Allergy Asthma Immunol Res. 2026 Jul;18(4):611-619
https://doi.org/10.4168/aair.2026.18.4.611
pISSN 2092-7355·eISSN 2092-7363

Allergy, Asthma & Immunology Research AAIR

Brief Communication

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# Subtype-Specific Efficacy of Topical *Streptococcus* Postbiotic Emollient in Adolescents and Adults With Atopic Dermatitis and Comorbid Allergies: A *Post-hoc* Analysis of a Randomized, Double-Blind, Vehicle-Controlled Trial

OPEN ACCESS

**Received:** Aug 14, 2025
**Revised:** Mar 17, 2026
**Accepted:** Mar 18, 2026
**Published online:** Jul 2, 2026

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## ABSTRACT

Topical *Streptococcus* postbiotic emollient (Strain CX) has shown efficacy for mild-to-moderate atopic dermatitis (AD) in a previous study; however, treatment responses according to allergic comorbidity status have not yet been explored. We conducted a *post hoc* analysis to evaluate the differential therapeutic effects of Strain CX in patients with AD stratified by the presence or absence of allergic comorbidities. This *post hoc* analysis was derived from a randomized, double-blind, vehicle-controlled trial (Clinical Research Information Service of South Korea, KCT0007876). A total of 98 patients with mild-to-moderate AD were stratified into placebo (n = 33), AD without allergic comorbidities (n = 29), and AD with allergic comorbidities (n = 36) groups. The primary outcomes were the Investigator's Global Assessment (IGA) score and the proportions of participants achieving 25% or 50% improvement in the Eczema Area and Severity Index (EASI), assessed at weeks 4 and 8. The secondary outcomes included a range of skin-related clinical and molecular measures, along with additional evaluations of serum inflammatory and allergic biomarkers as laboratory measures in the per-protocol analysis set. At week 8, 55.2% (16/29) of participants in the AD without allergic comorbidities group achieved an IGA score of 0 or 1 with ≥ 1 point reduction, compared to 30.6% (11/36) in the AD with allergic comorbidities group ($P$ = 0.0272). Both Strain CX intervention groups showed significant improvements in skin parameters, including EASI, skin moisture, and transepidermal water loss. Notably, the AD with allergic comorbidities group solely exhibited significant reductions in systemic

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**Trial Registration**
Clinical Research Information Service Identifier: KCT0007876

**Disclosure**
This study was conducted by two independent teams: one responsible for the clinical trial and the other for statistical analysis and manuscript drafting. While the clinical trial was funded by Cosmax BTI, the drafting and statistical analysis team conducted its work independently for academic purposes, without any funding support. The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the manuscript.

inflammatory markers, including sIL-2R (mean, −231.19; 95% confidence interval [CI], −378.82 to −83.57 pg/mL), CCL17 (−127.05; 95% CI, −251.80 to −2.31 pg/mL), and CCL22 (−578.40; 95% CI, −939.31 to −217.49 pg/mL). Clinical skin responses improved more in patients with AD without allergic comorbidities, while immunomodulatory benefits were observed in those with allergic comorbidities. These findings support patient stratification based on allergic comorbidity status for personalized Strain CX treatment strategies.

**Trial Registration**: Clinical Research Information Service Identifier: KCT0007876

**Keywords:** Atopic dermatitis; skin microbiome; post biotics; emollient; *Streptococcus*; therapeutic uses

## INTRODUCTION

Recently, the skin microbiota has emerged as a novel therapeutic target for inflammatory skin conditions, including atopic dermatitis (AD).[1,2] Among commensal microbes, *Streptococcus* species have been shown to enhance skin barrier integrity by promoting elasticity, facilitating desquamation, and improving hydration.[3] Based on these properties,[1] we previously conducted a proof-of-concept trial to evaluate the efficacy of a topical *Streptococcus* postbiotic emollient, specifically Strain CX, in patients with mild-to-moderate AD. As a result, we found that this formulation was a novel, safe, and effective therapeutic option for this population.[1]

AD is a clinically and immunologically heterogeneous disease, and treatment responses may vary substantially across patient subgroups.[4] While the underlying mechanisms linking AD to coexisting allergic diseases remain incompletely understood, type 2 inflammation and IgE sensitization appear to be key drivers.[5] Accordingly, AD, a chronic inflammatory pruritic skin disorder, can be phenotypically categorized into AD with or without allergic comorbidities (i.e., asthma, allergic rhinitis, atopic keratoconjunctivitis, or food allergy).[6]

Given that microbiome-based postbiotic therapies may exert both skin-targeted barrier effects and broader immunomodulatory influences, clinical and immunological responses to Strain CX may differ according to allergic comorbidity status.[7,8] Therefore, in this *post hoc* analysis, we aimed to characterize differential treatment responses by stratifying patients into allergic and non-allergic AD subtypes.

## MATERIALS AND METHODS

### Study design and population

This randomized, double-blind, vehicle-controlled proof-of-concept trial was conducted at three academic hospitals in South Korea and enrolled 100 patients aged 12–70 years with mild-to-moderate AD (Clinical Research Information Service of South Korea, KCT0007876). The 100 enrolled patients were randomized in a 1:2 ratio to receive either placebo (simple essence cream) or Strain CX cream for 4 or 8 weeks. In this *post hoc* analysis, patients with mild-to-moderate AD were stratified according to the presence of allergic comorbidities to explore treatment responses. After recruiting patients from three different hospitals, the research was conducted by the Korean Skin Research Center. All participants provided informed consent. This study followed the ethical guidelines of the Declaration of Helsinki,

the International Conference on Harmonization Good Clinical Practice, and relevant regulatory standards. This trial was approved by the Institutional Review Board of the Korean Skin Research Center in South Korea (HBABN01-220509-HRBR-E0113-01).[1]

The study considered eligible those patients who were diagnosed with AD (physician confirmed); an Investigator's Global Assessment (IGA) score ranging from 2 (mild) to 3 (moderate); and consistent use of a moisturizer (emollient) daily at an unchanging dose for a minimum of 7 days prior to the initial visit.[9] After the exclusion criteria were applied, two patients withdrew from the study, resulting in a total of 98 patients with mild-to-moderate atopic dermatitis. Further details of the study protocol, including the inclusion and exclusion criteria, are provided in the previous study.[1]

## *Streptococcus* postbiotic solution and randomization

The human skin-derived strains of *Streptococcus*, specifically *Streptococcus pneumoniae* BF00257 (KCCM12005P), *Streptococcus infantis* BF00247 (KCCM12642P), and *Streptococcus mitis* BF00251 (KCCM12656P), obtained from the COSMAX Microbiome Bank (CMB; COSMAX BTI Inc., Seongnam, Korea) were used to formulate the *Streptococcus* postbiotic solution designated as Strain CX solution (**Supplementary Fig. S1**).[1] The solution was incorporated into a 1% concentration water-based emollient gel formulated with Carbopol 980 for topical application (intervention group), while the control group received a vehicle emollient without the postbiotic solution. Details are provided in the **Supplementary Data S1** and previous study.[1]

Patients were randomly allocated by an independent person to the placebo or 1.0% Strain CX group in a 1:2 ratio according to a block randomization method. In this *post hoc* analysis, the Strain CX group was further stratified into AD without allergic comorbidities and AD with allergic comorbidities (stopiFigure). Comorbid allergies were defined as a history of physician-diagnosed asthma, allergic rhinitis, atopic keratoconjunctivitis, or food allergy.[10]

## Endpoints

The primary outcomes were defined as changes from baseline to each assessment, including the achievement of an Investigator's Global Assessment (IGA) score of 0 or 1 with a ≥ 1 point reduction, and ≥ 30% or ≥ 50% improvement in the Eczema Area and Severity Index (EASI) score.[11,12] Secondary endpoints included skin physiological parameters (skin moisture score and transepidermal water loss [TEWL]), patient-reported outcomes (pruritus visual analog scale [VAS], Dermatology Life Quality Index [DLQI], and Patient-Oriented Eczema Measure [POEM]), and stratum corneum barrier markers (filaggrin, loricrin, and involucrin) assessed by quantitative real-time polymerase chain reaction from tape-stripped corneocyte samples.[12,13] For the per-protocol analysis set, serum inflammatory and allergic biomarkers, including sIL-2R, IL-13, CCL17, CCL22, and IgE, were quantified by using an enzyme-linked immunosorbent assay.[14] Detailed information is provided in **Supplementary Data S1**.

## Statistical analysis

To evaluate whether clinical outcomes differed according to allergic comorbidity status in patients with mild-to-moderate AD, the primary and secondary endpoints were compared among the 3 groups: the placebo group, the AD without allergic comorbidities group, and the AD with allergic comorbidities group. Categorical variables were compared using Fisher's exact test, and continuous variables were analyzed using analysis of variance, with $P$ value< 0.05 considered significant.[15] Analysis of covariance was used to adjust for covariates, with *post hoc* comparisons conducted to evaluate significant differences among the three


https://doi.org/10.4168/aair.2026.18.4.611

groups.[11] Additionally, baseline characteristics between per-protocol and non-per-protocol populations were compared using independent *t*-test for continuous variables and Fisher's exact test for categorical variables.[16,17] All analyses were conducted using R (version 4.3.2; R Foundation, Vienna, Austria) and Python (version 3.12.10; Python Software Foundation, Beaverton, OR, USA).

## RESULTS

Between January 2022 and May 2023, 100 patients with AD were enrolled; however, two were excluded due to withdrawal of consent and failure to meet the inclusion criteria (**Supplementary Fig. S1**). Eligible 98 patients were included in the full intent-to-treat set and randomized in a 1:2 ratio into 2 groups, including a placebo group (n = 33) and a 1.0% Strain CX treated group (n = 65; AD without allergic comorbidities group, n = 29; AD with allergic comorbidities group, n = 36). Of 65 patients with Strain CX intervention, 36 (55.4%) reported at least one allergic comorbidity (allergic rhinitis only, 27.85%; food allergy only, 8.3%; atopic keratoconjunctivitis only, 5.6%; > 1 allergic comorbidity, 58.3%) in **Figure B**. Of these, 13 patients in the placebo group and 27 in the Strain CX group were excluded from the per-protocol set due to refusal to undergo blood sampling (**Figure**, **Table 1**, and **Supplementary Table S1**). The remaining 58 participants were included in the per-protocol analysis set, with baseline characteristics generally comparable between per-protocol and non-per-protocol populations (**Supplementary Table S2**).

At week 8, 55.2% (16/29) of participants in the AD without allergic comorbidities group achieved an IGA score of 0 or 1 with ≥ 1 point reduction from baseline, compared to 30.6% (11/36) of those in the AD with allergic comorbidities group ($P$ = 0.0272; **Tables 2** and **3**). Strain CX intervention groups, including both AD with and without allergic comorbidities groups, had significantly superior profiles across various skin parameters, including EASI, skin moisture, and TEWL scores (**Table 2**). Notably, the AD with allergic comorbidities group with Strain CX intervention solely exhibited significant improvements in systemic inflammatory markers, including sIL-2R (mean, −231.19; 95% confidence interval [CI], −378.82 to −83.57 pg/mL), CCL17 (−127.05; 95% CI, −251.80 to −2.31 pg/mL), and CCL22 (−578.40; 95% CI, −939.31 to −217.49 pg/mL) at week 8 compared to baseline. Results assessing outcomes at week 4 are shown in **Supplementary Table S3**. No significant differences in safety issues were reported (**Supplementary Table S4**).

## DISCUSSION

Despite the *post hoc* nature of this analysis and the fact that the original study was not primarily designed to evaluate treatment responses by allergic comorbidity status, our findings provide valuable insights into the potential of phenotype-based therapeutic approaches. Specifically, patients without allergic comorbidities showed a significantly higher clinical response to Strain CX treatment, as reflected in greater improvements in IGA scores compared to those with allergic comorbidities.

Several plausible mechanisms may explain these findings. While improvements in EASI, skin hydration, and TEWL were observed across both Strain CX subgroups compared to placebo, a higher IGA response was more pronounced in patients without


https://doi.org/10.4168/aair.2026.18.4.611

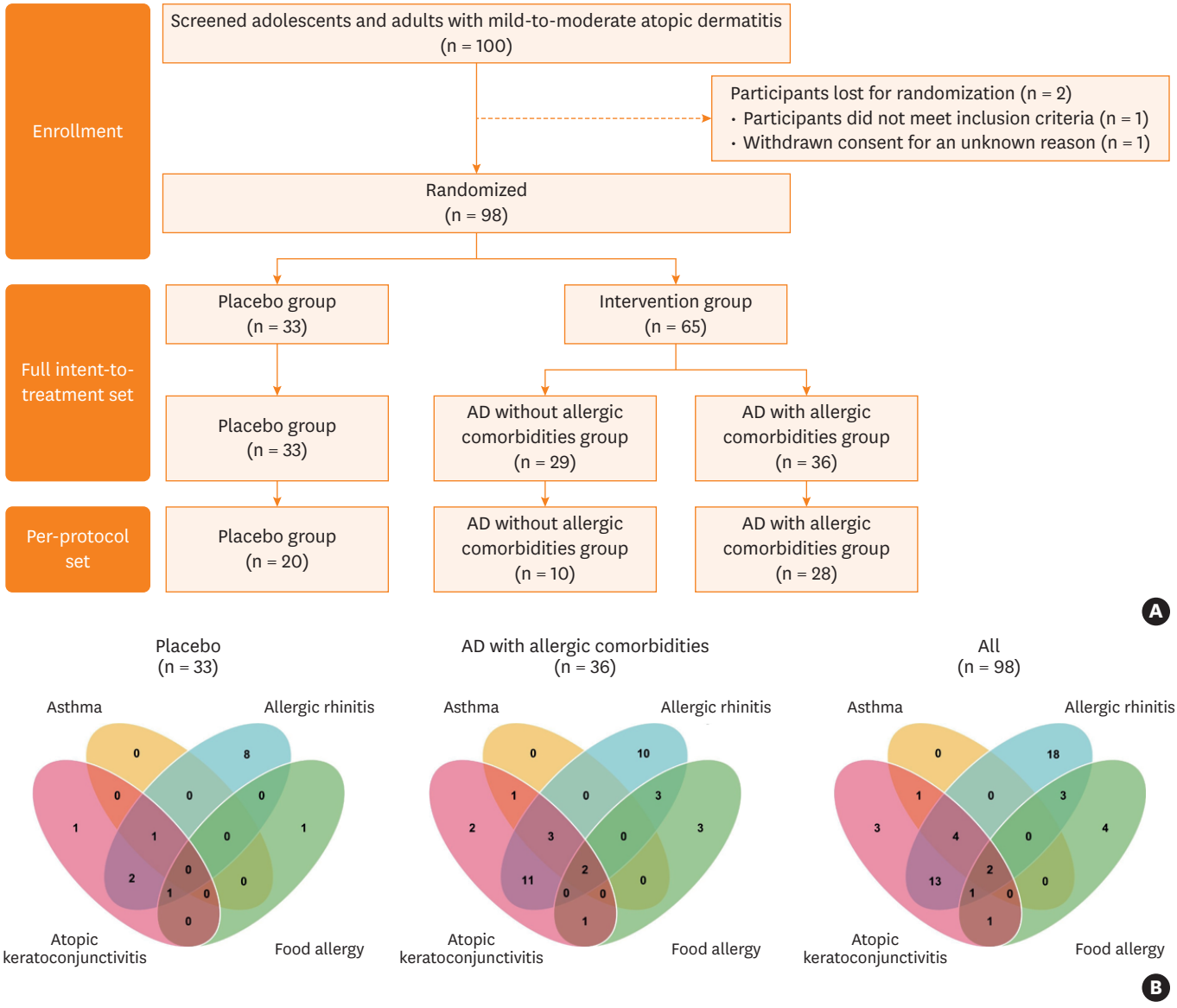



**Figure.** Study flow diagram for randomized controlled trials of 1.0% Strain CX intervention.
AD, atopic dermatitis.

allergic comorbidities. In contrast, patients with allergic comorbidities showed greater improvements in systemic inflammatory markers, including sIL-2R, CCL17, and CCL22, following treatment with Strain CX, suggesting differential clinical and immunologic response patterns by phenotype.

The differential clinical responses observed in this study may reflect distinct disease phenotypes in AD. Patients without allergic comorbidities may represent a more skin-dominant phenotype, in which local barrier repair and microbiome modulation are sufficient to achieve substantial clinical improvement.[18] In contrast, patients with AD and allergic comorbidities often exhibit persistent systemic type 2 inflammation, which may attenuate the magnitude of skin-focused clinical responses despite measurable immunologic improvements.[19]


https://doi.org/10.4168/aair.2026.18.4.611

**Table 1.** Baseline characteristics of participants in full analysis set

| Characteristics | Full analysis set (n = 98) | | | |
|---|---|---|---|---|
| | Placebo (n = 33) | AD without allergic comorbidities (n = 29) | AD with allergic comorbidities (n = 36) | *P* value* |
| Age (yr) | 42.6 ± 12.7 | 47.1 ± 14 | 39.4 ± 14.3 | 0.0866 |
| Sex | | | | 1.0000 |
| Male | 6 (18.2) | 5 (17.2) | 6 (16.7) | |
| Female | 27 (81.8) | 24 (82.8) | 30 (83.3) | |
| Family history of allergy | 16 (48.5) | 7 (24.1) | 19 (52.8) | 0.0507 |
| Smoking | | | | 0.3827 |
| Smoker | 3 (9.1) | 1 (3.4) | 5 (13.9) | |
| Non-smoker | 30 (90.9) | 28 (96.6) | 31 (86.1) | |
| IGA† | | | | 0.7411 |
| 2 (mild) | 18 (54.5) | 17 (58.6) | 23 (63.9) | |
| 3 (moderate) | 15 (45.5) | 12 (41.4) | 13 (36.1) | |
| EASI score | 6 ± 4.5 | 6 ± 3.5 | 6.7 ± 3.4 | 0.6897 |
| Skin moisture score | 24 ± 8.1 | 24.5 ± 8.7 | 24.6 ± 8.4 | 0.9399 |
| TEWL (g/m$^2$/h) | 15.8 ± 10.3 | 15 ± 6.2 | 15.2 ± 8.5 | 0.9446 |
| Pruritus VAS score | 5.4 ± 1.4 | 6.2 ± 1.3 | 6 ± 1.6 | 0.0827 |
| DLQI score | 27.6 ± 5.5 | 28.7 ± 4 | 29.2 ± 4.5 | 0.3551 |
| POEM score | 16.3 ± 4.8 | 15.4 ± 3.9 | 17.2 ± 6.1 | 0.3622 |
| Barrier profiles detected by tape strips | | | | |
| Filaggrin, ratio of filaggrin/GAPDH (%) | 0.7 ± 0.6 | 1.1 ± 1.7 | 1.2 ± 1.5 | 0.3325 |
| Loricrin, ratio of loricrin/GAPDH (%) | 1.2 ± 1.4 | 1 ± 1.5 | 1 ± 1.1 | 0.8306 |
| Involucrin, ratio of involucrin/GAPDH (%) | 0.9 ± 1 | 1.1 ± 2 | 1 ± 1.7 | 0.8315 |

Values are presented as mean ± standard deviation or number (%).
AD, atopic dermatitis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; IGA, Investigator's Global Assessment; POEM, Patient-Oriented Eczema Measure; TEWL, transepidermal water loss; VAS, visual analog scale.
*Comparisons among the 3 groups were conducted using an analysis of variance test, with *P* value < 0.05 was considered statistically significant.
†IGA was assessed according to the following degree: 0, clear; 1, almost clear; 2, mild; 3, moderate; 4, severe.

Conceptually, Strain CX differs from conventional emollients, which primarily provide passive barrier support, as it is a microbiome-derived postbiotic formulation intended to modulate host-microbe interactions and immune signaling.[2,8] Compared to commercially available postbiotic formulations that often focus on generalized barrier enhancement, Strain CX incorporates specific *Streptococcus*-derived components that may contribute to both local skin barrier improvement and systemic immunomodulatory effects.[1]

While these results are promising, these exploratory findings should be interpreted in the context of the *post hoc* design, nominal statistical thresholds, modest subgroup sizes, and absence of long-term biomarker data beyond week 24, and would benefit from validation in future prospective studies.

These findings suggest that while the clinical skin response is more prominent in patients without allergic comorbidities, microbiome-based postbiotic therapy may offer additional immunomodulatory benefits in those with allergic comorbidities. Taken together, our results highlight the potential importance of patient stratification based on allergic comorbidities when designing and selecting Strain CX interventions for AD, and support the future development of personalized, phenotype-guided treatment strategies for this intervention.

## ACKNOWLEDGMENTS

The clinical trial for this study was supported by Cosmax BTI. The preparation of the manuscript and the data analysis were supported by the Ministry of Health & Welfare, South

**Table 2.** Comparison of change in primary and secondary endpoints at week 8 among study participants

| Endpoints | Placebo | AD without allergic comorbidities | AD with allergic comorbidities | *P* value* |
|---|---|---|---|---|
| Primary endpoint (full analysis set) | n = 33 | n = 29 | n = 36 | |
| IGA† score of 0 or 1 and reduction of ≥ 1 point from baseline at week 8 | 4 (12.1) | 16 (55.2) | 11 (30.6) | **< 0.001** |
| EASI-30‡ score at week 8 | 2 (6.1) | 6 (20.7) | 7 (19.4) | 0.1716 |
| EASI-50‡ score at week 8 | 0 (0.0) | 0 (0.0) | 1 (2.8) | 0.9999 |
| Secondary endpoint (full analysis set)§ | n = 33 | n = 29 | n = 36 | |
| EASI score | 0.00 (−0.44 to 0.43) | **−0.73 (−1.22 to −0.24)** | **−0.67 (−1.08 to −0.27)** | **0.0243** |
| Skin moisture score | **4.36 (2.22 to 6.49)** | **10.06 (7.68 to 12.45)** | **8.51 (6.53 to 10.50)** | **0.0005** |
| TEWL | 0.00 (−1.98 to 1.98) | **−5.81 (−8.02 to −3.60)** | **−3.23 (−5.07 to −1.39)** | **0.0003** |
| Pruritus VAS score | **−3.25 (−3.91 to −2.60)** | **−4.29 (−5.03 to −3.56)** | **−3.66 (−4.27 to −3.05)** | 0.0820 |
| DLQI score | **8.84 (6.99 to 10.69)** | **9.11 (7.05 to 11.16)** | **7.00 (5.29 to 8.72)** | 0.1930 |
| POEM score | **−6.97 (−8.57 to −5.36)** | **−7.04 (−8.83 to −5.25)** | **−7.98 (−9.47 to −6.48)** | 0.5796 |
| Filaggrin | 0.21 (−0.31 to 0.73) | 0.36 (−0.22 to 0.94) | 0.25 (−0.24 to 0.73) | 0.2175 |
| Foricrin | −0.38 (−1.40 to 0.63) | 0.99 (−0.14 to 2.12) | 0.50 (−0.44 to 1.44) | 0.1383 |
| Involucrin | −0.25 (−1.03 to 0.53) | **1.28 (0.41 to 2.15)** | 0.18 (−0.54 to 0.91) | **0.0204** |
| Secondary endpoint (per protocol analysis set)§ | n = 20 | n = 10 | n = 28 | |
| sIL-2R (pg/mL) | **177.83 (5.60 to 350.05)** | −212.77 (−466.52 to 40.97) | **−231.19 (−378.82 to −83.57)** | **0.0010** |
| IL-13 (pg/mL) | **75.36 (7.42 to 143.31)** | −15.14 (−115.24 to 84.96) | −36.03 (−94.27 to 22.21) | **0.0356** |
| CCL17 (pg/mL) | 130.64 (−139.75 to 401.03) | −242.03 (−758.19 to 274.13) | **−127.05 (−251.80 to −2.31)** | 0.0769 |
| CCL22 (pg/mL) | 339.07 (−81.98 to 760.12) | −241.05 (−861.39 to 379.30) | **−578.40 (−939.31 to −217.49)** | **0.0043** |
| IgE (ng/mL) | 0.28 (−7.59 to 8.14) | −1.57 (−10.79 to 7.66) | −0.04 (−7.18 to 7.10) | 0.8322 |

Values are presented as number (%) or mean (95% confidence interval). Mean value was adjusted for age, sex, family history of allergy, and smoking status. Bold indicates a statistically significant difference ($P < 0.05$).
AD, atopic dermatitis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; POEM, Patient-Oriented Eczema Measure; TEWL, transepidermal water loss; VAS, visual analog scale.
*Comparisons among the three groups were conducted using Fisher's exact test for categorical variables and analysis of covariance for continuous variables, adjusting for age, sex, family history of allergy, and smoking status.
†IGA was assessed according to the following degree: 0, clear; 1, almost clear; 2, mild; 3, moderate; 4, severe.
‡EASI-30 and EASI-50 are defined as ≥ 30% and ≥ 50% improvement in EASI from baseline, respectively.
§Secondary endpoint is results assessing outcomes from baseline to week 8.

Korea (RS-2025-02220492). The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the manuscript.

## SUPPLEMENTARY MATERIALS

### Supplementary Data S1
Methods

### Supplementary Table S1
Baseline characteristics of participants in per-protocol analysis set

### Supplementary Table S2
Comparison of baseline characteristics between per-protocol and non-per-protocol populations

### Supplementary Table S3
Comparison of change in outcomes at week 4 among study participants

### Supplementary Table S4
Adverse events reported at the systemic and local levels

**Table 3.** Comparison of group differences in outcome measures

| Variables | Group pairwise comparisons (vs.) | | *P* value |
|---|---|---|---|
| Full analysis sets (n = 98) | | | |
| IGA* score of 0 or 1 and reduction of ≥ 1 point from baseline at week 8 | | | |
| Placebo vs. AD without allergic comorbidities | 4 (12.1) | 16 (55.2) | **0.0002** |
| Placebo vs. AD with allergic comorbidities | 4 (12.1) | 11 (30.6) | 0.0848 |
| AD without allergic comorbidities vs. AD with allergic comorbidities | 16 (55.2) | 11 (30.6) | **0.0272** |
| EASI score from baseline to week 8 | | | |
| Placebo vs. AD without allergic comorbidities | 0.00 (−0.44 to 0.43) | **−0.73 (−1.22 to −0.24)** | **0.0209** |
| Placebo vs. AD with allergic comorbidities | 0.00 (−0.44 to 0.43) | **−0.67 (−1.08 to −0.27)** | **0.0188** |
| AD without allergic comorbidities vs. AD with allergic comorbidities | **−0.73 (−1.22 to −0.24)** | **−0.67 (−1.08 to −0.27)** | 0.8462 |
| Skin moisture score from baseline to week 8 | | | |
| Placebo vs. AD without allergic comorbidities | **4.36 (2.22 to 6.49)** | **10.06 (7.68 to 12.45)** | **0.0002** |
| Placebo vs. AD with allergic comorbidities | **4.36 (2.22 to 6.49)** | **8.51 (6.53 to 10.50)** | **0.0037** |
| AD without allergic comorbidities vs. AD with allergic comorbidities | **10.06 (7.68 to 12.45)** | **8.51 (6.53 to 10.50)** | 0.3081 |
| TEWL from baseline to week 4 | | | |
| Placebo vs. AD without allergic comorbidities | −1.30 (−2.95 to 0.35) | **−4.14 (−5.98 to −2.30)** | **0.0155** |
| Placebo vs. AD with allergic comorbidities | −1.30 (−2.95 to 0.35) | **−2.16 (−3.69 to −0.62)** | 0.4277 |
| AD without allergic comorbidities vs. AD with allergic comorbidities | **−4.14 (−5.98 to −2.30)** | **−2.16 (−3.69 to −0.62)** | 0.0926 |
| TEWL from baseline to week 8 | | | |
| Placebo vs. AD without allergic comorbidities | 0.00 (−1.98 to 1.98) | **−5.81 (−8.02 to −3.60)** | **0.0001** |
| Placebo vs. AD with allergic comorbidities | 0.00 (−1.98 to 1.98) | **−3.23 (−5.07 to −1.39)** | **0.0142** |
| AD without allergic comorbidities vs. AD with allergic comorbidities | **−5.81 (−8.02 to −3.60)** | **−3.23 (−5.07 to −1.39)** | 0.0691 |
| Involucrin from baseline to week 8 | | | |
| Placebo vs. AD without allergic comorbidities | −0.25 (−1.03 to 0.53) | **1.28 (0.41 to 2.15)** | **0.0060** |
| Placebo vs. AD with allergic comorbidities | −0.25 (−1.03 to 0.53) | 0.18 (−0.54 to 0.91) | 0.3920 |
| AD without allergic comorbidities vs. AD with allergic comorbidities | **1.28 (0.41 to 2.15)** | 0.18 (−0.54 to 0.91) | 0.0505 |
| Per protocol analysis set (n = 58) | | | |
| sIL-2R (pg/mL), baseline to week 8 | | | |
| Placebo vs. AD without allergic comorbidities | **177.83 (5.60 to 350.05)** | −212.77 (−466.52 to 40.97) | **0.0094** |
| Placebo vs. AD with allergic comorbidities | **177.83 (5.60 to 350.05)** | **−231.19 (−378.82 to −83.57)** | **0.0004** |
| AD without allergic comorbidities vs. AD with allergic comorbidities | −212.77 (−466.52 to 40.97) | **−231.19 (−378.82 to −83.57)** | 0.8947 |
| IL-13 (pg/mL), baseline to week 8 | | | |
| Placebo vs. AD without allergic comorbidities | **75.36 (7.42 to 143.31)** | −15.14 (−115.24 to 84.96) | 0.1192 |
| Placebo vs. AD with allergic comorbidities | **75.36 (7.42 to 143.31)** | −36.03 (−94.27 to 22.21) | 0.0115 |
| AD without allergic comorbidities vs. AD with allergic comorbidities | −15.14 (−115.24 to 84.96) | −36.03 (−94.27 to 22.21) | 0.7037 |
| CCL22 (pg/mL), baseline to week 8 | | | |
| Placebo vs. AD without allergic comorbidities | 339.07 (−81.98 to 760.12) | −241.05 (−861.39 to 379.30) | 0.1073 |
| Placebo vs. AD with allergic comorbidities | 339.07 (−81.98 to 760.12) | **−578.40 (−939.31 to −217.49)** | **0.0010** |
| AD without allergic comorbidities vs. AD with allergic comorbidities | −241.05 (−861.39 to 379.30) | **−578.40 (−939.31 to −217.49)** | 0.3237 |

Values are presented as number (%) or mean (95% confidence interval). Mean value was adjusted for age, sex, family history of allergy, and smoking status.
Bold indicate a significant difference ($P < 0.05$).
AD, atopic dermatitis; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; TEWL, transepidermal water loss.
*IGA was assessed according to the following degree: 0, clear; 1, almost clear; 2, mild; 3, moderate; 4, severe.

**Supplementary Fig. S1**

Study flow chart. (A) Experimental schedule and (B) Production protocol for Strain CX postbiotic emollient.

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