

The AIMS1 protocol: study protocol of a randomized, double-blind, non-inferiority clinical trial in dermocosmetics dedicated to atopic dermatitis (Lipikar®, La Roche-Posay vs. Relipid®, NEUTRADERM)

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Study protocol

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Abstract

(171/350 words) Background: Severe and mild atopic dermatitis is classically treated with topical, i.e., moisturizer and topical steroids. The environment is competitive and dermatologists' prescriptions are guided more by habit than evidence based-medicine. Methods: Patients with non-severe atopic dermatitis (SCORAD <40) were enrolled. We aim to conduct a multi-center, comparative study with the emollient considered to be the gold standard well-documented in publications (Lipikar baume AP+M, La Roche Posay, L'Oréal), randomized in double-blind, parallel groups. Methods: A total of 37 subjects per group, i.e. a total of 74 participants, were required to demonstrate non-inferiority. In order to take account of 15% of patients lost to follow-up, we propose to include 86 patients. A sensory study preliminary to the trial is conducted to ensure that the blind cannot be lifted by recognizing the sensory elements of the cream (scent, application, silkiness, etc). Discussion: This is the first dermo-cosmetic study to propose a research protocol with rigorous design and statistics allowing the comparison of two topical active ingredients after ensuring sensory elements do not allow the blind to be lifted. Trial registration: Unique protocol ID: 2024-A02369-38; NCT 07358000 (ClinicalTrials.gov) the 20 th of January, 2026.

1. Background

Atopic dermatitis (AD), also known as atopic eczema, is a chronic inflammatory skin disease of increasing prevalence. According to data, it affects 10–20% of children, and while the majority of cases resolve by the age of five, around 10–15% persist into adulthood. It is noted that more significant skin sensitization occurs before 15 months of age in atopic children during the first decade of life (1). The condition generally has a genetic origin, either related to mutations in filaggrin or other skin barrier proteins, or at the immune level, involving mutations in receptors for pro-inflammatory molecules (2).

The skin's immunological barrier plays a crucial role, with specific pathologies-dedicated responses according to the pathogenic conditions encountered. A Th1 response triggers an inflammatory reaction, whereas a Th2 response limits excessive inflammation. However, in certain inflammatory skin diseases, these responses are dysregulated and become excessive, particularly in atopic dermatitis (3).

Patients suffering from inflammatory skin disorders often display unique imbalances in their skin microbiome, known as dysbiosis (4). Associated lesions with *Staphylococcus aureus* are frequently found in atopic dermatitis, especially during flare-ups (biofilms) (5). Atopic dermatitis typically involves the bacterium *Staphylococcus aureus* and more sporadically some *Staphylococcus epidermidis* strains, able to produce specific skin barrier-degrading proteases. These bacteria trigger a Th2-type immune response together with a reduction in microbiome diversity (2). During the manifestation of the disease, biomarkers of the Th2-immune pathway (MCP-1 (CCL2), TARC (CCL17), MDC (CCL22), IL-31, TSLP, MCP-4 (CCL13)) are overexpressed, as well as those of the Th1 pathway (IP-10, IFN γ), the Th17/Th22 pathway (IL-17a, IL-22, IL-23), and inflammatory molecules of the innate immune system (IL-1 β , IL-6, IL-8, IL-16, IL-18, IL-1Ra, TNF α , TNF β , VEGFa). In terms of the microbiome, biodiversity decreases with a significant drop in *Streptococcus* bacteria (6).

The production of Th2 cytokines, IL4 and IL6, reduces ceramide production. Maintaining an acidic skin pH and providing physiological lipids are beneficial for the skin and can help improve the severity of atopic dermatitis (7). Appropriate treatments can restore barrier function, notably with suitable emollients, helping to restore skin barrier integrity (interaction of the acid mantle, ceramide production, tight junction quality, and local immunology) (3). In summary, the pathophysiology of atopic dermatitis is very complex, involving multiple interactions between the immune system, epidermal cells, and the nervous system in the skin. Regular hydration with emollients can modify these interactions (8).

New-generation emollients aim to reduce *S. aureus* proteases and superantigens that cause barrier damage and inflammation while promoting the diversity of commensal bacteria, which produce *S. aureus*-targeting antibacterial molecules (4, 5). The mainstay of treatment for mild-to-moderate forms of AD is the combination of topical steroids and emollients. Daily application of emollients can be cumbersome, leading to poor compliance, treatment fatigue, and the need for rotation of emollients. They also present an economic burden, as they represent an ongoing expense for the patient, adding a financial strain in managing this chronic dermatosis. Thermal waters, rich in sodium bicarbonate (9) or sulfurous waters (10), i.e., mineral-rich thermal waters, can significantly change both the bacterial genera and skin-inhabiting species, resulting in an increase of beneficial bacteria (9). These mineral waters represent an interesting emollient base, which helps to reduce inflammation and to enhance the diversity of cutaneous microbiomes (9, 10). Laboratoires Gilbert has developed and patented an active ingredient processed from seawater (Active Oligo Skin™, AOS, patent FR2872046/FR1853214), designed and produced at their pharmaceutical production site in Hérouville-Saint-Clair. This active ingredient has shown *in vitro* promising results on *S. aureus* biofilms and in pre-clinical tests on the inflammatory mechanisms associated with sensitive and atopic skins (11). The process involves several consecutive filtrations of Iroise seawater: ultrafiltration, electrodialysis, and nanofiltration to obtain the AOS complex, the richest in minerals and trace elements on the market compared to other thermal waters from competitors.

Dermocosmetics or cosmetics studies typically follow a rigorous methodology to assess product efficacy, safety, and acceptability, with classic steps (12, 13). It can be concluded that cosmetics play a key role in daily life and are used by all genders, thereby increasing cosmetic usage and scope (14). In certain respects, the challenges and benefits of dermocosmetics can be paralleled by those of cosmeceuticals, as they enhance both the beauty and health of the skin. Thus, well-documented scientific evidence is required (15). The aim of the AIMSI (Active Ingredient & Microbiome Skin Impact) clinical study was design to compare the efficacy of the Laboratoires Gilbert emollient balm (Relipid + resplenishing balm, NEUTRADERM) with an emollient balm considered the "gold standard" and most widely prescribed on the market (Lipikar Baume AP + M, La Roche Posay, L'Oreal) in treating AD. The assumption is that, clinically, the balm will be at least as effective as the gold standard (non-inferiority), with a benefit for microbiome diversity, which remains a major issue in AD. Prior to the non-inferiority clinical study, we aim to conduct a preliminary sensory study to ensure that the sensory data provided to the consumers do not compromise the double-blind design, ensuring methodological robustness.

2. Objectives

Primary objective

The primary objective of the AIMS trial is to determine whether the emollient balm Relipid + lipid-replenishing balm (NEUTRADERM) is non-inferior to Lipikar AP + M balm (La Roche-Posay) in improving disease severity in patients with mild-to-moderate atopic dermatitis. The primary endpoint is the change in SCORAD (SCORing Atopic Dermatitis) index between baseline (V0) and Day 70 (V5). Non-inferiority will be concluded if the upper bound of the two-sided 95% confidence interval for the difference in mean SCORAD change between the experimental and control groups does not exceed the predefined non-inferiority margin of 5 points.

Secondary objectives

The secondary objectives of the AIMS trial are:

1. To evaluate changes in patient-reported quality of life using the Dermatology Life Quality Index (DLQI) between baseline and follow-up visits.
2. To assess changes in pruritus intensity using the Itch Numeric Rating Scale (Itch NRS).
3. To compare the cumulative use of topical corticosteroids between treatment groups during the study period.
4. To evaluate adherence to emollient application by quantifying product use and patient-reported compliance.
5. To perform a health economic evaluation comparing the direct costs associated with each treatment strategy, including emollient consumption and healthcare resource utilization.
6. To assess the safety profile of both interventions through systematic recording and evaluation of adverse events.

All secondary analyses will be considered exploratory.

Ancillary microbiome objective

An ancillary study conducted exclusively at Caen University Hospital aims to evaluate the effect of Relipid+ lipid-replenishing balm and Lipikar AP + M balm on skin microbiome diversity. The objective is to assess changes in bacterial alpha diversity, measured by the Shannon diversity index, after repeated application of emollients. Skin samples will be collected via standardized non-invasive swabbing at baseline (V0), mid-study (V3), and end-of-study (V5). The analysis will focus on changes in microbial diversity and composition over time in patients treated either with Relipid + or Lipikar AP + M balms.

Participation in the ancillary microbiome study is optional and independent from participation in the primary clinical trial.

3. Methods

This trial was reported in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) (16) reporting guidelines and the corresponding checklist is given in supplementary materials.

Design and settings

We aim to conduct a multi-center, double-blinded and comparative study with the emollient considered to be the gold standard well-documented in publications (Lipikar AP + M balm, La Roche Posay, L'Oréal), randomized in double-blind, parallel groups. Experimental design is given in Fig. 1.

Participants

Recruitment

Recruitment will be prospective and multicentric in several centers in the region, with hospitals (Caen, Cotentin, Avranches, St Lô) and private practices, to avoid recruitment bias.

Inclusion criteria

To be eligible, subjects must meet all the defined inclusion criteria:

- Patient (6 months-70 years) with mild-to-moderate atopic dermatitis (SCORAD < 40)
- Treatment time < 72 hours between initial treatment and application of the balm
- Affiliated with the social security system and French-speaking
- Patient or legal guardian informed of the study and having signed informed consent (if applicable, interventional research with minimal risks and constraints).
- Informed consent must be signed.

Table 1
Expected participant demographic characteristics according to Pro-EDI

PRO-EDI characteristics	Expected trial population	Rationale
Age	Participants aged 6 months to 70 years	The eligibility criteria allow inclusion across the paediatric and adult population with mild-to-moderate atopic dermatitis
Sex	All sexes eligible	Sex is not an eligibility criterion and both males and females will be eligible for participation
Gender	All genders eligible	Gender identity does not constitute an eligibility criterion
Race, ethnicity and ancestry	Not restricted by race, ethnicity or ancestry	No exclusion criterion is based on race, ethnicity or ancestry. The study is conducted in Normandy, France, and the expected distribution will reflect the population attending the participating centre(s).
Socioeconomic status	No specific socioeconomic restriction	Socioeconomic status is not an eligibility criterion. Participants must, however, be affiliated with the French national health insurance system, as specified in the eligibility criteria.
Geographic location	Primarily participants residing in Normandy / recruited at CHU Caen Normandie	The study is conducted at CHU Caen Normandie, with recruitment centred in the Normandy region

Subjects meeting only one of the non-inclusion criteria are not eligible to participate in the research i.e., patient refusing the study, patients under guardianship, curatorship, safeguard of justice or legal protection or patients with SCORAD requiring systemic therapy

Table 2
Details of schedule and provisional visits

Evaluations	Selection Visit (D-x..)	V0 (D0)	V1 (D7)	V2 (D14)	V3 (D21)	V4 (D28)	V5 (D42)	V6 (D56)	V7 (D70)
Inform subjects	X								
Verification of eligibility criteria	X								
Informed consent		X							
Randomization		X							
Clinical examination		x	x	x	x	x	x	x	x
SCORAD calculation		x	x	x		x		x	x
Microbiome sampling *		x				x			x
End-of-study visit									x
Collection of adverse events		X	X	X	X	X	x	x	x

* For patients at Caen University Hospital, samples will be taken at V0, V4 and V7. They will be transported to the CBSA laboratory, using the same transport arrangements as those used by Caen hospital.

Exclusion criteria

Exclusion criteria are:

1. Medication used: systemic therapies with immunomodulatory or immunosuppressive agents within the previous 4 weeks; topical or systematic therapies with antibiotics or antihistaminic drugs within the previous 2 weeks; phototherapy (such as PUVA, UVA, or UVB) within the previous 4 weeks; topical therapy with immunomodulator within the previous 2 weeks; or topical or systematic use of any over-the-counter drugs within the previous week.

Patients who are participating in any other clinical trial or had participated in a clinical trial within the previous month, or those who are considered as unfit for the trial are also excluded.

Patients may discontinue their participation in the study if they wish, at any time and for any reason, or at the investigator's discretion. Premature study termination may be due to:

- progression of the disease under study,
- patient refusal to continue,
- withdrawal of consent,
- protocol violations requiring study discontinuation,
- severe toxicity,
- unblinding,
- investigator's decision,
- sponsor's decision,
- participant non-compliance.

All exits must be documented and the investigator must specify the reason. The observation booklet must be completed until the participant leaves the trial. In the event of premature study discharge, the investigating team sends the discharge form to the Clinical Research Unit (URC) Clinical Research Associate. A patient may leave the study prematurely if:

- Withdrawal of consent
- In the event of a CTCAE (common terminology criteria for adverse effects) severe side effect
- If systemic treatment is required.

Follow-up will be carried out one month after discharge.

Interventions

Rescue and concomitant treatment

Routine treatment, such as urea ointment, is recommended for each group, even on non-lesional skin, based on doctors' recommendations. In cases of serious itching, cetirizine hydrochloride or levocetirizine is to be used as a rescue drug. Dosage and frequency have to be recorded for each use.

Randomization and blinding

Randomization will be 1:1 with an online, centralized randomization generator, with stratification on patient characteristics and hospital and/or liberal follow-up so as not to create a hospital recruitment bias.

Blinding will be maintained throughout the study. The emollients will be packaged by the research Department of Caen Normandy Hospital in neutral bottles, with no differentiating features. In the event of severe adverse events justifying discontinuation of emollient treatment, the blind may be lifted.

Maintaining the blind, or withholding information about the awarded intervention, is crucial for several reasons, as the bias reduction (which minimizes performance). Participants and investigators are unaware of which treatment is being administered, reducing the likelihood that their behaviors or

perceptions will influence the results. It enables results with high quality, since it improves the internal validity of the study by ensuring that observed differences between treatment groups are attributable to the interventions themselves and not to bias or expectations, and then enable scientific acceptance.

In order to ensure that blinding was possible before carrying out the study, we wanted to carry out a preliminary sensory study to ensure that the organoleptic characteristics of the different balms did not allow blinding to be lifted. The whole protocol is given for full consideration by L'Orphelin et al., Skin Health and disease, 2026, under press.

Outcome measures

The single primary objective of this study is to show the clinical benefit (SCORAD) of RELIPID+ lipid-resplenishing balm (NEUTRADERM) compared with Lipikar AP + M balm (La Roche Posay) in mild-to-moderate atopic dermatitis, with the assumption that it improves patients at least as well (non-inferiority study).

SCORAD

SCORAD (SCOring Atopic Dermatitis) is a clinical tool used to assess the severity of atopic dermatitis developed by a group of European dermatology experts (17), it quantifies the extent, intensity and subjective impact of the disease on the patient. The SCORAD is based on three main components:

1. Extent of skin involvement (affected body surface area): the rule of nines is used to estimate the percentage of body surface area affected. Each body region (head, trunk, limbs, etc.) represents a given percentage of the total body surface area. The total body surface affected is noted A.
2. Intensity of skin lesions: this section is based on the clinical assessment of six objective signs in a representative area of affected skin, i.e., erythema (redness), swelling, sweating/crusting, lichenification (thickening of the skin), dryness, scratching lesions. Each sign is graded on a scale of 0 to 3 (0 = absent, 1 = mild, 2 = moderate, 3 = severe), giving a total intensity score (graded B).
3. Subjective symptoms as pruritus (itching) and sleep disturbance. Each symptom is scored by the patient on a visual analog scale (from 0 to 10). This score is marked C.

Then, the general formula for calculating the final score is as follows:

$SCORAD = A/5 + 7B/2 + C$. The total score ranges from 0 to 103, with the following categories (18): mild AD (SCORAD < 25), moderate AD (25 < SCORAD < 50) and severe AD (SCORAD > 50).

Non inferiority

A non-inferiority study is designed to demonstrate that the efficacy of a new treatment is not inferior to that of an existing treatment by more than a predefined margin. To demonstrate that the new treatment (experimental treatment, Relipid+ lipid-resplenishing balm, NEUTRADERM) is not inferior to the reference treatment (standard treatment, Lipikar AP + M balm, La Roche Posay) by more than a predefined margin

of non-inferiority. The new treatment is inferior to the reference treatment by more than the non-inferiority margin (null hypothesis, H0) and the alternative hypothesis H1 is that the new treatment is not inferior to the reference treatment by more than the margin of non-inferiority.

The secondary objectives of the AIMS1 study are the improvement in quality of life (DLQI) and scratch score (Itch NRS), the reduction in the use of dermocorticoids, the compliance with emollient application and the reduced cost of emollient (cost-effectiveness study). The primary endpoint (evaluation criteria) will be a mixed clinical-symptom score (SCORAD) comparing the improvement in the score at V0 inclusion and at follow-up visits up to 3 months.

An adjudication committee made up of two dermatologists will be responsible for blindly assessing the patients' evaluations on randomly selected photographs. These pictures will be taken during the course of the study by the investigating physicians at the various inclusion centers.

Safety assessment

Adverse events (AEs) that occur during this trial will be recorded and reported to investigators, and the causality between AE and intervention will be assessed according to the WHO Uppsala Monitoring Centre System for Standardized Case Causality Assessment [WHO. The use of the WHO-UMC system for standardized case causality assessment. 2018. https://www.who-umc.org/media/164200/who-umc-causality-assessment_new-logo.pdf. Accessed June 2020.]. An independent data and safety monitoring committee will assess any safety data requested during the trial. Investigators will address AEs (Adverse events) using the IWRS (Interactive Web Response System) in a timely manner in cases of emergency. They will apply to break the blindness if necessary.

Sample size calculation

According to Navarro-Lopes et al.(19), in a randomized study, the standard deviation ranged from 3.4 to 5 points depending on the group. The clinically acceptable non-inferiority margin was defined by an expert panel and set at 5 points between the two arms for the SCORAD index change. In our study, the standard deviation was higher than that reported by Navarro-Lopes et al (19)., reaching 7 points due to the inclusion of patients with mild-to-moderate atopic dermatitis.

Assuming a true difference of 0 points between the two groups, a power of 85%, and a one-sided alpha risk of 2.5%, the required sample size was calculated to be 37 patients per group, for a total of 74 patients (Fig. 2). To account for an anticipated dropout rate of up to 15%, we planned to include 86 patients in total (43 per group).

The sample size calculation was based on the standard formula for non-inferiority clinical trials (20). Calculations were performed using SAS software version 9.4 (SAS Institute, Cary, NC) with the POWER procedure.

Data management and quality control

An adjudication committee will be set up to ensure that data remains consistent. A blind adjudication panel will be set up by two trained dermatologists, not taking part in the study, to judge the SCORAD on randomly selected photographs.

Ancillary study

The ancillary study will focus on the pathogen bestiary of cutaneous flora, measuring the Shannon score (alpha bacterial diversity). This study requires skin samples and reproducibility of the procedure, and will only be carried out in the investigating center at Caen University Hospital for patients, i.e., focusing on improving the diversity of patients' microbiomes following application of either the AOS-containing balm, Relipid+ resplenishing balm, from NEUTRADERM, or the Lipikar AP + M balm (La Roche Posay, L'Oréal).

The sampling protocol will be as follows:

Materials: Equipment will be sent by the Cosmetomics platform to the sampling site (Caen University Hospital).

- NaCl: VWR, ref. 27800.360
- Tween20: ACROS Organics, ref. 233362500
- Swab [cotton/wood swabs]: CML, ref. ETB, supplier reference: 8150CC
- Sterile hemolysis tubes or sterile Eppendorf tubes
- Collection masks (4 cm²), sterilized by UV exposure under PSM for 1h on each side. Storage and transport in sterile Petri dishes

The humidification solution (0.15 M NaCl, 0.1% Tween 20) will be prepared and autoclaved by the CRC in Caen Hospital and sent to the end user (collection site). The micro-organism collection area is located on a forearm (the same one for the duration of the study), close to the fold area, in an uninjured zone. The sampling area should not be washed or covered with any products, at least 4 h before the appointment for microbiological sampling. A 4 cm² skin sample will be collected. The number of swab passes should be 20 in 3 directions (i.e. 60 passes).

Identify collection tubes or Eppendorf cones and swabs according to pre-defined nomenclature.

Two (2) mL of moistening solution (NaCl-Tween20) are added to each tube. These tubes should be stored at 4°C before use.

The swabs are moistened by soaking in the 2 mL of solution already present in the tube, then gently wringing out the sides, just before sampling.

The sampling mask is held in the hand by the sampler (wearing gloves). Sampling is performed by passing the swab 20 times in each of 3 directions (horizontal, vertical and diagonal), as shown in the

Fig. 3. After use, the masks are discarded and must not be reused.

After collection, the swab is immediately inserted into the sterile tube containing the 2 mL humidification solution. The operation should be carried out under conditions of maximum cleanliness and, wherever possible, under SHP (Sterile Hood Plenum).

The stem of the swab should be cut as short as possible above the cotton so that the tube can be closed.

After collection from each volunteer, the samples can be immediately frozen and stored at -80°C before delivery to the carrier.

Safety assessment

All adverse events (AEs) and serious adverse events (SAEs) occurring during the study period will be recorded and assessed.

An AE is defined as any untoward medical occurrences in a participant receiving the study intervention, whether or not considered related to the intervention. A serious adverse event (SAE) is defined according to ICH-GCP standards as any event that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is otherwise considered medically significant.

The causal relationship between the intervention and any reported AE or SAE will be assessed using the WHO–Uppsala Monitoring Centre (WHO-UMC) standardized case causality assessment system. All SAEs will be reported to the sponsor within 24 hours of awareness by the investigator and subsequently notified to the appropriate regulatory authorities (CPP and ANSM) in accordance with French regulatory requirements.

An independent Data and Safety Monitoring Committee (DSMC) will oversee participant safety throughout the study. The DSMC is independent from the sponsor and investigators. Given the minimal-risk nature of the dermocosmetic intervention and the absence of systemic exposure, no interim efficacy analysis is planned. The DSMC will review safety data annually or upon occurrence of any SAE and may recommend continuation, modification, or termination of the study if necessary.

Data management and quality control

All participant data will be coded using a unique identification number to ensure pseudonymization. The correspondence table linking participant identity to study code will be kept securely by the principal investigator and will not be accessible to unauthorized personnel.

Data will be collected using standardized case report forms and stored in secure institutional databases compliant with applicable data protection regulations. All data will be retained for a period of 25 years in accordance with French regulatory requirements for clinical research.

Access to the final trial dataset will be restricted to the principal investigator and the senior biostatistician. No contractual agreement with the sponsor or funder restricts investigators' access to the data or their ability to analyze and publish the results independently.

Monitoring of the study will be conducted under the responsibility of the sponsor (CHU Caen Normandie). Quality control procedures will include regular data verification, source data checks, and compliance assessments to ensure adherence to the protocol, Good Clinical Practice standards, and applicable regulatory requirements.

Statistical analysis

Statistical analyses will be performed on an intention-to-treat (ITT) basis, meaning that each subject will be analyzed according to their randomized group. A per-protocol (PP) analysis will also be conducted, excluding protocol deviations (use of "Relipid+ lipid-resplenishing balm" or "Lipikar AP + M emollient balm") and subjects with missing data for the primary outcome. Missing data for the primary endpoint in the ITT analysis will be imputed as follows: missing values will be considered as no change in the score. Sensitivity analyses will be performed using alternative methods in the following order: multiple imputation (PROC MI) and complete-case analysis excluding missing data. Non-inferiority will be declared only if all analysis strategies yield consistent results, in accordance with the CONSORT guidelines for non-inferiority trials (Piaggio, JAMA).

Categorical variables will be described as counts and percentages. Continuous variables will be summarized using means and standard deviations or medians and interquartile ranges [Q1; Q3], depending on the normality assumption assessed by a non-significant Shapiro-Wilk test and/or histogram symmetry.

To compare changes in the SCORAD index between the two arms under a non-inferiority hypothesis, the differences between baseline and day 70 (delta SCORAD) will first be calculated within each group. Then, the difference in mean changes between the experimental and control groups will be computed along with the corresponding 95% confidence interval (CI). The upper bound of the CI will be compared to the predefined non-inferiority margin of 5 points. Non-inferiority will be concluded if this bound is less than 5 points in both ITT and PP analyses. Validity assumptions will be checked, including normality of data within each group (Shapiro-Wilk test or Q-Q plots).

A multiple linear regression will be conducted with delta SCORAD as the dependent variable and randomization group as the main explanatory variable, adjusting for stratification factors used during randomization.

If the 95% CI for the difference in means does not include zero, superiority tests may be performed using Student's t-test or the Mann-Whitney U test, depending on the data distribution.

Secondary quantitative endpoints will be compared using appropriate statistical tests. Changes in quality of life, pruritus scores, and Shannon index will be analyzed using mixed-effects models to

account for repeated measures. Use of topical corticosteroids and adherence to emollient application at day 70 will be compared between groups using Chi-square or Fisher's exact tests.

Statistical analyses will be performed using SAS software version 9.4 (SAS Institute, Cary, NC) or later, and/or R software version 4.4.1 or later (2024, The R Foundation for Statistical Computing). A two-sided p-value < 0.05 will be considered statistically significant. Analyses of secondary endpoints will be exploratory, and nominal p-values may be reported.

A health economic evaluation will be conducted to estimate cost minimization based on PMSI data and direct costs for each strategy (accounting for emollient volume used, calculated using the retail price of the product). In case of clinical events related to poor tolerance of a strategy, associated healthcare costs (including reductions in emergency visits and/or hospitalizations for exacerbations) will also be incorporated into the analysis.

4. Ethics and Dissemination

Ethics approval

This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Ethical approval was obtained from the Comité de Protection des Personnes (CPP IDF VIII), reference number 2024-A02369-38, on May 23, 2025.

Authorization was granted by the French National Agency for Medicines and Health Products Safety (ANSM) in accordance with Article L.1121-4 of the French Public Health Code.

The study is registered on ClinicalTrials.gov (NCT 07358000).

Consent to participate

Written informed consent will be obtained from all participants prior to any study-specific procedures. For minors, written informed consent will be obtained from a parent or legal guardian, in accordance with French regulations.

Participants followed at Caen University Hospital and enrolled in the ancillary microbiome study will provide additional specific written consent for non-invasive skin swab sampling and for the analysis of microbiome diversity. Participation in the ancillary study is optional and does not condition participation in the main trial.

Confidentiality and data protection

Personal data collected in the context of this study will be processed in compliance with the General Data Protection Regulation (EU 2016/679) and the French Data Protection Act.

The study complies with the MR-001 reference methodology established by the French Data Protection Authority (CNIL) for research involving human participants.

All data will be pseudonymized using coded identifiers. Only the principal investigator will retain the correspondence table linking participant identity to the study code. Access to identifiable data will be restricted to the medical team, authorized sponsor representatives for monitoring purposes, regulatory authorities, and the Data Protection Officer when necessary.

Participants have the right to access, rectify, restrict processing, object to processing, and request erasure of their personal data, in accordance with applicable regulations, subject to legal obligations related to research safety and regulatory requirements.

Protocol amendments

Any substantial protocol modifications (e.g., changes in eligibility criteria, outcomes, or analyses) will be submitted to the Ethics Committee (CPP), the competent authority (ANSM), and updated in the ClinicalTrials.gov registry prior to implementation. Investigators and study personnel will be informed accordingly

Access to data

The principal investigator and the senior biostatistician will have full access to the final trial dataset. No contractual agreement with the funder restricts investigators' access to data.

The sponsor and funders will not have authority to restrict the interpretation, analysis, or publication of the study results.

Dissemination policy

The full study protocol will be made publicly available upon publication of the primary results. The whole protocole is available on clinicaltrials.org

5. Trial status

Recruitment has not yet started at the time of manuscript submission. The protocol version is 1.2 (dated January 15, 2026). Recruitment is expected to begin in March 2026, with an anticipated completion date in December 2027.

6. Discussion

The primary endpoint in clinical trials for atopic dermatitis may vary. However, the primary endpoint used in clinical trials testing local therapies in atopic dermatitis generally includes composite measures of

improvement in disease severity and symptoms.

We design the AIMS study using SCORAD variations as our primary endpoints, which is commonly used in clinical trials and clinical practice to assess the severity of atopic dermatitis. SCORAD considers the extent and intensity of skin lesions, as well as subjective symptoms such as pruritus and loss of sleep. Consensus use of SCORAD will enable comparison with other studies available in the literature.

Blinding is essential to ensure the validity and reliability of randomized controlled studies in cosmetology. Although unique challenges exist due to the sensory characteristics of cosmetic products, strategies such as the use of placebos, identical packaging, double-blinding, investigator training and objective assessments can be employed to overcome these obstacles. By rigorously applying these strategies, researchers can minimize bias and produce results that are more credible and acceptable to the scientific community and regulatory bodies. Nevertheless, it remains big and unique challenges of blinding in cosmetology. Indeed, cosmetic products often have distinct sensory characteristics (smell, texture, color) that can reveal product identity, as immediate feelings and effects (i.e., visible or perceptible immediate effects, making it difficult to maintain blindness). As far as we know, this is the first time a dermo-cosmetic study has taken up the issue. In fact, we have imposed on ourselves the rigor of RCT applied in cosmetology and we are keen to ensure that blind is maintained with a preliminary sensory study.

Moreover, our study does not seek only clinical validation by comparison with gold standard treatment. The ancillary study on skin microbiome demonstrates a desire for translational research, enabling a much more scientific approach and providing an intellectual underpinning for clinical results.

As far as we know, this is the first dermo-cosmetic study to propose a research protocol with rigorous design and statistics allowing the comparison of two topical emollient balms composed of 2 different mineral waters. We propose a preliminary study to ensure the sensory elements of the creams cannot lift the blind. This protocol could be used for future topical trials.

Abbreviations

AD
Atopic dermatitis
RCT
Randomized Clinical Trial
SCORAD
SCORing Atopic Dermatitis

Declarations

Ethics Approval declaration: This study was performed in accordance with the principles of the Declaration of Helsinki. Approval was granted by the national Ethics Committee CPP IDF VIII, registration

number 2024-A02369-38, the 23rd of May, 2025.

Consent for publication: Not applicable. No individual person's data, images, or identifiable information are included in this manuscript.

Availability of data and materials: The datasets generated and/or analysed during the current study will be available from the corresponding author upon reasonable request. De-identified individual participant data (IPD), including the data dictionary and statistical analysis code, will be made available beginning 6 months and ending 5 years following publication of the primary results. Data sharing will be subject to a data access agreement and limited to researchers who provide a methodologically sound proposal consistent with the objectives of the AIMS trial. Data will be shared after de-identification, in compliance with the General Data Protection Regulation (EU 2016/679), French data protection laws, and the MR-001 reference methodology established by the CNIL. The full study protocol and statistical analysis plan will be made publicly available upon publication of the primary results. Biological specimens collected as part of the ancillary microbiome study will not be shared. However, anonymized derived microbiome sequencing data may be made available under the same conditions.

Authors' contributions: JMLO (Jean-Matthieu L'Orphelin) conceived the study, designed the clinical protocol, and drafted the manuscript. JJP (Jean-Jacques Parienti) designed the statistical analysis and the study plan and performed the sample size calculation. Anais Briant (AB) designed the statistical analysis. AB, JG, CL, and MF contributed to the study design, methodology, and critical revision of the manuscript. All authors read and approved the final manuscript.

Statements and Declarations / Competing interest

Jean-Matthieu L'Orphelin has received speaker and consultant honoraria from BMS, Novartis, MSD, Laboratoires Gilbert and Pierre Fabre Oncology.

Jean-Jacques Parienti has received speaker and consultant honoraria from Gilead Science, MSD and ViiV healthcare. Other authors have no conflict of interest to declare.

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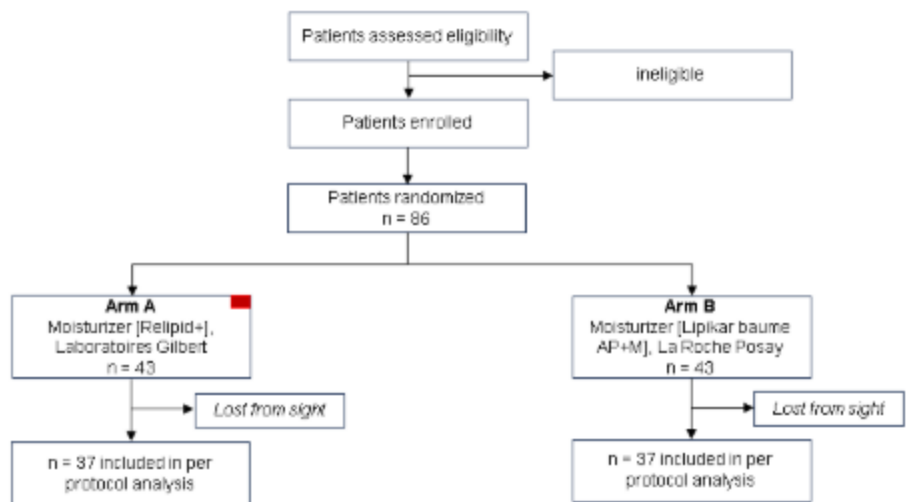
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Figures



■ Patients enrolled in Ceen hospital will be included in an ancillary study on impact of moisturizer on skin microbiome

Figure 1

AIMSI trial profile

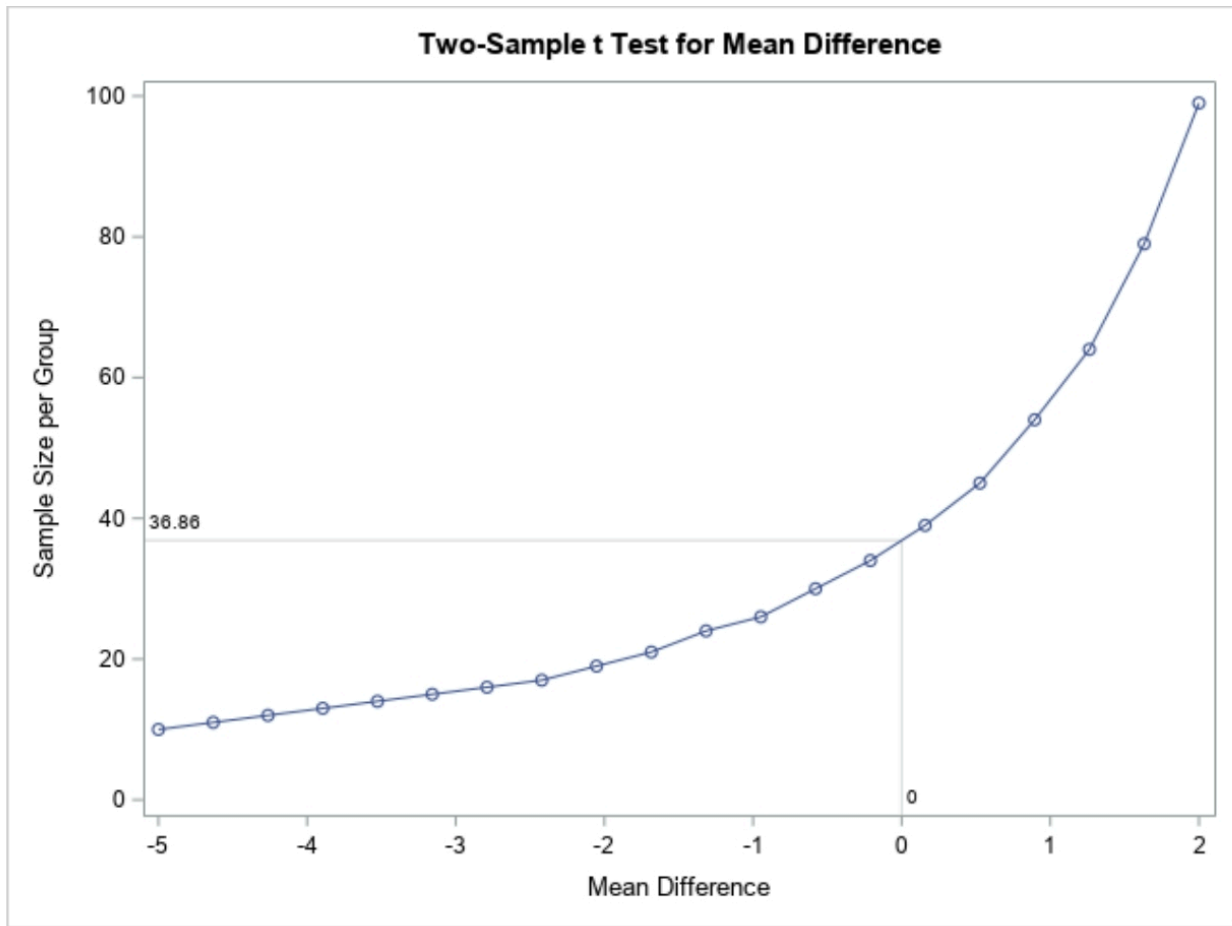


Figure 2

Sample size calculation for AIMS non-inferiority clinical trial

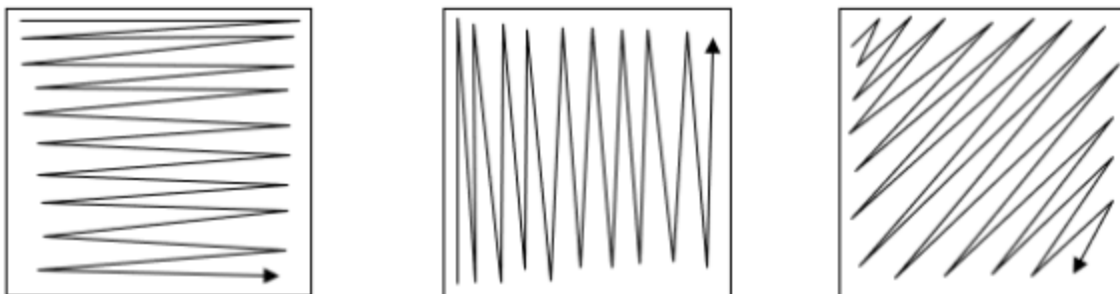


Figure 3

Sampling passing the swab in each of 3 directions