Effective Prevention of Atopic Dermatitis by Applying Fam’s Baby Moisturizer Twice Daily or Once Daily Compared with 2e Moisturizer Once Daily in High-Risk Neonates: Study Protocol for A Randomized, Blinded, Parallel, Three Group, Phase II Trial (PAF Study)

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Study Protocol

Keywords: Atopic dermatitis, moisturizer, neonate, randomized, controlled trial

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Abstract

Background

Atopic dermatitis (AD) is a chronic and inflammatory skin disease that commonly affects young children. AD causes health-related burdens associated with pruritus and poor quality of life. The efficacy of moisturizer application shows inconsistency on primary prevention of AD according to previous randomized, controlled trials. Which moisturizer is effective and how often moisturizer should be applied to prevent development of AD in infants remain unclear. We hypothesize that twice daily application of moisturizer using Fam's Baby is more effective than once daily application and that a sufficient amount of moisturizer application is effective for preventing development of AD in neonates and infants. Therefore, this study aimed to examine whether applying Fam's Baby twice daily or once daily prevents AD compared with 2e moisturizer once daily in neonates and infants with at least one parent or sibling who has had atopic dermatitis.

Methods

This study is a single-center, three-parallel group, assessor-blind, superiority, individually randomized, controlled, phase II trial. A newborn with at least one parent or sibling who has had AD is randomly assigned to application of Fam's Baby twice daily, Fam's Baby once daily, or 2e once daily in a 1:1:1 ratio until 32 weeks old. The primary outcome is the time to the first onset of AD during administration of the moisturizer.

Discussion

This is the first phase II randomized, controlled trial in Japan to investigate whether applying moisturizer (Fam's Baby) twice daily or once daily can prevent the incidence of AD compared with another moisturizer (2e) once daily in high-risk neonates. In this study, we will use 2e once daily as control moisturizer to confirm the efficacy for primary prevention of AD as found in our previous trial. Evaluation of application of moisturizers for preventing AD in this study is expected to contribute to a reduction in the prevalence of AD and a reduction in health care costs.

Trial registration

Japan Registry of Clinical Trials (jRCT); ID: jRCTs031200070. Registered on 20 July 2020.

Background

Background and rationale

Atopic dermatitis (AD) is a chronic and inflammatory skin disease that commonly affects young children. AD causes health-related burdens associated with pruritus and poor quality of life [1]. A systematic review and meta-analysis showed that parental history of AD increased the risk of AD in the offspring (pooled
odds ratio: 3.30, 95% confidence interval [CI]: 2.45–4.42) [2]. Genetically susceptible individuals of AD have a higher risk of AD.

According to an epidemiological study, which was conducted globally between 1994 and 1996, the prevalence of AD was 7.3% among children aged 6 to 7 years old and 7.4% among those aged 13 to 14 years old [3]. The prevalence of AD as confirmed by a physician’s examination in Japan is 12.8% in children aged 4 months old, 9.8% at 1.5 years old, and 13.2% at 3 years old, [1, 4]. We previously reported that 32.3% of children had been diagnosed with AD until the age of 9 years and identified four phenotypes of AD in Tokyo, Japan [5].

The possibility of percutaneous sensitization via inflammatory skin of AD is established on the basis of Lack’s dual-allergen-exposure hypothesis [6]. We found that early-onset infant AD was positively associated with later food allergy in a prospective cohort study [7]. AD is considered as an origin of atopic march and the first history of atopic manifestations in children [8]. Therefore, whether skin care intervention from an earlier stage of life is effective for primary prevention of allergic diseases, such as AD and food allergies, would be interesting to determine in the future.

In 2014, we performed a randomized, controlled trial (RCT) to evaluate whether moisturizer (2e, Shiseido Japan Co., Ltd., Tokyo, Japan) once daily prevents the incidence of AD at 32 weeks of age compared with a control group in which Vaseline was applied as required from birth [9]. This trial showed that the cumulative incidence of AD was significantly lower in the 2e application group compared with the control group (hazard ratio: 0·48, 95% CI: 0·27–0·86). Another pilot RCT, which was conducted in the United Kingdom and the United States, showed that applying moisturizer after birth was effective in primary prevention of AD (relative risk: 0·50, 95% CI: 0.28–0.90) [10]. Recently, the BEEP study showed that application of the moisturizer Doublebase Gel (Dermal Laboratories, Herts, UK) or Diprobase Cream (Bayer, Berks, UK), at least once daily from early birth had no preventive effect on AD (adjusted relative risk: 0.95 95% CI: 0.78–1.16, p=0.61) [11]. Similarly, the PreventADALL study (2×2 factorial design), which tested two primary prevention strategies of skin care and early food introduction, showed that an oil bath and application of a moisturizer to the infant’s face (Ceridal cream) at least 5 days per week from 0.5 to 9 months of age was not effective in preventing AD [12]. Therefore, unfortunately, these two large RCTs could not confirm the efficacy of moisturizer application for primary prevention of AD. The efficacy of applying moisturizer is inconsistent regarding primary prevention of AD based on data from previous RCTs. Therefore, which moisturizer is effective and how often moisturizer should be applied to prevent development of AD in infants remain unclear.

Fam’s Baby (Fam’s Inc., Tokyo, Japan) is a popular commercially available moisturizer in Japan. Fam’s Baby contains glycerin, stearic acid, dimethicone, liquefied petroleum gas, polyvinylpyrrolidone, triethanolamine, cetanol, caprylic/capric triglyceride, laureth-2, laureth-21, tocopheryl acetate, and phenoxyethanol. We hypothesize that twice daily moisturizer application using Fam’s Baby is more effective than once daily application and that a sufficient amount of moisturizer application is effective for preventing development of AD in neonates and infants.
Objectives

This study aimed to examine whether applying Fam's Baby moisturizer twice daily or once daily prevents AD compared with 2e moisturizer once daily in high-risk neonates.

Trial design

This study is a single-center, pragmatic, three-parallel group (1:1:1), assessor-blind, superiority, individually, randomized, controlled, phase II trial (Fig. 1).

Methods

Study setting

This study will recruit neonates in the National Children's Hospital (National Center for Child Health and Development [NCCHD], Tokyo, Japan).

Eligibility criteria

High-risk neonates with AD (N=60) who meet all of the following inclusion criteria and none of the exclusion criteria will be enrolled in this study.

Inclusion criteria

Neonates must meet the following inclusion criteria to be enrolled in the study:

1. Newborns aged younger than 6 days old at recruitment
2. Newborns with at least one parent or sibling who has a past history of AD (high-risk newborn)
3. Newborns whose parents provide written informed consent after receiving an explanation

Exclusion criteria

The following exclusion criteria will be used for the study:

1. Newborns using topical medications, such as steroids (excluding the mouth and anal areas)
2. Newborns with skin lesions, such as abnormal keratinization and bullous disease
3. Newborns who are born at <37 weeks in gestation
4. Newborns who are born by cesarean section
5. Multiple births (not singletons)
6. Newborns with serious complications
7. Newborns whose immediate family plans to move and who may not be able to visit the study site
8. Parents unable to understand Japanese
9. Physicians decide that the neonate is not appropriate for participation in the study
Interventions

Study physicians will provide guidance to the legal representative (parents) or their family members on how to bathe, how to apply cosmetics, and how to write a diary at the enrollment. These physicians will check the status of entries in the diary for each visit.

Intervention in each group

1. Group A: Fam’s Baby applied twice a day
   - Application site: the whole body, except for the scalp
   - Amount used once: size of a ping-pong ball (0.7 g/piece) with a total of six pieces (total of 4.2 g)
   - Number of applications: twice a day
   - Application period: until 32 weeks of age

2. Group B: Fam’s Baby applied once a day
   - Application site: the whole body, except for the scalp
   - Amount used once: size of a ping-pong ball (0.7 g/piece) with a total of six pieces (total of 4.2 g)
   - Number of applications: once a day
   - Application period: until 32 weeks of age

3. Group C: 2e applied once a day [9]
   - Application site: the whole body except for the scalp
   - Amount used once: one teaspoonful (4.0 g)
   - Number of applications: once a day
   - Application period: until 32 weeks of age

Criteria for discontinuing or modifying allocated interventions

Study physicians will discontinue the intervention if the research cannot be continued for the following reasons:

1. When AD is diagnosed
2. Parents request to withdraw the neonate from the study or consent is withdrawn
3. When the inclusion criteria are not met or the exclusion criteria are violated after registration
4. When the intervention is difficult to continue because of illness, etc.
5. When participants do not come to the study site owing to moving
6. Discontinuation of the study is deemed appropriate by the study physicians

Study physicians will consider whether to continue the study in the following cases:
1. When important information regarding the quality, safety, and efficacy of the intervention is obtained.
2. When completing the study is determined as difficult to complete owing to difficulty in recruiting study participants or frequent dropouts.
3. When accepting the intervention is determined as difficult because there is an instruction to change the study plan by the independent data monitoring committee or by the Certified Clinical Research Review Committee.

**Strategies to improve adherence to interventions**

The amount of moisturizer actually used will be calculated by collecting a container of moisturizer at each visit and by measuring the remaining amount, and the frequency of intervention will be confirmed from the diary written by the parents.

**Relevant concomitant care permitted or prohibited during the trial**

1. Once a day, the whole body will be washed with soap at the out of bathtub and the soap will be rinsed with water. The same soap will be distributed in the three groups.
2. Bath additives will not be used.
3. During the study period, applying other moisturizers, skin topical medicines, and skin application agents is prohibited (excluding the mouth and anal areas).
4. If a skin rash appears, physicians will judge whether application of the moisturizer should be interrupted or stopped, and the physicians will start treatment for the skin rash as necessary. If the study intervention is discontinued and treatment improves the condition of the skin, intervention will be resumed. Physicians will record the diagnosis, details of the treatment, and treatment period in an electronic medical chart.
5. When AD is diagnosed, the intervention will be stopped and physicians will carry out appropriate treatment.

**Provisions for post-trial care**

In case of discontinuation due to illness, we will follow-up participants as long as possible until the situation is restored. If a health issue occurs because of this study, treatment will be performed as much as possible.

**Primary outcome**

The primary outcome is the time to the first onset of AD during application of the moisturizer. The time to onset of AD is defined as the number of days between discharge of the newborn and the onset of AD. The U.K. Working Party’s diagnostic criteria [13] will be used as diagnostic criteria of AD.

**Secondary outcomes**
Efficacy endpoints include the following: (1) Eczema Area and Severity Index (EASI) scores [14] at 4, 12, 24, and 32 weeks after birth; (2) patient-oriented eczema measure (POEM) scores [15] during the study; (3) stratum corneum hydration at the date of registration at 4, 12, 24, and 32 weeks after birth; (4) total immunoglobulin E (IgE) antibody titer and specific IgE antibody titer (ImmunoCAP) at the diagnosis of AD or at 32 weeks after birth; and (5) serum thymus and activation-regulated chemokine levels at diagnosis of AD or at 32 weeks after birth [16].

Participants’ timeline

Sample size calculation

A total of 60 participants, with 20 in each group, will be enrolled in this study. This is an exploratory study and the target case size is set on the basis of feasibility. In our institute, the number of births exceeds approximately 2000 per year, and the number of singletons born at 37 weeks after pregnancy is approximately 1200 per year. An epidemiological study of AD showed that the prevalence of AD in adults was approximately 5%, and that in neonates with a high risk for either or both parents was approximately 10% [17]. Therefore, recruiting 60 neonates within the 8-month registration period should be possible.

Recruitment

We will place posters and pamphlets around the examination room at our institute. We will perform provisional enrollment and make a list if parents are willing to participate in the study and the offspring may meet the inclusion criteria. When a tentatively listed pregnant woman gives birth, we will reconfirm that the selection criteria are met and recruit the woman.

Assignment of interventions: allocation

Sequence generation

Participants will be assigned 1:1:1 to groups A, B, and C by the substitution block method in the order of registration. No allocation adjustment factor will be set.

Concealment mechanism/implementation

We will use VIEDOC4 (Pharma Consulting Group Japan K.K., Tokyo, Japan) for enrollment for this study, and will enroll the subjects and randomize them. The participant’s identification number and the assigned group will be displayed on electronic data capture, and a registration confirmation notification will be automatically sent to the study physicians and the data center by e-mail. The study physicians will print and store the registration confirmation notification email.

Assignment of interventions: blinding

Who will be blinded
The physicians who measure the EASI and diagnose AD will be blinded to the group allocations and will not look at documents and any other information about the study intervention.

**Data collection and management**

**Plans for assessment and collection of outcomes**

A summary of the data collection plan is shown in Table 1. Background information, the living environment, and nutrition will be provided by interview. Adherence and POEM scores will be obtained from the diary. The EASI score and the diagnosis of AD will be obtained by a blinded examination.

**Data management**

The electronic data capture system will be used for data in this study. All data management will be performed independently by the data center of the NCCHD.

**Confidentiality**

During conducting research, the staff involved in the study will establish safety management and systems to protect personal information.

**Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use**

The study physicians will properly store the samples obtained in this study until 5 years after the study is completed.

**Statistical methods**

**Statistical methods for outcomes**

Analysis will be performed according to the intention-to-treat principle. To assess whether group A or group B is more effective than group C in preventing the onset of AD, we will use two co-primary analyses using the log-rank test for the time to the onset of AD. The significance level of each comparison is 2.5%. For each group, Kaplan–Meier estimates of the AD-free rate will be determined. Additionally, the Cox proportional hazards model will be used to estimate the hazard ratios of groups A vs. C and groups B vs. C, and their 95% CIs. The CIs will be calculated using the Wald type method. The exact method will be applied to adjust for tied observation times. A test with Schoenfeld residuals will be used to assess the proportional hazard assumption. If a significance level of 10% rejects the validity of the proportional hazards assumption, group comparisons using the difference in the restricted mean survival time will be applied as a supplementary analysis of the co-primary analysis. For the secondary endpoints, the mean and standard deviation of continuous variables, and the frequency and proportion of discrete variables will be calculated for each treatment group and time point. For the safety endpoints, the frequency and proportion of adverse events occurring will be calculated for each treatment group.
Interim analyses

We do not plan an interim analysis.

Methods for additional analyses (e.g., subgroup analyses)

We do not plan additional analyses.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data

Analysis of the primary and secondary outcomes will be performed on the largest analysis group. As a reference, analysis will be performed on the target group that conforms to the research implementation plan. If there is a serious breach, such as a consent breach, the subject will be excluded from analysis of the target group.

(1) Largest analysis group: full analysis set

Among all randomized subjects, the following will be excluded:

1. Subjects who have never had study intervention
2. Subjects for whom data were not obtained since the start of the study intervention
3. Subjects found to be in violation of eligibility criteria after the fact

(2) Analysis target group conforming to the research protocol: per protocol set

A group of subjects in the full analysis set who do not have significant deviation from the implementation plan will be included. Subjects with the following will be excluded from this group:

1. Poor adherence (application amount is <70% of the planned application amount during the study intervention period, or the number of days that the correct number of applications can be performed is <70% of the planned application period during the study intervention period)
2. If adherence cannot be evaluated
3. When using bath salts for longer than 7 days
4. Cosmetics other than test cosmetics or control cosmetics, skin external medicines, and skin application agents are applied for 7 days or longer (excluding external use only around the mouth, pubic area, and anus)

Plans to provide access to the full protocol, participant level-data, and statistical code

We do not plan to provide access to the full protocol, participant level-data, and statistical code.

Oversight and monitoring
Composition of the coordinating center and trial steering committee

The coordinating center is located in the Allergy Center, NCCHD. YI is the principle investigator. KYH will coordinate the PAF study. KP is a biostatistician who will analyze the data. TM and YO will advise the study process.

Composition of the data monitoring committee, and its role and reporting structure

Central and onsite monitoring will be conducted to ensure that this study is conducted safely and according to the research protocol and that data are being collected accurately. Monitoring will be conducted by a person designated by the investigator. The study is independent from the sponsor and competing interests. An independent data monitoring committee will be established in this study to monitor the safety of the study.

Adverse event reporting and harms

In this study, all adverse events that occurred during the study intervention period (after discharge) will be investigated, and the investigators will report the following items to the data center: 1) event name; 2) date of onset; 3) severity (mild, moderate, and severe); 4) seriousness (serious, non-serious); 5) intervention measures (continuation, interruption, and discontinuation); 6) measures (none, yes [contents if yes]); 7) outcomes (recovery, remission, unrecovered, recovered but with sequelae, death, and unknown) and outcome confirmation date; and 8) causal relationship with cosmetics used (can be denied, cannot be denied).

Frequency and plans for auditing conduct of the trial

We do not plan auditing in this study.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants and ethical committees)

After the approved clinical research review committee at this facility approves a change in the research implementation plan, notification of this change will be submitted to the local welfare department. After approval by the accredited clinical research review board, approval of the administrator of the implementing medical institution regarding the revised content will be obtained. If permission is obtained, the investigators will send a copy of the permit to the Research Secretariat and changes to the research protocol will take effect.

Dissemination plans

Main research results will be submitted to academic journals after the final analysis. The co-authors will be decided in accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals of the International Committee of Medical Journal Editors.


Discussion

This is the first phase II, three-armed RCT in Japan to examine whether applying moisturizer (Fam's Baby) twice daily or moisturizer (Fam's Baby) once daily prevents the incidence of AD compared with another moisturizer (2e) once daily in high-risk neonates and infants. In this study, we will use 2e once daily as a control moisturizer, which we confirmed as effective for primary prevention of AD in our previous RCT [9].

Other similar studies

As mentioned above, two RCTs provided evidence that protecting the skin barrier with a moisturizer applied at the beginning of the neonatal period prevented development of infantile AD [9,10]. However, prevention of AD was not proven in the BEEP study [11] in high-risk neonates in the UK and in the PreventADALL study [12] in general populations of Norway and Sweden. Once daily moisturizer was proposed in the study protocols of these two previous studies [11, 12]. Reasons for the inconsistency in results for moisturizer interventions might be due to different countries and cultures, different types of moisturizers, and differences in adherence. Dissanayake et al [18] performed an RCT in Japan to examine whether combined synbiotics and skin moisturizers could prevent AD and food allergy. However, they did not show efficacy of moisturizer application two to three times/day against prevention of AD and food allergy. The actual amount of moisturizer application and adherence in their study were unclear. Lowe et al [19] reported that applying a sufficient amount of moisturizer twice daily (≥5 days per week, good adherence) in neonates was preventable for sensitization of IgE at the age of 12 months in a small pilot RCT. We believe that the key points of a strategy for preventing allergies by skin moisturizer are as follows: 1) applying a sufficient amount of moisturizer, 2) twice daily application of moisturizer, and 3) the quality of the moisturizer. An individual patient data meta-analysis is ongoing by an international collaboration group (SCiPAD) to identify whether skin care interventions in infants prevent development of AD and food allergy [20]. New evidence for skin care prevention, such as application of moisturizer, will be determined.

Potential benefits of the study

This is a pilot RCT to examine the efficacy of using Fam's Baby from the neonatal period for high-risk neonates to prevent AD. Based on the results of this study, we hope that a phase III study will be conducted to determine the optimal method for preventing AD by applying this moisturizer. If we establish a novel strategy for preventing development of AD by this skin moisturizer intervention for high-risk neonates, the prevalence of AD is expected to decrease and medical care costs will be reduced.

Trial status

Data are currently being collected. The protocol version number is 1.3 and the date is 13 May 2020. The date recruitment began at 21 August 2020, and will be completed by March 2021.

Abbreviations
Declarations

Acknowledgments

We thank Ellen Knapp, PhD, from Edanz Group (https://en-author-services.edanzgroup.com/ac) for editing a draft of this manuscript. Ms. Miwako Seike and Ms. Youndzi Mizuho developed a data management plan for this study. Dr. Mayumi Sako developed a data monitoring plan for this study. The members of the independent data monitoring committee are as follows: Dr. Osamu Natsume (Hamamatsu Medical University Hospital), Dr. Masaki Futamura (Nagoya Medical Center), and Dr. Rin Nishi (Yutenji Family Clinic). Clinical nursing support is provided by the Clinical Center of NCCHD.

Authors’ contributions

YI is the principle investigator of the PAF study. All authors contributed to conception and design of the study. YI wrote the first draft of the manuscript. All authors read and approved the final manuscript.

Funding

This study is funded by Fam’s Inc. (Tokyo, Japan).

Availability of data and material

Not applicable.

Ethics approval and consent to participate

This study follows the World Medical Association Declaration of Helsinki and Clinical Trials Act. The accredited clinical research review committee of the NCCHD reviewed and approved the study protocol on 30 April 2020 (IRB ID: jRCTs031200070). The implementation plan was submitted to the Minister of Health, Labor and Welfare. All parents will provide consent before neonates are enrolled into the trial.

Consent for publication

Not applicable.

Competing interests

This trial is conducted on the basis of a collaboration between the NCCHD and Fam’s Inc. Yukihiro Ohya received funding from Fam’s Inc. The other authors have no competing interests in relation to this study.
Fam's Inc. has only been involved in the design of the study and will not be involved in the collection, analysis, interpretation of data, or decision to submit results.

References

1. Kato N, Ohya Y, Ikeda M, Ebihara T, Katayama I, Saeki H, et al. Japanese Guidelines for Atopic Dermatitis 2020. Allergol Int. 2020; doi: 10.1016/j.alit.2020.02.006.

2. Ravn NH, Halling AS, Berkowitz AG, Rinnov MR, Silverberg JI, Egeberg A, et al. How does parental history of atopic disease predict the risk of atopic dermatitis in a child? A systematic review and meta-analysis. J Allergy Clin Immunol. 2020;145:1182-93.

3. Williams H, Robertson C, Stewart A, Aït-Khaled N, Anabwani G, Anderson R, et al. Worldwide variations in the prevalence of symptoms of atopic eczema in the International Study of Asthma and Allergies in Childhood. J Allergy Clin Immunol. 1999;103:125-38.

4. Saeki H, Iizuka H, Mori Y, Akasaka T, Takagi H, Kitajima Y, et al. Prevalence of atopic dermatitis in Japanese elementary schoolchildren. Br J Dermatol. 2005;152:110-4.

5. Yamamoto-Hanada K, Yang L, Saito-Abe M, Sato M, Inuzuka Y, Toyokuni K, et al. Four phenotypes of atopic dermatitis in Japanese children. A general population birth cohort study. Allergol Int. 2019;68:521-3.

6. Lack G. Epidemiologic risks for food allergy. J Allergy Clin Immunol. 2008;121:1331-6.

7. Shoda T, Futamura M, Yang L, Yamamoto-Hanada K, Narita M, Saito H, et al. Timing of eczema onset and risk of food allergy at 3 years of age: a hospital-based prospective birth cohort study. J Dermatol Sci. 2016;84:144-8.

8. Dharmage SC, Lowe AJ, Matheson MC, Burgess JA, Allen KJ, Abramson MJ, et al. Atopic dermatitis and the atopic march revisited. Allergy. 2014;69:17-27.

9. Horimukai K, Morita K, Narita M, Kondo M, Kitazawa H, Nozaki M, et al. Application of moisturizer to neonates prevents development of atopic dermatitis. J Allergy Clin Immunol. 2014;134:824-30.

10. Simpson EL, Chalmers JR, Hanifin JM. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. J Allergy Clin Immunol. 2014;134:818-23.

11. Chalmers JR, Haines RH, Bradshaw LE, Montgomery AA, Thomas KS, Brown SJ, et al. Daily emollient during infancy for prevention of eczema: the BEEP randomised controlled trial. Lancet. 2020;395:962-72.

12. Skjerven HO, Rehbinder EM, Vettukattil R, LeBlanc M, Granum B, Haugen G, et al. Skin emollient and early complementary feeding to prevent infant atopic dermatitis (PreventADALL): a factorial, multicentre, cluster-randomised trial. Lancet. 2020;395:951-61.

13. Williams HC, Burney PG, Hay RJ, Archer CB, Shipley MJ, Hunter JJ, et al. The U.K. Working Party's diagnostic criteria for atopic dermatitis. Br J Dermatol. 1994;131:383-96.

14. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol.
15. Charman CR, Venn AJ, Williams HC. The patient-oriented eczema measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients' perspective. Arch Dermatol. 2004;140:1513-9.

16. Fujisawa T, Nagao M, Hiraguchi Y, Katsumata H, Nishimori H, Iguchi K, et al. Serum measurement of thymus and activation-regulated chemokine/CCL17 in children with atopic dermatitis: elevated normal levels in infancy and age-specific analysis in atopic dermatitis. Pediatr Allergy Immunol. 2009;20:633-41.

17. Saeki H, Oiso N, Honma M, Iuzuka H, Kawada A, Tamaki K. Prevalence of atopic dermatitis in Japanese adults and community validation of the U.K. diagnostic criteria. J Dermatol Sci. 2009;55:140-1.

18. Dissanayake E, Tani Y, Nagai K, Sahara M, Mitsuishi C, Togawa Y, et al. Skin care and synbiotics for prevention of atopic dermatitis or food allergy in newborn infants: a 2 × 2 factorial, randomized, non-treatment controlled trial. Int Arch Allergy Immunol. 2019;180:202-11.

19. Lowe AJ, Su JC, Allen KJ, Abramson MJ, Cranswick N, Robertson CF, et al. A randomized trial of a barrier lipid replacement strategy for the prevention of atopic dermatitis and allergic sensitization: the PEBBLES pilot study. Br J Dermatol. 2018;178:e19-21.

20. Kelleher MM, Cro S, Cornelius V, Axon E, Lodrup Carlsen KC, Skjerven HO, et al. Skincare interventions in infants for preventing eczema and food allergy. Cochrane Database of Systematic Reviews. 2020(2); doi: 10.1002/14651858.CD013534.
| Table 1 | Assessment schedule |
|---------|---------------------|
|         | Study period | Endpoint | Unscheduled medical examination (appearance of skin rash, etc.) | When the study intervention is discontinued (including when atopic dermatitis is diagnosed) |
| **Visit** | 1 | 2 | 3 | 4 | 5 |
| **Time point** | Entry (6 days old) | 4 weeks after entry (±7 days) | 12 weeks after entry (±14 days) | 24 weeks after entry (±28 days) | 32 weeks after entry (±28 days) |
| **ENROLLMENT:** | | | | | |
| Eligibility screen | X | | | | |
| Informed consent | X | | | | |
| Allocation | X | | | | |
| **ASSESSMENTS:** | | | | | |
| Background information | X | | | | |
| Living environment | X | | X | | X |
| Nutrition | X | | X | | X |
| Body height | X | X | X | X | X | X | X |
| Body weight | X | X | X | X | X | X | X | X |
| Evaluation of the presence or absence of atopic dermatitis by a blinded physician | X | X | X | X | X | X | X | X |
| EASI score by a blinded physician | X | X | X | X | X | X | X |
| POEM score by caregivers | → | → | → | → | → | → | → | → |
| Stratum corneum hydration | X | X | X | X | X | X | X | X |
| Study period                                                                 | Endpoint                        | Unscheduled medical examination (appearance of skin rash, etc.) | When the study intervention is discontinued (including when atopic dermatitis is diagnosed) |
|-------------------------------------------------------------------------------|---------------------------------|-----------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| Total IgE, egg white, ovomucoid, milk, wheat, peanut, and *Dermatophagoides farinae*-specific IgE and TARC in serum | X                               | X                                                              | X                                                                                           |
| Check the diary                                                              | X                               | X                                                              | X                                                                                           |
| Amount of emollients used                                                     | X                               | X                                                              | X                                                                                           |
| Combination therapy                                                          | X                               | X                                                              | X                                                                                           |
| Adverse events                                                                | X                               | X                                                              | X                                                                                           |

EASI, Eczema Area and Severity Index; POEM, patient-oriented eczema measure; TARC, thymus and activation-regulated chemokine; IgE, immunoglobulin E.

**Figures**
Figure 1

Trial scheme. Newborns with at least one parent or sibling who has had atopic dermatitis will be recruited and enrolled. Participants will be assigned 1:1:1 to groups A, B, and C, and evaluated if they have AD at 4, 12, 24, and 32 weeks for each group.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SPIRITChecklist.doc