Asivatrep, a TRPV1 antagonist, for the topical treatment of atopic dermatitis: Phase 3, randomized, vehicle-controlled study (CAPTAIN-AD)

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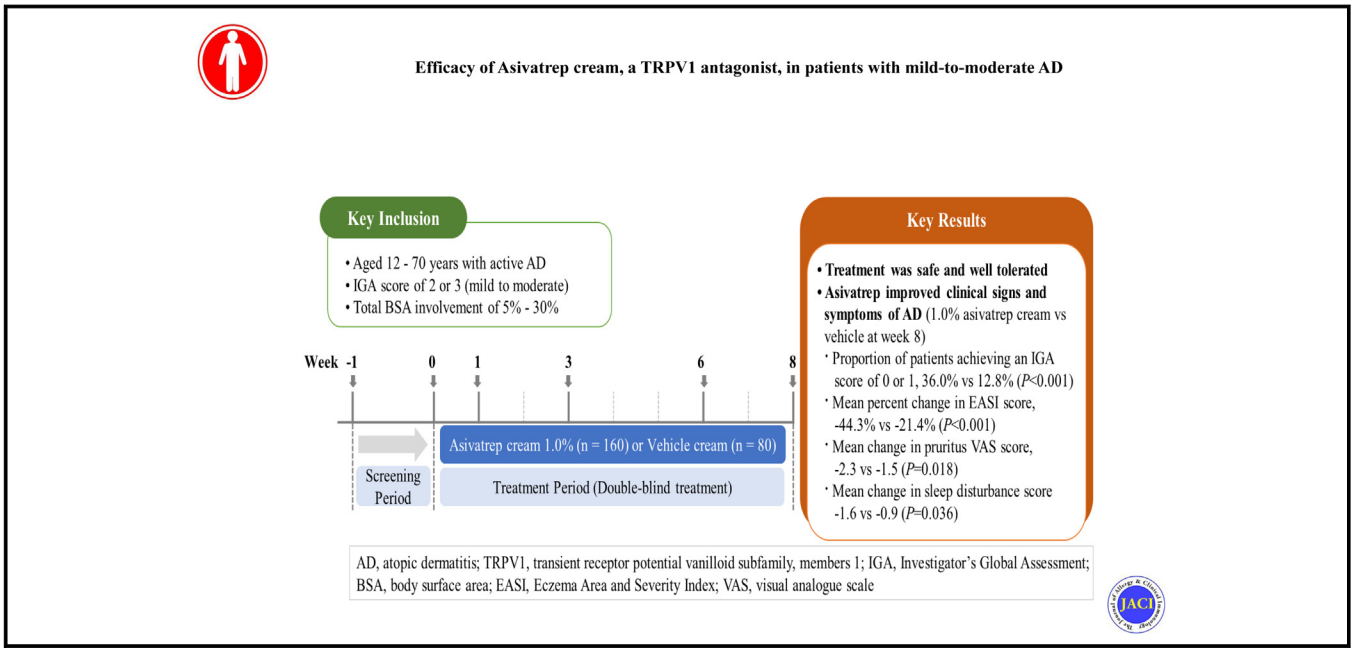
GRAPHICAL ABSTRACT



Background: Asivatrep is a potent and selective antagonist of transient receptor potential vanilloid subfamily V member 1 (TRPV1), which plays an important role in itch and inflammation in atopic dermatitis (AD).

Objective: This current study aimed to evaluate the efficacy and safety of asivatrep cream in patients with AD.

Methods: For this phase 3 double-blind, vehicle-controlled study, patients aged ≥12 years with mild to moderate AD were

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Disclosure of potential conflict of interest: B. J. Kim has served as consultant and investigator for AMOREPACIFIC. Y. W. Lee has been investigator or consultant of AMOREPACIFIC, Galderma, Lilly, SCM Lifescience Co Ltd, and Therabest Co Ltd. C. Won has been an investigator for AstraZeneca, Celltrion, Dermira, Medipl, and Kangstem Biotech. D. H. Lee has been a consultant, investigator, and/or advisory board member for AbbVie, AMOREPACIFIC, Cutisbio, EHL Bio, HaplnScience, Kangstem Biotech, Novartis, Sanofi, and SCM Lifescience. K. Jung, H.-J. Nam, G. Choi, Y.-H. Park, and M. Park are employees of AMOREPACIFIC. The rest of the authors declare that they have no relevant conflicts of interest.

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enrolled and randomly assigned 2:1 to the 1.0% asivatrep or vehicle group for 8 weeks of twice-daily application (n = 240). The primary end point was the proportion of patients with an Investigator's Global Assessment score (IGA) of 0 or 1 at week 8. Standard safety assessments were conducted.

Results: At week 8, significantly more patients in the asivatrep group (36.0%) than in the vehicle group (12.8%) had IGA scores of 0 or 1 ($P < .001$); significantly more had ≥2 points of improvement on the IGA from baseline score (20.3% vs 7.7%; $P = .01$). The mean percentage reduction in the Eczema Area and Severity Index (EASI) score was 44.3% for the asivatrep group and 21.4% for the vehicle group at week 8 ($P < .001$). Significantly more asivatrep-treated patients experienced an improvement of at least 50%, 75%, and 90% on the EASI than the vehicle group. The mean ± SD change in the pruritus visual analog scale score at week 8 was −2.3 ± 2.4 for the asivatrep group and −1.5 ± 2.4 for the vehicle group ($P = .02$). No significant safety issues were reported.

Conclusion: Asivatrep improved clinical signs and symptoms of AD and was well tolerated. (J Allergy Clin Immunol 2022;149:1340-7.)

Key words: *Atopic dermatitis, asivatrep, transient receptor potential vanilloid subfamily member 1 (TRPV1), pruritus*

Atopic dermatitis (AD) is a chronic inflammatory pruritic skin disease that flares periodically and has a high prevalence of approximately 25% in children and 10% in adults, although it depends on the countries surveyed.[1-4] Both genetic and environmental factors have been implicated as risk factors for the progression of AD. Importantly, the pathophysiology of AD is complex and multifactorial, involving alterations in the T-helper type 2 cell–mediated immune response, IgE-mediated hypersensitivity, and epidermal barrier dysfunction.[5-7] Currently, there are 3 classes of topical therapies for AD that have been approved by the US Food and Drug Administration: topical corticosteroids (TCSs), topical calcineurin inhibitors (TCIs), and one phosphodiesterase 4 inhibitor.[8-11] However, novel topical treatment options that are more effective and safe are still needed for long-term disease management as a result of safety concerns and increased patient nonadherence. In particular, long-term use of TCSs may lead to cutaneous adverse reactions, such as thinning of the skin and telangiectasia.[8-10] TCIs often cause symptoms of irritation, such as burning and stinging, at the application site, especially in the initial phase of treatment, and there is patient and physician reluctance as a result of black-box warnings regarding a possible cancer risk.[8-10]

The transient receptor potential vanilloid subfamily V member 1 (TRPV1), a nonselective cation channel, is expressed in keratinocytes, mast cells, and cutaneous sensory nerves, indicating that it plays an important role in cutaneous physiology and disease.[12,13] TRPV1 is involved in the pathogenesis of inflammation and serves as a key downstream signaling molecule for histamine-independent and -dependent itch in patients with AD.[13-16] The axon reflexive flare accompanying itch occurs through the TRPV1-controlled release of neuropeptides, such as substance P and calcitonin gene–related peptide, which increases pruritogenic stimuli.[17-19] Interestingly, TRPV1 is overexpressed in the skin lesions of AD, and its activation results in the release of molecules that enhance both pruritus and inflammation.[15,20,21]

Abbreviations used

AD:	Atopic dermatitis
EASI:	Eczema Area and Severity Index
EASI-50:	At least 50% improvement in EASI score
EASI-75:	At least 75% improvement in EASI score
EASI-90:	At least 90% improvement in EASI score
IGA:	Investigator's Global Assessment
TCI:	Topical calcineurin inhibitor
TCS:	Topical corticosteroid
TEAE:	Treatment-emergent adverse event
TRPV1:	Transient receptor potential vanilloid subfamily V member 1
VAS:	Visual analog scale

Thus, TRPV1 inhibition may be a potential therapeutic target for the treatment of AD.

Asivatrep (PAC-14028, $C_{21}H_{22}F_5N_3O_3S$) cream (1.0%) is a nonsteroidal TRPV1 antagonist designed to treat mild to moderate AD.[22] Preclinical analyses in rats and mice revealed asivatrep to be noncarcinogenic and effective at suppressing AD-like skin inflammation.[23-25] Subsequently, a phase 2 clinical trial was conducted in adult patients with mild to moderate AD over 8 weeks (ClinicalTrials.gov NCT02757729). During that trial, 3 different concentrations of asivatrep (0.1%, 0.3%, and 1.0%) were compared to a vehicle cream.[26,27] The 1.0% asivatrep was superior to the vehicle cream in terms of ameliorating the signs and symptoms of AD. The application of asivatrep twice daily for 8 weeks also had a good safety profile, with a far lower incidence of treatment-related adverse events compared to vehicle.

The present phase 3 study investigated the efficacy and safety of 1.0% asivatrep cream in patients aged 12 years or older with mild to moderate AD over an 8-week period.

METHODS

Study design

CAPTAIN-AD (NCT02965118) was conducted in a phase 3, randomized, double-blind, vehicle-controlled manner at 6 hospitals in the Republic of Korea in patients aged 12 to 70 years with mild to moderate AD. The included patients (240 of 254 screened) were randomized at a ratio of 2:1 to the 1.0% asivatrep or the vehicle cream group for 8 weeks. During the treatment period, patients underwent clinical and safety assessments at weeks 1, 3, 6, and 8 (Fig 1).

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines, and applicable regulatory requirements. The institutional review boards at each hospital in the Republic of Korea approved the study protocol, informed consent form, and relevant supporting data.

Patient population

Eligible patients were aged 12 years or older, had mild to moderate AD, and met the following inclusion criteria: a physician's diagnosis of AD according to the Hanifin and Rajka diagnostic criteria; AD affecting 5% to 30% of their body surface area; an Investigator's Global Assessment (IGA) score of 2 (mild) or 3 (moderate); and had been applying a moisturizer (emollient) at least once daily at a stable dose for at least the 7 days immediately before the baseline visit.

Patients were excluded from participation for any of the following reasons: serious skin diseases other than AD or widespread scarring at the AD lesion site; skin diseases resulting from other medical, psychologic, or neuropathic causes; active pruritus caused by chronic urticaria or allergens such as scabies

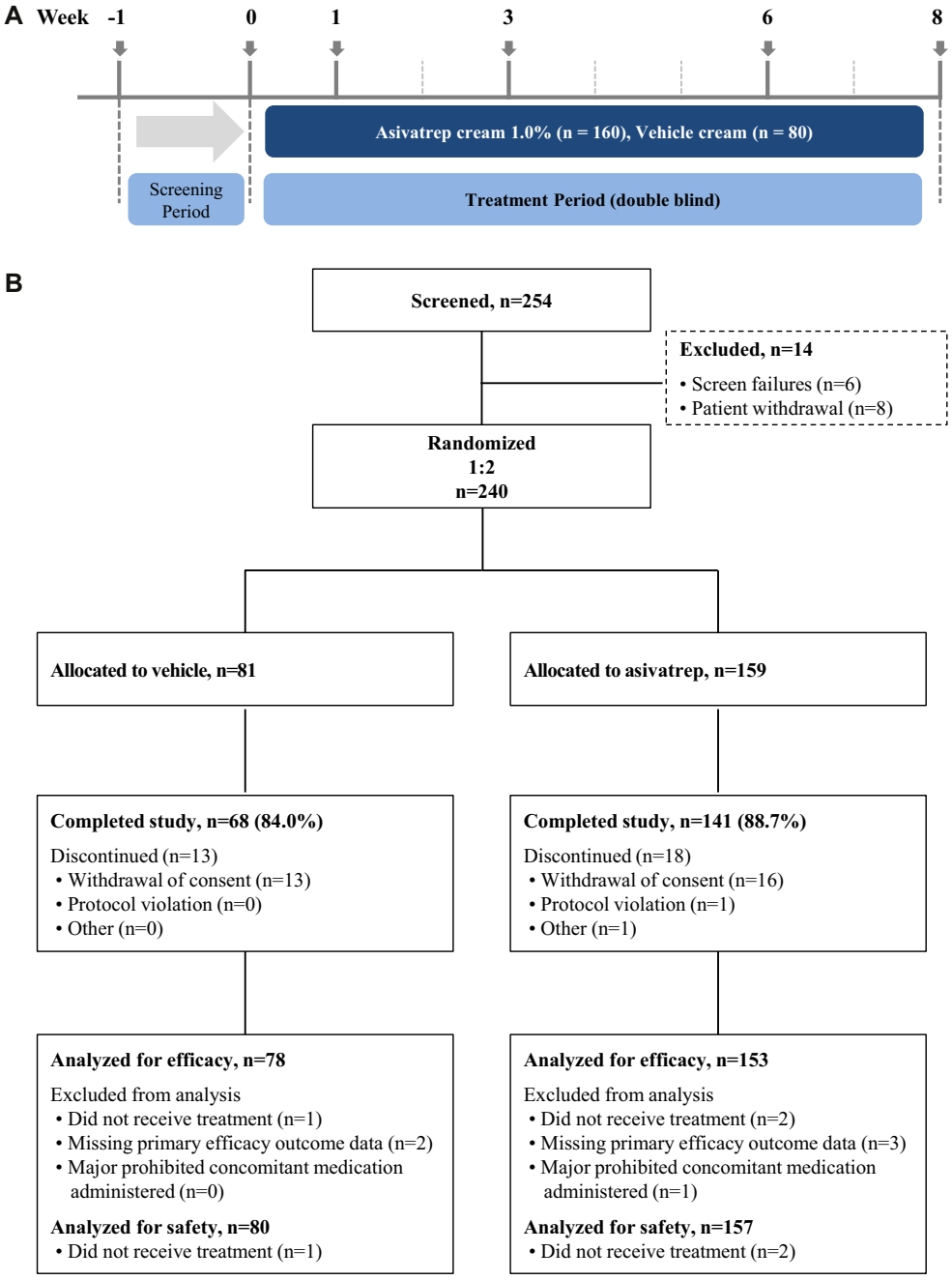

FIG 1. **A,** Study design. **B,** Patient disposition.

and insect bites; acute or chronic hepatitis or known liver cirrhosis; an unstable or uncontrolled chronic medical disease; history of a malignant tumor or an active malignant tumor; prior receipt of corticosteroids, antibiotics, or immunosuppressants for systemic treatment; phototherapy or immunotherapy treatment in the preceding 28 days; a history of treatment with biological products (eg, omalizumab and infliximab) in the preceding 16 weeks; and the receipt of TCSs, TCIs, or antibiotics in the preceding 14 days.

Randomization, blinding, and treatment

An independent statistician assigned the patients randomly at a ratio of 2:1 to the asivatrep or the vehicle cream group through the stratified block randomization method considering the 6 hospitals using SAS version 9.3 (SAS Institute, Cary, NC). Blinded and coded kits containing asivatrep or the vehicle cream were used to conceal the assigned treatment. The physical appearance, color, texture, and homogeneity of each of the strengths of the asivatrep and vehicle cream were kept consistent.

During the 8-week treatment period, patients were required to apply the investigational cream to areas of AD twice daily by rubbing it evenly to form a thin film. Furthermore, a moisturizer, which was provided to all patients at the time of randomization, could be used on dry skin other than the skin lesions affected by AD regularly for 8 weeks. Assessments were conducted at baseline and at weeks 1, 3, 6, and 8 by the same assessor for consistency.

Study end points

The primary efficacy end point was the proportion of patients with an IGA score of 0 or 1 in the score at week 8 as evaluated by a physician using the

6-point IGA scale (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe, and 5 = very severe). A key secondary end point was to determine the proportion of patients who had an IGA score of 0 or 1 with a 2-point or greater improvement from baseline to week 8.

The other key secondary end points included changes or percentage changes from baseline in Eczema Area and Severity Index (EASI) score, pruritus visual analog scale (VAS) score, and sleep disturbance score at weeks 1, 3, 6, and 8. The EASI score ranges from 0 to 72, with higher scores indicating greater severity and an increased extent of erythema, induration, papulation and edema, excoriation, and lichenification. The VAS and sleep disturbance scores were self-assessed by patients at each visit through recalling symptoms experienced in the preceding 3 days. The numerical rating scale ranges from "no itching" (0) to "worst imaginable itching" (10). Additional secondary end points were the proportion of patients with an improvement in the EASI of at least 50% (EASI-50), 75% (EASI-75), and 90% (EASI-90) at week 8.

Over the 8-week treatment period, safety parameters were evaluated by adverse event reporting, clinical laboratory testing, electrocardiogram recordings, vital signs, and physical examinations.

Statistical analyses

The sample size calculation was based on the results from the phase 2b study of asivatrep cream in adult patients with AD.[26] A total of 240 patients were required to adequately assess safety and to have at least 80% power to detect a significant difference between the 1.0% asivatrep and vehicle groups in the primary efficacy end point (the proportion of patients with an IGA score of 0 or 1 at week 8). The number of patients was calculated using the statistical program PASS 13 (NCSS Statistics Software, Kaysville, Utah).

The full analysis set population, which included all randomized patients who were administered investigational products at least once and from whom data efficacy data could be obtained at least once at baseline or after, was used for the efficacy analyses. For the full analysis set, the last observation carried forward method was used for missing data. The Pearson chi-square test or the Fisher exact test were used to determine any differences in the IGA success rate between the 2 groups. Analyses of the EASI, pruritus VAS, and sleep disturbance scores were performed using a 2-sample *t* test or Wilcoxon rank-sum test.

For the safety analysis, all patients who were administered the investigational product at least once were included. Differences between the groups in terms of treatment-emergent adverse events (TEAEs), adverse drug reactions, and serious adverse events were analyzed using the Pearson chi-square test or Fisher exact test. The TEAEs, adverse drug reactions, and serious adverse events were coded using the system organ classes and the MedDRA version 21.0 preferred terms.

RESULTS

Patient population

Of 254 patients screened, 240 eligible patients (94.5%) with mild to moderate AD were randomized in a 2:1 ratio to either the 1.0% asivatrep cream (n = 159) or vehicle cream (n = 81) group (Fig 1, *A*). Most patients in the asivatrep (141/159, 88.7%) and vehicle (68/81, 84.0%) groups completed the study to week 8. In particular, 18 of the patients assigned to the asivatrep group discontinued study treatment because of patient withdrawal of consent (n = 16), major protocol violation (n = 1), or worsening of AD considered unrelated to treatment (n = 1). A total of 231 patients (asivatrep, 153 patients; vehicle, 78 patients) were included in the full analysis set analysis, while all 237 patients (asivatrep, 157 patients; vehicle, 80 patients) who received at least 1 dose of the study treatment were included in the safety population (Fig 1, *B*).

The randomized groups were well balanced in terms of demographics and baseline characteristics (Table I).

TABLE I. Patient demographics and baseline characteristics

Characteristic	Vehicle cream (n = 80)	Asivatrep cream (n = 157)
Age (years), mean ± SD	25.3 ± 8.0	26.0 ± 8.3
Age		
12-19 years	12 (15.4)	24 (15.7)
19-70 years	66 (84.6)	129 (84.3)
Female	37 (47.4)	67 (43.8)
Total body surface area (%), mean ± SD	12.3 ± 7.5	13.4 ± 7.6
IGA score		
2 (mild)	34 (43.6)	61 (39.9)
3 (moderate)	44 (56.4)	92 (60.1)
EASI, mean ± SD	7.9 ± 4.6	8.6 ± 4.8
Pruritus VAS, mean ± SD	5.4 ± 2.0	5.6 ± 1.8

Data are presented as no. (%) of patients unless otherwise indicated.

Efficacy

IGA success. At week 8, the IGA score in the asivatrep treatment group was significantly lower than that in the vehicle-treated group. The proportion of patients who had an IGA score of 0 (clear) or 1 (almost clear) was 36.0% (55/153) in the asivatrep group and 12.8% (10/78) in the vehicle group ($P < .001$) (Fig 2, *A,* and see Table E1 in this article's Online Repository at www.jacionline.org). Additionally, compared to the vehicle group, a greater proportion of patients in the asivatrep group had an IGA score of 0 or 1 and an improvement of at least 2 points on the IGA from baseline score (20.3% vs 7.7%; $P = .01$) (Fig 2, *B,* and Table E1). The proportion of patients who had an IGA score of 0 or 1 in the asivatrep group also continued to decrease significantly at week 3, 6, and 8 after treatment, compared to that in the vehicle group (Fig 2, *C,* and see Table E2 in this article's Online Repository at www.jacionline.org).

EASI score. The mean percentage change in the EASI score from baseline to week 8 was greater in the asivatrep treatment group than in the vehicle-treated group (Fig 3, *A,* and Table E2). The greatest significant difference was observed at week 8, with a reduction of 44.3% in the asivatrep group versus 21.4% in the vehicle group ($P < .001$). Additionally, significantly more patients in the asivatrep group experienced an improvement of at least 50% (EASI-50), 75% (EASI-75), and 90% (EASI-90) (50.3%, 23.5%, and 9.8%) compared to the vehicle group (28.2%, 11.5%, and 2.6%) at week 8 ($P = .001$, $P = .03$, and $P = .046$, respectively) (Fig 3, *B,* and Table E1). Asivatrep was found to effectively reduce disease severity, as evidenced by the reduction in signs of AD. Representative clinical images are shown in Fig 4.

Pruritus and sleep. Patient-reported assessments of itch in the asivatrep treatment group were lower than those in the vehicle-treated group at week 1, which was maintained until week 8 (Fig 5, *A,* and Table E2). At week 8, the mean ± SD change in the patient-reported pruritus VAS scores from baseline was significantly greater among patients who received asivatrep (reduction of 2.3 ± 2.4) compared to those who received the vehicle (reduction of 1.5 ± 2.4) ($P = .018$).

Similarly, asivatrep-treated patients had a greater reduction in sleep disturbance caused by itching than the vehicle-treated patients at weeks 3, 6, and 8 (Fig 5, *B,* and Table E2). Significantly, more patients receiving the asivatrep cream (reduction

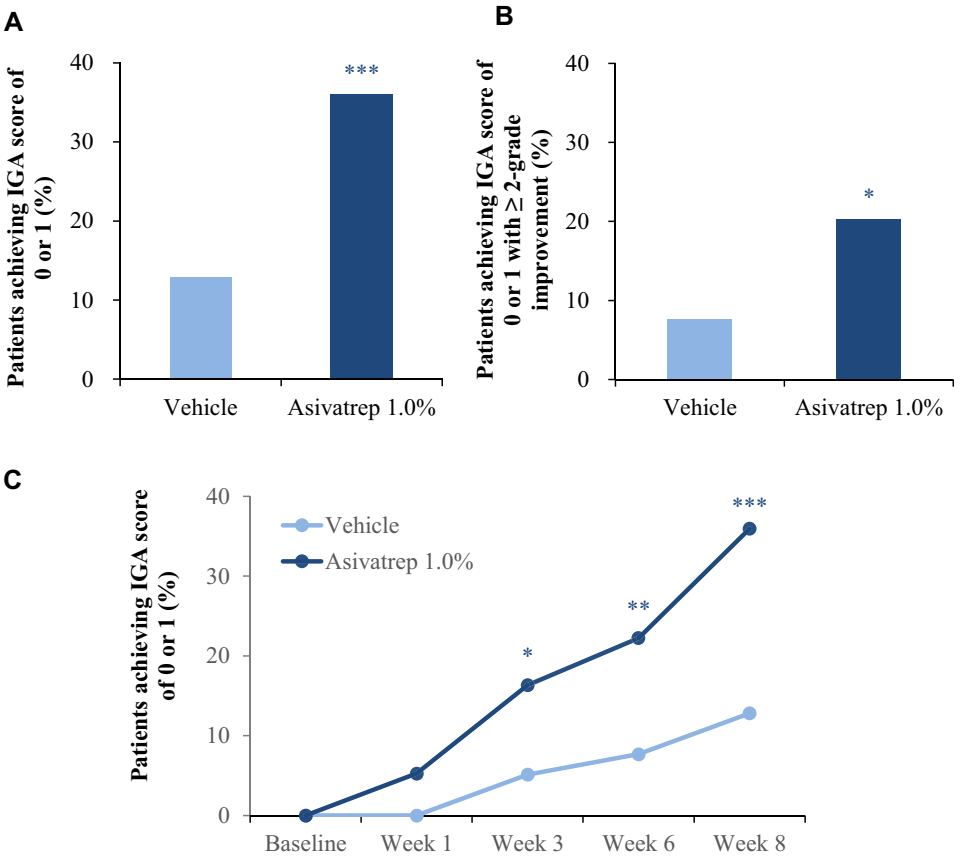

FIG 2. IGA score. **A,** Proportion of patients with an IGA score of 0 or 1 (clear or almost clear) at week 8. **B,** Proportion of patients with an IGA score of 0 or 1 with ≥2-point improvement from baseline at week 8. **C,** Proportion of patients with an IGA score of 0 or 1 at weeks 1, 3, 6, and 8. *P < .05, **P < .01, ***P < .001 vs vehicle.

of 1.6 ± 2.5) had an improved sleep disturbance score at week 8 compared to those who received the vehicle (reduction of 0.9 ± 2.4) (P = .036).

Safety

The asivatrep cream was well tolerated and was not associated with clinically significant application site reactions (Table II and see Table E3 in this article's Online Repository at www.jacionline.org). Overall, the incidence of TEAEs was reported in 14.7% (23/157) of patients treated with asivatrep and 6.3% (5/80) of patients treated with vehicle cream. There was a slightly greater incidence of TEAEs with asivatrep compared to vehicle cream, which was not statistically significant (P = .06). The most common TEAEs (≥2% of patients treated with asivatrep cream) were nasopharyngitis (2.6%), urticaria (1.3%), burning sensation (1.3%), and rhinorrhea (1.3%), which were similar in the vehicle group. No adverse events led to discontinuation. Although a larger proportion of patients in the vehicle group (16.0%) prematurely discontinued the study than in the asivatrep group (11.3%), there were no adverse events leading to discontinuation (Fig 1, *B*). The incidence of adverse drug reactions was 6.4% (10/157) in the asivatrep treatment group and 5.0% (4/80) in the vehicle treatment group (P = .78). The most common adverse drug reactions (≥2% of patients treated with asivatrep) were nasopharyngitis (1.3%), urticaria (1.3%), and a burning sensation (1.3%). Serious adverse events were not reported. The occurrence of overall TEAEs and adverse drug reactions was acceptable and comparable between the groups.

In addition, no clinically relevant changes in laboratory parameters, vital signs, electrocardiography results, or physical examinations were found in any of the treatment groups.

DISCUSSION

This phase 3 trial demonstrated that treatment with asivatrep cream resulted in a greater amelioration of clinical signs and symptoms of AD, as assessed by IGA, EASI, and pruritus VAS scores, compared to vehicle cream. The present study provides additional evidence that topical TRPV1 antagonist is a promising topical medication for patients with AD.

Our findings confirm and expand the results of the previous phase 2b trial of asivatrep cream in patients with mild to moderate AD.[26] This phase 3 clinical trial included patients aged 12 years or older with mild to moderate AD. The primary end point of efficacy, evaluated by comparing the proportion of patients with an IGA score of 0 or 1 between the groups at week 8, was significantly higher in the asivatrep treatment group (36.0% vs 12.8%;

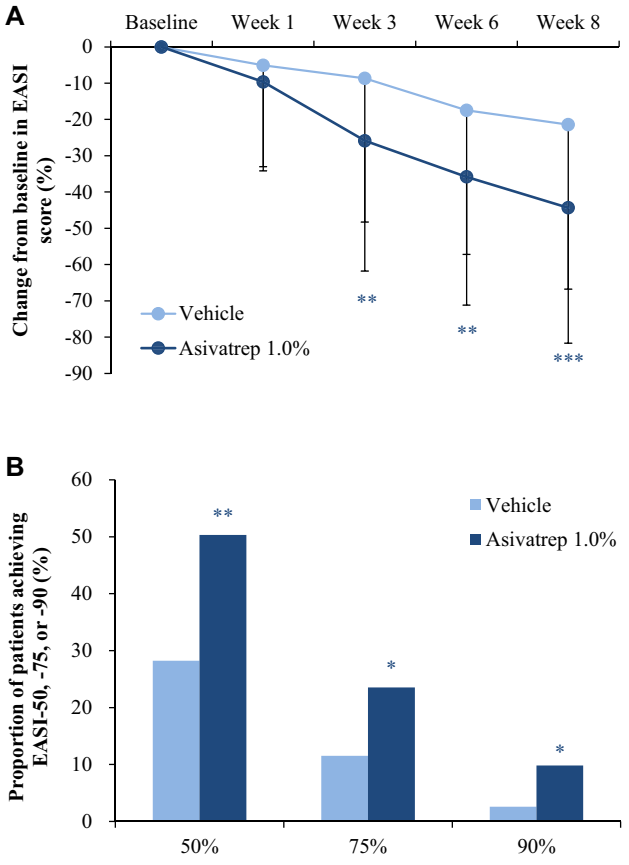

FIG 3. EASI score. **A,** Mean percentage change from baseline in EASI scores at weeks 1, 3, 6, and 8. **B,** Proportion of patients with an improvement from baseline of at least 50%, 75%, or 90% on the EASI at week 8. *$P < .05$, **$P < .01$, ***$P < .001$ vs vehicle.

$P < .001$). The IGA success rates in the asivatrep group showed greater improvement from week 1 to week 8. Moreover, at week 8, significantly more patients in the asivatrep group had an IGA score of 0 or 1 and an improvement of 2 points or more from baseline compared to the vehicle cream group (20.3% vs 7.7%; $P = .01$). However, the efficacy shown in this study was less than the results found in the asivatrep phase 2b study at 8 weeks, particularly with the 1.0% concentration, with IGA success rates of 36.0% vs 57.5%, respectively.[26] This difference observed between phase 3 and 2b trials is probably due to the differences in the drug compliance (90% vs 96%), the mean duration of AD (15 vs 6.9 years), and/or the patient population with or without the inclusion of children.

The application of asivatrep cream twice a day significantly improved the mean percentage change from baseline for the EASI score versus the vehicle group at week 8 (−44.3% vs −21.4%; $P < .001$); the data were consistent across all clinical signs, including IGA response. Significant improvements of at least 50%, 75%, and 90% in the EASI score at week 8 were observed in more patients receiving asivatrep than among those receiving vehicle (50.3%, 23.5%, and 9.8% vs 28.2%, 11.5%, and 2.6%, respectively). Although IGA success/IGA 0 or 1 has been generally accepted to be correlated with EASI-90, the current data found a discrepancy between the EASI-90 and the IGA 0 or 1 in asivatrep-treated patients (9.8% vs 36.0%, respectively). Because the IGA focuses on erythema and papulation, but lacks consideration for the disease extent (percentage of body surface area affected), this discrepancy may be attributed to some patients with just perceptible erythema but remaining chronic lichenification, or in a rather large area of involvement at the end of treatment. In addition, 1-grade improvement of IGA in patients with baseline mild AD (IGA score of 2) could have a relatively high probability of experiencing an IGA score of 1. However, considering the EASI-75 (23.5%) and the proportion of patients with an

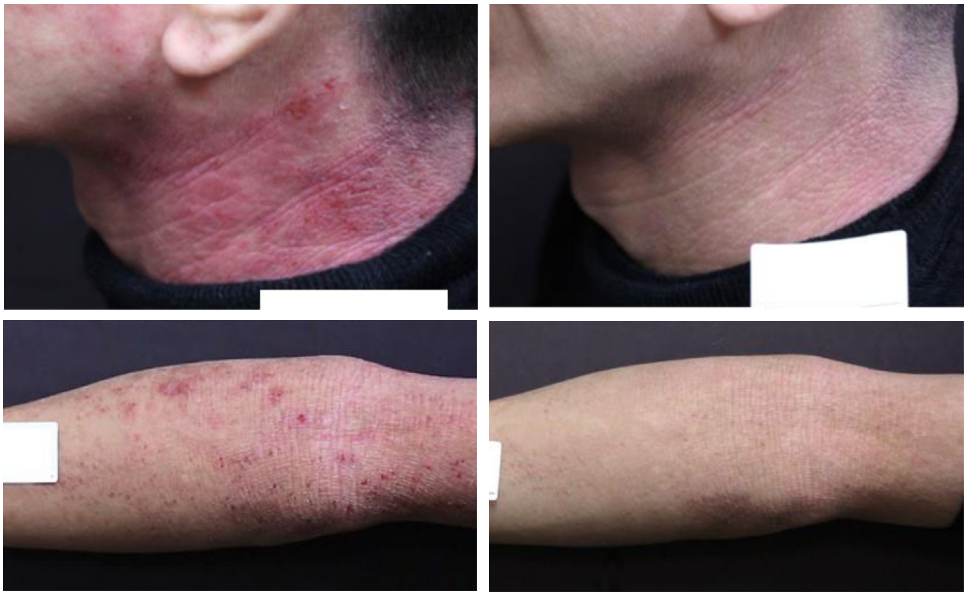

FIG 4. Representative photographs of patients treated with asivatrep cream.

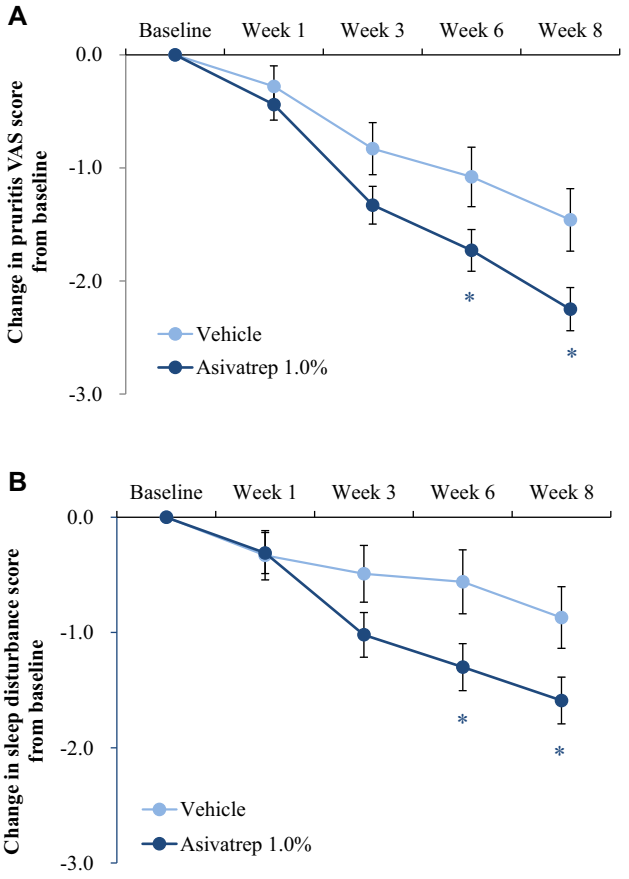

FIG 5. Pruritus VAS and sleep disturbance score. **A,** Mean change from baseline in pruritus VAS score at weeks 1, 3, 6, and 8. **B,** Mean change from baseline in sleep disturbance score at weeks 1, 3, 6, and 8. Data are presented as means (SDs). *$P < .05$ vs vehicle.

TABLE II. Summary of adverse events

Characteristic	Vehicle cream (n = 80)	Asivatrep cream (n = 157)
TEAEs	5 (6.3)	23 (14.7)
Adverse drug reactions	4 (5.0)	10 (6.4)
Serious adverse events	0	0
TEAEs leading to discontinuation	0	0
TEAEs occurring in ≥2 patients		
Nasopharyngitis	5 (6.3)	4 (2.6)
Urticaria	1 (1.3)	2 (1.3)
Burning sensation	0	2 (1.3)
Rhinorrhea	0	2 (1.3)

Data are presented as no. (%) of patients.

IGA score of 0 or 1 and an improvement of 2 points on the IGA (20.3%) in the asivatrep group, these values are not that far apart.

In addition, marked and lasting improvements during treatment period in patient-reported symptoms of AD, including pruritus and sleep, were also observed in the asivatrep group. The improvement in pruritus VAS scores in the asivatrep group was significantly greater than those observed in the vehicle group at week 8 (−2.3 vs −1.5; $P = .02$). These results show that significant improvements were found for all efficacy parameters in the asivatrep group compared to the vehicle group for both adolescent and adult patients. Sensitivity analyses showed that the efficacy results were not affected by the proportion of patients with missing data (n = 23, 10.0%) handled with the last observation carried forward and were also the same as the primary analysis (see Table E4 in this article's Online Repository at www.jacionline.org).

Asivatrep is a potent and selective TRPV1 antagonist.[25,28] TRPV1, a nonselective cation channel, is well characterized in the skin and has been implicated in itch signaling and inflammation regulation.[28,29] In AD-like murine models, topically administered asivatrep cream led to effective suppression of the inflammatory response, decreasing the levels of type 2 cytokines (IL-4 and IL-13).[25] This directly inhibits the increased release of neuropeptides substance P and calcitonin gene–related peptide, which decreases pruritogenic tone. Intriguingly, asivatrep cream promotes skin barrier function by producing epidermal differentiation markers such as loricrin, filaggrin, involucrin, and suprabasal/differentiation-related keratins. Therefore, the efficacy of asivatrep cream may be explained by the decrease in the expression and activation of TRPV1 in the lesioned skin leading to the attenuation of dermatitis and pruritus, and by the concomitant improvement in the integrity of the epidermal barrier. However, further research is needed to confirm this potential mechanism.

Treatment with asivatrep cream was well tolerated over the 8-week treatment period in patients with AD aged 12 years and older. Although the incidence of TEAEs was higher in the asivatrep-treated group (14.7%) than in the vehicle group (6.3%), the TEAEs reported were generally mild in severity. All these events recovered or stabilized during the treatment period; most TEAEs were unrelated to asivatrep. Moreover, hyperthermia, which is commonly elicited by systemic TRPV1 antagonists, was not reported during the 8 weeks of treatment with asivatrep cream, which was consistent with a previous study.[26] Overall, the safety results suggest that asivatrep cream has a favorable safety profile as a topical agent for AD. Consequently, considering that the mainstay of treatment in the management of AD is TCSs, which are associated with systemic and cutaneous adverse reactions, or TCIs with black-box warnings, asivatrep cream, with its minimal adverse events, can provide a new alternative treatment for adolescents and adults, although long-term safety data have not yet been reported.

The present study has a few limitations. First, the 8-week treatment period could not address the efficacy and safety of long-term treatment. Second, this trial evaluated adolescents and adults but not the pediatric population (birth to age 11 years), in whom AD is more prevalent. A recent study evaluated the pharmacokinetics, preliminary efficacy, and safety of asivatrep in children (NCT02748993). Third, while the sample size was considered large in terms of determining the therapeutic efficacy of asivatrep versus the vehicle cream, further clinical studies with a larger sample size and with non-Korean patients who may have different phenotypes and endotypes of AD are required to confirm the results of the present study. Fourth, the current study did not cover a numerical rating scale, and the score on the Dermatology Life Quality Index, which are valuable tools recommended by the Harmonising Outcome Measures for Eczema initiative for evaluating pruritus and quality of life in AD, respectively. A future study incorporating these outcome measures will provide further insight into the efficacy of asivatrep in terms of patient-related outcomes.

In conclusion, treatment with asivatrep cream resulted in marked and sustained relief of signs and pruritus associated with AD in adolescents and adults, along with an acceptable safety profile. The results show that asivatrep cream may be a novel and effective topical medication for patients with AD.

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Clinical implications: Asivatrep cream ameliorated signs and symptoms, with a favorable safety profile in patients with AD. The first-in-class topical TRPV1 antagonist asivatrep may be a promising therapeutic option for AD.

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TABLE E1. Summary of efficacy results from baseline at week 8

Characteristic	Vehicle cream (n = 78)	Asivatrep cream (n = 153)	*P* value vs vehicle
IGA score			
IGA score of 0 or 1	10 (12.8)	55 (36.0)	< .001
IGA score of 0 or 1 and reduction of ≥2 points	6 (7.7)	31 (20.3)	.014
EASI score			
EASI score, mean % change (SD)	−21.4 (45.3)	−44.3 (37.3)	< .001
EASI-50	22 (28.2)	77 (50.3)	.001
EASI-75	9 (11.5)	36 (23.5)	.030
EASI-90	2 (2.6)	15 (9.8)	.046

Data are presented as no. (%) of patients unless otherwise indicated.

TABLE E2. Summary of efficacy results at week 1, 3, 6, and 8 after treatment of asivatrep

Characteristic	Vehicle cream (n = 78)	Asivatrep cream (n = 153)	*P* value vs vehicle
IGA score of 0 or 1, no. (%)			
Week 1	0	8 (5.3)	.053
Week 3	4 (5.1)	25 (16.3)	.015
Week 6	6 (7.7)	34 (22.2)	.006
Week 8	10 (12.8)	55 (36.0)	< .001
EASI score, mean % change (SD)			
Week 1	−5.1 (29.1)	−9.6 (23.4)	.724
Week 3	−8.7 (39.6)	−25.9 (35.9)	.003
Week 6	−17.5 (39.7)	−35.8 (35.3)	.001
Week 8	−21.4 (45.3)	−44.3 (37.3)	< .001
VAS score, mean change (SD)			
Week 1	−0.3 (1.6)	−0.4 (1.7)	.423
Week 3	−0.8 (2.0)	−1.3 (2.1)	.084
Week 6	−1.1 (2.3)	−1.7 (2.3)	.043
Week 8	−1.5 (2.4)	−2.3 (2.4)	.018
Sleep disturbance score, mean change (SD)			
Week 1	−0.3 (1.9)	−0.3 (2.2)	.890
Week 3	−0.5 (2.2)	−1.0 (2.4)	.157
Week 6	−0.6 (2.5)	−1.3 (2.5)	.033
Week 8	−0.9 (2.4)	−1.6 (2.5)	.036

TABLE E3. All TEAEs by system organ class and preferred term

Characteristic	Vehicle cream (n = 80)	Asivatrep cream (n = 157)
Infections and infestations	5 (6.3)	9 (5.7)
Nasopharyngitis	5 (6.3)	4 (2.6)
Bronchitis	0	1 (0.6)
Ear infection	0	1 (0.6)
Eczema herpeticum	0	1 (0.6)
Folliculitis	0	1 (0.6)
Herpes zoster	0	1 (0.6)
Hordeolum	1 (1.3)	0
Skin and subcutaneous tissue disorders	1 (1.3)	4 (2.6)
Urticaria	1 (1.3)	2 (1.3)
Hyperhidrosis	0	1 (0.6)
Pigmentation disorder	0	1 (0.6)
Nervous system disorders	0	3 (1.9)
Burning sensation	0	2 (1.3)
Headache	0	1 (0.6)
Gastrointestinal disorders	0	3 (1.9)
Colitis	0	1 (0.6)
Constipation	0	1 (0.6)
Enteritis	0	1 (0.6)
Respiratory, thoracic, and mediastinal disorders	0	2 (1.3)
Rhinorrhea	0	2 (1.3)
Injury, poisoning and procedural complications	0	1 (0.6)
Ligament sprain	0	1 (0.6)
Investigations	0	1 (0.6)
Blood creatine phosphokinase abnormal	0	1 (0.6)
Musculoskeletal and connective tissue disorders	0	1 (0.6)
Arthralgia	0	1 (0.6)
Reproductive system and breast disorders	0	1 (0.6)
Acquired phimosis	0	1 (0.6)
Vascular disorders	0	1 (0.6)
Hypertension	0	1 (0.6)

Data are presented as no. (%) of patients.

TABLE E4. Sensitivity analysis of efficacy results from baseline at week 8

Primary analysis	Vehicle cream (n = 78)	Asivatrep cream (n = 153)	*P* value vs vehicle
IGA score			
IGA score of 0 or 1	10 (12.8)	55 (36.0)	< .001
IGA score of 0 or 1 and reduction of ≥2 points	6 (7.7)	31 (20.3)	.010
EASI score			
EASI score, mean % change (SD)	−21.4 (45.3)	−44.3 (37.3)	< .001
EASI-50	22 (28.2)	77 (50.3)	.001
EASI-75	9 (11.5)	36 (23.5)	.030
EASI-90	2 (2.6)	15 (9.8)	.046
Sensitivity analysis	**Vehicle cream (n = 68)**	**Asivatrep cream (n = 140)**	***P* value vs vehicle**
IGA score			
IGA score of 0 or 1	9 (13.2)	54 (38.6)	< .001
IGA score of 0 or 1 and reduction of ≥2 points	6 (8.8)	31 (22.1)	.014
EASI score			
EASI score, mean % change (SD)	−28.8 (40.1)	−48.4 (33.0)	.001
EASI-50	21 (30.9)	77 (55.0)	.001
EASI-75	9 (13.2)	36 (25.7)	.040
EASI-90	2 (2.9)	15 (10.7)	.055

Data are presented as no. (%) of patients unless otherwise indicated. The primary analysis was performed on the full analysis set with missing values imputed by the last observation carried forward method. The sensitivity analysis excludes all patients with missing data: asivatrep, 13 patients (8.5%); vehicle, 10 patients (12.8%).