Intervention with Tralokinumab in patients with moderate-to-severe Atopic Dermatitis with genital impact

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Protocol Synopsis

Study title	A non-interventional, prospective 52-week clinical study investigating improvements in patient-reported outcomes (PROs) in individuals with moderate-to-severe atopic dermatitis (AD) involving the genital region, treated with tralokinumab as part of routine care.
Hypothesis	Treatment with tralokinumab in patients with moderate-to-severe AD involving the genital region is expected to lead to significant improvements in PROs and clinical disease severity. These improvements will be assessed using genital-specific scoring systems, validated PRO instruments, and non-invasive imaging techniques, including optical coherence tomography (OCT), confocal microscopy, or line-field optical coherence tomography (LC-OCT).
Objectives	To investigate improvements in genital scores and PROs in patients with moderate-to-severe AD involving the genital region during treatment with tralokinumab in routine clinical care. Clinical assessment of genital AD severity will be conducted using genital-specific scoring systems [e.g., Genital-Numerical Rating Scale (g-NRS), Genital-Investigator Global Assessment (g-IGA)], validated PRO instruments [e.g., Patient-Oriented Eczema Measure (POEM), Atopic Dermatitis Control Tool (ADCT)], and non-invasive imaging techniques (e.g., confocal microscopy, OCT, LC-OCT).
Study design	This is a prospective, open, exploratory, non-randomized, non-blinded study. A total of 30 patients diagnosed with moderate-to-severe AD involving the genital region will be treated with tralokinumab in routine clinical care, in accordance with the tralokinumab Summary of Product Characteristics, over a period of 52 weeks. Data acquisition will take place at treatment initiation and during routine follow-up visits at baseline, week 4, week 16, week 24, and week 52.
Timelines	First patient first visit: October 2025 Patient recruiting: 12 months Last patient last visit: October 2027 Study Closure: June 2028
Sample size	A total of 30 patients with moderate-to-severe AD involving the genital region, for whom the clinical decision to initiate treatment with tralokinumab has been made independently of the study, will be offered enrollment. Patients will be recruited at two centers: approximately two-

	thirds at the Institute and Comprehensive Center for Inflammation Medicine (CCIM) of the University Medical Center Schleswig-Holstein (UKSH), Campus Lübeck, Lübeck, Germany and approximately one-third at the Department of Dermatology of the University Hospital Augsburg (UKA), Augsburg, Germany.
Study site location	The study will be conducted at two centers: primarily at the Institute and Comprehensive Center for Inflammation Medicine at the University of Lübeck, Lübeck, Germany, and additionally at the Department of Dermatology, University Hospital Augsburg, Augsburg, Germany.
Subject eligibility criteria Inclusion	• Subjects must be able to understand and communicate with the investigator and comply with the requirements of the study and must give written, signed and dated informed consent before any study related activity is performed. • Subjects must be at least 18 years of age at time of enrollment. • Subjects starting treatment with tralokinumab and for whom the clinical decision has been made independent of the study according to licensed product specifications and treatment guidelines prior to participation in the study. • Subjects diagnosed with moderate-to-severe AD and genital involvement eligible for systemic therapy according to the local label.
Subject eligibility criteria Exclusion	• Exclusion criteria will comply with the licensed specifications for tralokinumab. • Subjects incapable of giving full informed consent. • Current participation in another study with any investigational products (noninterventional or registries are allowed). • Currently pregnant or nursing women will be excluded from this study. • Subjects without genital involvement.
Early termination	• Treatment failure, defined as no improvement or worsening of EASI at week 16. • Change in therapy. • More than 20% of the total treatment duration (i.e., >73 cumulative, non-consecutive days) without receiving the study drug.

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List of abbreviations

AD	Atopic Dermatitis
ADCT	Atopic Dermatitis Control Tool
AE	Adverse Event
BMI	Body Mass Index
BSA	Body Surface Area
CCIM	Comprehensive Center for Inflammation Medicine
DLQI	Dermatology Quality of Life Index
EASI	Eczema Area and Severity Index
GCP	Good Clinical Practice
g-IGA	Genital- Investigator Global Assessment
g-NRS	Genital-Numeric Rating Scale
HADS	Hospital Anxiety and Depression Scale
IGA	Investigator Global Assessment
IL-13	Interleukin-13
l-SCORAD	localized SCORing Atopic Dermatitis
LC-OCT	Line-field Optical Coherence Tomography
MGISD	Mean Global Index of Sexual Dysfunction
OCT	Optical Coherence Tomography
POEM	Patient-Oriented Eczema Measure
PRO	Patient-Reported Outcomes
SAE	Serious Adverse Event
SBQ-G	Sexual Behavior Questionnaire
SCORAD	SCORing Atopic Dermatitis
UKA	University Hospital Augsburg
UKSH	University Medical Center Schleswig-Holstein

1. Background/Rationale

Atopic dermatitis (AD) is a common, chronic, and highly pruritic inflammatory skin disease that significantly impacts quality of life and poses a considerable socioeconomic burden (1). It is often associated with reduced health-related quality of life, sleep disturbances, and impaired work productivity (2,3).

Genital involvement in AD, reported in 10.3% to 45% of cases, can severely affect patients' well-being, particularly sexual health (4, 5). However, genital examination is often omitted in routine clinical practice, and patients may hesitate to disclose symptoms in this area. As a result, genital AD remains frequently overlooked and under-reported.

Tralokinumab is a fully human IgG4 monoclonal antibody that specifically neutralizes interleukin-13 (IL-13) by inhibiting its binding to IL-13 receptors (6). IL-13 plays a central role in AD pathogenesis and is a key driver of inflammation and skin barrier dysfunction (7). Tralokinumab is approved for the treatment of moderate-to-severe AD.

Certain anatomical regions, such as the head and neck and the genital area, are considered difficult-to-treat areas in AD. While treatment efficacy in the head-and-neck region can be assessed retrospectively through regional EASI analysis, evaluating the impact of treatment on genital involvement and its associated patient-reported outcomes (PROs) requires prospective study designs.

A post hoc analysis of adult patients with moderate-to-severe AD has shown that tralokinumab provides sustained improvement in head-and-neck involvement for up to four years, including in patients with severe baseline disease (8). These improvements were accompanied by enhanced quality of life, particularly regarding reductions in skin discomfort and feelings of self-consciousness or embarrassment due to visible skin involvement (8).

In contrast, data on genital involvement remain limited. A recent case series by Paolino *et al.* suggested that tralokinumab may be particularly effective in this area (9). After four months of treatment in 12 patients with genital AD, the genital Investigator Global Assessment (IGA) score was reduced by approximately 60% ($p = 0.001$), with a median decrease from 3 to 1 ($p = 0.001$).

Further studies with larger patient populations are warranted to confirm these findings, assess long-term clinical benefits, and investigate the corresponding improvements in patient-reported outcomes.

2. Study Purpose

This study aims to investigate improvements in genital PROs in patients with moderate-to-severe AD involving the genital region during treatment with tralokinumab in routine clinical care over a 52-week period. Additionally, the study will assess changes in both local (genital-specific) and general clinical scoring systems, as well as evaluate skin changes using non-invasive imaging techniques such as confocal microscopy, optical coherence tomography (OCT), or line-field optical coherence tomography (LC-OCT).

3. Study Objectives

Primary Endpoint	Improvement of ≥50% in Genital-Numerical Rating Scale (g-NRS) or ≥2 points in Genital-Investigator Global Assessment (g-IGA) in patients with moderate-to-severe AD treated with tralokinumab over a 52-week period.
Secondary Endpoints	Improvement in general PRO instruments [e.g., Patient-Oriented Eczema Measure (POEM), Atopic Dermatitis Control Tool (ADCT), Dermatology Life Quality Index (DLQI), Hospital Anxiety and Depresssion Scale (HADS)] in patients with moderate-to-severe AD undergoing treatment with tralokinumab over a 52-week period.
	Improvement in overall disease severity [e.g., Eczema Area and Severity Index (EASI), SCORing Atopic Dermatitis (SCORAD), Investigator Global Assessment (IGA)] in patients with moderate-to-severe AD undergoing treatment with tralokinumab over a 52-week period.
	Exploratory assessment of skin changes using non-invasive imaging techniques (OCT, confocal microscopy, or LC-OCT) will be performed, where feasible and acceptable to participants, in patients with moderate-to-severe AD receiving tralokinumab over a 52-week period. Imaging will be conducted at both centers. Image analysis will be carried out at the Department of Dermatology, University Hospital Augsburg (UKA), Augsburg, Germany.

4. Study Design

This is a prospective, open-label, exploratory, non-randomized, non-blinded study. A total of 30 patients diagnosed with moderate-to-severe AD involving the genital region will be treated with tralokinumab as part of routine clinical care, in accordance with the Summary of Product Characteristics for tralokinumab, over a 52-week period.

Tralokinumab is prescribed in accordance with the terms of its marketing authorization. The decision to prescribe tralokinumab is clearly independent of the decision to include the patient in the study. The medicinal product is obtained through standard distribution channels.

Data will be collected at treatment initiation and during routine follow-up visits at baseline, week 4, week 16, week 24, and week 52.

5. Study Population

The study will consist of a total of 30 patients (both male and female) with moderate-to-severe AD involving the genital region, for whom the clinical decision to initiate treatment with tralokinumab has been made independently of the study in accordance with the terms of the marketing authorization and local clinical guidelines. Patients will be recruited at two centers: approximately two-thirds at the Institute and Comprehensive Center for Inflammation Medicine (CCIM) of the University Medical Center Schleswig-Holstein (UKSH), Campus Lübeck, Lübeck, Germany, and approximately one-third at the Department of Dermatology of the UKA, Augsburg, Germany.

Participation in the study is entirely voluntary, and subjects may withdraw at any time without providing a reason and without any consequences to their ongoing medical care.

5.1. Inclusion Criteria

The investigator must ensure that only patients who meet the following inclusion criteria and do not fulfill any of the exclusion criteria are offered enrollment in the study.

Subjects eligible for inclusion in this study must fulfill **all** of the following criteria:

- Subjects must be able to understand and communicate with the investigator and comply with the requirements of the study and must give written, signed and dated informed consent before any study related activity is performed.
- Subjects must be at least 18 years of age at time of enrollment.

- Subjects starting treatment with tralokinumab and for whom the clinical decision has been made independent of the study according to licensed product specifications and treatment guidelines prior to participation in the study.
- Subjects diagnosed with moderate-to-severe AD and genital involvement eligible for systemic therapy according to the local label.

5.2. Exclusion Criteria

Subjects fulfilling any of the following criteria are not eligible for inclusion in this study:

- Subjects not fullfilling the approved (licensed) indication for treatment with tralokinumab.
- Subjects incapable of giving full informed consent.
- Current participation in another study with any investigational products (noninterventional or registries are allowed).
- Currently, pregnant and nursing women, or those planning to become pregnant or breastfeed, will be excluded from this study.
- Subjects without genital involvement.

5.3. Reproductive Status

Data on tralokinumab use during pregnancy are limited. Animal studies have shown no evidence of reproductive toxicity; however, as a precaution, use during pregnancy should be avoided. It is unknown whether tralokinumab is excreted in human milk; therefore, use during lactation is not recommended. Regarding fertility, animal studies revealed no adverse effects on male or female reproductive organs or on sperm parameters (count, motility, or morphology).

5.4. Management and Reporting of Adverse Events and Other Experiences

An Adverse Event (AE) is defined, in accordance with Good Clinical Practice (GCP) regulations, as any novel medical occurrence or worsening of a preexisting medical condition in a participant that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship of AEs to the study drug is determined by a physician for all AEs. The causal relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE. The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

Following the subject's written consent to participate in the study, all non-serious AEs and Serious Adverse Event (SAEs), whether related or not related to study drug, are collected and will be reported as described in the following sections.

A non-serious AE is an AE not classified as serious. The collection of non-serious AE information begins following the subject's written consent to participate in the study. All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 30 days following the last dose of study treatment. Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. Non-serious AE are to be provided to BMS and to health authorities as per applicable law. AEs will be reported by using the adverse event reporting form and will be documented within the case report form.

A SAE is defined, in accordance with GCP regulations, as any medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- requires inpatient hospitalization or causes prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may endanger the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above. Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

The following hospitalizations are not considered SAEs in this study:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

A SAE report will be completed for any event where doubt exists regarding its seriousness and for the above-mentioned criteria. In this trial SAEs will be documented following the subject´s written consent to participate in the study through 30 days of discontinuation of dosing and the completed report will be sent within 24 hours of awareness to LEO Pharma Global Safety via drug.safety@leo-pharma.com in the form of a list according to current regulations. If a follow-up SAE report is necessary, SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report will be sent within 24 hours of awareness to drug.safety@leo-pharma.com. All SAE will be followed to resolution or stabilization.

Pregnancy

After initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, the investigational product will be immediately and permanently discontinued.

A pregnancy will be reported to LEO Pharma Global Safety and the completed report will be sent within 24 hours of awareness to drug.safety@leo-pharma.com.

Any pregnancy that occurs in a female partner of a male study participant will be reported to LEO Pharma if the female partner has signed an informed consent for disclosure of pregnancy information. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported to LEO Pharma.

Product Quality Complaints

Product Quality Complaints are any communication about Tralokinumab that alleges deficiencies related to identity, quality, durability, reliability, safety, effectiveness, performance,

tampering, diversion, or counterfeiting/falsification of a drug, combination product, or device after it is released for distribution to market or clinic by either: (1) LEO Pharma or (2) distributors or partners for whom LEO Pharma manufactures the material. This includes all components co-packaged with the drug, such as drug containers, delivery system, labelling, and inserts.

Product Quality Complaints will be reported to LEO Pharma within one business day of awareness. The report should include as much product information as possible (e.g. description of quality complaint, impacted batch number, photographs).
The affected product will be quarantined immediately at the investigational site and should not disposed unless retention presents a risk to personnel (e.g. cytotoxic).

5.5. Recruitment of Study Participants

Recruitment is expected to take approximately 12 months. Eligible patients will be identified and recruited at two study sites: approximately two-thirds at the Institute and CCIM of the UKSH, Campus Lübeck, Lübeck, Germany, and approximately one-third at the Department of Dermatology of the UKA, Augsburg, Germany.

Eligible patients are those initiating systemic treatment with tralokinumab for moderate-to-severe AD, independently of the study, as part of routine clinical care. Patients are identified by their treating physician and are informed about the study during regular consultation hours. Initial study information is provided through a short information leaflet (Kurzinformation).

6. Study Timeline

The study is planned to commence with the first patient's first visit in October 2025. The recruitment period will span 12 months, during which eligible patients will be screened and enrolled. The last patient's last visit is anticipated in October 2027. Following this, data analysis and reporting will be conducted, with study closure expected by June 2028.

7. Visit Schedule and Assessments

7.1. Procedures for Informing and Obtaining Consent

Eligible patients will be asked during their regular consultation whether they are interested in participating in the study. If they express interest, they will receive detailed written patient information and a general introduction to the study. Patients will be informed both verbally and in writing. Sufficient time will be provided for them to review the study information, consider their participation, and ask any questions during or after the consultation. If the patient decides to participate, the informed consent form will be signed and dated by both the patient and the physician. The study will only commence after full and independent informed

consent has been obtained. Written informed consent is a mandatory prerequisite for study participation.

7.2. Study Methodology

The study involves clinical documentation, clinical scoring, PRO instruments, safety monitoring, and imaging techniques including OCT, confocal microscopy, or LC-OCT.

Local/genital assessment tools include the patients‘ g-NRS, g-IGA, the Lindenmeyer Sexuality Questionnaire, the Sexual Behavior Questionnaire (SBQ-G), and the localized SCORAD (l-SCORAD).
Clinical scores include the EASI, IGA, SCORAD.
Patient-reported outcomes will be assessed using the DLQI, POEM, ADCT, and HADS.

7.3. First Visit

During the regular consultation, participants will be screened for eligibility according to the inclusion and exclusion criteria. A complete physical examination will be performed, and eligibility for treatment with tralokinumab will be assessed. Informed consent will then be obtained and signed by both the participant and the physician.

Following consent, clinical documentation will be completed, including demographics, disease history, concomitant medications, clinical scores, and patient-reported outcomes. Imaging assessments will also be conducted. Upon completion of baseline assessments, participants will begin treatment with tralokinumab as per the product's summary of characteristics.

7.4. Schedule of Visits

The schedule of visits, including timelines for clinical documentation, clinical scoring, patient questionnaires, and imaging procedures, is outlined in Table 1. All procedures listed in Table 1 represent standard clinical assessments routinely performed in the care of patients with atopic dermatitis. The Genital-Investigator Global Assessment (g-IGA) is a scale used to evaluate the severity of genital skin inflammation in affected patients. Assessment of skin changes using non-invasive imaging techniques (OCT, confocal microscopy, or LC-OCT) will be performed, where feasible and acceptable to participants. OCT is a non-invasive, non-injurious imaging modality that is safe for patients and is frequently employed in routine dermatological care. Imaging will be conducted at both centers. Image analysis will be carried out at the Department of Dermatology, UKA, Augsburg, Germany.

Table 1: Schedule of visits, clinical documentation, clinical scores, patient questionnaires, and imaging.

Visit	**1**	**2**	**3**	**4**	**5**
Week	**0**	**4**	**16**	**24**	**52**
Procedure:					
Informed consent	X				
Confirmation of eligibility	X				
Patient demographics	X				
Medical history, prior and concomitant therapies as well as surgeries	X				
Weight, Height, body mass index (BMI)	X				
Genital-Investigator Global Assessment (g-IGA)	X	X	X	X	X
Eczema Area and Severity Index (EASI)	X	X	X	X	X
Investigator Global Assessment (IGA)	X	X	X	X	X
SCORing Atopic Dermatitis (SCORAD)	X	X	X	X	X
Localized SCORing Atopic Dermatitis (l-SCORAD)	X	X	X	X	X
Genital-Numeric Rating Scale (g-NRS)	X	X	X	X	X
Sexuality Questionnaire Lindenmeyer	X	X	X	X	X
Sexual Behavior Questionnaire (SBQ-G)	X	X	X	X	X
Dermatology Life Quality Index (DLQI)	X	X	X	X	X
Patient-Oriented Eczema Measure (POEM)	X	X	X	X	X
Atopic Dermatitis Control Tool (ADCT)	X	X	X	X	X
Hospital Anxiety and Depression Scale (HADS)	X		X		X
Non-invasive imaging*	X	X	X	X	X

**Exploratory assessment of skin changes using non-invasive imaging techniques (OCT, confocal microscopy, or LC-OCT) will be performed, where feasible and acceptable to participants. Imaging will be conducted at both centers. Image analysis will be carried out at the Department of Dermatology, UKA, Augsburg, Germany.*

7.4.1. Clinical, demographic and imaging assessments

The following assessments will be conducted during the study. Items 1 to 5 focus on gathering general patient information. Clinical signs will be assessed using the g-IGA, EASI, IGA, SCORAD and l-SCORAD for the genital area. Symptoms will be evaluated with the Genital-NRS. Quality of life will be assessed using the Sexuality Questionnaire Lindenmeyer, SBQ-G, DLQI, POEM, ADCT, and HADS.

7.4.2. Clinical documentation and safety

Clinical Documentation & Safety will be asked at first visit on week 0 and until week 52 depending on the item. Data is consisting of:

- Date of birth / age
- Gender
- Medical/Surgical history and previous medications
- Adverse Events / SAEs
- Concomitant therapy
- Initial diagnosis of AD
- AD treatment history

- Weight
- Height

Patients' height will be measured and documented in the beginning, the weight throughout the study. The body mass index (BMI) will be calculated using the formula.

BMI= (weight in kilograms / (height in meters x height in meters)).

7.4.3. Scores Assessing Clinical Signs

The following scores will be recorded at baseline and at each scheduled follow-up visit throughout the study.

Genital-Investigator Global Assessment (g-IGA)

The g-IGA is a clinician-reported tool used to assess the severity of genital involvement in AD, as previously described (9). It utilizes a 5-point scale developed, incorporating morphological criteria:

- **0 – Clear**: No signs of inflammation (e.g., erythema, induration, lichenification, oozing, or crusting). Postinflammatory hyper-/hypopigmentation may be present.
- **1 – Almost Clear**: Minimal erythema and slight induration or lichenification; no oozing or crusting.
- **2 – Mild**: Mild erythema (pink), slight induration or lichenification; no oozing or crusting.
- **3 – Moderate**: Noticeable erythema (dull red), induration, or lichenification; oozing/crusting may occur.
- **4 – Severe**: Marked erythema (bright/deep red), pronounced thickening, and/or widespread lesions; oozing or crusting may be present.

Eczema Area and Severity Index (EASI)

The EASI is used to assess the severity and extent of signs of AD in patients. It evaluates four key parameters: Erythema, infiltration, excoriation, and lichenification, each rated on a scale of 0 to 3 (0 = none, 3 = severe). These parameters are assessed across four body regions: Head/neck, upper limbs, trunk, and lower limbs.

The total EASI score is calculated by combining the severity of the four parameters with the affected body surface area (BSA) (expressed as a percentage of the total body surface area). The resulting score ranges from 0 to 72, with higher scores indicating more severe eczema.

Investigator's Global Assessment (IGA)

The IGA is a clinician-assessed scale used to evaluate the overall severity of AD. The IGA is based on a visual inspection of the patient's skin and is rated on a 5-point scale:

0 = Clear (no signs of AD)

1 = Almost Clear (few residual lesions)

2 = Mild (slight redness, itching, and/or scaling)

3 = Moderate (moderate redness, itching, and/or scaling)

4 = Severe (intense redness, itching, scaling, and/or thickened skin)

SCORing Atopic Dermatitis (SCORAD)

The SCORAD is a validated clinical tool used to assess the extent and severity of AD. It integrates both objective clinical signs and patient-reported symptoms into a composite score ranging from 0 to 103. The extent of the disease is calculated using the "rule of nines" to estimate the percentage of body surface area affected. Intensity is assessed based on six clinical signs: erythema, edema/papulation, excoriation, lichenification, oozing/crusts, and dryness, each scored on a 4-point scale: 0 = none, 1 = mild, 2 = moderate, and 3 = severe. Subjective symptoms, specifically pruritus and sleep disturbance, are recorded by the patient using visual analogue scales ranging from 0 to 10.

Localized SCORAD for the Genital Area (l-SCORAD)

The l-SCORAD is an adapted version of the SCORAD designed to evaluate the severity of AD in the genital area. This tool focuses solely on the intensity of skin lesions within the localized site and excludes overall body surface area and patient-reported symptoms. The same six clinical signs (erythema, edema/papulation, excoriation, lichenification, oozing/crusts, and dryness) are assessed and scored on a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe).

7.4.4. Scores Assessing Symptoms

The following scores will be recorded at baseline and at each scheduled follow-up visit throughout the study.

Genital-Numeric Rating Scale (Genital-NRS)

The Genital Numeric Rating Scale (g-NRS) is a patient-reported measure that subjectively assesses the severity of genital involvement in AD on a scale from 0 to 10, as previously described (9).

Patient-Oriented Eczema Measure (POEM)

The POEM is a questionnaire designed to evaluate the symptoms of AD over the past week. It consists of seven questions addressing symptoms such as itching, sleep disturbance, bleeding, oozing, skin cracks, scaling, and dryness. For each question, the patient indicates the number of days in the past week they experienced the symptom (0 to 7 days). Each response is scored from 0 to 4 (0 = no days, 4 = every day), and the total score is the sum of these individual scores. The total score ranges from 0 to 28, with higher scores reflecting a greater symptom burden and more severe disease.

Atopic Dermatitis Control Tool (ADCT)

The ADCT is a patient-reported measure to assess the control of AD symptoms over the past week. It includes six questions on itching, sleep disturbance, daily activities, and emotional impact, with responses scored from 0 to 4 (0 = no symptoms, 4 = extreme symptoms). The total score, ranging from 0 to 24, indicates the level of control. A score of 7 or higher, or an increase of 5 points or more since the last assessment, suggests poor disease control.

7.4.5. Scores Assessing Quality of Life of Patients

The following scores will be recorded at baseline and at each scheduled follow-up visit throughout the study, except for the HADS, which will be assessed at Visits 1, 3, and 5 only.

Sexuality Questionnaire Lindenmeyer

The Sexuality Questionnaire Lindenmeyer is designed to assess various aspects of an individual's sexual health and well-being. It includes questions about the respondent's relationship status, satisfaction with their partnership, and the frequency of sexual contact. It also explores the individual's sexual behaviour, including their satisfaction with sexual activity and whether they use contraception. The questionnaire addresses any perceived sexual problems, including whether these issues may be related to alcohol or drug use. Finally, it asks whether the individual has sought medical or psychological treatment for sexual difficulties in the past and whether they currently wish for help in managing these issues. Through a combination of multiple-choice and open-ended questions, the questionnaire collects information to better understand the respondent's sexual health and identify areas where therapeutic support may be needed.

Sexual Behaviour Questionnaire SBQ-G

The SBQ-G is a standardized tool used to assess sexual function and satisfaction over the past three months. It includes questions on various aspects of sexuality, such as sexual desire, frequency of sex and masturbation, arousal, enjoyment, and overall satisfaction. Additionally, it addresses specific sexual problems like erectile dysfunction in men, premature or delayed ejaculation, orgasm ability in women, and pain during intercourse. For men, the questionnaire also includes questions about the ability to achieve and maintain an erection, as well as satisfaction with orgasm. For women, it covers orgasm frequency and satisfaction, pain during sex, and menstrual regularity. Responses are scored on a scale from 0 to 3, and a Mean Global Index of Sexual Dysfunction (MGISD) is calculated by summing specific items and computing a weighted average. Higher scores indicate greater sexual dysfunction.

Dermatology Life Quality Index (DLQI)

The DLQI is a patient-administered, ten-question, quality of life questionnaire that covers six domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment (10). The DLQI has a one-week recall period.

Response categories include:

not relevant = score of 0
not at all = score of 0
a little = score of 1
a lot = score of 2
very much = score of 3

The DLQI will be self-administered by the patient at visits indicated in the activity schedule. The DLQI will be analyzed under six headings (10 questions) as follows:

Table 2: Analysis of DLQI.

Domain	Question number	Score
Symptoms and feelings	Question 1 and 2	Score maximum 6
Daily activities	Question 3 and 4	Score maximum 6
Leisure	Question 5 and 6	Score maximum 6
Work and school	Question 7	Score maximum 3
Personal relationships	Question 8 and 9	Score maximum 6
Treatment	Question 10	Score maximum 3

Hospital Anxiety and Depression Scale (HADS)

The HADS is a self-report tool designed to assess the levels of anxiety and depression experienced over the past week. Participants are asked to select a score between 0 and 3 for

each statement**.** The scale includes questions related to feelings of tension, enjoyment, restlessness, and panic. Based on the total scores, the results are interpreted as follows: A score between 0 and 7 indicates normal levels, 8 to 10 suggests borderline abnormal levels, and a score between 11 and 21 indicates abnormal levels, which may require further evaluation. This tool helps to identify individuals who may be experiencing anxiety or depression, aiding in the decision for further assessment or intervention.

7.4.6. Imaging

Assessment of skin changes using non-invasive imaging techniques (OCT, confocal microscopy, or LC-OCT) have become an optional routine analysis of inflammatory skin diseases and will be performed on an availability-dependent basis. These assessments will be conducted depending on patient willingness and availability at the respective visits. Confocal microscopy, OCT, and LC-OCT will be performed at the Department of Dermatology, University Hospital Augsburg (UKA), Germany. OCT will also be conducted at the Institute and CCIM, University Hospital Schleswig-Holstein (UKSH), Lübeck, Germany.
All imaging data will be analyzed at the Department of Dermatology in Augsburg. To facilitate this, anonymized image data will be securely transferred to Augsburg on encrypted storage devices for extraction and analysis.

Confocal microscopy

Confocal microscopy is a high-resolution imaging technique, allowing non-invasive examination of skin, mucosa, hair, and nails (11). In dermatology, confocal microscopy is effective for identifying various cutaneous infections and infestations, as well as for monitoring treatment progress (12).

OCT Imaging

The VivoSight OCT System (Michelson Diagnostics Ltd, Kent, UK) will be utilized in this study. According to the manufacturer’s specifications, the laser product is laser class 1 and eye safe meaning that safety goggles are not required. The emission wavelength is 1.305 nm. The optical resolution is <7.5 µm lateral and <5 µm axial. The scan area is 6 mm x 6 mm. The penetration depth is about 1-2 mm. Images will be acquired as vertical B-scans and en-face scans. The images will be saved as TIFF, TIFF stack, and DICOM formats. OCT scans will be obtained of a non-lesional skin site and a lesional skin site at investigaors and subjects discretion:

- The non-lesional skin site will be at the left or right volar forearm. The same skin site will be used for all evaluations throughout the study. A body map will be used for reference so that the location is used consistently for all subsequent evaluations.

- The AD lesional skin site will be at predilection site e.g. at the elbow. The same skin site will be used for all evaluations throughout the study. A body map will be used for reference so that the location is used consistently for all subsequent evaluations.

LC-OCT Imaging

The LC-OCT is a non-invasive imaging technique that combines the depth penetration of OCT with the high lateral resolution of confocal microscopy, allowing for real-time, high-resolution visualization of skin architecture in both cross-sectional and en-face modes.

8. Data Handling

During the study, the protocol and GCP guidelines will be strictly followed. Study data will be initially documented as source data in the patient's medical records and study-specific documents by the designated study personnel immediately after each visit.Pseudonymized data, using identifiers such as 'P01' for Lübeck and 'P51' for Augsburg, followed by the corresponding visit number (e.g., P01V2), will be annotated and transferred to a paper-based case report form. Pseudonymized data will also be stored electronically using Microsoft Excel. Standard security measures for using Microsoft Excel will be implemented, including password protection of files, restricted access to authorized personnel only, regular data backups, and storage on secure, access-controlled institutional servers to ensure data confidentiality and integrity. To minimize transcription and transfer errors, a two-step internal monitoring process will be implemented: a second independent study team member will review and verify all data entries on the CRFs against the original source documents, as well as the electronic entries against the paper CRFs. Any discrepancies identified will be resolved promptly through source data verification. All source data will remain at the Institute and CCIM Lübeck. Electronic data may be exchanged between the UKSH, Campus Lübeck, and the UKA Augsburg via secure systems and may be accessed by authorized study personnel for analysis. Image analysis will be carried out at the Department of Dermatology, UKA, Augsburg, Germany. Access to electronic data will be restricted to authorized study personnel only.

9. Termination of the Study

Study participation may be discontinued early in the following cases:

- if treatment failure occurs, defined as no improvement or a worsening of the EASI score at week 16.
- if there is a change in therapy.
- if the participant misses more than 20% of the total treatment duration, corresponding to more than 73 cumulative, non-consecutive days without receiving the study drug.

10. Statistical analysis

Descriptive and inferential statistical analyses will be conducted to evaluate the efficacy of tralokinumab in patients with moderate-to-severe AD over a 52-week period. For the primary endpoint, changes in genital/local patient-reported outcome (PRO) instruments (e.g., Genital-NRS) will be analyzed using paired t-tests or Wilcoxon signed-rank tests, depending on data distribution, to assess within-subject improvement from baseline to week 52. Repeated measures ANOVA or mixed-effects models may be applied to assess longitudinal trends over multiple time points. For the secondary endpoints, similar methods will be used to analyze changes in general PROs (e.g., POEM, ADCT, DLQI, HADS) and clinical severity scores (e.g., EASI, SCORAD, IGA). Missing data will be handled using appropriate imputation methods or sensitivity analyses. For the exploratory imaging analyses, changes in structural and morphological features as measured by confocal microscopy and OCT will be evaluated descriptively and, where possible, compared over time using non-parametric tests or image-derived quantitative metrics. All statistical tests will be two-sided, and a p-value of <0.05 will be considered statistically significant. All questionnaires and clinical scores used in this study, except the newly developed Genital-Investigator Global Assessment (g-IGA), are standardized and validated instruments widely applied in dermatological research and practice. The selection of these instruments was made by Prof. Dr. Andreas Wollenberg and Prof. Dr. Diamant Thaci in consultation with Prof. Dr. Uwe Gieler to ensure clinical relevance. Prof. Gieler will also be involved in the data analysis to ensure appropriate interpretation of the results.

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