect the clinical assessment of psoriasis; a history of chronic and recurrent infectious disease; blood pressure higher than 140 mmHg/90 mmHg; a former malignant tumor; having received local anti-psoriasis treatment within 2 weeks prior to the screening (including local use of nonweak glucocorticosteroids, salicylic acid, etc.); and allergy to any ingredient of the study drug.

Treatment

Subcutaneous AK111 injection of 75 mg, 150 mg, 300 mg, or 450 mg or matching placebo was administered subcutaneously at weeks 0, 1, 4, and 8 through two or three injections at different sites. A total of 28 days after the last subject in each dose group received the first dose, the investigator evaluated the PK profile and safety data separately with the sponsor in a blinded manner. Third-party investigators were invited to evaluate the unblended data independently. If a lower dose level had good safety and tolerability, a decision on dose escalation to the next higher dose level was made by the study investigator, the third-party unblinded investigator, and the sponsor.

Study Endpoints

Primary endpoints: incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs).

Assessment of PK parameters: terminal elimination half-life ($T_{1/2}$), area under the curve (AUC), C_{max} and time to maximum plasma concentration (T_{max}).

Secondary endpoints: proportion of subjects who achieved at least a PASI75 response, a PASI90 response, and a PASI100 response at week 12.

Proportion of subjects who achieved a sPGA of 0 or 1 at week 12 and number and proportion of subjects with detectable anti-drug antibodies (ADAs).

Statistics

Statistical analysis was performed using SAS9.4 (or higher) statistical software, and the non-compartmental model used WinNonlin8.2 (or higher) to calculate PK parameters, including but not limited to the time of occurrence of C_{max} (T_{max}), C_{max}, AUC, volume of distribution (V_d), and $T_{1/2}$. Continuous variables are summarized as the number, mean value, standard deviation, median value, maximum value, and minimum value, and were compared between the AK111 injection group and the placebo group. Categorical data are presented as frequency and percentage. Placebo subjects in different dose groups were combined for statistical calculations. The percentage of subjects with PASI75, PASI90, and PASI100 responses at each time point were calculated, and the changes and percentage changes in PASI scores and the proportion of sPGA of 0/1 scores from baseline are summarized at each time point.

RESULTS

Subject Baseline

A total of 92 subjects were screened; 44 failed the screening and 48 were randomized. A total of 36 subjects were randomized to the AK111

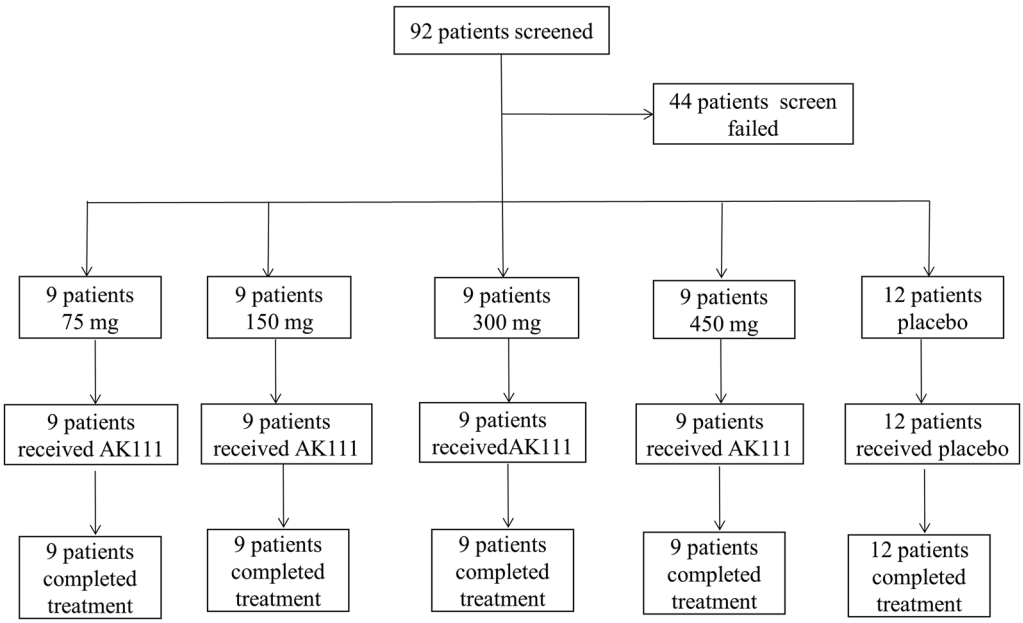

Fig. 1 Patient disposition, subject selection, and completion

group, with 9 patients for each dose level, and 12 subjects were randomized to the placebo group, with 3 subjects in each dose's placebo group. All 48 enrolled subjects completed the study and were included in the full analysis set (FAS), safety analysis set (SS), and pharmacodynamic analysis set (PDS) population. One subject in the 450 mg group was excluded from the pharmacokinetic analysis set (PKS) population due to delayed administration, and the remaining 35 subjects were included in the PKS. The subject flow chart is shown as (Fig. 1).

The demographic characteristics and baseline characteristics were similar between the different dose groups and the placebo group (Table 1). Among the 36 subjects randomized to the AK111 group, the mean (± SD) age was 38.1 (± 9.03) years, the mean weight was 67.06 (± 9.468) kg, and the mean course of psoriasis disease was 15.54 (± 5.762) years.

Pharmacokinetic and Pharmacodynamic Assessment

The parameter elimination rate constant (λz) was calculated using the best fit method. The calculation of λz was based on quantifiable concentration data of the terminal elimination phase from at least three different time points. Due to the limited blood collection time window after the first to third doses in this study, the complete elimination phase was not achieved, so λz and parameters derived from λz [area under the curve from 0 to infinity ($AUC_{0-\infty}$), $T_{1/2}$, mean residence time from 0 to infinity ($MRT_{0-\infty}$), apparent total body clearance following extravascular administration (CL/F), and apparent volume of distribution following extravascular administration (V_d/F)] could be predicted and descriptive statistical analysis could be performed only on the fourth dose.

After the fourth subcutaneous injection of 75 mg, 150 mg, 300 mg, and 450 mg AK111, the average C_{max} was 18.38 mg/L, 24.30 mg/L, 43.82 mg/L, and 73.85 mg/L, respectively. The average AUC_{0-t} was 1001.07, 1240.98, 2280.00, and 3960.61 mg/L per day. The mean Rac (C_{max}) was between 1.13 and 1.57, indicating only slight accumulation after repeated administration. The mean terminal half-life values for the 75 mg, 150 mg, and 300 mg groups ranged from 26 to 28 days. The AK111 PK parameters C_{max} and AUC_{0-t} showed approximate dose proportionality following injection doses of 150 mg,

Table 1 Baseline demographics and disease characteristics

Characteristic	75 mg (*N* = 9)	150 mg (*N* = 9)	300 mg (*N* = 9)	450 mg (*N* = 9)	AK111Total (*N* = 36)	Placebo (*N* = 12)
Male, *n* (%)	7 (77.8)	7 (77.8)	7 (77.8)	7 (77.8)	28 (77.8)	10 (83.3)
Age in years, mean (SD)	33.4 (6.88)	41.7 (11.17)	39.0 (7.91)	38.3 (9.07)	38.1 (9.03)	38.7 (8.44)
BMI (kg/m^2), mean (SD)	23.54 (2.981)	23.87 (2.444)	24.48 (1.365)	23.27 (2.967)	23.79 (2.458)	24.53 (2.885)
Duration of plaque psoriasis (years), mean (SD)	14.73 (5.393)	16.34 (5.012)	18.29 (5.726)	12.77 (6.300)	15.54 (5.762)	15.80 (4.923)
Psoriatic arthritis (%)	0	0	0	2 (22.2)	2 (5.6)	1 (8.3)
BSA (%), mean (SD)	30.56 (12.259)	30.83 (15.174)	38.72 (16.358)	36.50 (18.682)	34.15 (15.519)	30.75 (11.153)
PASI score, mean (SD)	19.12 (4.655)	16.93 (3.770)	22.79 (6.399)	22.84 (7.437)	20.42 (6.059)	18.47 (3.355)
sPGA score, mean (SD)	3.3 (0.50)	3.0 (0.00)	3.3 (0.50)	3.7 (0.50)	3.3 (0.48)	3.3 (0.49)
Conventional systemic treatment	9 (100.0)	9 (100.0)	9 (100.0)	9 (100.0)	36 (100.0)	12 (100.0)
Biologic treatment *n* (%)	0	2 (22.2)	1 (11.1)	1 (11.1)	4 (11.1)	0

SD standard deviation, *BMI* body mass index, *BSA* body surface area, *sPGA* a static physician global assessment, *PASI* psoriasis area and severity index

300 mg, and 450 mg (Table 2). The mean concentration–time profile of AK111 following multiple-dose subcutaneous injection administration is shown in Fig. 2A.

Serum total IL-17A levels can indirectly reflect the status of AK111 binding to IL-17A in humans. After multiple subcutaneous injections of AK111, the serum total IL-17A level was rapidly increased in each dose group of 75–450 mg, which indirectly indicated that AK111 quickly bound to its target IL-17A after entering the body and reached its highest concentration from 1 to 3 weeks after administration. The AK111 75 mg dose rose the fastest on the first week (measured on day 8), with an average increase of 126.167 pg/ml. The AK111 150 mg dose rose the fastest before the third week, with an average increase of 164.426 pg/ml. The AK111 300 mg dose rose the fastest on the first week, with an average increase of 232.657 pg/ml (measured on day 8). The AK111 450 mg dose rose the fastest, up to 261.188 pg/ml before the drug administration at week 2, then gradually dropped. The changes between the dose groups were somewhat linear. The placebo group showed total IL-17A levels before and after administration all below the lower limit of detection. A line plot of total IL-17A values of serum in each dose group is shown in Fig. 2B.

Efficacy Assessment

Disease activity was assessed with the use of the PASI (a composite evaluation instrument for psoriasis severity, with subscores for erythema, induration, scaling, and percentage of body surface area affected) and the sPGA [a 6-point instrument for rating the physician's impression of the overall severity of the psoriasis, on a scale from 0 (clear) to 5 (severe)]. PASI75, PASI90, and PASI100 were defined as participants who achieved ≥ 75%, ≥ 90%, and 100%

Table 2 Mean (SD) pharmacokinetic parameters of the fourth dose

Parameter[b]	75 mg (N = 9)	150 mg (N = 9)	300 mg (N = 9)	450 mg (N = 8)
C_{max} (mg/L)	18.379 (6.4947)	24.300 (3.1556)	43.822 (11.4861)	73.850 (36.5472)
T_{max} (day)	0.238 (0.237,27.831)	0.239 (0,24.731)	0.242 (0,25.869)	11.956 (0,23.687)
AUC_{0-t} (mg/L per day)	1001.072 (375.0724)	1240.978 (204.2806)	2280.001 (675.4220)	3960.608 (2022.1303)
$AUC_{0-\infty}$ (mg/L per day)	1210.187 (481.1155)	1456.488 (293.0662)	2354.667 (853.3135)	NR[c]
$T_{1/2}$ (day)	27.789 (5.2200)	26.291 (3.2957)	26.319 (4.5613)	NR
V_d/F (L)	3.157 (2.0976)	3.971 (0.4577)	5.151 (1.1104)	NR
CL/F (L/day)	0.085 (0.0750)	0.107 (0.0203)	0.143 (0.0528)	NR
$MRT_{0-\infty}$ (day)	43.033 (6.7869)	40.202 (4.6820)	40.782 (5.6375)	NR
Rac (C_{max})	1.128 (0.2801)	1.572 (0.2108)	1.561 (0.4496)	1.312 (0.2541)

C_{max} maximum observed concentration, T_{max} time of occurrence of C_{max}, AUC_{0-t} area under the curve from 0 to the time of the last quantifiable concentration, $AUC_{0-\infty}$ area under the curve from 0 to infinity, $T_{1/2}$ terminal elimination half-life, V_d/F apparent volume of distribution following extravascular administration, CL/F apparent total body clearance following extravascular administration, $MRT_{0-\infty}$ mean residence time from 0 to infinity, Rac (C_{max}) C_{max} after the fourth dose divided by C_{max} after the first dose, NR not reported [in the 450 mg dose group, no PK samples were collected on day 113, resulting in quantifiable concentration data of the terminal elimination phase being less than 3. Therefore, the parameters derived from λ_Z ($AUC_{0-\infty}$, $T_{1/2}$, $MRT_{0-\infty}$, CL/F, V_z/F) are not reliable and will not be reported in this paper.]
*T_{max} is expressed as median (minimum, maximum), and other parameters are expressed as mean (standard deviation, SD)

reduction from baseline, respectively. sPGA 0/1 was defined as achieving sPGA clear (0) or almost clear (1). The key effective endpoints of the study were the proportions of subjects who achieved PASI75, PASI90, PASI100, and sPGA 0/1 responses at week 12. Efficacy endpoint assessment was analyzed on the basis of the FAS. For all efficacy endpoints, the response rates were higher in each AK111 dose group than in the placebo group at week 12. The rates of PASI90 and sPGA0/1 response rates in the 150 mg and above doses of AK111 groups were numerically superior to the rates observed in the 75 mg dose group. More details are shown in Table 3 and Fig. 3.

TEAE and Immunogenicity Assessment

All 48 participants were included in the SS. This study was unblinded at 12 weeks, at which time the study ended for the placebo group. The adverse event observation period of the placebo group was 12 weeks. The AK111 group continued to be followed up until 20 weeks. During the 20-week follow-up period, the TEAE and treatment-related adverse event (TRAE) incidence of the AK111 group were 75.0% (27/36) and 66.7% (24/36), respectively. Within its 12 weeks, the incidence of TEAEs and TRAEs in the placebo group was 66.7% (8/12) and 33.3% (4/12), respectively. Taking into account the different observation periods, the patients who received each regimen of AK111 had a comparable rate of adverse events to patients who received the placebo. The incidence of TEAE in the 75 mg, 150 mg, 350 mg, and 450 mg AK111 groups was 88.9% (8/9), 55.6% (5/9), and 77.8% [7.8% (7/9), respectively, with no significant correlation between adverse events and dose]. Six subjects had a total of seven TEAEs of severity grade $\geq$ 3 (the AE terms were elevated triglycerides or hypertriglyceridemia), including five subjects (13.9%) in the AK111 group (total) and one subject (8.3%) in the placebo group. All

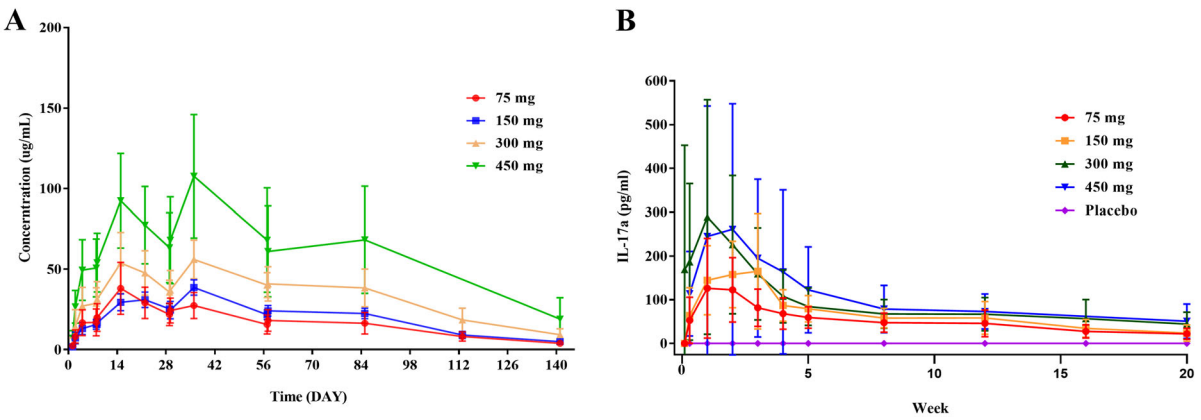

Fig. 2 Pharmacokinetics and pharmacodynamics after drug administration

Table 3 Efficacy at week 20

Parameter	75 mg ($N = 9$) *n* (%)	150 mg ($N = 9$) *n* (%)	300 mg ($N = 9$) *n* (%)	450 mg ($N = 9$) *n* (%)	AK111 total ($N = 36$) *n* (%)	Placebo ($N = 12$) *n* (%)
PASI75	8 (88.9)	8 (88.9)	9 (100.0)	9 (100.0)	34 (94.4)	1 (8.3)
PASI90	4 (44.4)	8 (88.9)	5 (55.6)	9 (100.0)	26 (72.2)	1 (8.3)
PASI100	2 (22.2)	5 (55.6)	3 (33.3)	4 (44.4)	14 (38.9)	0
sPGA0/1	6 (66.7)	7 (77.8)	5 (55.6)	8 (88.9)	26 (72.2)	1 (8.3)

PASI psoriasis area and severity index, *sPGA* static physician global assessment

grade ≥ 3 TEAEs were assessed as probably unrelated to the investigational product by investigators. The remaining TEAEs were grade 1 or grade 2. Among patients who received AK111, the most commonly reported AEs included hypertension and hyperglycemia (Table 4). No SAE or TEAE that resulted in withdrawal or death occurred.

A total of 48 subjects were included in the immunogenicity analysis set (ADAS). The ADA positive rate at baseline was 2.1% (1/48). After administration, ADAs were detected in one subject in the AK111 450 mg group, who was detected as positive at baseline, and the titer did not increase after administration. All other subjects were ADA negative. Therefore, there was no treatment-emergent ADA, defined as either no ADA-positive response at baseline but with any positive response in the post-baseline period or a positive ADA response at baseline and the titer increasing > twofold in the post-baseline period. Neutralizing antibodies (NAbs) were not detected in any subject. We did no formal analysis on the impact of ADA on PK or efficacy due to the small proportion of ADA-positive subjects.

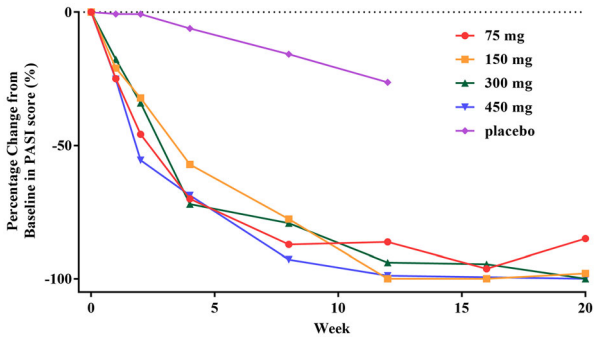

Fig. 3 Percentage change in PASI score in each group after treatment (%)

Table 4 Overview of treatment-emergent adverse events (safety analysis population)

SOC/PT	75 mg (*N* = 9)	150 mg (*N* = 9)	300 mg (*N* = 9)	450 mg (*N* = 9)	AK111 Total (*N* = 36)	Placebo (*N* = 12)
Any TEAE	8 (88.9)	5 (55.6)	7 (77.8)	7 (77.8)	27 (75.0)	8 (66.7)
Hypertension	1 (11.1)	1 (11.1)	1 (11.1)	1 (11.1)	4 (11.1)	2 (16.7)
Death	0	0	0	0	0	0
AE leading to study treatment discontinuation	0	0	0	0	0	0
Increased γ-glutamyl transferase	1 (11.1)	1 (11.1)	1 (11.1)	0	3 (8.3)	0
Increased heart rate	1 (11.1)	0	0	2 (22.2)	3 (8.3)	0
Elevated alanine aminotransferase	0	0	1 (11.1)	1 (11.1)	2 (5.6)	0
Elevated aspartate aminotransferase	0	0	1 (11.1)	1 (11.1)	2 (5.6)	0
Low platelet count	0	0	0	1 (11.1)	1 (2.8)	0
Hyperglycemia	2 (22.2)	2 (22.2)	1 (11.1)	1 (11.1)	6 (16.7)	0
Kaliopenia	2 (22.2)	1 (11.1)	0	0	3 (8.3)	0
Hyperuricemia	1 (11.1)	0	1 (11.1)	0	2 (5.6)	0
Hyperphosphatemia	0	0	1 (11.1)	0	1 (2.8)	0
Hypotension	1 (11.1)	1 (11.1)	1 (11.1)	0	3 (8.3)	0
Upper respiratory tract infection	2 (22.2)	0	0	0	2 (5.6)	0
Oral and pharyngeal pain	1 (11.1)	0	0	0	1 (2.8)	0
Injection site pain	1 (11.1)	0	0	0	1 (2.8)	0
Drowsiness	1 (11.1)	0	0	0	1 (2.8)	0
Urticaria	1 (11.1)	0	0	0	1 (2.8)	0
Erythrocytes in urine	0	0	0	1 (11.1)	1 (2.8)	1(8.3)
TEAE with severity ≥ 3						
Hypertriglyceridemia	0	1 (11.1)	1 (11.1)	2 (22.2)	4 (11.1)	0
Elevated blood triglycerides	1 (11.1)	0	0	0	1 (2.8)	1 (8.3)

EXPLORATORY RESEARCH

Psoriatic Skin Tissue Biomarkers

Nine patients were analyzed for biomarkers, including three patients in the 75 mg dose group, four patients in the 300 mg dose group and two patients in the placebo group. The exploratory biomarkers included chemokine C–C motif chemokine ligand 20 (CCL20), Human beta-defensin 2 (HBD-2), IL-17A, and chemokine C–X–C motif chemokine ligand 1 (CXCL1) mRNA expression levels.

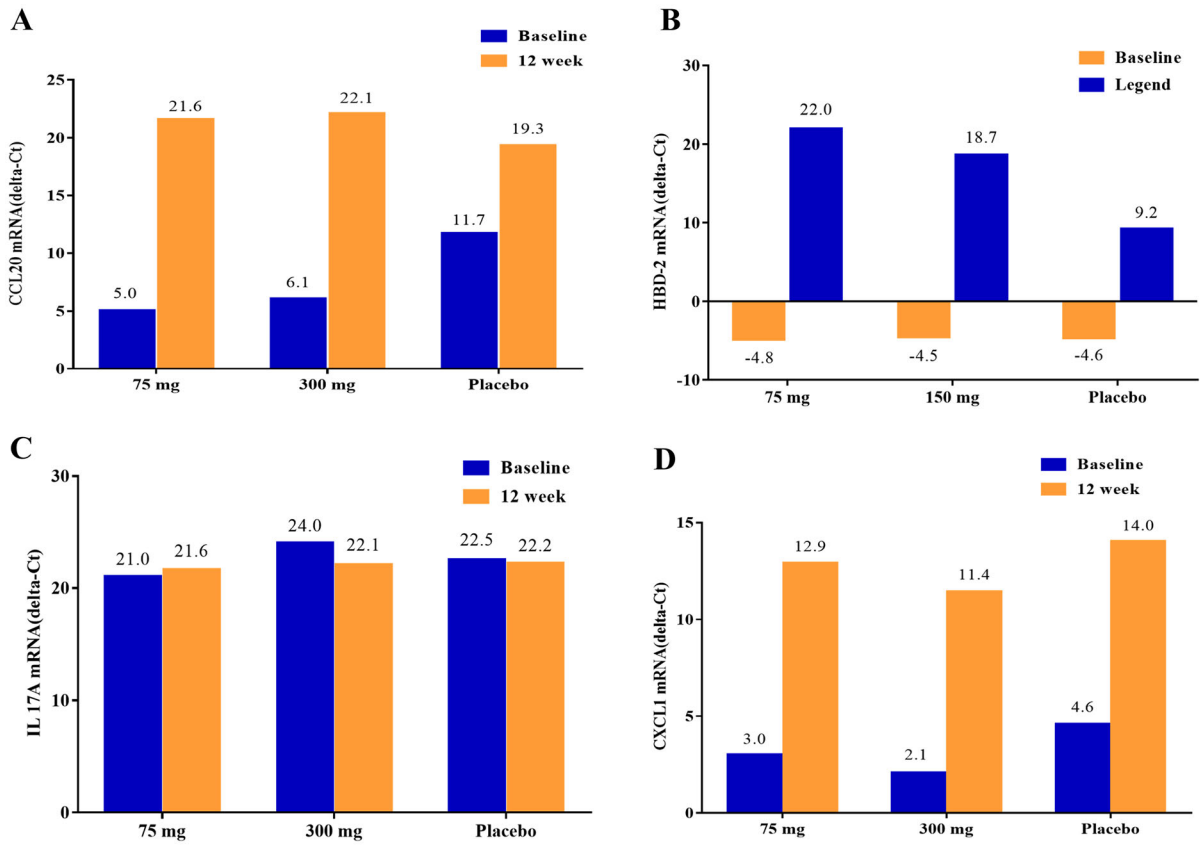

Fig. 4 Psoriasis-related biomarker mRNA expression levels. **A**, **B** The decreases in CCL20 and HBD-2 expression in the AK111 75 mg and AK111 300 mg groups were more than those in the placebo group. **C**, **D** The decreases in the levels of IL17A and CXCL1 expression in the AK111 75 mg and AK111 300 mg groups were not different from those in the placebo group

Due to the limited data, the RT-PCR results were only used to find any expression change trends of IL-17A, HBD-2, CCL20, and CXCL1 mRNA. The biomarker exploratory index showed that after multiple subcutaneous injections of AK111, HBD-2 and CCL20 expression were significantly inhibited at week 12 compared with those in the placebo group. There was no obvious change trend in the other indicators (Fig. 4A–D).

DISCUSSION

This study is the first human experiment of AK111 in an Asian population providing 20 weeks of study data. The results are similar to those of a previous clinical trial conducted in New Zealand. Patients with moderate and severe plaque psoriasis showed good safety, tolerability, and efficacy. The study reached its expected primary and secondary study endpoints. AK111 quickly reached PASI50 in 100% of patients in the week 8. All patients in the 450 mg group achieved PASI75 and PASI90, and 88.9% of the patients achieved PASI100 in this group, compared with only 33.3% of patients in the 75 mg group, indicating a potentially better efficacy improvement at higher dose levels. With a marketed product for psoriasis of the same drug class, M1095, which also acts on the IL-17 pathway, a 100% PASI75 and PASI90 response rate and a 56% response rate to PASI100 were demonstrated in the 240 mg group [18]. In a large phase III clinical trial of bimekizumab, another IL-17 mAb, 68% of

patients achieved PASI100 [19]. Guselkumab targets IL-23 to treat psoriasis by acting on the IL-23/Th17 axis. Its therapeutic effect increased to 82.6% of PASI100 from 52 weeks to 56 weeks [20]. In the current clinical trial, many patients reached sPGA0/1, including 100% of the patients in the AK111 450 mg group. By comparison with the above biological drugs, the current study data showed excellent clinical efficacy of high-dose AK111. The AK111 75–300 mg dose groups showed a longer half-life of 26–28 days, which could meet the maintenance dose frequency of every 4 weeks (Q4W). These data will help evaluate the efficacy of Q4W in the future and provide a basis for the drug regimens of phase II clinical trials.

Accumulating evidence highlights the central role of IL-17A in the pathogenesis of psoriasis, providing the basis for its clinical benefit [21]. The IL-17 pathway is involved in multiple immunomodulatory functions, such as antibacterial bacteria, playing a role in controlling nonsystemic fungal infections, especially those caused by Candida on the oral mucosa [19]. When IL-17A/F is inhibited, the common adverse reactions reported for biologics in this drug class are upper respiratory tract infection, skin mucosal infection, Candida, nasopharyngeal disease, etc. [22]. Common adverse reactions to apremilast are nausea, vomiting, headache, and diarrhea [23]. The main common adverse effects of secukinumab and ustekinumab are upper respiratory tract infection, nasopharyngitis, and arthralgia [24]. In the current trial, only two (5.6%) subjects in the test group had an upper respiratory tract infection. Other commonly reported adverse reactions in this study were high blood pressure, hyperglycemia, and accelerated heart rate, which were grade 1 or grade 2 and resolved without intervention. Similar experiences with adverse reactions are reported in previous studies [25–27]. No rare adverse reactions occurred, and the only tertiary adverse reaction was hypertriglyceridemia. The investigator judged that no TEAEs led to withdrawal from the study and no TEAEs led to death. In addition, the results indicate that there is no clear dose–response relationship with the overall incidence of AEs. Probably due to the small sample size, no inactive reactions occurred in this study.

AK111 is also associated with reversing the pathological hyperplasia of the diseased skin and reducing the RNA levels of proinflammatory genes upregulated by IL-17A/F and various IL-17-induced psoriatic plaques [28]. When we explored some epidermis-related psoriasis biomarkers, we found that the mRNA expression levels of CCL20 and HBD-2 were significantly different from those in the placebo group. Preliminary results showed that the improvement of psoriasis was not related to CXCL1 in the psoriatic epidermis, while IL-17A was at the lower limit of detection, so we did not assess the statistical gap between the test group and the control group. Due to limited data, the RT-PCR results were only used to find the expression change trends of IL-17A, HBD-2, CCL20, and CXCL1 mRNA.

The limitations of this clinical study include its small clinical sample size, short treatment period, and relatively short follow-up time of only 20 weeks. The results from this study are to be validated in trials with a large scale.

CONCLUSION

AK111, a monoclonal antibody designed to selectively inhibit IL-17A and IL-17F, showed a rapid and favorable clinical response, with the 450 mg dose of AK111 being safe in patients with moderate-to-severe psoriasis. The clear findings on the indicators of psoriasis and the skin improvement were dose dependent. Psoriasis plaque was completely lost in most of the patients in the highest dose group of 450 mg. In the future, we will further analyze and evaluate the safety and efficacy of AK111 in patients with plaque psoriasis.

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Compliance with Ethics Guidelines. The study was designed, implemented and reported by the guidelines of Good Clinical Practice (GCP), the current Declaration of Helsinki and the National Medical Products Administration (NMPA). The study protocol was approved by the ethics committee of the First Affiliated Hospital of Bengbu Medical college. All participants signed informed consent to participate in the trials.

Data Availability. All data used in this study are available from the corresponding author upon reasonable request.

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