

Efficacy and safety of CM310 in moderate-to-severe atopic dermatitis: A multicenter, randomized, double-blind, placebo-controlled phase 2b trial

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Abstract

Background: Atopic dermatitis (AD) affects approximately 10% of adults worldwide. CM310 is a humanized monoclonal antibody targeting interleukin-4 receptor alpha that blocks interleukin-4 and interleukin-13 signaling. This trial aimed to evaluate the efficacy and safety of CM310 in Chinese adults with moderate-to-severe AD.

Methods: This multicenter, randomized, double-blind, placebo-controlled, phase 2b trial was conducted in 21 medical institutions in China from February to November 2021. Totally 120 eligible patients were enrolled and randomized (1:1:1) to receive subcutaneous injections of 300 mg CM310, 150 mg CM310, or placebo every 2 weeks for 16 weeks, followed by an 8-week follow-up period. The primary endpoint was the proportion of patients achieving $\geq 75\%$ improvement in the Eczema Area and Severity Index (EASI-75) score from baseline at week 16. Safety and pharmacodynamics were also studied.

Results: At week 16, the proportion of EASI-75 responders from baseline was significantly higher in the CM310 groups (70% [28/40] for high-dose and 65% [26/40] for low-dose) than that in the placebo group (20% [8/40]). The differences in EASI-75 response rate were 50% (high *vs.* placebo, 95% CI 31%–69%) and 45% (low *vs.* placebo, 95% CI 26%–64%), with both *P* values < 0.0001 . CM310 at both doses also significantly improved the EASI score, Investigator's Global Assessment score, daily peak pruritus Numerical Rating Scale, AD-affected body surface area, and Dermatology Life Quality Index compared with placebo. CM310 treatment reduced levels of thymus and activation-regulated chemokine, total immunoglobulin E, lactate dehydrogenase, and blood eosinophils. The incidence of treatment-emergent adverse events (TEAEs) was similar among all three groups, with the

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most common TEAEs reported being upper respiratory tract infection, atopic dermatitis, hyperlipidemia, and hyperuricemia. No severe adverse events were deemed to be attributed to CM310.

Conclusion: CM310 at 150 mg and 300 mg every 2 weeks demonstrated significant efficacy and was well-tolerated in adults with moderate-to-severe AD.

Trial Registration: ClinicalTrials.gov, NCT04805411.

Keywords: CM310; Moderate-to-severe atopic dermatitis; Interleukin-4 receptor alpha; Adults

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease that has a global prevalence of up to 20% in children and 10% in adults.^[1] Approximately 20% of AD patients experience moderate-to-severe AD.^[2] Typical characteristics of moderate-to-severe AD include intense pruritus and chronic or relapsing disease course,^[3] which significantly impairs patients' quality of life.^[4] Despite topical corticosteroids combined with optimal skin care being the mainstay of AD treatment, many patients with moderate-to-severe AD do not achieve adequate disease control and require systemic immunosuppressants.^[5]

As with other atopic diseases, AD is characterized by immune dysregulation, including aberrant activation of type 2 T helper (Th2) cytokines.^[6] Th2 immune mediators, including interleukin-4 (IL-4) and IL-13, are known to participate in the pathophysiology of AD by promoting inflammation, fibrosis, impaired epidermal barrier function, and immunoglobulin E (IgE) production.^[7-9] *In vivo* data have identified a potential reduction of chronic pruritus after sensory neuron-specific deletion of IL-4 receptor alpha (IL-4R α) in mice.^[10] Therefore, developing biologics targeting IL-4, IL-13, and IL-4R α has emerged as a new strategy in the treatment of AD.

Dupilumab, an anti-IL-4R α antibody, has shown notable therapeutic benefits in multiple phase 3 clinical trials for moderate-to-severe AD.^[11-14] These trials have demonstrated significant amelioration in AD clinical manifestations, as assessed by established metrics such as Investigator's Global Assessment (IGA), Eczema Area and Severity Index (EASI), and pruritus Numerical Rating Scale (NRS) score. These findings underscore the favorable efficacy and safety profile of anti-IL-4R α antibody for individuals with moderate-to-severe AD.

CM310 is a humanized monoclonal antibody that specifically binds to IL-4R α , preventing its interaction with IL-4 and IL-13. A phase 1b/2a trial (NCT04893941) involving adults with moderate-to-severe AD showed that CM310 was well-tolerated and produced significant improvements in AD signs and symptoms. The epitope of CM310 to IL-4R α differs from that of dupilumab, as evidenced by the differential cross-species reactivity of CM310 binding to humans, rats, and cynomolgus monkeys, whereas dupilumab binds only to human IL-4R α . This divergence indicates distinct mechanisms in precluding IL-4R α signaling and leads to different clinical outcomes. The present study reports findings from a phase 2b trial evaluating the efficacy and safety of CM310 monotherapy in adults with moderate-to-severe AD.

Methods

Ethics approval

This trial was conducted in compliance with the Good Clinical Practice guidelines issued by National Medical Products Administration, and relevant regulations. This study was approved by the Institutional Review Board and Independent Ethics Committee of the Peking University People's Hospital (No. 2020PHA073-001) and the participating study centers. Patients signed a written informed consent form.

Trial design and participants

This multicenter, randomized, double-blind, placebo-controlled, phase 2b trial (ClinicalTrials.gov, NCT04805411) was conducted across 21 study sites in China. The 28-week study period comprised an up to 4-week screening period, followed by 16 weeks of treatment and 8 weeks of follow-up periods. Patients aged 18–70 years, who had been diagnosed with moderate-to-severe AD for at least 12 months (with baseline IGA score of ≥ 3 , EASI score of ≥ 16 , $\geq 10\%$ body surface area (BSA) of AD involvement, and peak pruritus NRS [PP-NRS] score of ≥ 4), and who were inadequately controlled with topical corticosteroids, were enrolled in the trial. Detailed inclusion/exclusion criteria are listed in Supplementary Table 1, <http://links.lww.com/CM9/B608>.

Randomization and blinding

The enrolled patients were randomly allocated to the placebo group or CM310 groups. Patient and drug randomization lists were generated via SAS (version 9.4, SAS Institute Inc., Cary, USA) with a permuted block size of six and then imported into Interactive Web Response System. All patients and trial personnel were blinded to all randomization procedures.

Procedures

Eligible patients were randomized 1:1:1 to receive high-dose CM310 at a dose of 300 mg (loading dose, 600 mg), low-dose CM310 at a dose of 150 mg (loading dose, 300 mg), or matching placebo subcutaneously every 2 weeks for 16 weeks. Throughout the trial, patients were required to apply moisturizer daily. If medically indicated (i.e., to control intolerable AD symptoms), rescue medications with topical corticosteroids, topical calcineurin inhibitors, or systemic glucocorticoids were given at the discretion of the investigator. Patients who were given systemic glucocorticoids were discontinued from the study drug, but continued study evaluations were required.

Outcomes

The primary endpoint was the proportion of EASI-75 responders (EASI scores improved by $\geq 75\%$ from baseline) at week 16. The secondary efficacy endpoints included the following responder rates at all scheduled time points from baseline to end-of-study (EOS; 24 weeks): achieving IGA 0/1 with ≥ 2 -grade improvement; ≥ 2 -grade improvement in IGA score; EASI-75; EASI-50 and EASI-90 ($\geq 50\%$ and $\geq 90\%$ improvements from baseline, respectively); and ≥ 3 - or ≥ 4 -point improvements in weekly average of daily PP-NRS score. Additional secondary efficacy outcomes were the percent changes at all scheduled time points in EASI score, weekly average of daily PP-NRS score, and percentage of BSA (%BSA) of AD involvement, as well as the change at all scheduled time points in Dermatology Life Quality Index (DLQI) score.

Safety assessments involved monitoring of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), physical examination, vital signs, a 12-lead electrocardiogram, and clinical laboratory parameters.

To reflect the pharmacodynamics of CM310 in moderate-to-severe AD, serum biomarkers were evaluated, including thymus and activation-regulated chemokine (TARC), total IgE, lactate dehydrogenase, and blood eosinophils.

Statistical analysis

Sample size calculation is based on the primary endpoint (the proportion of participants achieving EASI-75 at week 16). Assuming that CM310 had similar efficacy results to dupilumab,^[15] an enrollment of 30 participants per group would provide the trial with 80% power to detect a 36.6% difference between the CM310 high-dose group and the placebo group (51.3% vs. 14.7%) in the primary endpoint. Statistical tests were two-sided and performed at the 0.05 significance level. Factoring a dropout rate of 25%, 40 participants per group were required with a total of 120 participants.

Both full analysis set and safety set included all randomized participants who received at least one dose of study drug. Full analysis set was used for efficacy analysis by treatment groups as randomized; while safety set was adopted for safety analysis by treatment group as actually received. Pharmacodynamic concentration analysis set included all randomized patients who received any study drug and had at least one corresponding qualified result.

The binary efficacy endpoints (e.g., responders for EASI-50, EASI-75, EASI-90, and IGA 0/1) were analyzed using Wald method and Fisher's exact test. If rescue medication was used or participants had missing value of endpoints for any visit, the patient would be treated as a non-responder from when the rescue was used.

Continuous endpoints (e.g., percent change in EASI score) were analyzed using mixed-effect model for repeated measures, using response variable, group, visit, and group-by-visit interaction as fixed effect and the baseline value as covariates. An unstructured covariance

matrix was used to model within-patient errors. Continuous efficacy data were deemed missing once rescue medication was initiated or study withdrawal occurred, and no imputation was made. Least-squares (LS) means estimated by treatment group were provided, along with the difference between these estimates vs. placebo, as well as corresponding standard errors (SEs) and associated 95% confidence intervals (CIs). For biomarker analysis, descriptive statistics were computed, followed by a two-sample *t*-test to compare each pair of groups.

The following three sensitivity analyses were prespecified to assess the robustness of primary endpoint: (1) the patients would be treated as "non-responders" after rescue medication; and last observation carried forward (LOCF) method was used to impute the missing EASI score at week 16 and further derive the corresponding EASI-75; (2) no handling of efficacy data after rescue medication and non-responder imputation for all missing data; and (3) no handling of efficacy data after rescue medication; and the LOCF method was used to impute the missing EASI score at week 16 and further derive the corresponding EASI-75. The following two sensitivity analyses were prespecified to evaluate the robustness of response for continuous variable EASI (percent change in EASI score from baseline to week 24): (1) data after rescue medication (excluding the onset day) were deemed missing and were analyzed using an analysis of covariance (ANCOVA) model after LOCF imputation; and (2) no handling of efficacy data after rescue medication; all observed values of EASI scores would be included in mixed-effect model for repeated measures (MMRM) for analysis.

We performed *post hoc* efficacy endpoint analyses on the proportions of responders for EASI-75 and an IGA score of 0/1 with ≥ 2 -point reduction at week 16, which selectively excluded the confounding impact of coronavirus disease 2019 (COVID-19). SAS (SAS Institute Inc., Cary, USA) was used for statistical analysis.

Results

Participants

From February to November 2021, 120 patients were randomized to the study treatment ($n = 40$ per group) [Figure 1]. Altogether 108 (90.0%) patients completed the study, with 12 patients discontinuing the study mainly due to withdrawal of consent.

No obvious differences in terms of demographic and baseline characteristics were identified between the treatment groups [Table 1]. All patients were adults with a mean age of 34.5 years, and most were male (79, 65.8%). About half (55, 45.8%) of the patients had moderate AD (IGA score of 3) and the other half (65, 54.2%) had severe AD (IGA score of ≥ 4).

Efficacy

In the full analysis set, the proportions of EASI-75 responders at week 16 were 70% (28/40), 65% (26/40),

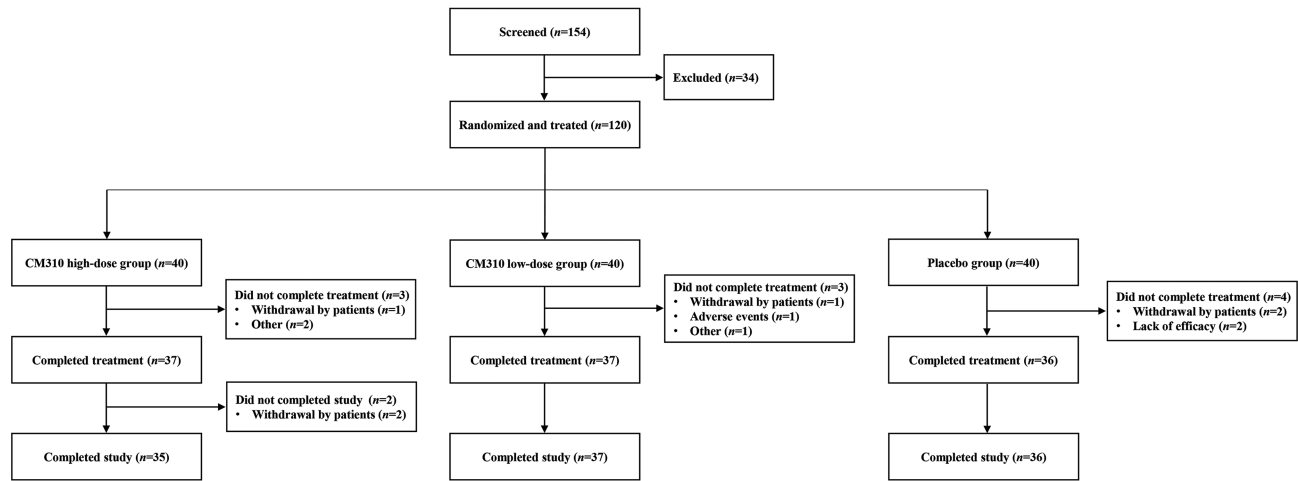


Figure 1: Flow diagram of the recruitment of patients with moderate-to-severe atopic dermatitis.

and 20% (8/40) in high-dose, low-dose, and placebo groups, respectively. The differences in EASI-75 response rate were 50% (high *vs.* placebo, 95% CI 31%–69%) and 45% (low *vs.* placebo, 95% CI 26%–64%), with both *P* values <0.0001. For both EASI-90 and EASI-50 response rates, the CM310 groups demonstrated statistically significant superiority over placebo at week 16 (high *vs.* placebo, *P* = 0.0038 and 0.0004, respectively; low *vs.* placebo, *P* = 0.0033 and 0.0172, respectively) [Table 2]. The proportions of EASI-50, EASI-75, and EASI-90 responders from baseline at each time point are shown in Supplementary Figure 1A–C, <http://links.lww.com/CM9/B608>.

The proportions of patients achieving an IGA score of 0/1 and a reduction of ≥2 points from baseline at week 16 were numerically higher in high-dose and low-dose groups than that in the placebo group (high *vs.* placebo, 22% *vs.* 12%, *P* = 0.3781; low *vs.* placebo, 30% *vs.* 12%, *P* = 0.0993); significant differences between high-dose and placebo groups were observed from weeks 20 to 24. The proportions of patients achieving ≥2-point reduction in IGA score from baseline at week 16 were statistically significantly higher in the CM310 groups (high *vs.* placebo, 48% *vs.* 12%, *P* = 0.0012; low *vs.* placebo, 55% *vs.* 12%, *P* = 0.0001) [Table 2 and Supplementary Figure 1D, E, <http://links.lww.com/CM9/B608>]. In addition, EASI-75 (high-dose [73%] and low-dose [71%] *vs.* placebo [18%]; both *P* values <0.0001) and IGA score of 0/1 with ≥2-point reduction (35% and 32% *vs.* 9%, *P* = 0.023 and 0.033, respectively) in the *post hoc* efficacy analysis were consistent with the full analysis set (data not shown).

The proportions of patients achieving ≥3-point improvements in the weekly average of daily PP-NRS scores from baseline at week 16 were statistically higher in the CM310 groups than that in the placebo group (high *vs.* placebo, 60% *vs.* 25%, *P* = 0.003; low *vs.* placebo, 58% *vs.* 25%, *P* = 0.006); similar results were observed in the case of the proportions of patients achieving ≥4-point improvements (high *vs.* placebo, 45% *vs.* 12%,

P = 0.0026; low *vs.* placebo, 38% *vs.* 12%, *P* = 0.0188). The LS mean percent change from baseline in weekly average of daily PP-NRS score favored CM310 *vs.* placebo starting as early as week 2 (LS mean differences, −1.2% [95% CI −1.8% to −0.5%] for high *vs.* placebo and −0.8% [95% CI −1.5% to −0.2%] for low *vs.* placebo), and improved incrementally over the 16-week treatment period. Greater LS mean percent reductions in EASI score and %BSA affected from baseline to EOS and LS mean change in DLQI were found in the CM310 groups *vs.* placebo [Table 2 and Supplementary Figure 2, <http://links.lww.com/CM9/B608>].

Across prespecified subgroups based on the demographics and baseline disease characteristics (IGA score, EASI score, and %BSA affected), CM310 generally increased the proportions of patients achieving EASI-75, IGA 0/1 with ≥2-grade improvement, and a reduction of ≥3- and ≥4-point in weekly average of daily PP-NRS score at week 16 [Supplementary Figures 3 and 4, <http://links.lww.com/CM9/B608>].

During the trial, rescue medication use was less frequent in the CM310 groups than in the placebo group (high-dose, 5%; low-dose, 18%; placebo, 35%). In the sensitivity analyses, the proportion of EASI-75 responders at week 16 remained significantly higher in the CM310 groups than that in the placebo group [Supplementary Table 2, <http://links.lww.com/CM9/B608>]. Furthermore, both CM310 dose regimens showed greater improvements in the LS mean percent change in EASI score from baseline at week 16 compared to placebo [Supplementary Table 2, <http://links.lww.com/CM9/B608>].

Safety

The overall rates of TEAEs were similar between the CM310 and placebo groups (62/80 [78%] *vs.* 30/40 [75%]). Most TEAEs were mild or moderate [Table 3], and no deaths were reported. Four SAEs were reported in 3 (2%) out of 120 patients: hepatitis E in one patient in the low-dose group; infected dermal cyst in one

Table 1: Demographic and clinical characteristics of patients with moderate-to-severe atopic dermatitis at baseline (full analysis set).

Characteristics	CM310 high-dose (n = 40)	CM310 low-dose (n = 40)	Placebo (n = 40)	Total (n = 120)
Age (years)	33.2 ± 13.2	36.7 ± 16.4	33.7 ± 14.9	34.5 ± 14.9
Male	26 (65)	29 (73)	24 (60)	79 (66)
Height (cm)	169.81 ± 8.90	168.73 ± 9.26	166.46 ± 8.61	168.33 ± 8.96
Weight (kg)	70.75 ± 14.66	68.91 ± 12.73	65.85 ± 13.48	68.51 ± 13.68
BMI (kg/m ²)	24.40 ± 3.95	24.19 ± 4.14	23.64 ± 3.71	24.08 ± 3.92
Baseline EASI score	26.25 ± 10.41	30.07 ± 13.76	26.28 ± 11.14	27.53 ± 11.90
Baseline IGA score of 3	21 (52)	14 (35)	20 (50)	55 (46)
Baseline IGA score of ≥4	19 (48)	26 (65)	20 (50)	65 (54)
Baseline weekly average of daily PP-NRS score	7.38 ± 1.62	7.48 ± 1.38	7.42 ± 1.62	7.43 ± 1.53
Baseline %BSA affected by AD	42.96 ± 22.59	47.86 ± 22.00	43.31 ± 23.01	44.71 ± 22.46
%BSA affected by AD				
≥10 to <30	13 (32)	10 (25)	14 (35)	37 (31)
≥30 to <50	13 (32)	17 (42)	13 (32)	43 (36)
≥50	14 (35)	13 (32)	13 (32)	40 (33)
Baseline DLQI score	19.60 ± 5.90	17.90 ± 5.70	17.50 ± 6.40	18.30 ± 6.00
Medical history reported in ≥10% of patients				
Rhinitis allergic	14 (35)	16 (40)	16 (40)	46 (38)
Hyperlipidemia	8 (20)	4 (10)	2 (5)	14 (12)
Hepatic steatosis	7 (18)	5 (12)	2 (5)	14 (12)
Hyperuricemia	6 (15)	4 (10)	3 (8)	13 (11)
Asthma	2 (5)	5 (12)	6 (15)	13 (11)
Conjunctivitis*	2 (5)	4 (10)	2 (5)	8 (7)
Eczema	4 (10)	1 (2)	2 (5)	7 (6)
Prior systemic treatment				
Systemic glucocorticoids	6 (15)	9 (22)	5 (12)	20 (17)
Immunosuppressants	3 (8)	3 (8)	4 (10)	10 (8)
JAK inhibitors	3 (8)	2 (5)	0	5 (4)
Dupilumab	2 (5)	3 (8)	0	5 (4)

Data are presented as *n* (%) or mean ± standard deviation, unless otherwise indicated. *Conjunctivitis (MedDRA preferred term) included conjunctivitis and conjunctivitis allergic. %BSA: Percentage of body surface area; AD: Atopic dermatitis; BMI: Body mass index; DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; IGA: Investigator's Global Assessment; JAK: Janus kinase inhibitors; MedDRA: Medical Discovery for Regulatory Activities; PP-NRS: Peak pruritus Numerical Rating Scale.

patient and two spinal compression fractures in one patient in the placebo group. Spinal compression fractures led to drug discontinuation, while hepatitis E led to drug and study discontinuation. These four SAEs were considered unrelated to the study drug.

The most common TEAEs (≥10% in any treatment group) were upper respiratory tract infection, AD, hyperlipidemia, and hyperuricemia [Table 3]. Of these, there was no imbalance in upper respiratory tract infection between the CM310 groups and the placebo group. Patients dosed with placebo reported higher incidence of

AD than those treated with CM310 (placebo, 10%; high-dose, 0; low-dose, 8%), whereas hyperlipidemia and hyperuricemia were more common in CM310-treated patients. Conjunctivitis (MedDRA preferred term: conjunctivitis, conjunctivitis allergic, and conjunctivitis bacterial) occurred at a low rate, with one patient receiving 300 mg CM310 and two patients receiving placebo (all moderate) reporting the condition.

No significant abnormalities were observed in physical examination, vital signs, 12-lead electrocardiogram, or laboratory tests among the three groups.

Table 2: Efficacy analysis of patients with moderate-to-severe atopic dermatitis (full analysis set).

Items	CM310 high-dose (n = 40)	CM310 low-dose (n = 40)	Placebo (n = 40)
Patients with EASI-75 at week 16			
Number, n (%)	28 (70)	26 (65)	8 (20)
Difference (95% CI) vs. placebo, %	50 (31, 69)	45 (26, 64)	
P value vs. placebo	<0.0001	<0.0001	
Patients with IGA 0–1 and ≥2-point improvement from baseline at week 16			
Number, n (%)	9 (22)	12 (30)	5 (12)
Difference (95% CI) vs. placebo, %	10 (–6, 26)	18 (–0, 35)	
P value vs. placebo	0.3781	0.0993	
Patients with ≥2-point improvement in IGA from baseline at week 16			
Number, n (%)	19 (48)	22 (55)	5 (12)
Difference (95% CI) vs. placebo, %	35 (16, 54)	42 (24, 61)	
P value vs. placebo	0.0012	0.0001	
Patients with EASI-90 at week 16			
Number, n (%)	16 (40)	19 (48)	4 (10)
Difference (95% CI) vs. placebo, %	30 (12, 48)	38 (19, 56)	
P value vs. placebo	0.0038	0.0004	
Patients with EASI-50 at week 16			
Number, n (%)	34 (85)	32 (80)	21 (52)
Difference (95% CI) vs. placebo, %	32 (14, 52)	28 (8, 47)	
P value vs. placebo	0.0033	0.0172	
Patients with ≥3-point reduction in weekly average of daily PP-NRS score from baseline at week 16			
Number, n (%)	24 (60)	23 (58)	10 (25)
Difference (95% CI) vs. placebo, %	35 (15, 55)	33 (12, 53)	
P value vs. placebo	0.0030	0.0060	
Patients with ≥4-point reduction in weekly average of daily PP-NRS score from baseline at week 16			
Number, n (%)	18 (45)	15 (38)	5 (12)
Difference (95% CI) vs. placebo, %	33 (14, 51)	25 (7, 43)	
P value vs. placebo	0.0026	0.0188	
LS mean percent change in weekly average of daily PP-NRS score from baseline to EOS, mean ± SE			
	–47.6 ± 5.8	–33.0 ± 5.8	–17.1 ± 6.4
Difference (95% CI) vs. placebo, %	–30.5 (–47.6, –13.5)	–15.8 (–33.0, 1.3)	
LS mean percent change in EASI score from baseline to EOS, mean ± SE			
	–81.9 ± 5.2	–70.5 ± 5.3	–51.2 ± 5.9
Difference (95% CI) vs. placebo, %	–30.7 (–46.4, –15.0)	–19.2 (–35.0, –3.4)	
LS mean percent change in AD-affected %BSA from baseline to EOS, mean ± SE			
	–74.2 ± 6.7	–62.6 ± 6.7	–33.6 ± 7.6
Difference (95% CI) vs. placebo, %	–40.6 (–60.6, –20.6)	–29.0 (–49.0, –9.0)	
LS mean change in DLQI score from baseline to EOS, mean ± SE			
	–10.3 ± 1.1	–6.5 ± 1.1	–4.1 ± 1.2
Difference (95% CI) vs. placebo, %	–6.2 (–9.4, –2.9)	–2.4 (–5.6, 0.9)	

%BSA: Percentage of body surface area; AD: Atopic dermatitis; CI: Confidence interval; DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; EOS: End-of-study; IGA: Investigator’s Global Assessment; LS: Least-squares; PP-NRS: Peak pruritus Numerical Rating Scale; SE: Standard error.

Table 3: Adverse events of patients with moderate-to-severe atopic dermatitis (safety set).

Items	CM310 high-dose (n = 40)	CM310 low-dose (n = 40)	Placebo (n = 40)
No. of TEAEs	64	79	83
Any TEAE	30 (75)	32 (80)	30 (75)
Grade 3	0	1 (2)	1 (2)
Grade 4/5	0	0	0
No. of study drug-related TEAEs	10	5	13
Any study drug-related TEAE	8 (20)	5 (12)	5 (12)
Grade 3	0	0	0
Any SAE	0	1 (2)	2 (5)
TEAE leading to treatment discontinuation	0	1 (2)	1 (2)
TEAE leading to study discontinuation	0	1 (2)	0
Death	0	0	0
TEAEs occurring in ≥5% of patients in any treatment group (MedDRA SOC or PT)			
Investigations	13 (32)	14 (35)	15 (38)
Blood bilirubin increased	3 (8)	2 (5)	1 (2)
White blood cells urine positive	3 (8)	2 (5)	0
Blood uric acid increased	2 (5)	2 (5)	1 (2)
Alanine aminotransferase increased	1 (2)	2 (5)	2 (5)
Blood creatine phosphokinase increased	2 (5)	1 (2)	2 (5)
Urinary occult blood positive	0	2 (5)	2 (5)
Blood triglycerides increased	1 (2)	1 (2)	2 (5)
Blood lactate dehydrogenase increased	1 (2)	2 (5)	1 (2)
Red blood cells urine positive	0	0	3 (8)
Aspartate aminotransferase increased	2 (5)	0	1 (2)
White blood cell count increased	0	0	2 (5)
Blood glucose increased	0	2 (5)	0
Infections and infestations	14 (35)	9 (22)	13 (32)
Upper respiratory tract infection	8 (20)	2 (5)	4 (10)
Urinary tract infection	2 (5)	0	2 (5)
Skin infection	0	3 (8)	0
Nasopharyngitis	0	2 (5)	1 (2)
Folliculitis	1 (2)	0	2 (5)
Skin and subcutaneous tissue disorders	5 (12)	6 (15)	10 (25)
Dermatitis atopic	0	3 (8)	4 (10)
Urticaria	3 (8)	0	0
Erythema	0	0	2 (5)
Skin erosion	0	0	2 (5)
Metabolism and nutrition disorders	5 (12)	6 (15)	6 (15)
Hyperlipidemia	4 (10)	2 (5)	1 (2)
Hyperuricemia	0	5 (12)	1 (2)
Gastrointestinal disorders	1 (2)	4 (10)	3 (8)
Dental caries	0	2 (5)	0
Hepatobiliary disorders	1 (2)	0	2 (5)
Hepatic function abnormal	0	0	2 (5)
General disorders and administration site conditions	1 (2)	2 (5)	0
Injection site reaction	0	2 (5)	0

Data are presented as *n* (%), unless otherwise indicated. MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred term; SAE: Serious adverse event; SOC: System organ class; TEAE: Treatment-emergent adverse event. Unless otherwise stated, data are presented as the number and percentage of patients. TEAEs were encoded by MedDRA v24.1.

Biomarker

The mean percent change in serum TARC decreased from baseline at week 16 in CM310-treated patients, but increased in placebo-treated patients (high *vs.* placebo, -63.42% *vs.* 29.89% , $P = 0.0003$; low *vs.* placebo, -49.99% *vs.* 29.89% , $P = 0.0035$). However, unlike the high-dose group, where serum TARC remained almost unchanged at week 24 (-61.35%), the mean percent change in serum TARC increased to 2.78% in the low-dose group. The mean percent change in serum total IgE also declined from baseline in CM310-treated patients, but increased in placebo-treated patients (at week 24: high *vs.* placebo, -54.92% *vs.* 43.53% , $P < 0.0001$; low *vs.* placebo, -44.52% *vs.* 43.53% , $P = 0.0001$). At week 16, the mean change in lactate dehydrogenase from baseline was higher in the high-dose and low-dose groups than in the placebo group (high *vs.* placebo, -65.21 U/L *vs.* -4.57 U/L, $P = 0.0001$; low *vs.* placebo, -75.72 U/L *vs.* -4.57 U/L, $P = 0.0005$); the mean changes in blood eosinophil count were $-0.099 \times 10^9/L$, $-0.193 \times 10^9/L$, and $-0.006 \times 10^9/L$ in the high-dose, low-dose, and placebo groups, respectively (both P values > 0.05) [Supplementary Figure 5, <http://links.lww.com/CM9/B608>].

Discussion

Over a 16-week treatment period, both CM310 regimens (150 mg and 300 mg every 2 weeks) produced marked improvements in AD clinical manifestations, including pruritus, skin lesions, and quality of life. Furthermore, CM310 was well-tolerated with a favorable safety profile.

Clinical trials of dupilumab have shown that dupilumab improves AD symptoms by blocking IL-4R α .^[12,16] Similar to dupilumab, CM310 also specifically binds to the IL-4R α , blocking the signaling of both IL-4 and IL-13, thereby reducing type 2 inflammatory activity. A phase 3 study of dupilumab in China showed that 57.3% of patients with moderate-to-severe AD achieved EASI-75 response after 16-week treatment, along with an acceptable safety profile.^[17] In this trial of CM310, a statistically significant higher proportion of CM310-treated patients achieved EASI-75 compared with placebo starting at week 4 and sustained through week 24. Notably, EASI-75 response rates were maintained in more patients receiving CM310 at 300 mg than 150 mg after drug withdrawal.

The CM310 groups did not exhibit significant superiority in the response rate for achieving an IGA score of 0/1 with ≥ 2 -point reduction at week 16 compared with placebo. However, the response rate of IGA ≥ 2 -point reduction was significantly higher in the CM310 groups than in the placebo group. Excluding the confounding impact of COVID-19, a significantly higher proportion of patients in the CM310 groups achieved an IGA score of 0/1 with ≥ 2 -point reduction than placebo-treated patients.

Pruritus is a debilitating symptom of AD that causes patients to scratch, resulting in further aggravation of

AD.^[18] In the current trial, 16-week CM310 monotherapy, particularly the high-dose, displayed rapid and substantial amelioration in pruritus, as assessed by PP-NRS. More patients in the CM310 groups *vs.* the placebo group achieved ≥ 3 - and ≥ 4 -point improvements in the weekly average of daily PP-NRS score from weeks 4 and 6, respectively. Superiority over placebo was also found in the CM310 groups regarding percent change from baseline at week 16 in PP-NRS score. Moreover, in comparison with the CM310 low-dose group, the improvement in pruritus persisted up to week 24 in the CM310 high-dose group, suggesting that the high-dose regimen produced better clinical benefits in improving pruritus symptoms. Achieving an improvement in pruritus may contribute to the improvement of life quality.

CM310 demonstrated favorable tolerability and safety profile. The overall incidence of adverse events was similar across the CM310 and placebo groups, except for higher risks of skin and subcutaneous tissue disorders (including AD, erythema, and skin erosion) in placebo-treated patients. This difference could be attributed to the effect of CM310 in restoring skin-barrier function and decreasing scratching. Patients receiving 300 mg CM310 had a higher incidence of upper respiratory tract infection than those receiving 150 mg, but the incidence of treatment-related upper respiratory tract infection was similar between the two groups (5% *vs.* 2%). The findings may be impacted by possible external interference and limited sample size. Unlike more common TEAEs (e.g., conjunctivitis, injection site reaction, and nasopharyngitis) reported in dupilumab trials,^[19,20] elevated rates of hyperlipidemia and hyperuricemia were observed in CM310-treated patients, presumably due to their daily diet. A higher incidence of hyperuricemia was found in the low-dose group (none was considered to be study drug-related), which might be affected by transient elevations of uric acid. In addition, the incidence of conjunctivitis was low in each cohort. Further studies of CM310 (e.g., ongoing phase 2 extension study and phase 3 study) are necessary to evaluate these AEs.

AD activity and severity have been reported to be associated with Th2-related biomarker levels.^[21] In this trial, CM310 led to marked reductions in serum levels of total IgE and lactate dehydrogenase, with IgE decreasing slowly and continuously until week 20 and lactate dehydrogenase showing a rapid initial decrease during the first 4 weeks, followed by a subtle incremental decrease over the remainder of the treatment duration. TARC is a chemotactic factor that selectively attracts Th2 cells.^[22] This study showed rapid decrease in serum TARC with CM310 *vs.* placebo from baseline to week 4, which was maintained through week 16. During safety follow-up period, however, serum TARC level returned to prior treatment in low-dose group and remained unchanged in high-dose group; similar trends were also seen in both CM310 groups regarding DLQI and PP-NRS, suggesting that TARC might be more sensitive to the efficacy of CM310 than other pharmacodynamic biomarkers.

This phase 2b study presents limitations as it focuses solely on Chinese patients with moderate-to-severe AD, and has a small sample size as well as a short treatment duration. Subsequent trials, such as the extension trial (CM310AD100), are underway to assess the long-term efficacy and safety of CM310 in a broader population with moderate-to-severe AD.

In conclusion, both CM310 regimens (150 mg and 300 mg every 2 weeks) significantly improved AD signs and symptoms and quality of life in adults with moderate-to-severe AD, with a favorable safety profile. This trial provides further evidence that IL-4R α is a key target in the treatment of AD and that CM310 is a promising biologic therapy for adults with moderate-to-severe AD.

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Conflicts of interest

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