Clinical trial protocol

GEDACNE-1 STUDY

A phase III study to assess efficacy and safety of N-Acetyl-GED-0507-34-LEVO gel [redacted]%, applied once daily for 12 weeks in patients with acne vulgaris (GEDACNE-1)

Confidential

PPM Services S.A
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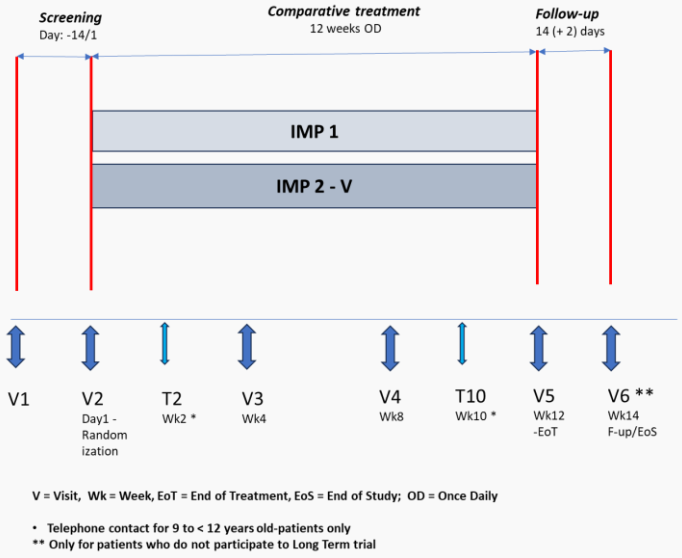
Synopsis

Sponsor	PPM Services S.A., Switzerland
Trial no.	**NAC-GED-0507-ACN-01-23-A**
EU CT No.	**2023-510339-12-00**
Title	A phase III study to assess efficacy and safety of N-Acetyl-GED-0507-34-LEVO gel [redacted]%, applied once daily for 12 weeks in patients with acne vulgaris (GEDACNE-1)
Phase	Phase 3 (Pivotal)
International coordinating investigators	Prof. Mauro Picardo Prof Christos C. Zouboulis
Study centers	At least *40* sites, located in at least *4* European countries will participate in this study.
Study period (planned)	Q3-2024 – Q2-2026. Duration of patient participation is approximately 16 weeks (14-day screening and 12 weeks of treatment +2 weeks of follow-up) and will require up to 6 visits (V). The planned duration of recruitment, from First Patient In (FPI) to Last Patient In (LPI), is approximately 10 months.
Objective(s)	The objective of the study is to evaluate the efficacy and the safety of N-Acetyl-GED-0507-34-Levo [redacted]% gel [IMP 1], in comparison to the corresponding vehicle gel [IMP 2-V], applied once daily (OD) for 12 weeks in patients with acne vulgaris.
Study design	Multicenter, randomized, parallel-group, vehicle-controlled, double-blind efficacy and safety study.



Number of patients (planned)	Four Hundred (400) patients will be recruited, to obtain at least 366 patients in the full analysis set (FAS). Patients will be randomly allocated to one of the two treatment arms (IMP 1 or IMP 2-V) in a 1:1 ratio: 200 patients in the IMP 1 arm and 200 patients in the IMP 2-V arm.
DSMB	A Data Safety Monitoring Board will be established to undertake periodic risk-benefit assessments during the clinical trial; the appropriate written charter prescribes its establishment and management.
Study medication/ Investigational medicinal product (IMP)	**IMP 1 arm** N-Acetyl-GED-0507-34-Levo [redacted]% gel ([redacted] mg/100 mg), PPM Services S.A., Switzerland **IMP 2/Vehicle arm (V)** N-Acetyl-GED-0507-34-Levo corresponding vehicle, PPM Services S.A., Switzerland
Dose	Each patient will apply a fingertip unit of gel (IMP 1 or IMP 2-V) as a thin film, once daily (OD), to the entire facial skin area and the affected skin areas of the trunk accessible for self-application (i.e., shoulders, upper back, and upper anterior chest). The application is to dry and, cleansed skin, avoiding the eyes, lip region, and mucous membranes. Details will be provided in the Investigator Manual and in the patient's diary.
Justification of dose	The large available nonclinical safety studies package is considered adequate to support the proposed Phase 3 clinical study with once daily topical administration of NAC-GED-0507 [redacted]% gel, as also agreed with EMA in the Scientific Advice procedures EMEA/H/SA/4021/1/2018/I and EMA /SA/0000066556, and with FDA in the Type B meeting procedure PIND 143424 (ref id: 4473308). Previous results indicate that NAC-GED-0507 has a well characterized, very favorable safety profile both: (i) in terms of dermal toxicity and tolerability, as demonstrated by administering twice daily NAC-GED-0507 [redacted]% gel to minipigs and mice. Noteworthy NAC-GED-0507 [redacted]% gel was well tolerated and no toxicology findings were observed, following chronic twice daily application for 39 weeks in minipigs, aged 9 weeks at the beginning of treatment, corresponding to 9 years old children and (ii) in terms of systemic toxicity at very high clinical exposure margins of NAC-GED-0507, as demonstrated in the oral toxicity studies performed in the rat with NAC-GED-0507 (13 weeks oral treatment) and with the parent compound GED-0507 (6-month oral treatment) test items. In these two studies, NAC-GED-0507 exposure margins above [redacted] and above [redacted] were achieved, respectively (based on the clinical PK data obtained in study NAC-GED-0507-ACN-02-17, upon 12-week once daily administration of NAC-GED-0507 [redacted]% gel). Moreover, in the closed patch test in guinea pigs for delayed-type hypersensitivity (according to Buehler) NAC-GED-0507 [redacted]% gel caused no reactions identified as sensitization, NAC-GED-0507 was not genotoxic in

the full battery of genetic toxicology tests and proved safe at large clinical exposure margins achieved in the oral fertility and embryo-fetal development toxicity studies performed in the rat and in the rabbit.

Regardless of the reassuring preclinical data of systemic and local safety and tolerability, demonstrated for exposures well above regular human exposures, identifying the dose for Phase 3 program of NAC-GED-0507 [redacted]% gel mainly considered the results of two large Phase 2 studies. These showed a safety and tolerability profile, indistinguishable from that of the vehicle alone and without any signal of proportionality in relation to the dose, for the range between [redacted]% and [redacted]% (see the Investigator's Brochure).

A comparison of results from two or more controlled trials with single fixed doses is usually sufficiently informative for dose selection.

This is particularly true for topical drugs, where systemic absorption is negligible and cannot provide valuable PK data and where, for practical reason, the exact extent of the exposure is more imprecise than for systemic products.

Based on these assumptions, the dose-response relationship in the two Phase 2 studies conducted, both double-blind controlled, was considered. [redacted] both studies showed a clear dose-response relationship on the absolute lesion count, always statistically significant versus vehicle.

Moreover, regarding NAC-GED-0507 [redacted]% gel, a post-hoc analysis of the Phase 2b study [redacted] has been performed.

The objective of the post-hoc analysis was to further analyze the differences between treatment groups in detail, focusing on determining the most effective product dose.

To evaluate the most effective product dose, orthogonal contrasts and several adjustment methods for multiple comparisons were applied (Tuckey-Kramer, Scheffè, and Bonferroni's methods) to analyze the pairwise comparisons of treatment groups in terms of LS Means differences.

The results confirmed that:

a) NAC-GED-0507 [redacted]% gel was found to have a higher effect (p=0.0002) in the reduction from baseline of total lesion count's percentage than the NAC-GED-0507 [redacted]% gel, which, in turn, was more effective than the placebo

b) the higher concentration was more effective (p=0.044) than NAC-GED-0507 [redacted]% gel in increasing the IGA success rate after 12 weeks of treatment.

Pediatrics. In children, like adults, the skin exposure to the active ingredient is a function of the surface area of the lesions which in children - with the same anatomical areas of the body involved - is substantially related to the body surface and therefore to the amount of product used topically to treat the affected skin areas.

	Noteworthy, no significant age-related histological differences concerning the composition of dermal barrier are present between the proposed pediatric population and adults, and the functional barrier property of skin does not vary with age (Michel et al., 1997). Indeed, systemic absorption of the active substance was observed to be minimal both in adults and in the pediatric patients already enrolled in the performed clinical studies. The sub-analysis conducted on the large Phase 2B study confirms that the response to treatment with NAC-GED-0507 [redacted]% gel is not influenced by patient's age. The results in the >18 years and ≤18 years subgroups, despite the relatively small number of younger patients, show that: a) At Wk12 the mean reduction in percent is similar for NAC-GED-0507 [redacted]% gel (n=87) compared to vehicle (n=91): -59.0% vs -33.4% for patients ≤18 years and -54.6% vs -34.6% for patients >18 years, respectively and the percent change from baseline versus vehicle remained highly statistically significant in both age groups (p<0.0001) b) The rate of IGA success between NAC-GED-0507 [redacted]% gel and vehicle present a similar difference: 41.4 % vs 20.9% (+20.5%) in ≤18 age and 50.8% vs 28.8% (+22%) in the >18 group. The above provides the rationale for the use of NAC-GED-0507 [redacted]% gel both in the adults and pediatric populations. In conclusion, due to both safety and efficacy evidence, NAC-GED-0507 [redacted]% gel is considered the dose with the most favorable efficacy / safety ratio in both adults and children among the tested concentrations.
Duration of treatment	12- week treatment period (84 applications).
Mode of administration	Topical application. Upon completion of all screening/baseline assessments, the first dose will be applied by the patient at the site (V2, Day 1) under supervision of the investigator or study nurse. The other doses will be applied by the patients at home, once daily application to dry skin at night after cleansing/washing following the instructions received at the site by the investigator/study nurse for the correct IMP application method. No formal rescue medication is foreseen. Patient's requiring substitutive treatments for acne, as per Investigator's judgment, will be discontinued from the study and relevant details documented.
Study population	Male and female patients aged ≥ 9 and <50 years and affected by acne vulgaris

Selection criteria

Criteria for inclusion:

1. *Informed consent obtained**

   * Written informed consent, before any study-related procedure, personally signed and dated by the patient if the patient is ≥ 18 years old (or different age based on local regulations), or signed and dated by the parents or the legal guardian(s) (or only one parent depending on local regulations) if the patient is ≥ 9 to < 18 years old (or different age based on local regulations). An additional informed assent form must be signed by patient if ≥ 9 to <18 years old (or different age based on local regulations) to confirm his willingness to participate in the study. If the patient becomes 18 years of age (or different age based on local regulations) during the study, the patient must provide written informed consent at that time to continue study participation

2. *Sex and age:* Male and female patients aged ≥ 9 and <50 years

3. *Diagnosis <u>at screening and baseline visits</u>:*

   a) Patients affected by facial acne vulgaris with:

   Investigator's Global Assessment (IGA) score:

   - equal to 3–4 if patient is > 14 and < 50 years old
   - ≥ 2 if the patient is ≥ 9 and ≤ 14 years old.

   Face Inflammatory lesions: ≥ 20 and ≤ 100 inflammatory lesions (papules and pustules) and ≤ 1 nodules on the face

   Face Non-inflammatory lesions: ≥ 20 and ≤ 100 non-inflammatory lesions (open and closed comedones) on the face

   b) Patients affected also by truncal acne (optional criteria)**:**

   The patient has a truncal acne on areas of the trunk (shoulders, upper back and upper anterior chest) accessible for patient's self-application of study medication with a severity grade equal to 2 or 3 on the Physician Global Assessment (PGA) scale.

   The patient has a minimum of 20 inflammatory lesions (papules and pustules) and 20 non-inflammatory lesions (open and closed comedones) but no more than 100 non-inflammatory lesions on areas of the trunk (shoulders, upper back and upper anterior chest) reachable to patient's self-application of study medication at screening and baseline

4. *Full comprehension:* Patients and their parents/legal guardian(s) (for <18 years old patients, or different age based on local regulations and possibly only one parent depending on local regulations) can comprehend the whole nature and purpose of the study, including possible risks and side effects, and are able to cooperate with the Investigator and to comply with the requirements of the entire study

5. *Contraception and fertility:* Women of childbearing potential must be using an effective contraception method during the entire duration of the study (effective contraception methods are those considered at least "acceptable" according to *CTCG Recommendations*). A prior stable treatment period is required for the following reliable methods of contraception:
    a. Hormonal oral, implantable, transdermal, or injectable contraceptives must be stable for at least 6 months before the baseline visit
    b. A non-hormonal intrauterine device (IUD) must be started at least 2 months before the baseline visit.

Criteria for exclusion:

1. *Acne:*
    - Patients with a known history of acne persistent and unresponsive to topical and/or oral treatments within 6 months before randomization
    - Patients with generalized or localized acne forms other than acne vulgaris, e.g., acne conglobata, acne fulminans, acne rosacea, secondary acne (chloracne, drug-induced acne, etc), nodule-cystic acne
    - Patients with acne requiring systemic treatment
2. *Beard and facial/body hair, tattoos*:
    - Patients with a beard or who intend to grow a beard and/or to perform a facial tattoo during the study
    - Patients with facial hair or facial tattoos that could interfere with study assessments in the investigator's opinion
    - For patients with truncal acne: body hair, tattoos (or who intend to perform them) on the shoulders, upper back or upper anterior chest accessible to self-application of study medication by the patient (evaluable area) that may interfere with the study assessments in the investigator's opinion
3. *Skin diseases:* Patients with other active skin diseases (e.g., urticaria, atopic dermatitis, sunburn, seborrheic dermatitis, perioral dermatitis, rosacea, skin malignancies) or active skin infections in the facial or truncal region (bacterial, fungal, or viral) or any other facial or truncal disease or condition that might interfere with the evaluation of acne or place the patient at unacceptable risk
4. *Allergy:* Known or suspected hypersensitivity to any active or inactive ingredient in the study medications. Patients with a history of an allergic reaction or significant sensitivity to the formulations' ingredients
5. *Topical therapies:* Patients who are currently using, will use during

the study, or discontinued less than 4 weeks before study baseline the use of prescribed and/or over-the-counter topical therapies for the treatment of acne, including but not limited to: corticosteroids, antibiotics, azelaic acid, benzoyl peroxide, salicylates, α-hydroxy/glycolic acid, any other topical cosmetic therapy for acne and retinoids on the face/trunk

6. *Topical skin care products and procedures:* Patients who are currently using, will use during the study, or discontinued less than 4 weeks before study baseline the use of products for facial/truncal application containing glycolic or other acids, masks, washes or soaps containing benzoyl peroxide or salicylic acid, non-mild cleansers or moisturizers containing retinol, salicylic or alpha- or beta-hydroxy acids, facial/truncal procedures such as chemical peel, laser treatment, photodynamic therapy, acne surgery, cryodestruction or chemodestruction, x-ray therapy, intralesional steroids, dermabrasion
7. *Phototherapy:* Patients who are currently using, will use during the study, or discontinued less than 4 weeks before study baseline phototherapy for the treatment of acne, including but not limited to: UV-A, UV-B, heliotherapy. Patients who have the need or plan to be exposed to artificial tanning devices or excessive sunlight during the study
8. *Systemic therapies*: Patients who are currently using, will use during the study, or discontinued less than 12 weeks before study baseline the use of systemic therapies for the treatment of acne, including but not limited to: antibiotics, isotretinoin. Other systemic therapy that could affect the patient's acne (i.e., anabolics, lithium, EGRF inhibitors, iodides, systemic corticosteroids - except inhaled corticosteroids or intrathecal corticosteroids - or other immunosuppressants), in the opinion of the investigator
9. *Known systemic diseases that can lead to acneiform eruptions:*
    a. Increased androgen production. 1) Adrenal origin: e.g., Cushing's disease, 21-hydroxylase deficiency; 2) Ovarian origin: e.g., polycystic ovarian syndrome, ovarian hyperthecosis
    b. Cryptococcosis disseminated
    c. Dimorphic fungal infections
    d. Behçet's disease
    e. Systemic lupus erythematosus (SLE)
10. *Investigative studies*: Participation in the evaluation of any investigational product or device within 24 weeks before study baseline
11. *Diseases*: Patients with underlying uncontrolled or unstable

conditions (including but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal and auto-immune), which, in the Investigator's opinion, could significantly compromise the patient's safety and/or place the patient at an unacceptable risk. Any condition that in the investigator's opinion would make it unsafe for the patient to participate in the study

12. *Alcohol and other substance abuse*: History of alcohol or other substance abuse within one year before screening
13. *Communication:* Patient(s) and parents/legal guardian(s) (if applicable and possibly only one parent depending on local regulations) unable to communicate or cooperate with the investigator due to e.g., language problems, impaired cerebral function, impaired mental conditions
14. *Reliability:* Patients who may be unreliable for the study including patients who are unable to return for the scheduled visits
15. *Pregnancy*:* Pregnant or breastfeeding women or women of childbearing potential who are planning to become pregnant during the study.

*For all female patients of childbearing potential, pregnancy test result must be negative at screening.

Efficacy assessments and endpoints

Efficacy assessments

Efficacy will be assessed by the investigator using acne lesion count and IGA (primary efficacy variables) at V2/Day 1 (Baseline), V3/Wk4, V4/Wk8 and V5/Wk12 (End of Treatment [EoT]). Acne lesion count and IGA will also be performed for inclusion at V1 (screening) and in case of Early Termination Visit [ETV].

Acne lesion count: Inflammatory (papules, pustules and nodules) and non-inflammatory (open [blackheads] and closed [whiteheads] comedones) lesions on the face (including the nose) and on the trunk will be accurately counted and recorded at each visit as detailed in the study schedule. Total lesions will be calculated as the sum of inflammatory plus non-inflammatory lesions.

IGA (Face): Overall severity of acne will be assessed using a 5-point scale from 0 = clear to 4 = severe at each visit as detailed in the study schedule.

PGA (Trunk): Overall severity will be assessed using a 5-point scale from 0 = clear to 4 = severe at each visit as detailed in the study schedule.

Two co-primary efficacy endpoints:

To evaluate the efficacy of N-Acetyl-GED-0507-34-Levo [redacted]% gel in comparison to IMP 2-V after 12 weeks of treatment, the following family of primary efficacy endpoints will be analyzed:

a. Endpoint 1 (E1): the relative change from baseline in total lesion count

(inflammatory plus non-inflammatory) at V5/Wk12 on the face

b. Endpoint 2 (E2): proportion of patients with an IGA success (face) at V5/Wk12.

IGA success is defined according to the patient's age as:

- a score of "clear" (score = 0) or "almost clear" (score = 1) for patients aged ≥ 9 and ≤ 14 years
- a score of "clear" (score = 0) or "almost clear" (score = 1) and at least a 2-score point reduction in IGA at V5/Wk12 for patients aged > 14 and < 50 years.

Main Secondary efficacy endpoints:

To evaluate the efficacy of [redacted]% N-Acetyl-GED-0507-34-Levo gel in comparison to IMP 2-V after 12 weeks of treatment on the following parameters:

FACE

a. Absolute change from baseline in total lesion count at V5/Wk12
b. Percentage of patients who achieve an IGA success over the study duration (i.e., score of 1 [almost clear] or 0 [clear] for patients aged ≥ 9 and ≤ 14 years; score of 1 [almost clear] or 0 [clear] and at least a two-grade improvement from baseline for patients aged > 14 and < 50 years)
c. Change from baseline in total lesion count over the study duration
d. Change from baseline in inflammatory lesion count over the study duration
e. Change from baseline in non-inflammatory lesion count over the study duration.

TRUNK

a. Absolute change from baseline in total lesion count at V5/Wk12
b. Percentage of patients who achieve a PGA score of 1 (almost clear) or 0 (clear) and at least a two-grade improvement from baseline over the study duration
c. Change from baseline in truncal total lesion total count over the study duration
d. Change from baseline in truncal inflammatory lesion count over the study duration
e. Change from baseline in truncal non-inflammatory lesion count over the study duration.

OTHER

a. Dermatology Life Quality Index (DLQI) / Children's Dermatology Life Quality Index (C-DLQI for patients from 9 to 16 years old), completed by the patient at the Baseline and Week 12/EoT visits (prior

to any Investigator assessments to not impact the patient's answers to the quality of life questionnaire)

b. [redacted] at the Baseline and Week 12/EoT visits

c. [redacted] (not mandatory, following specific consent) at the Baseline and Week 12/EoT visits.

Tolerability and safety assessments/endpoints

Safety and tolerability endpoints

- Incidence of all Adverse Events (AEs), Treatment-Emergent Adverse Events (TEAEs), Adverse Drug Reactions (ADRs), Serious Adverse Events (SAEs) throughout the study; with special attention to local TEAEs concerning the treated area (local dermal safety), and systemic TEAEs
- Frequency of discontinuation of treatment due to TEAEs
- Changes from baseline of vital signs during the study
- Physical examination during the study
- Changes from baseline of laboratory test at V5/Wk12
- Change from baseline of local tolerability - Application site signs/symptoms during the study*
- Assessment of overall application site irritation at V5/Wk12.

*Local tolerability will be evaluated on the basis of the following signs and symptoms: application site non-lesional erythema, application site exfoliation, and application site dryness, stinging, burning, itching. For each sign/symptom, a severity score will be assigned using a 4-point scale from 0 = absent to 3 = severe.

Only a sign/symptom occurring after the first application of study medication that requires additional therapy or discontinuation of treatment or judged clinically significant by the Investigator, will be documented as a TEAE.

Study procedures

Visits 1-2: Screening/Baseline visits should be conducted within 14 days. At Screening visit, study staff will explain the study procedures and an informed consent/assent must be signed prior to the initiation of any study-related procedures.

If more than 3 days occur between screening and baseline (Day1) visits, physical examination including vital signs, body weight, clinical evaluations (lesions counts, IGA, PGA) need to be repeated. Prior and concomitant therapy and concomitant medications/procedures will be reviewed; lab examination (CBC/diff., glycemia, [redacted] transaminases, cholesterol, triglycerides) and pregnancy test will be performed at Screening. At baseline, if eligibility is confirmed after check of all inclusion/exclusion criteria, patients will be randomized and assigned a test article kit number; test article and Patient Diary will be dispensed. Patients and parents/guardian(s) (if applicable and possibly only one parent

depending on local regulations) will be instructed on how to apply the test article and to record applications in the Patient Diary. The first dose will be applied during this visit under supervision of the investigator. Adverse events (AEs) will be assessed. The patients will be scheduled for the first follow-up visit.

Visits 3-4 (Wk4, Wk8): Patients will return for safety and clinical evaluations (lesion counts, IGA/PGA, AEs), and review of concomitant medications/procedures. Test article application and compliance will be checked (only from Patient Diary at V3/Wk4 and from Patient Diary and test article accountability at V4/Wk8); a new supply of test article and Patient Diary will be dispensed at V4/Wk8.

Visit 5 (Wk12): Patients will return for safety and clinical evaluations (lesion counts, IGA/PGA, AEs,), and review of concomitant medications/procedures. Test article application and compliance will be reviewed (from Patient Diary), test article and Patient Diary will be returned. Lab examination (CBC/diff., glycemia, [redacted] transaminases, cholesterol, triglycerides, pregnancy test) will be repeated. The patient will be scheduled for the next follow-up visit.

Visit 6 (Wk14) is a telephone contact for safety monitoring.

Moreover, patients aged 9 to < 12 years old will have additional phone contact (in the presence of parents or legal guardian(s) who signed the Informed Consent or only one parent depending on local regulations) at Week 2 and at Week 10 of treatment, to ensure that any local tolerability or safety issues are promptly identified. The Investigator will be asked to fill in the eCRF page relating to the phone contact promptly. In case of safety issues, an immediate automatic notification will be sent to the DSMB.

Rationale for sample size

The sample size is based on the two co-primary endpoints: relative change from baseline in total lesion count on the face (inflammatory plus non-inflammatory) and IGA success at V5/Wk12 to reach a power of 90% at a level of 0.05, since these are considered the most relevant clinical endpoints.

The formal calculation of sample size is based on the paper from T. Sozu et al. Sample size for co-primary continuous and binary endpoint (2012), assuming the normality of the relative change from baseline distribution and making the following assumptions:

- an error I type of [redacted]%
- a statistical power of [redacted]%
- a relative change from baseline in total lesion count on the face at V5/Wk12 in the IMP 2-V arm (placebo arm) of [redacted]% (data retrieved from the Study NAC-GED-0507-ACN-01-18)
- a Standard Deviation (SD) of the difference between treatment arms of [redacted]% (data retrieved from the Study NAC-GED-0507-ACN-01-18).

	- a rate of IGA success on the face at V5/Wk12 in the IMP 2-V arm (placebo arm) of [redacted]% (data retrieved from the Study NAC-GED-0507-ACN-01-18) - a difference between the two treatment arms in terms of the relative change from baseline in total lesion count on the face (inflammatory plus non-inflammatory) at V5/Wk12 equal to or greater than [redacted]% and a difference in IGA successes equal or greater than [redacted]% (data retrieved from the Study NAC-GED-0507-ACN-01-18) A sample size of 366 evaluable patients will be adequate to find a significant difference between the two treatment arms in terms of the relative change from baseline in total lesion count on the face (inflammatory plus non-inflammatory) at V5/Wk12 and in IGA successes. Considering a drop-out rate close to [redacted]% of non-evaluable patients for any reason, a total of 400 patients will have to be enrolled in the study (sample allocation ratio 1:1). A second pivotal Phase 3 study (NAC-GED-0507-ACN-01-23-B) with an identical study design to the present study is planned to be performed with an equivalent sample size of 400 patients in total.
Analysis sets	**Analysis sets** *Screened Analysis Set (SCR):* all patients who sign the informed consent form receive a screening number, regardless of whether they have completed all the screening procedures. *Enrolled Set (ENR):* All patients included in the study, excluding screening failures. *Randomized Set (RND):* all enrolled patients who are randomized. *Full Analysis Set* (FAS): all randomized patients who receive at least one dose of the study medication and have at least one valid post- baseline efficacy assessment for both primary endpoints. The analyses on FAS will be performed with the Intention-To-Treat (ITT) principle. *Per-Protocol Set (PPS)* all patients included in the FAS who complete the study without major protocol deviations*. *Safety Set (SS):* all patients who receive at least one dose of study medication. ** Major protocol deviation will be identified in the SAP and/or during a blind medical review.*
Statistical methods	Continuous data will be summarized with standard descriptive statistics (i.e. mean, SD, median, interquartile range [IQR], minimum and maximum). Categorical data will be summarized by frequency and percentage. 95% confidence intervals (CIs) will be provided as relevant. All data will be presented by treatment arm and overall and, if relevant, by study visit. Statistical test will be performed for between-arm differences in demographic

and baseline features (medical and efficacy data).

Medical history and adverse events (AEs) will be described according to System Organ Classes (SOC) and Preferred Terms (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) and will be presented by treatment arm. Previous/concomitant medications will be presented by treatment arm using the World Health Organization Drug Dictionary (WHO-DD).

All analyses will be performed using SAS® software, the latest applicable version.

Analysis of primary variables

The primary variables will be analyzed presenting descriptive statistics (mean, SD, median, IQR, minimum and maximum for total lesion count endpoint and count and percentage for IGA success rate endpoint) overall, by treatment arm and, if deemed relevant, by study visit.

Subgroup analyses will be performed for: gender (M; F), age (≥ 9 and ≤ 18 years; vs ≥ 19 and < 50 years; and also, in the following subgroups ≤12; 13 to 18; ≥19;), Race/ethnicity (white; black; Asian, Latino; other); Fitzpatrick skin type; country.

Absolute and relative differences in terms of total lesion count between baseline and EoT will be also presented.

To evaluate if the difference in terms of the relative change vs baseline of total lesion count on the face at V5/Wk12 between the two treatment arms can be considered statistically significant, an independent t-test (or Wilcoxon test if the Normality is violated) will be applied.

To evaluate if the difference in terms of the proportion of patients with an IGA success at V5/Wk12 between the two treatment arms can be considered statistically significant, an independent Chi-Square test (or Fisher exact test if the successes in one of the two treatment groups is lower than 5) will be applied.

A p-value equal to or lower than 0.05 will be considered statistically significant.

Analysis of secondary variables

Secondary variables will be analyzed presenting descriptive statistics overall, by treatment arm and, if deemed relevant, by study visit.

Subgroup analyses will be performed for: gender (M; F), age (≥ 9 and ≤ 18 years; vs ≥ 19 and < 50 years; and also, in the following subgroups ≤12; 13 to 18; ≥19;), IGA/PGA Score at Baseline, Race/ethnicity (white; black; Asian, Latino; other); Fitzpatrick skin type; country.

All statistical tests that will be applied, if any, will have exploratory purposes only.

Safety analysis

The number and percentage of patients with at least an AE recorded during

	the study, as well as the number and types of events (i.e. AEs, TEAEs, ADRs, Serious Adverse Events (SAEs)) of events will be summarized according to SOC and PT of MedDRA dictionary. A patient with multiple AEs within a SOC will only be counted once towards the total of the SOC. Descriptive statistics will be computed for all other safety endpoints (i.e., vital signs, physical examination, laboratory test, local tolerability-Application site signs/symptoms, overall application site irritation) at applicable time points, as well as changes from baseline by treatment arm. Patient data listings will be provided as appropriate. The analysis of baseline and demographics' characteristics will be performed on the RND population. The primary and secondary analyses will be performed on the FAS having the PP as supportive for the primary analysis. The safety analyses will be performed on the SAF. More details on the statistical analyses will be provided in the Statistical Analysis Plan (SAP).
Date of issue	24JAN2025 (UK)

Signatures of Sponsor

Title A phase III study to assess efficacy and safety of N-Acetyl-GED-0507-34-LEVO gel [redacted]%, applied once daily for 12 weeks in patients with acne vulgaris (GEDACNE-1)

Protocol no: NAC-GED-0507-ACN-01-23-A

Protocol version: Final V2.0 (UK only)

Protocol date: 24JAN2025

Document History:

Version	Date	Description of change	Reason for change
1.1	17MAY2024	Original Version	NA
1.2	13AUG2024 (UK ONLY)	Harmonized the information in par. 10.3 with the Patient Information Sheet, in respect of information on treatment choices available to participants, and who they should contact in the circumstances they experience worsening acne. Added in paragraph 5.5.1 that the study visits for school age children should be undertaken outside of school hours. Minor improvements in Appendix C. Minor typos corrections.	MHRA RFI
2.0	24JAN2025 (UK ONLY)	Text added/modified to make processes and procedures more clear. Minor typos corrections.	Need to align the UK version with the one applied in the EU countries

This clinical trial protocol was subject to critical review and has been approved by the Sponsor. The information it contains is consistent with:

- the current risk-benefit evaluation of the investigational product
- the moral, ethical, and scientific principles governing clinical research as set out in the currently valid revision of the Declaration of Helsinki and the principles of good clinical practice (GCP) as described in ICH GCP.

The investigator will be supplied with details of any significant or new findings, including adverse events (AEs), relating to treatment with the IMP.

For the Sponsor:

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Signature of International Coordinating Investigators

Title A phase III study to assess efficacy and safety of N-Acetyl-GED-0507-34-LEVO gel [redacted]%, applied once daily for 12 weeks in patients with acne vulgaris (GEDACNE-1)

Protocol no: NAC-GED-0507-ACN-01-23-A

Protocol version: Final V2.0 (UK only)

Protocol date: 24JAN2025

I confirm with my signature

- that I agree to conduct the trial in accordance with regulations as laid down in this clinical trial protocol/amendment, in the currently valid revision of the Declaration of Helsinki and in the ICH-GCP guideline and applicable national laws and regulations. Changes to this protocol require written agreement of both investigator and Sponsor
- that I have acquainted myself with the results of the pharmacological and toxicological studies of the investigational product and the results of other trials as described in the investigator's brochure, or other appropriate information.

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List of in-text Tables and Figures

1. Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BP	Benzoyl peroxide
CA	Competent Authority
CAH	Congenital adrenal hyperplasia
C-DLQI	Children Dermatology Life Quality Index
CI	Confidence Interval
CRA	Clinical Research Associate
CRO	Contract Research Organization
CRF	Case Report Form
CTCAE	Common Terminology Criteria For Adverse Events
CTCG	Clinical Trials Coordination Group
CTP	Clinical Trial Protocol
CTR	Clinical Trial Regulations
CS	Clinically Significant
DLQI	Dermatology Life Quality Index
DMP	Data Management Plan
DSMB	Data Safety Monitoring Board
E	Endpoint
EC	Ethics Committees
EDC	Electronic Data Capture
EMA	European Union Agency
ENR	Enrolled
EoT	End Of Treatment
EoS	End of Study
ETV	Early Termination Visit
EU	European Union
FAS	Full Analysis Set
FPI	First Patient In
FDA	Food And Drug Administration
FSH	Follicle Stimulating Hormone

GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
HbA1c	Glycated Hemoglobin
HDL-C	High-Density Lipoprotein Cholesterol
IB	Investigator's Brochure
ICE	Intercurrent Event
ICF	Informed Consent Form
ICH	International Conference On Harmonization
IEC	Independent Ethics Committees
IGA	Investigator's Global Assessment
IMP	Investigational Medicinal Product
IMP 2-V	Vehicle (placebo)
IQR	Interquartile Range
ITT	Intent-To-Treat Set
IUD	Intra-Uterine Device
IWRS	Interactive Web Response System
LDL-C	Low-Density Lipoprotein Cholesterol
LLOQ	Lower Limit Of Quantification
LOCF	Last Observation Carried Forward
LPI	Last Patient In
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDra	Medical Dictionary For Regulatory Activities
NCE	New Chemical Entity
NCS	Not Clinically Significant
OD	Once Daily
PDCO	Paediatric Committee (EMA)
PDF	Portable Document Format
PGA	Physician Global Assessment
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
POS	Polycystic Ovary Syndrome
PPAR	Peroxisome Proliferator-Activated Receptors
PPS	Per-Protocol Analysis Set

PT	Preferred Term
PV	Pharmacovigilance
Q	Quarter
QoL	Quality of Life
QP	Qualified Person
QPPV	Qualified Person For Pharmacovigilance
RBC	Red Blood Cell
ROI	Region Of Interest
RND	Randomized Analysis Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
[redacted]	[redacted]
SCR	Screened Analysis Set
SC	Stratum Corneum
SD	Standard Deviation
SG	Sebaceous Gland
SLE	Systemic Lupus Erythematosus
SOP	Standard Operating Procedure
SOC	System Organ Class
SS	Safety Set
SSL	Skin Surface Lipids
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Telephone
TEAE	Treatment-Emergent Adverse Event
TLC	Total Lesion Count
TMF	Trial Master File
UPT	Urine Pregnancy Test
UV	Ultraviolet
V	Visit
WBC	White Blood Cell
WOCBP	Women Of Childbearing Potential
WK	Week

2. Introduction

Acne is a complex disorder of the pilosebaceous unit and is considered to be one of the most frequent skin diseases (Moradi Tuchayi S, 2015). Acne occurs primarily during adolescence and epidemiological studies in the western industrialized countries estimate prevalence that ranges between 50% and 95% among the adolescent population (Ghodsi SZ, 2009). Moreover, a significant number of patients experience acne after adolescence (Dreno B, 2018), with three distinct sub-types of disease: persistent acne (a continuation of the disease from adolescence into adulthood, mainly in female patients. A community-based UK study estimated the prevalence of facial acne in adult women aged between 26 and 44 years to be 14%- (Williams C, 2006); relapsing acne, with regression after adolescence and recurrence in adulthood; and late-onset acne, which first presents well after puberty (commonly in the early- to mid-twenties). The mean age at presentation for adult acne treatment is around 24 years.

Although acne is not a life-threatening condition, it can be a significant source of distress for patients and can be associated with depression, anxiety and poor self-esteem (Aslam I, 2015). A stepwise approach to acne management includes topical agents for mild to moderate acne and escalation to oral agents for more resistant cases (Das S, 2014; Zeichner Jushua A, 2016). The mainstay of acne therapy includes: topical retinoids, topical antibiotics, benzoyl peroxide (alone or in combination) for mild to moderate acne, and for severe acne oral antibiotics or hormonal agents in conjunction with a topical retinoid or oral isotretinoin alone. However, side effects are associated to available therapies. Antibiotic resistance is an issue, benzoyl peroxide (BP) is an alternative bactericidal oxidizing agent that circumvents the problem of resistance, but patients sometimes complain of skin irritation, peeling, itching, and redness. Topical retinoids also commonly cause skin irritation and oral isotretinoin has the most significant side effect profile, including joint pain, headaches, dry skin, itching, depression, and is a potent teratogen (Aslam I, 2015). Even if fixed-dose combinations topical products were recently marketed, drug products with new active pharmaceutical ingredients have not become available in the last couple of decades for the treatment of acne. Moreover, the management of acne patients by the dermatologists has become increasingly difficult, due to easily accessible medical devices and cosmetic products that make it troublesome to appropriately treat acne pathogenic aspects using pharmacologically active medicinal products.

Therefore, the need to develop new chemical entities with improved side effects profiles and that target different aspects of acne pathogenesis is strongly felt.

Several primary and secondary factors are believed to contribute to the onset and development of acne (Kurokawa I, 2009). Specifically, the basic disease mechanism is thought to involve: (i) increased sebum production, (ii) keratinocyte hyperproliferation, (iii) inflammation, and (iv) altered bacterial colonization, primarily by Propionibacterium acnes.

The exact sequence of these events is unclear, but the major pathophysiologic factor is likely to be an androgen-induced increase in sebum production and secretion, coupled with qualitative changes in sebum. Characteristic changes in sebum composition reported in acne patients include reduced levels of linoleic acid, increased levels of squalene and lipid peroxides, and an increased ratio of saturated/mono-unsaturated fatty acids (Kurokawa I, 2009; Ottaviani M, 2010; Zouboulis CC, 2014).

Hormones, the environment, neurologic and inflammatory mediators, and lipid metabolism have all been implicated in the regulation of sebum production (Zouboulis CC, 2014).

The quantitative and qualitative changes in sebum production have also been implicated in colonization of the follicular duct by P. acnes. Notably, sebum quality may influence skin microbiome composition, particularly in terms of the abundance and strains of P. acnes populating the pilosebaceous unit. P. acnes is thought to contribute to acne pathogenesis through several different mechanisms including interaction with innate cutaneous immunity and keratinocyte and sebocytes function, leading to amplification of the three key pathologic processes implicated in acne development: inflammation, keratinization, and sebogenesis (Beylot C, 2014). Support for the development of therapies that target molecules implicated in the activation of innate immunity is provided by several research findings. These include a confirmed association between sebaceous lipid synthesis and inflammation and evidence of elevated levels of CD3+ and CD4+ T cells and inflammatory markers in early subclinical acne lesions (microcomedones) (Dreno B, 2015). Furthermore, recent studies highlight the important contributory role of Toll-like receptor activation and subsequent interleukin-1 alpha secretion by keratinocytes in comedogenesis (Dreno B, 2015).

The pilosebaceous unit and resident sebocytes also play an active role in skin endocrine function. Androgen hormones as well as growth-promoting hormones and growth factors control sebaceous gland function, and recent attention has focused on insulin/insulin growth factor-1 signaling and its ability to stimulate sebocyte proliferation and differentiation. Importantly, endocrine changes closely related to pubertal rises in insulin resistance have been reported to affect acne onset and development, leading to a re-evaluation of nutritional influences and endocrine factors involved in the promotion of acne development (Smith RN, 2008). The Western diet, characterized by a high glycemic load, may be an environmental factor linking acne to hyperinsulinemia and may represent a targetable adjunctive aspect of acne pathogenesis. A low-glycemic-load diet appears to ameliorate the signs of acne, reducing the number of both inflammatory and non-inflammatory lesions and affecting the fatty acid composition of sebum triglycerides through reduced fatty acid mono-unsaturation (Kurokawa I, 2009; Smith RN, 2008).

Evidence also suggests that peroxisome proliferator-activated receptors (PPAR) expressed in sebaceous-gland cells and their ligands play an important role in the regulation of human sebum production and acne development (Makrantonaki E and Zouboulis CC, 2007; Chen W, 2003).

Sebum alterations and inflammation represent the primary events in acne pathogenesis, indicating that these phenomena should be the primary therapeutic targets. In line with this view, molecules to control sebum production and the inflammatory process should be developed for the treatment of acne.

Based on the demonstration of combined anti-inflammatory and lipid modulating properties in the main cell populations of the pilosebaceous unit, the Sponsor decided to exploit the use of NAC-GED-0507 for the treatment of acne. The pharmaceutical form developed is a gel to be applied on the skin affected by acne, designed to act locally and to minimize systemic adsorption.

N-Acetyl-GED-0507-34-Levo

N-Acetyl-GED-0507-34-Levo [redacted] is a new chemical entity (NCE) under development for the topical treatment of acne vulgaris and psoriasis (see Investigator's Brochure [IB]).

In vitro non-clinical pharmacology studies demonstrate that N-Acetyl-GED-0507-34-Levo has significant anti-inflammatory properties on human keratinocytes and human sebocytes and an ability to regulate sebogenesis on human sebocytes.

For the clinical treatment of acne with N-Acetyl-GED-0507-34-Levo, a topical aqueous [redacted] gel formulation has been chosen, designed to act locally so that the drug substance reaches the primary target cells i.e., keratinocytes and sebocytes while minimizing systemic adsorption of the active pharmaceutical ingredient. Acne patients frequently exhibit oily skin, for which the application of an aqueous gel is optimal. Moreover, the majority of acne patients are young, and the application of a gel is preferred and improves the dosing compliance.

Non-clinical and clinical studies in support of the development of N-Acetyl-0507-34-Levo for the treatment of facial acne are presented in the IB.

Rationale for this clinical trial NAC-GED-0507-ACN-01-23-A

The present clinical trial belongs to the pivotal clinical program of NAC-GED-0507. It is a Phase 3, multi-center, randomized, parallel-group, double-blind, vehicle-controlled efficacy and safety study. N-Acetyl-GED-0507-34-Levo [redacted]% gel will be topically administered in patients affected by facial acne vulgaris or by facial and trunk acne vulgaris, once daily (OD) over a treatment duration of 12 weeks (as recommended in FDA Guidelines Acne Vulgaris: Developing Drugs for Treatment).

The dose selection rationale and the decision to include the NAC-GED-0507 [redacted]% gel in this study, is based on the results obtained in the previous Phase 2 clinical study (Study GED-0507-ACN-01-16), on the results of the Phase 1b trial (NAC-GED-0507-ACN-02-17) and on the results of the Phase 2b trial NAC-GED-0507-ACN-01-18.

- In the Phase 2 Study GED-0507-ACN-01-16, NAC-GED-0507 gel [redacted]%, [redacted]% and vehicle (same semi-solid formulation that will be employed in this clinical study), were tested in a population affected by mild-to-moderate acne. In this study, significant results versus vehicle were observed with the active gels. Noteworthy, taking into consideration the sub-group analysis performed in the acne population who presented ≥ 20 inflammatory lesions and ≥ 20 non-inflammatory lesions, a clinically significant trend of increased efficacy was observed by increasing the gel concentration.
- The Phase 1b study with NAC-GED-0507 [redacted]% gel (Study nr. NAC-GED-0507-ACN-02-17) was an open label study performed in a total 25 patients, whose age ranged from 12 to 29 years, who were treated with N-Acetyl-GED-0507-34-Levo [redacted]% gel as single daily application for 12 consecutive weeks, followed by a two-week follow-up period. Plasma samples withdrawn at Day1 (Pre-dose) and at Week 12 (End of Treatment) from the 25 patients enrolled in the study, were analyzed to evaluate NAC-GED-0507 concentration, using a validated analytical method with a LLOQ of 1 ng/mL. Results on the plasmatic concentration of NAC-GED-0507 were below LLOQ for all pre-dose samples. Results on the plasmatic

concentration of NAC-GED-0507 on Week 12 samples were: below LLOQ for 8 samples, measurable but below [redacted]ng/mL for 15 samples, and slightly above [redacted]ng/mL for 2 samples ([redacted] and [redacted] ng/mL, respectively).

- The objectives of the NAC-GED-0507-ACN-01-18 Phase 2b study was to evaluate the efficacy and safety of NAC-GED ([redacted]% and [redacted]%) in patients with moderate-to-severe facial acne vulgaris. It was a double-blind randomized controlled clinical trial conducted at 36 sites in Germany, Italy and Poland. Patients aged 12-30 years with facial acne, an IGA score of 3-4, and an inflammatory and non-inflammatory lesion count of 20-100 were randomized to topical application of the study medication ([redacted]% or [redacted]%) or placebo (vehicle), once daily for 12 weeks. The co-primary efficacy endpoints were percentage change from baseline in total lesion count (TLC) and IGA success at week 12; the safety endpoints were adverse events (AEs) and serious AEs. Between Q1 in 2019 and Q1 in 2020 450 patients [n = 418 (92·9%) IGA 3; n = 32 (7·1%) IGA 4] were randomly assigned to NAC-GED [redacted]% (n = 150), NAC-GED [redacted]% (n = 150) or vehicle (n = 150). The percentage change in TLC reduction was statistically significantly higher in both the NAC-GED [redacted]% [-57·1%, 95% confidence interval (CI) -60·8 to -53·4; P < 0·001] and NAC-GED 2% (-44·7%, 95% CI -49·1 to -40·1; P < 0·001) groups compared with vehicle (-33·9%, 95% CI -37·6 to -30·2). A higher proportion of patients treated with NAC-GED [redacted]% experienced IGA success (45%, 95% CI 38-53) vs. the vehicle group (24%, 95% CI 18-31; P < 0·001). The IGA success rate was 33% in the NAC-GED [redacted]% group (P = not significant vs. vehicle) [redacted]

Moreover, regarding NAC-GED-0507 [redacted]% gel, a post-hoc analysis of the Phase 2b study (Prot. N° NAC-GED-0507-ACN-01-18) has been performed.

The objective of the post-hoc analysis was to further analyze the differences between treatment groups in detail, focusing on determining the most effective product dose.

To evaluate the most effective product dose, orthogonal contrasts and several adjustment methods for multiple comparisons were applied (Tuckey-Kramer, Scheffè, and Bonferroni's methods) to analyze the pairwise comparisons of treatment groups in terms of LSMeans differences.

The results confirmed that:

a) NAC-GED-0507 [redacted]% gel was found to have a higher effect (p=0.0002) in the reduction from baseline of total lesion count's percentage than the NAC-GED-0507 [redacted]% gel, which, in turn, was more effective than the placebo

b) The higher concentration was more effective (p=0.044) than NAC-GED-0507 [redacted]% gel in increasing the IGA success rate after 12 weeks of treatment.

Pediatrics. In children, like adults, the skin exposure to the active ingredient is a function of the surface area of the lesions which in children - with the same anatomical areas of the body involved - is substantially related to the body surface and therefore to the amount of product used topically to treat the affected skin areas. Noteworthy, no significant age-related histological differences concerning the composition of dermal barrier are present between the proposed pediatric population and adults, and the functional barrier property of skin does not vary with age (Michel et al., 1997).

Indeed, systemic absorption of the active substance was minimal in adults and pediatric patients enrolled in the previous clinical studies.

The sub-analysis conducted on the large Phase 2b study confirms that the response to treatment with NAC-GED-0507 [redacted]% gel is not influenced by patient's age. The results in the >18 years and ≤18 years subgroups show that:

a) At Wk12, the mean percentage reduction in TLC was similar for NAC-GED-0507 [redacted]% gel (n=87) compared to vehicle (n=91): -59.0% vs -33.4% for patients ≤18 years and -54.6% vs -34.6% for patients >18 years, respectively. The percentage change from baseline versus vehicle remained highly statistically significant in both age groups (p<0.0001)

b) The rate of IGA success between NAC-GED-0507 [redacted]% gel and vehicle presents a similar difference: 41.4 % vs 20.9% (+20.5%) in ≤18 age and 50.8% vs 28.8% (+22%) in the >18 groups.

In conclusion, the use of [redacted]% formulation is justified by the following evidences: (a) sub-optimal efficacy clinical results were obtained from [redacted]% and [redacted]% topical formulations, (b) in agreement with long term *in vivo* studies, negligible systemic absorption is obtained upon application of [redacted]% gel in humans and (c) the topical application of NAC-GED [redacted]% reduced TLC, increased the IGA success rate and was safe for use in patients with acne vulgaris.

3. Risk-benefit evaluation

3.1. Stress/risks due to trial procedures

The non-invasive procedures (clinical assessments: lesion count and IGA/PGA, as well as tolerability assessments and vital signs) do not pose a risk or stress for the patients.

The blood sampling procedure poses the same very small risk is typically associated with this procedure (e.g., infection, bleeding into the surrounding tissue, and very rarely inflammation of the vein or formation of blood clots). Therefore, blood withdrawal will be performed exclusively by qualified medical personnel.

3.2. Stress/risks due to the investigational medicinal product (IMP)

Pre-clinical considerations

On the basis of the available non-clinical and clinical data, there is no evidence that using N-Acetyl-GED-0507-34-Levo gel will raise to major safety concerns.

In the embryo-fetal development toxicity studies performed in the rat and in the rabbit and in the fertility study performed in the rat, no adverse effects were observed on embryofetal development, teratogenicity and on fertility parameters, upon systemic exposure of animals to very high NAC-GED-0507 plasma concentrations.

Negative results were obtained in all genotoxicity studies performed with both NAC-GED-0507 and GED-0507.

The UV-Vis spectra recorded on NAC-GED-0507 [redacted]% gel and the results obtained by testing NAC-GED-0507 in the Balb/C 3T3 Cell Phototoxicity Assay with neutral red uptake, are predictive of no phototoxicity.

Clinical considerations

NAC-GED-0507 [redacted]%, [redacted]% and [redacted]% topical formulation proved safe in the clinical studies performed in acne patients upon a 12-week treatment, and negligible systemic absorption (below LLOQ of [redacted] ng/mL) was observed for the formulation with higher dosage.

Overall, clinical data confirm a very good safety profile of NAC-GED-0507 [redacted]% when administered for 12 consecutive weeks, poorly distinguishable from the safety profile of vehicle. In a large randomized double blind controlled clinical trial (NAC-GED-0507-ACN-01-18), the percentage of patients who had one or more AEs was 19%, 16% and 19% in the NAC-GED [redacted]%, NAC-GED [redacted]% and vehicle groups, respectively.

Considerations about safety in children

Based on the following considerations, a positive opinion for the Paediatric Investigation Plan (EMEA-002674-PIP01-19) in a population from 9 years to less than 18 years of age was awarded by the Paediatric Committee (PDCO) of the European Medicines Agency.

Negligible systemic absorption upon administration of NAC-GED-0507 [redacted]% gel for 12 consecutive weeks has been demonstrated in the performed clinical study NAC-GED-0507-ACN-02-17 in acne patients aged ≥12 years. Moreover, a favorable safety and local tolerability profile of NAC-GED-0507 gel has been demonstrated in acne patients aged ≥ 12 years.

The Sponsor expects the same exposure and safety/local tolerability profile in acne patients aged 9 to < 12 years, based on skin permeability and physiology characteristics. The percutaneous absorption of molecules is largely dependent on the skin barrier function, primarily attributed to the stratum corneum (SC) containing lipids, such as cholesterol, free fatty acids, and ceramides. However, also the sebaceous gland (SG) secretion intervenes in shaping the lipidic composition of the epidermal permeability barrier. Indeed, skin surface lipids (SSL) result from the mixture deriving from two main sources: epidermal lipids produced during keratinocytes differentiation in the stratum corneum (SC), and sebum, an amorphous lipid matrix secreted by the sebaceous gland (SG). Sebum and SC have a remarkably diverse and unique lipid composition. Sebum, whose abundance is consistent with the sebaceous gland density, can be regarded as a surface active biofluid that impacts physical properties of the skin. Untargeted lipidomic approaches demonstrated that the SG secretion intervenes in shaping the lipid composition of the epidermal permeability barrier.

Acne is a complex and multifactorial skin disorder of the pilosebaceous unit. It occurs when small and inactive infant sebaceous glands are activated by hormonal secretion. In particular, androgens are sebotropic hormones essential for the adolescent development of SGs and for maintaining sebum production in adulthood. Increased sebogenesis is pivotal in the pathogenesis of acne and predisposes skin to deregulated inflammatory responses and both quantitative and qualitative modifications of

sebaceous lipids likely trigger inflammatory responses causative of acne lesions commonly called comedones.

The presence of acne in a patient, independently on patient's age, can therefore occur only when sebaceous glands are functional and have an impact on the skin barrier properties through sebogenesis.

Therefore, the skin physiology of patients affected by acne aged 9 to < 12 years is equivalent to those affected by acne aged ≥ 12. Thus, no difference in the NAC-GED-0507 absorption is expected in acne patients aged 9 to < 12 years compared to those ≥ 12 years.

For the same reason, no difference in the NAC-GED-0507 local tolerability and safety profile of the product is expected in acne patients aged 9 to < 12 years with respects to those ≥ 12 years.

The nonclinical toxicology data are considered suitable to support the treatment of patients aged 9 years and older in the proposed Phase 3 clinical studies, since a 39- week dermal tolerance and toxicity study has been performed in minipigs aged 9 weeks at the beginning of treatment (corresponding to 9 year old children). Moreover, safety of the molecule at high exposure margins was demonstrated in several nonclinical studies performed not only in the minipigs but also in mice and rats.

Despite the above, in order to carefully monitor the safety of the product in the upcoming pivotal clinical studies in the patient population aged 9 to < 12, it is proposed that:

- In the 12-week pivotal Studies, beyond the post-Baseline site visits already foreseen in the protocol at 4 weeks, 8 weeks and at 12 Weeks (end-of Treatment Visit) during which the safety assessment will be performed, additional phone calls will be included for all patients aged 9 to < 12 years enrolled in the study. The calls among the Principal Investigator and the enrolled patient aged 9 to < 12 (in the presence of parents or legal guardian(s) who signed the Informed Consent or only one parent depending on local regulations) will be performed at week 2 and at week 10 of treatment, to ensure that any local tolerability or safety issues are promptly identified. The Investigator will be asked to promptly fill in the eCRF page relating to the phone contact. In case of safety issues, an immediate automatic notification will be sent to the DSMB.

3.3 Conclusions about risk-benefit evaluation

Against the above-described minimal risks stands the benefit of information on the efficacy of a promising topical product which is intended to be used in the treatment of acne vulgaris.

As far as concern potential benefit on children, actual therapy of prepuberal acne is similar to that of adolescents and the main problem in this age group is lack of compliance. Combination therapy is actually most successful, and every therapeutic regimen should include a topical comedolytic, such as a topical retinoid, benzoyl peroxide, azelaic acid, or salicylic acid. Differently from adolescent, hormonal therapy is rarely considered in children, unless CAH, POS, or precocious puberty from another cause is proven (Cantatore et al, 2006).

Side effects associated with available therapies, such as antibiotic resistance and skin irritation, highlight the need to develop new chemical entities with improved efficacy profiles, such as the study medication, targeting different acne pathogenesis simultaneously. Moreover, a simple gel application once daily could improve patient compliance.

Taking into account these risks and benefits, the performance of the trial can be considered ethically sound for all ages considered, since the expected benefits appear greater at present than the risks for the volunteers. The clinical trial protocol will be submitted to the responsible ethics committees for approval.

4. Trial objectives

The objective of the study is to evaluate the efficacy and the safety of [redacted]% N-Acetyl-GED-0507-34-Levo gel, in comparison to the corresponding vehicle gel, applied once daily (OD) for 12 weeks in patients with acne vulgaris.

5. Investigational plan

5.1. Overall trial design and plan - description

This is a multicenter, randomized, parallel-group, vehicle-controlled, double-blind, efficacy and safety study. At least 40 sites located in at least 5 European countries will participate in this trial.

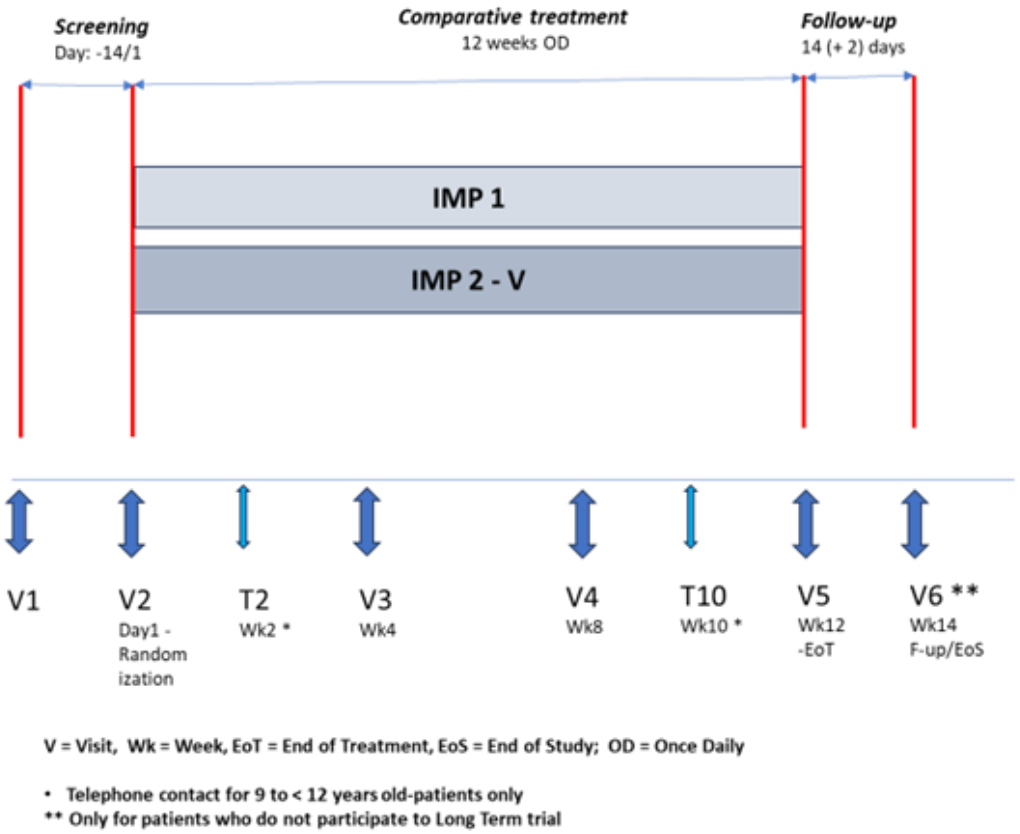
Approximately 400 patients (males and female aged ≥ 9 and <50 years) affected by facial acne vulgaris are planned to be randomized in order to have at least 366 patients in the full analysis set (FAS) and will be randomly allocated to one of the 2 treatment arms (NAC-GED-0507-34-Levo [redacted]% gel, or vehicle gel) in a 1:1 ratio. Recruitment will be competitive between the sites.

Stratified randomization will be conducted to guarantee the followings:

- Subset 9 to < 12 years: 5% of patients, corresponding to 20 patients.

The trial design consists of a 14-day screening period, a 12-week comparative treatment period, and a 2-week treatment-free follow-up period. Each patient will have 6 visits: V1-screening, V2-Day 1, V3/Wk4-Day 29, V4/Wk8-Day 57, V5/Wk12-Day 85 (EoT) (primary endpoint visit), V6/Wk14-Day 99 safety follow-up visit (Phone contact). Patients who complete 12 weeks of treatment can be eligible to continue treatment with NAC-GED-0507-34-Levo gel [redacted]%, in a separate open-label long-term study NAC-GED-0507-ACN-01-23-LT (GEDACNE-LT). In this case, the V6/Wk14-Day 99 follow-up visit (Phone contact) will not be performed. (**Figure 1**). Additionally, two telephone contacts will be performed in 9 to < 12 years old patients, at Wk2 and Wk10.

Figure 1- Study design



IMP will be topically applied OD by the patient to the entire face (including nose; avoiding eyelid and lip region) and to skin areas of the trunk accessible for self-application (shoulders, upper back, and upper anterior chest) if those are affected by acne. The study medication is applied by patients at home, except for the first dose, which will be applied at the site (V2, Day 1) under the Investigator's or study nurse's supervision. The gel will be applied to dry and, cleansed skin at night, following the instructions received at the site by the Investigator/study nurse on the correct method of IMP application.

Assessment of the patient's acne will be undertaken by a qualified, experienced and successfully trained investigator (see Section 10.8) using the evaluation tools at each site visit as detailed in the study schedule: lesion count (inflammatory and non-inflammatory lesions) and investigator's global assessment (face: IGA 5-point scale, trunk: PGA 5-point scale - the two scales are overlapping, the different naming is used in trials for easily distinguish trunk and face assessment, see Sections 5.5.2.2, 5.5.2.3 and 5.5.5).

Dermatology Life Quality Index (DLQI) / Children's Dermatology Life Quality Index (C-DLQI for patients from 9 to 16 years old), will be completed by the patient at the Baseline and Week 12/EoT visits (prior to any Investigator assessments to not impact the patient's answers to the quality-of-life questionnaire).

[redacted] at the Baseline and Week 12/EoT visits will be done. In a pool of

selected sites [redacted] will be performed.

As detailed in the study schedule, safety parameters (primary objective) will be monitored from signing the informed consent form (ICF) until the last visit. They will include: standard laboratory tests, pregnancy tests, vital signs, local tolerability assessment (application site non-lesional erythema, application site exfoliation, application site dryness, stinging, burning, itching) using a 4-point scale, recording of adverse events (AEs) and serious adverse events (SAEs), extent of exposure. Furthermore, overall application site irritation will be assessed at baseline (only presence/absence) and at the end of the study treatment, using a 4-point scale.

A Data Safety Monitoring Board will undertake periodic risk-benefit assessments during the clinical trial; the establishment and management of the Data Safety Monitoring Board (DSMB) is prescribed by the appropriate written charter.

DSMB will be promptly notified of safety issues recorded in the corresponding eCRF section.

The schedule of all trial procedures for all visits is displayed in **Appendix A.**

5.2. Discussion of trial design, including the choice of control groups

A double-blind design (patients and investigators blinded) is chosen to ensure the study assessments are carried out without bias.

Parallel group comparison is a common method and provides optimal conditions for examining efficacy (ICHE9 Guidance, Statistical Principles for Clinical Trials).

A randomization in a 1:1 ratio to either NAC-GED-0507 gel [redacted]% or vehicle gel is chosen as considered the most reliable and impartial method of determining differences between the IMP vs. vehicle gel.

Block randomization is a commonly used technique in clinical trial design to reduce bias and achieve balance in the allocation of participants to treatment arms. This method increases the probability that each arm will contain an equal number of individuals by sequencing participant assignments by block.

The randomization will also be stratified by age group to ensure the comparability of the two treatment arms within each stratum.

The vehicle gel, containing the same excipients as NAC-GED-0507 [redacted]% without the active substance, will serve as an external validity check for the study results and will show what an agent-free therapy contributes to in terms of efficacy and safety.

To evaluate a therapeutic effect, both clinical assessments using counting of inflammatory and non-inflammatory lesions and the IGA/PGA to assess the overall acne severity will be used as primary measures which largely follows the S-3 Guideline for Treatment of Acne (Nast A, 2016) and the FDA Draft ‘Guidance for Industry - Acne Vulgaris: Establishing Effectiveness of Drugs Intended for Treatment’ (May 2018). This combination allows for a balanced approach toward the evaluation of acne severity.

Experience has shown that once daily application on 84 consecutive days is adequate for the purpose of this study. If a treatment success occurs, it is largely seen during this time period of 12 weeks.

A separate open-label long-term extension study is planned. Patients completing the treatment-phase of this trial will be offered the opportunity to participate in this follow-on study (A long-term safety and efficacy study of N-Acetyl-GED-0507-34-LEVO [redacted]% gel, in subjects with acne vulgaris (GEDACNE-LT; EU CT Number: 2023-510342-24-00). In this open label study, all patients will apply the active medication (NAC-GED-0507 [redacted]% gel) Once Daily for up to 9 additional months of treatment (for a total of up to 12 months; 0 or 3 months in the pivotal Phase 3 trial and an additional 9 months in the open-label long-term extension study).

5.3. Selection and discontinuation/withdrawal of patients

5.3.1. Selection of patients

The selection of patients will be in accordance with the requirements of the national laws as well as the recommendations of the Helsinki Declaration and its currently valid revision of the Helsinki Declaration and in the ICH-GCP guideline. Advertisement (e.g., newspaper, online portal, bus or metro) will be used only after positive approval by the responsible EC.

The patients will be selected according to defined inclusion and exclusion criteria.

A gender specific subdivision into groups is not necessary in this clinical trial.

Males and females aged ≥ 9 to < 50 years are eligible for this clinical trial if they have confirmed diagnosis of acne vulgaris (see Section 5.3.3, inclusion criterion 3). Anti-acne efficacy is likewise detectable in men and women.

5.3.2. Justification of patient population

Acne occurs primarily during adolescence, with a prevalence that may reach 95% (Maronas, Jimenez, 2016). Acne may also be the first sign of pubertal maturation; the presence of acne in a patient, independently on patient's age, can occur when sebaceous glands are functional and have an impact on the skin barrier properties through sebogenesis; acne in early childhood is very rare. Generally, girls have an earlier onset, with an average age between 11 and 13 years, compared with boys, between 13 and 14 years, with more intense and severe forms (Bhate et al 2013).

In agreement with the Scientific Advice from EMA and with the opinion of Paediatric Committee (PDCO) on the Paediatric Investigation Plan, the Sponsor plans to run the current clinical study in acne patients ≥9 and ≤ 50 years old. Due to the low prevalence of acne in pediatric subset from birth to less than 9 years, and the fact that most diagnosed with infantile acne have a moderate course at best requiring no treatment, the enrollment of patient under the age of 9 would result in a lack of feasibility and PDCO granted a waiver for this age range.

Since acne in patients 9 to 14 years is usually less severe in grade, inclusion of patients with IGA 2 will be allowed for this age class.

The non-clinical studies package confirms the safety profile of NAC-GED-0507 and that it has no effects on the reproductive system in case of systemic exposure at large exposure margins for

adolescents and children. It includes a 13-week repeat-dose dermal tolerance study in minipigs. The age of the minipigs at the start of the study corresponds to that of human adolescents. This package also encompasses toxicity studies, which include chronic toxicity, and a 39-week dermal tolerance and toxicity study. The latter was performed on minipigs aged nine weeks at the beginning of the treatment, corresponding to children aged nine years old.

This study expects little or no dermal absorption. This assumption is based on available clinical and non-clinical data, as well as a Phase 1 open-label clinical study in patients affected by acne with NAC-GED-0507 [redacted]% gel (Study NAC-GED-0507-ACN-02-17, EudraCT 2017-003796-58), performed in patients aged 12-30.

Skin physiology of patients affected by acne aged 9 to < 12 years is considered equivalent to skin physiology of patients affected by acne aged ≥ 12 years. Therefore, no difference in the NAC-GED-0507 absorption is expected in acne patients aged 9 to < 12 years with respects to those ≥ 12 years. For the same reason, no difference in the NAC-GED-0507 local tolerability and safety profile of the product is expected in acne patients aged 9 to < 12 years with respects to those ≥ 12 years.

5.3.3. Inclusion criteria

The following criteria have to be met for inclusion of a patient in this trial:

1. *Informed consent obtained**

   * Written informed consent, before any study-related procedure, personally signed and dated by the patient if the patient is ≥ 18 years old (or different age based on local regulations), or signed and dated by the parents or the legal guardian(s) (or only one parent depending on local regulations) if the patient is ≥ 9 to < 18 years old (or different age based on local regulations). An additional informed assent form must be signed by patient if ≥ 9 to <18 years old (or different age based on local regulations) to confirm his willingness to participate in the study. If the patient becomes 18 years of age (or different age based on local regulations) during the study, the patient must provide written informed consent at that time to continue study participation.

2. *Sex and age:* Male and female patients aged ≥ 9 and <50 years

3. *Diagnosis <u>at screening and baseline visits</u>:*

   a) Patient affected by facial acne vulgaris with:

   Investigator's Global Assessment (IGA) score:

   - equal to 3–4 if patient is > 14 and < 50 years old
   - ≥ 2 if the patient is ≥ 9 and ≤ 14 years old

   Face Inflammatory lesions: ≥ 20 and ≤ 100 inflammatory lesions (papules and pustules) and ≤ 1 nodules on the face

   Face Non-inflammatory lesions: ≥ 20 and ≤ 100 non-inflammatory lesions (open and closed comedones) on the face

b) Patients affected also by truncal acne (optional criteria):

The patient has a truncal acne on areas of the trunk (shoulders, upper back and upper anterior chest) accessible for patient's self-application of study medication with a severity grade equals to 2 or 3 on the Physician Global Assessment (PGA) scale.

The patient has a minimum of 20 inflammatory lesions (papules and pustules) and 20 non-inflammatory lesions (open and closed comedones), but no more than 100 non-inflammatory lesions on areas of the trunk (shoulders, upper back and upper anterior chest) reachable to patient's self-application of study medication at screening and baseline

4. *Full comprehension:* Patients and their parents/legal guardian(s) (for <18 years old patients or different age based on local regulations and possibly only one parent depending on local regulations) can comprehend the whole nature and purpose of the study, including possible risks and side effects, and are able to cooperate with the Investigator and to comply with the requirements of the entire study

5. *Contraception and fertility:* Women of childbearing potential must be using an effective contraception method during the entire duration of the study (effective contraception methods are those considered at least "acceptable" according to *CTCG Recommendations* – *See* ***appendix C***). A prior stable treatment period is required for the following reliable methods of contraception:

a) Hormonal oral, implantable, transdermal, or injectable contraceptives must be stable for at least 6 months before the baseline visit

b) A non-hormonal intrauterine device (IUD) must be started at least 2 months before the baseline visit.

5.3.4. Exclusion criteria

The following conditions are considered as exclusion criteria:

1. *Acne:*

- Patients with a known history of acne, persistent and unresponsive to topical and/or oral treatments within 6 months before randomization
- Patients with generalized or localized acne forms other than acne vulgaris, e.g., acne conglobata, acne fulminans, acne rosacea, secondary acne (chloracne, drug-induced acne, etc), nodule-cystic acne
- Patients with acne requiring systemic treatment

2. *Beard and facial/body hair, tattoos*:

- Patients with a beard or who intend to grow a beard and/or to perform a facial tattoo during the study

- Patients with facial hair or facial tattoos that could interfere with study assessments in the investigator's opinion
- For patients with truncal acne; body hair, tattoos (or who intend to perform them) on the shoulders, upper back or upper anterior chest accessible to self-application of study medication by the patient (evaluable area) that may interfere with the study assessments in the investigator's opinion

3. *Skin diseases:* Patients with other active skin diseases (e.g., urticaria, atopic dermatitis, sunburn, seborrheic dermatitis, perioral dermatitis, rosacea, skin malignancies) or active skin infections in the facial or truncal region (bacterial, fungal, or viral) or any other facial or truncal disease or condition that might interfere with the evaluation of acne or place the patient at unacceptable risk
4. *Allergy:* Known or suspected hypersensitivity to any active or inactive ingredient in the study medications. Patients with a history of an allergic reaction or significant sensitivity to the formulations' ingredients
5. *Topical therapies:* Patients who are currently using, will use during the study, or discontinued less than 4 weeks before study baseline the use of prescribed and/or over-the-counter topical therapies for the treatment of acne, including but not limited to: corticosteroids, antibiotics, azelaic acid, benzoyl peroxide, salicylates, α-hydroxy/glycolic acid, any other topical cosmetic therapy for acne and retinoids on the face/trunk
6. *Topical skin care products and procedures:* Patients who are currently using, will use during the study, or discontinued less than 4 weeks before study baseline the use of products for facial/truncal application containing glycolic or other acids, masks, washes or soaps containing benzoyl peroxide or salicylic acid, non-mild cleansers or moisturizers containing retinol, salicylic or alpha- or beta-hydroxy acids, facial/truncal procedures such as chemical peel, laser treatment, photodynamic therapy, acne surgery, cryodestruction or chemodestruction, x-ray therapy, intralesional steroids, dermabrasion
7. *Phototherapy:* Patients who are currently using, will use during the study, or discontinued less than 4 weeks before study baseline phototherapy for the treatment of acne, including but not limited to: UV-A, UV-B, heliotherapy. Patients who have the need or plan to be exposed to artificial tanning devices or excessive sunlight during the study
8. *Systemic therapies*: Patients who are currently using, will use during the study, or discontinued less than 12 weeks before study baseline the use of systemic therapies for the treatment of acne, including but not limited to: antibiotics, isotretinoin. Other systemic therapy that could affect the patient's acne (i.e., anabolics, lithium, EGRF inhibitors, iodides, systemic corticosteroids - except inhaled corticosteroids or intrathecal corticosteroids - or other immunosuppressants), in the opinion of the investigator
9. *Known systemic diseases that can lead to acneiform eruptions:*
    i. Increased androgen production. 1) Adrenal origin: e.g., Cushing's disease, 21-hydroxylase deficiency; 2) Ovarian origin: e.g., polycystic ovarian syndrome,

ovarian hyperthecosis

ii. Cryptococcosis disseminated

iii. Dimorphic fungal infections

iv. Behçet's disease

v. Systemic lupus erythematosus (SLE)

10. *Investigative studies:* Participation in the evaluation of any investigational product or device within 24 weeks before study baseline

11. *Diseases:* Patient with underlying uncontrolled or unstable conditions (including but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal and auto-immune), which, in the Investigator's opinion, could significantly compromise the patient's safety and/or place the patient at an unacceptable risk. Any condition that in the investigator's opinion would make it unsafe for the patient to participate in the study

12. *Alcohol and other substance abuse:* History of alcohol or other substance abuse within one year before screening

13. *Communication:* Patient(s) and parents/guardian(s) (if applicable and possibly only one parent depending on local regulations) unable to communicate or cooperate with the investigator due to e.g., language problems, impaired cerebral function, bad mental conditions

14. *Reliability:* Patients who may be unreliable for the study including patients who are unable to return for the scheduled visits

15. *Pregnancy*:* Pregnant or breastfeeding women or women of childbearing potential who are planning to become pregnant during the study.

    *For all female patients of childbearing potential, pregnancy test result must be negative at screening.

5.4. Study medication

The investigator(s) take responsibility for and shall take all steps to maintain appropriate records to ensure appropriate handling, storage, distribution and use of trial materials in accordance with the protocol and applicable laws and regulations. Pharmaceutical technical faults associate with the IMP must be reported to Sponsor-PV.

5.4.1. Study medication specification

There will be two treatment arms:

IMP 1 arm (IMP 1)
N-Acetyl-GED-0507-34-Levo [redacted]% gel ([redacted] mg/100 mg), PPM Services S.A., Switzerland

IMP 2 Vehicle arm (IMP 2-V)
N-Acetyl-GED-0507-34-Levo corresponding vehicle, PPM Services S.A., Switzerland

Each patient will apply the gel (IMP 1 or IMP 2-V), Once Daily for 12 Weeks, to the entire facial skin area, to dry skin at night after washing, excluding the eyelid and lip region, and to skin areas of the trunk accessible for patient's self-application (i.e., shoulders, upper back, and upper anterior chest), if those are affected by acne.

5.4.2. Identity of study medication

All IMP will be labelled according to the requirements of local law and legislation. A copy of the labels will be filed in the trial master file (TMF). The release of IMP will be done by qualified person (QP). The coordination of distribution to sites will be performed by the Sponsor (or its designee).

At the sites, all IMP to be used during the trial will be stored in accordance with instructions given and will be inaccessible to unauthorized personnel.

Details of the IMP are given in the **Table** below:

Table 1: Details of IMP

Generic name/brand name/INN	**IMP 1:** N-Acetyl-GED-0507-34-Levo [redacted]% gel	**IMP 2-V:** N-Acetyl-GED-0507-34-Levo placebo gel (vehicle)
Formulation	Gel for topical use	Gel for topical use
Active ingredient	N-Acetyl-GED-0507-34-Levo	-
Amount per unit	[redacted] mg/100mg	-
Additional ingredients	Please refer to the IB	Please refer to the IB
Batch number	To be added in the TMF after delivery	To be added in the TMF after delivery
Packaging	35 g Aluminium tubes. Two types of kits will be available. Face kit: containing 2 boxes: Box 1 treatment Wk1-8, containing 8 tubes, Box 2 for treatment Wk9-12, containing 4 tubes Face + trunk kit: contains 3 boxes: Box1 treatment Wk1-4, containing 8 tubes, Box2 treatment Wk5-8, containing 8 tubes, Box3 treatment Wk9-12, containing 8 tubes (Box 1 and 2 will be dispensed together at V2))	35 g Aluminium tubes. Two types of kits will be available. Face kit: containing 2 boxes: Box 1 treatment Wk1-8, containing 8 tubes, Box 2 for treatment Wk9-12, containing 4 tubes Face + trunk kit: contains 3 boxes: Box1 treatment Wk1-4, containing 8 tubes, Box2 treatment Wk5-8, containing 8 tubes, Box3 treatment Wk9-12, containing 8 tubes (Box 1 and 2 will be dispensed together at V2
Storage condition	[redacted]	[redacted]

5.4.3. Assignment of treatments and randomization

Patient identification

Upon signature of informed consent each patient receives an 8-digit patient screening number via IWRS, which is composed of:

Digits 1 and 2: country code

Digits 3 and 4: trial site (01, 02, 03, etc.)

Digits 5, 6, 7 and 8: hyphen and individual screening number within the site (consecutively in the order of screening within the site: 001, 002, etc.)

The patient will keep the patient number as identifier throughout the trial (i.e. IT01-001).

Treatment assignment

Only patients who satisfy all the inclusion and none of the exclusion criteria will be randomized.

Patients will be randomized to one of 2 treatment arms:

IMP 1 arm
N-Acetyl-GED-0507-34-Levo [redacted]% gel ([redacted] mg/100 mg): 200 patients

IMP 2 Vehicle arm (V)
N-Acetyl-GED-0507-34-Levo corresponding vehicle: 200 patients

Treatment allocation will be on a 1:1 ratio in a blinded manner.

Enrollment will be performed competitively between all sites until approximately 400 patients are randomized in the trial to have 366 evaluable patients.

The randomization schedule will be constructed using SAS (Statistical Analysis System, SAS, Cary, NC).

Randomization will be stratified to include:

- Subset 9 to < 12 years: 5% of patients, corresponding to 20 patients.

Randomization

Patients who are eligible for enrollment into the trial will be randomized and assigned a randomization/kit number (randomization number = kit number). This randomization/kit number is different from the patient number and will only serve for treatment assignment, not for patient identification. The randomization/kit number will be recorded in the eCRF and the source documents, thus an allocation is possible at any time.

The patients will be randomized at V2/Day 1 by the interactive web response system (IWRS) to ensure study medication assignment according to stratification.

Patient kits will be dispensed according to the randomization/kit number assigned.

The treatment group designation will remain blinded to the sites until the final database is locked.

5.4.4. Study Medication administration

Patients will be instructed by the site staff on the correct usage of IMP at the trial site during V2/Day 1 and they will receive also written instructions with the diary.

Patients will be instructed to apply once daily (at night) for the duration of their participation. Once the treatment is started, it will be continued until the end of the study, even if IGA/PGA score=0 is reached. Last dose will be applied the day before V5.

Investigational site staff should demonstrate to patients correct application amount and techniques and patients will be requested to apply the first application at the investigational site to confirm correct application technique. All other applications will be generally undertaken at home.

Trial personnel will ensure that the patients can identify the treatment area of face (including nose, excluding eyelids and lips) and, if applicable, the areas of trunk (shoulders, upper back and upper anterior chest) reachable for patient's self-application of study medication.

Patients will be instructed to wash hands before and after application, not to take the IMP orally or apply it to mucous membranes, or to other body regions.

Application of the respective IMP should be made at night, on cleansed and dry skin, only, after showering or bathing, not before. Patients should not wash the treated area for at least 6 hours after the application.

Typically, the IMP will be applied by dabbing small amounts gently on multiple regions of the face (a fingertip unit for each area: forehead, nose, cheeks, chin avoiding eyes, lips and mucous membranes) and (if applicable) of the trunk (shoulders, upper back and upper anterior chest), accessible for self-application (excluding axillary regions and neck); then, using a fingertip, the IMP will be spread to provide a thin, uniform layer of the gel over the entire surface.

Cosmetics (e.g., makeup) should be applied only after IMP is completely absorbed. Facial makeup may be applied according to the patient's normal daily routine; however, patients should be instructed not to wear makeup during study visits as it may interfere with the evaluator's assessments.

5.4.5. Blinding

The trial will be performed in a double-blind manner. All IMPs will be supplied in identical form, color, odor and general appearance so that treatment blind maintains.

The IMPs will be blinded via the labelling procedure.

The trial blind should not be broken except in case of a medical emergency (where knowledge of the IMP received would affect the treatment of the emergency) or regulatory requirement (e.g., for SUSAR). The unblinding of a patient treatment allocation is possible via the IWRS module and only the Investigators (Principal Investigator and his/her delegate) can perform this procedure.

If unblinding occurs, the patient must be discontinued from the trial.

If the blind is broken, the date, time, person who broke the blind and the reason must be recorded in the patient's eCRF, and any associated AE report.

The treatment code will only be broken after all the clinical database is locked.

5.4.6. Restrictions during the clinical trial

Intentional, prolonged exposure to the sun or UV rays will be disallowed during the whole duration of the study. Sun avoidance measures for the treated surface include use of sunscreens and/or hats, minimizing sun exposure whenever possible and no tanning bed use.

Study patients will be instructed to accurately avoid over-cleansing the face during the whole study duration. A harsh cleansing may damage or weaken skin keratinization. Cleansing of the face will be allowed before each IMP application. The patients will be instructed to avoid any facial contact with water (including showers) for at least 6 hours after topical formulation application.

Moreover, patients will be instructed to use through the study the same facial cleanser, moisturizer and sunscreen and not to change products during the study. Patients must also agree to use non-comedogenic makeup during the study if they use makeup and use the same cosmetics through the study. At each visit, patients are asked if they have changed their cleansing/skin care/makeup routine.

Patients will be requested not to apply the IMP, or any makeup before the visits/assessments to avoid any effect on the assessment area.

Treatments as precluded by the exclusion criteria are not permitted. Permitted treatments are documented in Section 5.4.7.

5.4.7. Prior and concomitant therapy

Any medication the patient takes other than the IMP, including herbal and other non-traditional remedies, is considered a concomitant medication. At screening, patients will be asked about any previous acne treatments they have received, if applicable, as well as any concomitant medications they have taken. All prior medications taken in the 6 weeks before the first dose must be recorded in the eCRF. The last used acne treatment will be recorded independently from the period when it was used. The following information must be recorded in the eCRF for each concomitant medication: brand name, route of administration, start date, stop date, dosage, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRF.

At each subsequent trial visit, patients will be asked whether there have been any changes to concomitant medication(s) or if any new medication(s) was/were taken since the previous site visit.

The Investigator should examine the acceptability of all concomitant procedures, medications, topical preparations and dietary supplements not explicitly prohibited in this study. In order to ensure appropriate concomitant therapy is administered, patients will be instructed to consult with the Investigator before taking any medication (either self-administered nonprescription drugs or prescription therapy prescribed by another physician).

For a detailed list of forbidden medications see Exclusion Criteria.

Medication and skin care products allowed during the trial:

- Topical mild soap-free liquid face cleansers (acid and/or pH balanced and free of abrasives and alcohol), moisturizers, sunscreens, non-comedogenic cosmetics. Patients will be asked to use the same products through all the study duration: at each subsequent trial visit, patients will be asked whether there have been any changes. Non-medicated moisturizers, soaps, and makeup should not be recorded as concomitant medications.
- Contraceptives (see Inclusion Criteria).

Prohibited medication:

- All treatment as specified in exclusion criteria.

Concomitant medications should be kept to a minimum during the clinical trial. However, if they are considered necessary for the patient's welfare and are unlikely to interfere with the study objectives, they may be allowed at the discretion of the investigator. For a detailed list of forbidden medication see exclusion criteria. In case of doubts the Sponsor should be asked.

Rescue medication:

No formal rescue medication is foreseen. Patient requiring substitutive treatment for acne, as per Investigator's judgement will be discontinued from the study and relevant details documented.

5.4.8. Treatment compliance

Patients will administer treatment at night at home, except for the first one, which will be applied at the site under the supervision of the investigator at V2/Day 1.

All missing treatment administrations documented in the diary will be counted and documented in patient's chart and in the eCRF.

In case of inadequate usage, the patient will be instructed again on the correct study medication application.

5.4.9. IMP accountability

Upon receipt of the IMP, the IWRS will be updated to acknowledge receipt. All dispensed kits (used and unused) will be collected and counted at V4 and V5. The results will be documented in the eCRF and drug account form.

5.5. Efficacy and safety variable(s)

5.5.1. Procedures

A schedule of trial procedures is provided in **Appendix A** to this trial protocol.

Screening/Baseline visits should be conducted within 14 days.

In any case, if more than 3 days occur between screening and baseline (Day1) visits, physical examination including vital signs, body weight, clinical evaluations (lesions counts, IGA, PGA) need to be repeated.

Maximal effort should be put into ensuring that study visits for school age children will be planned outside of school hours.

Screening period (Visit 1, from Day -14 to V2)

Between Day -14 and Day 1 prior to randomization patients will undergo for initial screening. Patients and parents/guardian(s) (or only one parent depending on local regulations) for minors will be allowed sufficient time to review and evaluate their participation in the clinical trial. Patients and parents/guardian(s) (or only one parent depending on local regulations) must also be notified that they are free to discontinue from the trial at any time. The patients and parents/guardian(s) (or only one parent depending on local regulations) should be given the opportunity to ask questions and allowed sufficient time to consider the written information provided. At the Screening Visit the Investigator has to ensure the Patient Compliance to the Trial.

If the patient wishes to participate, he/she will be requested to consent. After the patient and parents/guardian(s) (or only one parent depending on local regulations) has signed and dated the ICF the patient will be allocated a patient number (a combination of site and screening number), and the following screening assessments will be performed:

- Consent process documented (patient information signed and documented in source notes)
- Documentation of demographic data (age, sex, race/ethnicity, Fitzpatrick scale for skin type – see Appendix G) and food consumption habits (in terms of days per week patient consumes foods such as sweets, salty snacks, soft drinks, or other indulgent treats)
- Documentation of previous/concomitant medications/therapies
- Documentation of relevant medical, surgical and acne history (including initial diagnosis and date of first treatment of acne, if applicable)
- Physical examination* and measurements of height, body weight, vital signs (blood pressure and heart rate [pulse]) **The physical examination will focus on the skin but will also include an orientative examination of the heart, lung, abdomen, basic neurological status and general examination of the eyes, ears, nose, and throat*
- Collection of samples for determination of laboratory parameters (see Section 5.5.3):
  - Standard safety laboratory examinations
  - Blood pregnancy test in childbearing potential women (see **Appendix C** for definition of WOCBP). *If menarche occurs after the Screening visit, blood pregnancy tests will be performed at the visit where there was a change in status and according to the schedule for females of childbearing potential. For pre-menstrual patients, re-confirm pre-menses status*

at every visit and, in case of status change, collect information on contraceptive method and perform a UPT. Additional UPTs may be performed at the Investigator's discretion.

- Clinical assessments (lesion count [inflammatory and non-inflammatory lesions] and IGA/PGA)
- Check inclusion/exclusion criteria
- Recording AEs before start of treatment (= non-treatment emergent AEs, i.e. occurring after signature on consent form).

Treatment period

Visit 2 (Day 1)

- Update of concomitant medications/therapies, and AEs
- Final eligibility check of the inclusion/exclusion criteria
- The following assessments are performed also at Visit 2, and considered as baseline assessments, only if the screening visit is performed > 3 days before Visit 2, Day 1. If the screening visit is performed ≤ 3 days before Visit 2, the assessments will not be repeated during Visit 2 and will be considered as baseline assessments:
  - Physical examination and measurements of body weight, vital signs (blood pressure and heart rate [pulse])
  - Clinical assessments (lesion count [inflammatory and non-inflammatory lesions] and IGA/PGA.
- Randomization (following confirmation of in-/exclusion criteria) to one of 2 treatment arms
- [redacted]
- [redacted] (not mandatory, following specific consent)
- Assessment of local signs during the visit (before administration of first IMP dose). The patient will be questioned if he/she experienced any subjective symptoms in the past 24 hours. Presence or absence of signs/symptoms in the past 14 days will be collected, Presence or absence of overall application site irritation in the last 2 weeks will be recorded.
- Dermatology Life Quality Index (DLQI) / Children's Dermatology Life Quality Index (C-DLQI for patients from 9 to 16 years old), completed by the patient (prior to any Investigator assessments to not impact the patient's answers to the quality of life questionnaire)
- Dispensing of IMP and Patient Diary and instruction on use of IMP, administration of first dose by patient under supervision of site staff
- Schedule next visit.

Days 2–28

Daily (OD) treatment by the patient at home, in the evening after cleansing/washing, and update of diary.

T2 - Wk2, Day15 (± 2 days)

For patients aged 9 to < 12 only, a phone contact will be kept at Wk2 (in the presence of parents or legal guardian(s) (or only one parent depending on local regulations) who signed the Informed Consent), to check concomitant medications/therapies, IMP compliance, AEs and assessment of local tolerability by local signs/symptoms (the patient will be questioned if he/she experienced any of these subjective symptoms from the last visit, by checking the diary).

Patients will also be asked to report signs and symptoms experienced within the last 24 hours prior to the phone contact.

The Investigator must promptly record the call results in the eCRF. In case of safety issues, an immediate automatic notification will be sent to the DSMB.

Visit 3 (Wk4, Day 29) (± 2 days)

- Check concomitant medications/therapies and AEs
- Physical examination and measurements of vital signs (blood pressure and heart rate [pulse])
- Clinical assessments (lesion count [inflammatory and non-inflammatory lesions] and IGA/PGA). PGA will be evaluated only if the trunk is treated
- Assessment of local tolerability by local signs/symptoms. The patient will be questioned if he/she experienced any of these subjective symptoms within the last 24 hours prior to the visit
- Collection of diary and assessment of patient compliance by diary check
- Dispensing a new diary
- Schedule next visit.

Days 29–56

Daily treatment (OD) by the patient at home, in the evening after cleansing/washing, and update of the diary (including the day of the V3/Wk4).

Visit 4 (Wk8 Day 57) (± 2 days)

- Check concomitant medications/therapies and AEs
- Physical examination and measurements of vital signs (blood pressure and heart rate [pulse])
- Clinical assessments (lesion count [inflammatory and non-inflammatory lesions] and IGA/PGA). PGA will be evaluated only if the trunk is treated

- Assessment of local tolerability by signs/symptoms. The patient will be questioned if he/she experienced any of these subjective symptoms within the last 24 hours prior to visit
- Collection of IMP and diary and assessment of patient compliance by diary check, and counting of tubes
- Dispensing of IMP and diary
- Schedule next visit.

Days 57–84

Daily treatment (OD) by the patient at home, in the evening after cleansing/washing, and update of the diary (including the day of the V4/Wk8). Treatment should be discontinued the night before EoT.

T10 - Wk10, Day71 (± 2 days)

For patients aged 9 to < 12 only, a phone contact will be kept at Wk10 (in the presence of parents or legal guardian(s) (or only one parent depending on local regulations) who signed the Informed Consent), to check concomitant medications/therapies, IMP compliance, AEs and assessment of local tolerability by local signs/symptoms (the patient will be questioned if he/she experienced any of these subjective symptoms from the last visit, by checking the diary).

Patients will also be asked to report signs and symptoms experienced within the last 24 hours prior to the phone contact.

The Investigator must promptly record the call results in the eCRF. In case of safety issues, an immediate automatic notification will be sent to the DSMB.

Visit 5 (Wk12, end of treatment [EoT] Day 85 (+ 3days)

- Check concomitant medications/therapies and AEs
- Physical examination, body weight and height (for minors) and vital signs (blood pressure and heart rate [pulse])
- Collection of samples for determination of laboratory parameters:
  - Standard safety laboratory examinations
  - Blood pregnancy test in childbearing potential women (see **Appendix C** for definition of WOCBP)
- Clinical assessments (lesion count [inflammatory and non-inflammatory lesions] and IGA/PGA). PGA will be evaluated only if the trunk is treated
- Assessment of local tolerability by local signs/symptoms. The patient will be questioned if he/she experienced any of these subjective symptoms within the last 24 hours prior to visit
- Patient’s assessment of overall application site irritation

- [redacted]
- [redacted] (not mandatory, following specific consent)
- Dermatology Life Quality Index (DLQI) / Children's Dermatology Life Quality Index (C-DLQI for patients from 9 to 16 years old), completed by the patient (prior to any Investigator assessments to not impact the patient's answers to the quality of life questionnaire)
- Collection of IMP and diary and assessment of patient compliance by diary check, and counting of tubes
- Schedule next visit.

Follow-up

Visit 6 (Wk14) End of trial Day99 (+ 2days) or ETV in case of withdrawal after EoT – Telephone contact

- Check concomitant medications/therapies and AEs
- End of trial.

If clinically significant out of range or clinically significant values are found at V5, patient will be asked to return at site to perform additional laboratory examinations of the significant out of range values.

This visit will be performed only for patients who are not included in the long-term study.

UNSCHEDULED VISITS (Early termination visit [ETV])

Any time the trial is permanently discontinued for any reason during the treatment phase, an Early Termination visit should be performed:

- Check concomitant medications/therapies and AEs
- Physical examination and measurements of vital signs (blood pressure and heart rate [pulse])
- Collection of samples for determination of laboratory parameters:
  - Standard safety laboratory examinations
  - Blood pregnancy test in childbearing potential women (see **Appendix C** for definition of WOCBP)
- Clinical assessments (lesion count [inflammatory and non-inflammatory lesions] and IGA/PGA). PGA will be evaluated only if the trunk is treated
- [redacted]
- [redacted] (not mandatory, following specific consent)

- Dermatology Life Quality Index (DLQI) / Children's Dermatology Life Quality Index (C-DLQI for patients from 9 to 16 years old), completed by the patient (prior to any Investigator assessments to not impact the patient's answers to the quality of life questionnaire)
- Evaluation of local tolerability signs/symptoms. The patient will be questioned if he/she experienced any of these subjective symptoms within the last 24 hours prior to visit
- Patient's assessment of overall application site irritation
- Collection of IMP and diary and assessment of patient compliance by diary check, and counting of tubes
- End of trial.

In case the discontinuation is during the Follow-up phase, the Visit 6 (Wk14) End of trial (± 2 days) – Telephone contact procedures will be performed.

5.5.2. Clinical Assessments

5.5.2.1. Lesion Counts

Non-inflammatory lesions (closed and open comedones), inflammatory lesions (papules, pustules, and nodules, if applicable) on the face, including the nose, and on the trunk (shoulders, upper back and upper anterior chest) will be counted and recorded separately at each scheduled site visit throughout the study.

Lesions are defined as follows:

Non-inflammatory lesions:

- Comedones – open (blackheads)
- Comedones – closed (whiteheads).

Inflammatory lesions:

- Papules – raised inflammatory lesions with no visible purulent material
- Pustules – raised inflammatory lesions with visible purulent material
- Nodules – any circumscribed, inflammatory mass greater than or equal to 5 mm in diameter with or without cystic changes.

The investigator/evaluator should use standard, good lighting and magnification as necessary to visualize lesions and a systematic counting procedure to ensure consistent and accurate counts.

The overall number of inflammatory lesions and non-inflammatory lesions for each of the two regions (face and trunk) will be reported separately in the eCRF. The overall number of total lesions

(inflammatory plus non-inflammatory lesions) will be calculated by the electronic data capture (EDC) system.

For the face, the total lesions will be calculated as the sum of inflammatory plus non-inflammatory lesions, including the nose.

For the trunk, the total lesions will be calculated as the sum of inflammatory plus non-inflammatory lesions of the anterior part of the trunk, excluding the neck and axillary regions.

Assessments per patient should be done by the same trained investigator throughout the study, if possible, to minimize the possibility for introduction of bias.

5.5.2.2. Investigator's Global Assessment (IGA) (face)

The IGA scale to be used in the study is a measure of static evaluation of qualitative overall acne severity for face. IGA is an ordinal scale with 5 severity grades (reported only in integers, e.g., 0 to 4). Each grade is defined by a distinct and clinically relevant morphologic description to minimize inter-observer variability (**Table 2)**. The grades on the scale have been sufficiently defined to appropriately and unambiguously represent each severity grade on the scale. The investigator is required to perform IGA scoring at each scheduled site visit. IGA scores will be documented in the eCRFs.

In case of worsening of acne, the investigator may consider treatment discontinuation according to section 8.3.1.

Table 2: IGA Scale For Acne Vulgaris*

Grade	Description	
0	CLEAR	Clear skin with no inflammatory or non-inflammatory lesions
1	ALMOST CLEAR	A few scattered comedones and a few small papules
2	MILD	Easily recognizable: less than half the face is involved. Some comedones and some papules and pustules
3	MODERATE	More than half of the face is involved. Many comedones, papules and pustules. One small nodule may be present
4	SEVERE	Entire face is involved. Covered with comedones, numerous papules and pustules. Few nodules may or may not be present

* Areas other than the face and nose are not included in assessment

Assessments per patient should be done by the same trained investigator throughout the study, if possible, to minimize the possibility for introduction of bias.

5.5.2.3. Physician Global Assessment (PGA) (trunk)

The PGA scale to be used in the study is a measure of static evaluation of qualitative overall acne severity for trunk. PGA is an ordinal scale with 5 severity grades (reported only in integers, e.g., 0 to

4). Each grade is defined by a distinct and clinically relevant morphologic description to minimize inter-observer variability (**Table 3)**. The grades on the scale have been sufficiently defined to appropriately and unambiguously represent each severity grade on the scale. The investigator is required to perform PGA scoring at each scheduled site visit. PGA scores will be documented in the eCRFs. The areas defined for PGA assessment are shoulders, upper back and anterior chest which are accessible to self-application by the patient, i.e., the regions that the patient can easily reach and apply the study medication without assistance.

Table 3: PGA Scale For Acne Vulgaris

Grade	Description	
0	CLEAR	Clear skin with no inflammatory or non-inflammatory lesions
1	ALMOST CLEAR	A few scattered comedones and a few small papules
2	MILD	Easily recognizable: less than half the surface is involved. Some comedones and some papules and pustules
3	MODERATE	More than half of the surface is involved. Many comedones, papules and pustules. One small nodule may be present
4	SEVERE	Entire surface is involved. Covered with comedones, numerous papules and pustules. Few nodules may or may not be present

Assessments per patient should be done by the same trained investigator throughout the study, if possible, to minimize the possibility for introduction of bias.

5.5.2.4. Dermatology life quality index (DLQI/ C-DLQI)

Dermatology Life Quality Index (DLQI) (age 17 and older)/Children's Dermatology Life Quality Index (C-DLQI) (for 16 years and younger) will be completed by each patient at Baseline and EoT. If the patient completed a CDLQI at the Baseline visit, a C-DLQI should be completed at the Week 12/ET Visit, regardless of the patient's age at the Week 12/ET visit.

The DLQI/C-DLQI measures dermatology-related limitations of functional ability on patients' lives. The questionnaires will be conducted prior to any acne assessment by the investigator, to avoid influencing the patient's answers. The higher the score (ranging from 0 to 30), the more the QOL is impaired (Morgan M, 1997; Lewis-Jones MS 1995).

English master version of both questionnaires is in **Appendix F** (validated versions in local languages will be used). Authorization to use will be obtained.

5.5.2.5. [redacted]

[redacted]

[redacted]

Table 4: [redacted]

[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Assessments per patient should be done by the same trained investigator throughout the study, if possible, to minimize the possibility for introduction of bias.

[redacted] the following assessment will be done at V2-Day1 (baseline) and V5/Wk12, EoT:

[redacted]

[redacted] will be performed at the clinical site by a trained investigator for patients participating in the [redacted] portion of the study.

[redacted] be undertaken with regard to collection, transmission, storage and use of [redacted] Collection of [redacted] is not mandatory; patients will be able to participate in the study even if they refuse to participate in [redacted] of patients will be obtained in [redacted]

The independent Third Party-Vendor [redacted] will perform the [redacted]

[redacted] will be performed in [redacted]

[redacted] **Methodology**

[redacted]

[redacted]

5.5.2.6. Local tolerability assessment

Local safety and tolerability will be evaluated on the basis of the following signs and symptoms:

Objective symptoms

- application site non-lesional erythema
- application site exfoliation
- application site dryness
- overall application site irritation.

Subjective symptoms

- stinging
- burning
- itching.

For all the site visits, objective symptoms (signs of erythema, exfoliation, dryness) will be assessed and scored by the Investigator and the patient will be questioned if he/she experienced any of the subjective symptoms (stinging, burning, itching) within the last 24 hours prior to visit.

During telephone contacts (patients aged 9 to < 12 only), patient will be questioned if he/she experienced any of the above sign/ symptoms within the last 24 hours prior to visit.

For each sign/symptom, a severity score will be assigned using a 4-point scale from 0 = none to 3 = severe (**Tables 5-7** and **9-11**).

Moreover, at baseline, the presence or absence of any of these signs/symptoms in the past 14 days will be collected.

The overall application site irritation will be assessed at baseline (only presence /absence assessment) and the end of study treatment (V5).

At V5, the overall application site irritation will be assigned using a 4-point scale from 0 = excellent to 3 = poor (see **Table 8**).

Only sign/symptom occurring after the first application of study medication that requires additional therapy or discontinuation of treatment or judged clinically significant by the Investigator, will be documented as a TEAE.

Table 5: Scoring of application site non-lesional erythema

Severity	Score	Description
None	0	No erythema
Mild	1	Light pinkness present
Moderate	2	Definite redness, easily recognized
Severe	3	Intense redness

Table 6: Scoring of application site exfoliation

Severity	Score	Description
None	0	No scaling
Mild	1	Barely perceptible shedding, noticeable only on light scratching or rubbing
Moderate	2	Obvious but not profuse shedding
Severe	3	Heavy scale production

Table 7: Scoring of application site dryness

Severity	Score	Description
None	0	No dryness
Mild	1	Slight barely perceptible fine superficial scale
Moderate	2	Clearly perceptible fine scale giving skin a powdery appearance
Severe	3	Marked roughness, cracked skin with fissures

Table 8: Scoring of overall application site irritation

Grades	Score	Description
Excellent	0	No signs of irritation during the study
Good	1	Slight signs of irritation during the study which might resolve by the end of the study
Fair	2	Signs of irritation throughout the study
Poor	3	Patient discontinued due to irritation
Irritation is defined as any sign or symptom of intolerance.		

Table 9: Scoring of stinging

Severity	Score	Description
None	0	No stinging
Mild	1	Slight sharp, tingling/stinging sensation; not really bothersome
Moderate	2	Definite sharp, tingling/stinging sensation; that was somewhat bothersome

Severe	3	Sharp, tingling/stinging sensation that had caused definite discomfort

Table 10: Scoring of burning

Severity	Score	Description
None	0	No burning
Mild	1	Slight warm, burning sensation; not really bothersome
Moderate	2	Definite warm, burning sensation; that was somewhat bothersome
Severe	3	Hot, burning sensation that has caused definite discomfort

Table 11: Scoring of itching

Severity	Score	Description
None	0	No itching
Mild	1	Slight itching; not really bothersome
Moderate	2	Definite itching that was somewhat bothersome, without loss of sleep
Severe	3	Intense itching that had caused pronounced discomfort; night rest interrupted and excoriation of the skin from scratching might have been present

5.5.3. Measurement of safety parameters

Relevant medical history and AEs will be recorded.

Spontaneously noted complaints will be recorded along with their duration, intensity and probability of a correlation with the IMP (see Section 7.3, Evaluation of adverse events).

Laboratory examinations

The following laboratory parameters will be collected at screening (V1) and at the end of the comparative treatment phase (V5/Wk12, EoT) (**see Table 12**).

If clinically significant out of range or clinical significant values are found at V5, additional laboratory examinations will be performed at V6 (Follow-up/ETV visit).

Table 12: Laboratory examinations

Parameter	Screening examination V1 Day -14 to -1	Final examination V5 Wk12, Day 85 + 3 days (EoT)	ETV
Hematology			
RBC	X	X	X
WBC	X	X	X
Hemoglobin	X	X	X
Hematocrit	X	X	X

Parameter	Screening examination V1 Day -14 to -1	Final examination V5 Wk12, Day 85 + 3 days (EoT)	ETV
MCH	X	X	X
MCV	X	X	X
MCHC	X	X	X
Platelets	X	X	X
CBC/Differential	X	X	X
Clinical Chemistry			
AST (GOT)	X	X	X
ALT (GPT)	X	X	X
Total cholesterol	X	X	X
Triglycerides	X	X	X
HDL-C	X	X	X
LDL-C	X	X	X
Plasma glucose	X	X	X
[redacted]	X	X	X
[redacted]	X	X	X
Pregnancy test	X	X	X
Fasting status	X	X	X

Hematology, clinical chemistry examinations and pregnancy test will be performed centrally.

Details on all laboratory procedures, collections, shipment of samples and reporting of results, alerting of extreme values and notable values by the central laboratory will be provided to investigators in the laboratory manual. The central laboratory will provide the sponsor with a copy of the laboratory certification and tabulation of the reference ranges. Details on collection and handling of laboratory samples are provided in the laboratory manual/instruction.

Any out of range laboratory results that are deemed clinically significant by the investigator will be recorded as medical history if detected at screening.

In case of unexpected laboratory out-of-range values in the blood samples collected at screening, which in the Investigator's opinion may pose the patient at increased risk during participation to the clinical trial, the patient/parents (or only one parent depending on local regulations) will be contacted to discontinue the treatment and will be withdrawn from the study. At all visits clinically significant laboratory results will be recorded as AEs.

5.5.4. Vital signs

Blood pressure and pulse rate will be measured at V1-screening, V2/Day 1 (only in case of V1 > 3 days before V2), V3/Wk4, V4/Wk8, V5/Wk12, ETV if applicable.

Blood pressure will be measured according to the National Institutes of Health, National Heart, Lung, and Blood Institute Guidelines [NIH 1997] with the following standardized techniques:

– patients are seated in a chair; blood pressure measurement begins after at least 10 minutes of rest

– the appropriate cuff size is used to ensure accurate measurement

– measurements will be taken with a sphygmomanometer.

Only one reading is required.

5.5.5. Appropriateness of measurements

Lesion count and IGA are widely used, non-invasive methods for examining overall acne severity. Both measures are described in the S-3 Guideline for Treatment of Acne (Nast A, 2016) and the FDA Draft 'Guidance for Industry - Acne Vulgaris: Developing Drugs for Treatment' (May 2018).

Investigators global assessment and PGA scores have been used in clinical studies of truncal acne in patients presenting with acne on the trunk and face, (Del Rosso J.Q, Hoffman L.K, 2018) and in addition, the PGA was used to assess efficacy in 2 recent registration studies that resulted in Food and Drug Administration's approval of trifarotene (Tan J, 2019; Blume-Peytavi 2020), indicating the current Food and Drug Administration endorsement of the PGA as an appropriate clinician-reported outcome measure for truncal acne in clinical trials.

Assessments should be conducted by investigators who are experienced and have been trained on the use of these evaluation tools. Assessments per patient should be done by the same trained investigator throughout the study, if possible, to minimize the possibility for introduction of bias.

The use of quality of life and psychosocial questionnaires is considered essential to adequately understanding just how the disease is affecting the patient, and to better understand the progress of the disease and the acne impact on QoL can drive the choice of therapy by clinicians (S-3 Guideline for Treatment of Acne, Nast A 2016; Simpson NB, 2004).

5.5.6. Primary efficacy variable

There are two primary efficacy variables: lesion count and IGA.

The primary variables are chosen in accordance with the S-3 Guideline for Treatment of Acne (S-3 Guideline for Treatment of Acne, Nast A 2016) and the FDA Guidance for industry. Acne vulgaris: developing drugs for treatment (May 2018). Experience with topical anti-acne medication has shown that a 12-week treatment period is in general sufficient to demonstrate efficacy. Thus, Wk12 (V5) should be suitable for the evaluation of the primary endpoints.

6. Data analysis and statistics

The statistical evaluation will be performed using the software program SAS (Statistical Analysis System, SAS, Cary, NC).

Based on the following description of statistical methods a detailed statistical analysis plan will be generated and finalized prior to database closure.

6.1. Generation of data base

Data from the source documents will be captured in an eCRF by a software package that can be customized for remote data entry procedure and that maintains an electronic audit trail. Only authorized site personnel will be able to enter/modify/correct data to the eCRF. The investigator/coordinator or designee must enter the information required by the protocol as soon as possible after the visit into the eCRF. The data will be checked for consistency. Queries for discrepant data may be generated automatically by the system upon entry or generated manually by the monitor or the trial data manager. All queries, generated by the system or by a user, will be electronic. All data management procedures will be detailed in a separate, specifically identified file that collectively will be referenced as the data management plan (DMP). The database structure will be validated by the vendor. The eCRFs will be developed in the EDC system in accordance with vendor standard operating procedures (SOPs) under supervision in agreement with the Sponsor. Once all the queries are closed and Data Management has verified the data, the Investigator will sign the eCRF (eSignature), and the database will be locked.

AEs and medical history will be coded with MedDRA (MedDRA version will be defined in the DMP); previous and concomitant therapy will be coded according to ATC. In case of general discontinuation of a specific treatment the common terminology criteria for adverse events (CTCAE) classification will be used and documented in the respective eCRF section as free text.

Patient data generated from the eCRF in portable document format (PDF)will be provided to the site at the end of the trial.

6.2. Analysis sets and type of analysis

Screened Analysis Set (SCR)

This analysis set includes all patients who signed the informed consent form and received a screening number, regardless of whether they completed all the screening procedures.

Enrolled Set (ENR)

All patients included in the study, excluding screening failure.

Randomized Set (RND)

All enrolled patients who are randomized to a treatment arm.

Full Analysis Set (FAS)

The Full Analysis Set (FAS) includes all randomized patients who receive at least one dose of the study medication and have at least one valid post- baseline efficacy assessment for both primary endpoints.

The analyses on FAS will be performed with the Intention-To-Treat (ITT) principle.

Per-Protocol Set (PPS)

The Per-Protocol Set (PPS) comprises all patients included in the FAS who complete the study without major protocol deviations. Major protocol deviation will be identified in the SAP and/or during a blind medical review.

The analysis of efficacy will be conducted on the FAS and PPS sets, with the FAS considered as the primary set for statistical analysis, based on treatment as randomized.

Safety Set (SS)

The Safety Set (SS) includes all patients who received at least one dose of study treatment. Safety analyses will be performed on the Safety Set based on treatment as received.

6.3. Efficacy endpoints

Efficacy will be assessed by the investigator using acne lesion count and IGA (primary efficacy variables) at V2/Day 1 (Baseline), V3/Wk4, V4/Wk8 and V5/Wk12 (End of Treatment [EoT]). Acne lesion count and IGA will also be performed for inclusion at V1 (screening) and in case of Early Termination Visit [ETV].

Acne lesion count: Inflammatory (papules, pustules and nodules) and non-inflammatory lesions (open [blackheads] and closed [whiteheads] comedones) on the face (including the nose) and on the trunk will be accurately counted and recorded at each visit as detailed in the study schedule. Total lesions will be calculated as the sum of inflammatory plus non-inflammatory lesions.

IGA (Face): Overall severity of acne will be assessed using a 5-point scale from 0 = clear to 4 = severe at each visit as detailed in the study schedule.

PGA (Trunk): Overall severity will be assessed using a 5-point scale from 0 = clear to 4 = severe at each visit as detailed in the study schedule.

6.3.1. Primary efficacy endpoint

To demonstrate the efficacy of a 12 weeks treatment with N-Acetyl-GED-0507-34-Levo [redacted]% gel, the following family of primary efficacy endpoints will be analyzed:

a. Endpoint 1 (E1): the relative change from baseline in total lesion count (inflammatory plus non-inflammatory) at V5/Wk12 on the face

b. Endpoint 2 (E2): proportion of patients with an IGA success at V5/Wk12.

IGA success is defined according to the patient's age as:

- a score of "clear" (score = 0) or "almost clear" (score = 1) for patients aged ≥ 9 and ≤ 14 years
- a score of "clear" (score = 0) or "almost clear" (score = 1) and at least a 2-score point reduction in IGA at V5/Wk12 for patients aged > 14 and < 50 years.

6.3.2. Secondary efficacy endpoints

To evaluate the efficacy of [redacted]% N-Acetyl-GED-0507-34-Levo gel in comparison to IMP 2-V after 12 weeks of treatment on the following parameters:

FACE

a. Absolute change from baseline in total lesion count at V5/Wk12

b. Percentage of patients who achieve an IGA success over the study duration (i.e., score of 1 [almost clear] or 0 [clear] for patients aged ≥ 9 and ≤ 14 years; score of 1 [almost clear] or 0 [clear] and at least a two-grade improvement from baseline for patients aged > 14 and < 50 years)

c. Change from baseline in total lesion count over the study duration

d. Change from baseline in inflammatory lesion count over the study duration

e. Change from baseline in non-inflammatory lesion count over the study duration.

TRUNK

a. Absolute change from baseline in total lesion count at V5/Wk12

b. Percentage of patients who achieve a PGA score of 1 (almost clear) or 0 (clear) and at least a two-grade improvement from baseline over the study duration

c. Change from baseline in truncal total lesion total count over the study duration

d. Change from baseline in truncal inflammatory lesion count over the study duration

e. Change from baseline in truncal non-inflammatory lesion count over the study duration.

OTHER

a. Dermatology Life Quality Index (DLQI) / Children's Dermatology Life Quality Index (C-DLQI for patients from 9 to 16 years old), completed by the patient at the Baseline and Week 12/EoT visits (prior to any Investigator assessments to not impact the patient's answers to the quality of life questionnaire)

b. [redacted]

c. [redacted] (not mandatory, following specific consent) at the Baseline and Week 12/EoT visits.

6.4. Safety and tolerability endpoints

1. Incidence of all Adverse Events (AEs), Treatment-Emergent Adverse Events (TEAEs), Adverse Drug Reactions (ADRs), Serious Adverse Events (SAEs) throughout the study with special attention to local TEAEs concerning the treated facial area (local dermal safety), and systemic TEAEs
2. Frequency of discontinuation of treatment due to TEAEs
3. Changes from baseline of vital signs during the study
4. Physical examination during the study
5. Changes from baseline of laboratory test at V5/Wk12
6. Change from baseline of local tolerability- Application site signs/symptoms during the

study*

7. Assessment of overall application site irritation at V5/Wk12.

*Local tolerability will be evaluated on the basis of the following signs and symptoms: application site non-lesional erythema, application site exfoliation, and application site dryness, stinging, burning, itching. For each sign/symptom, a severity score will be assigned using a 4-point scale from 0 = absent to 3 = severe.

Only a sign/symptom occurring after the first application of study medication that requires additional therapy or discontinuation of treatment or judged clinically significant by the Investigator, will be documented as a TEAE.

6.5. Rationale for the sample size

The sample size is based on the two co-primary endpoints: relative change from baseline in total lesion count on the face (inflammatory plus non-inflammatory) and IGA success at V5/Wk12 to reach a power of 90% at a level of 0.05, since this are considered the most relevant clinical endpoints.

The formal calculation of sample size is based on the paper from T. Sozu et al. Sample size for co-primary continuous and binary endpoint (2012), assuming the normality of the relative change from baseline distribution and making the following assumptions:

- an error I type of [redacted]%
- a statistical power of [redacted]%
- a relative change from baseline in total lesion count on the face at V5/Wk12 in the IMP 2-V arm (placebo arm) of [redacted]% (data retrieved from the Study NAC-GED-0507-ACN-01-18)
- a Standard Deviation (SD) of the difference between treatment arms of [redacted]% (data retrieved from the Study NAC-GED-0507-ACN-01-18).
- a rate of IGA success on the face at V5/Wk12 in the IMP 2-V arm (placebo arm) of [redacted]% (data retrieved from the Study NAC-GED-0507-ACN-01-18)
- a difference between the two treatment arms in terms of the relative change from baseline in total lesion count on the face (inflammatory plus non-inflammatory) at V5/Wk12 equal to or greater than [redacted]% and a difference in IGA successes equal or greater than [redacted]% (data retrieved from the Study NAC-GED-0507-ACN-01-18).

A sample size of 366 evaluable patients (183 in each treatment arm), will be adequate to find a significant difference between the two treatment arms in terms of the relative change from baseline in total lesion count on the face (inflammatory plus non-inflammatory) at V5/Wk12 and in IGA successes.

Considering a drop-out rate close to [redacted]% of non-evaluable patients for any reason, a total of 400 patients will have to be enrolled in the study (sample allocation ratio 1:1).

A second pivotal Phase 3 study (NAC-GED-0507-ACN-01-23-B) with an identical study design to the present study is planned to be performed with an equivalent sample size of 400 patients in total.

6.6. Statistical methods

The data documented in this study and the parameters measured will be evaluated and compared Continuous data will be summarized with standard descriptive statistics (i.e. mean, SD, median, interquartile range [IQR], minimum and maximum). Categorical data will be summarized by frequency and percentage. 95% confidence intervals (CIs) will be provided as relevant.

All data will be presented by treatment arm and overall and, if relevant, by study visit.

Statistical test will be performed for between-arm differences in demographic and baseline features (medical and efficacy data).

Medical history and adverse events (AEs) will be described according to System Organ Classes (SOC) and Preferred Terms (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) and will be presented by treatment arm. Previous/concomitant medications will be presented by treatment arm using the World Health Organization Drug Dictionary (WHO-DD).

All analyses will be performed using SAS® software, the latest applicable version..

A p-value equal to or lower than 0.05 will be considered statistically significant.

6.6.1. Efficacy analyses

6.6.1.1. Primary analysis

The primary variables will be analyzed presenting descriptive statistics (mean, SD, median, IQR, minimum and maximum for total [redacted] endpoint and count and percentage for IGA success rate endpoint) overall, by treatment arm and, if deemed relevant, by study visit.

Subgroup analyses will be performed for: gender (M; F), age (≥ 9 and ≤ 18 years; vs ≥ 19 and < 50 years; and also in the following subgroups ≤12; 13 to 18; ≥19;), IGA/PGA, Race/ethnicity (White; Black; Asian, Latino; other); Fitzpatrick skin type; country.

Absolute and relative differences in terms of total [redacted] between baseline and EoT will be also presented.

Estimands for the primary Endpoint 1 (E1)

The estimand for the primary E1 is defined as follows:

1. Treatment: 12 weeks administration of NAC-GED-0507 gel [redacted]% or vehicle gel.

2. Target population: Male and female patients aged ≥ 9 and <50 years affected by facial acne vulgaris. Full Analysis Set.

3. Variable: relative change from baseline in total [redacted] (inflammatory plus non-inflammatory) at V5/Wk12 on the face.

4. Intercurrent events (ICEs) and strategies to handle them:

- Treatment discontinuation

- Study withdrawal
- Use of prohibited medications listed in section 5.4.7

A treatment policy strategy will be applied where all observed values will be used regardless of the occurrence of the ICEs. Missing data due to any reason will be handled by using a LOCF imputation

5. Population-level summary: the difference in the relative change from baseline to V5/Wk12 in total [redacted] between the two treatment groups will be assessed by an independent t-test (or a Wilcoxon test if the Normality is violated). A p-value equal to or lower than 0.05 will be considered statistically significant.

Estimands for the primary Endpoint 2 (E2)

The estimand for the primary E2 is defined as follows:

1. Treatment: 12 weeks administration of NAC-GED-0507 gel [redacted]% or vehicle gel.

2. Target population: Male and female patients aged ≥ 9 and <50 years affected by facial acne vulgaris. Full Analysis Set.

3. Variable: proportion of patients with an IGA success at V5/Wk12.

4. Intercurrent events (ICEs) and strategies to handle them:

- Treatment discontinuation
- Study withdrawal
- Use of prohibited medications listed in section 5.4.7.

A treatment policy strategy will be applied where all observed values will be used regardless of the occurrence of the ICEs. Missing data due to any reason will be handled by using a LOCF imputation

5. Population-level summary: the difference in terms of the proportion of patients with an IGA success at V5/Wk12 between the two treatment arms will be assessed with an independent Chi-Square test (or Fisher exact test if the successes in one of the two treatment groups is lower than 5). A p-value equal to or lower than 0.05 will be considered statistically significant

6.6.1.2. Secondary analyses

Secondary variables will be analyzed presenting descriptive statistics overall, by treatment arm and, if deemed relevant, by study visit.

Subgroup analyses will be performed for: gender (M; F), age (≥ 9 and ≤ 18 years; vs ≥ 19 and < 50 years; and also in the following subgroups ≤12; 13 to 18; ≥19;), IGA Score at Baseline, Race/ethnicity (White; Black; Asian, Latino; other); Fitzpatrick skin type; country.

All statistical tests that will be applied, if any, will have exploratory purposes only.

The analyses of the secondary endpoints will be conducted on the FAS and PPS sets.

LOCF imputation methodology will be used to impute missing values for the lesions count and the IGA in the FAS.

6.6.1.3. Sensitivity analysis

The same analysis performed on the primary endpoints will be conducted on the PPS as sensitivity analysis.

Additionally, a second sensitivity analysis performed on the FAS will be conducted using the following specifications:

Sensitivity Estimands for the primary Endpoint 1 (E1)

1. Treatment: 12 weeks administration of NAC-GED-0507 gel [redacted]% or vehicle gel.

2. Target population: Male and female patients aged ≥ 9 and <50 years affected by facial acne vulgaris. Full Analysis Set.

3. Variable: relative change from baseline in total [redacted] (inflammatory plus non-inflammatory) at V5/Wk12 on the face.

4. Intercurrent events (ICEs) and strategies to handle them:

- Treatment discontinuation
- Study withdrawal
- Use of prohibited medications listed in section 5.4.7

A treatment policy strategy will be applied where all observed values will be used regardless of the occurrence of the ICEs. Missing data due to any reason will be handled by using a multiple imputation approach with a missing-at-random (MAR) assumption

5. Population-level summary: the difference in the relative change from baseline to V5/Wk12 in total [redacted] between the two treatment groups will be assessed by an independent t-test (or a Wilcoxon test if the Normality is violated).

Sensitivity Estimands for the primary Endpoint 2 (E2)

1. Treatment: 12 weeks administration of NAC-GED-0507 gel [redacted]% or vehicle gel.

2. Target population: Male and female patients aged ≥ 9 and <50 years affected by facial acne vulgaris. Full Analysis Set.

3. Variable: proportion of patients with an IGA success at V5/Wk12.

4. Intercurrent events (ICEs) and strategies to handle them:

- Treatment discontinuation
- Study withdrawal
- Use of prohibited medications listed in section 5.4.7

A treatment policy strategy will be applied where all observed values will be used regardless of the occurrence of the ICEs. Missing data due to any reason will be handled by using a multiple imputation approach with a missing-at-random (MAR) assumption

5. Population-level summary: the difference in terms of the proportion of patients with an IGA success at V5/Wk12 between the two treatment arms will be assessed with an independent Chi-Square test (or Fisher exact test if the successes in one of the two treatment groups is lower than 5).

6.6.2. Safety analyses

The analysis of safety will be conducted on the Safety Set.

Adverse events (AEs) will be coded by System Organ Class (SOC) and Preferred Term (PT), using the Medical Dictionary for Regulatory Activities (MedDRA).

Treatment-emergent adverse events (TEAEs), i.e. AEs with an onset on or after the time of the first IMP application, will be analyzed. TEAEs will be summarized by primary system organ class (SOC), preferred term (PT), severity and relationship to IMP.

All local tolerability signs and symptoms (both objective and subjective) will be listed and summarized at each visit by treatment and severity using frequency tables.

The overall application site irritation requested at the end of the study treatment will be listed and summarized using frequency tables by treatment group.

Vital signs will be listed and presented descriptively by visit, including changes from baseline.

Regarding laboratory assessments, the overall investigator's interpretation (as normal [N], abnormal but not clinically significant [NCS] or abnormal and clinically significant [CS]) will be listed and summarized by treatment group using shift tables from Visit 1 to Visit 5/Wk12.

6.6.3. Interim analyses

Not applicable

6.7. Handling of dropouts and missing data

Last observation carried forward (LOCF) imputation methodology will be used to impute missing values for the lesions count and the IGA/PGA in the FAS set.

7. Adverse events

7.1. Evaluation of adverse events

An adverse event (AE) is any untoward medical occurrence in a patient to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment (see Regulation (EU) No 536/2014).

Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Worsening of acne, in the treated area, is not to be recorded as an AE unless it results in the discontinuation of the patient from the trial or the use of further treatment for acne.

The observation period for AEs extends from when the patient provides informed consent until the trial is completed. AEs still present after the last patient's scheduled visit will be followed up within 14 days of receiving the last IMP dose by means of a phone call or site visit, as considered appropriate. After that time point the need for additional follow-up of ongoing AEs/SAEs will be discussed between the investigator and the Sponsor. However, in the event of discrepancies, the investigator's criteria will prevail. AEs occurring after the end of the clinical trial must be reported if the investigator considers there is a causal relationship with the investigational product.

The investigator will be responsible for the necessary acute medical treatment of any AEs required during the trial and will ensure that appropriate medical care will be maintained thereafter, if necessary.

All patients experiencing AEs - whether considered related with the use of the IMP or not - will be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report will be supplied, if possible. "Related" means a reasonable possibility that the event may have been caused by the IMP. All findings will be reported on an "adverse event"/ "serious adverse event" page in the case report form.

All AEs, including intercurrent illnesses, will be reported and documented as described below.

AEs are divided into the categories "serious" and "nonserious". This determines the procedure for reporting/documenting the AE (see below).

Surgical procedures themselves are not AEs but therapeutic measures for conditions requiring surgery. The condition for which the surgery is required is an AE, if it occurs or is detected during the trial period. Planned surgical measures permitted by the clinical trial protocol and the condition(s) leading to these measures are not AEs, if the condition(s) was (were) known before the start of treatment with investigational product. In the latter case the condition should be reported as medical history.

7.2. Definition of serious and nonserious adverse events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- results in death or is life-threatening
- results in permanent or significant disability/incapacity
- requires inpatient hospitalization* or prolongation of hospitalization
- results in a congenital abnormality/birth defect.

Medical and scientific judgment will be exercised in classification of other important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

AEs which do not fall into these categories are defined as nonserious.

**Hospitalization solely for the purpose of diagnostic tests, even if related to an AE, elective hospitalization for an intervention which was already planned before the inclusion of the patient in the clinical trial, and admission to a day-care facility may not themselves constitute sufficient grounds to be considered as a SAE.*

7.3. Reporting/documentation of adverse events

7.3.1. Reporting of adverse events

AEs either reported by the patient, or observed by the investigator **must be recorded on the adverse event page of the CRF** and should be described in the following manner:

The **nature** of the event will be described in precise, standard medical terminology (i.e. not necessarily the exact words used by the patient). A specific diagnosis should be stated (e.g., allergic contact dermatitis) if known.

The **intensity** of the AE will be described in terms of mild, moderate or severe according to the investigator's clinical judgment.

- **Mild**: The AE does not interfere in a significant manner with the patient's normal functioning level, but may be an annoyance
- **Moderate**: The AE produces some impairment of functioning but is not hazardous to health, but is uncomfortable and/or an embarrassment
- **Severe**: The AE produces significant impairment of functioning or incapacitation and is a hazard to the patient.

The **duration** of the event will be described by the start date and end date.

The **location** for cutaneous AEs will be described as at or just around the application area (≤2 cm from the application area) or distant (>2 cm from the application area).

The **causal relationship** between the event and the use of the IMP will be described in terms of:

Certain: the AE

- occurs in a plausible time relationship to IMP administration, and cannot be explained by concurrent disease or other drugs or chemicals, and
- follows a clinically plausible response to withdrawal of the IMP, and
- is definitive based on recognized pharmacological or other parameter associated with the IMP, and
- is confirmed by rechallenge procedure, if performed.

Probable: the AE

- follows a reasonable temporal sequence from administration of the IMP, and
- is unlikely to be attributed to a disease or other drug/s, and
- disappears or decreases on withdrawal of the IMP.

Possible: the AE

- follows a reasonable temporal sequence from administration of the IMP, but
- can also be explained by disease or other drugs, and
- information on drug withdrawal may be lacking or unclear.

Unlikely: the AE

- does not follow a reasonable temporal sequence from administration of the IMP, and
- can be reasonably explained by disease or other drug/s, and
- does not follow a known pattern of response to the IMP, and
- does not reappear or worsen upon re-challenge, if performed.

Not related: the AE

- occurs prior to IMP administration.

The **outcome** of the event will be described in terms of:

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown.

It will also be recorded if the study product use is continued, interrupted or discontinued.

Note: Insofar as possible all AEs should be followed-up to determine the final outcome of the event. Details of follow-up should be given (e.g., discontinuation of IMP, if specific treatment is required, if hospitalization is required etc.).

7.3.2. Reporting of serious adverse events

The investigator shall report all SAEs immediately within 24 hours after he becomes aware of the event by fax or e-mail to the Sponsor-PV. General information on the patient (pseudonymized), the randomization number, diagnosis and measures already taken are to be reported. The immediate report shall be followed by detailed written reports, sent within 5 business days. The investigator is obliged to completely document the course of the event and the measures taken, if possible, including the original findings and using the form for SAEs. Additional documentation is carried out on the case report forms.

SAE reports should be emailed/faxed to Sponsor-PV:

QPPV: [redacted] (business hours)

Email: [redacted]

Mobile: [redacted]

FaxToMail: [redacted]

The Sponsor will notify the Investigators of any Suspected Unexpected Serious Adverse Reactions (SUSAR) in accordance with local regulatory requirements and ICH GCP. In accordance with European Union (EU) Regulation 536/2014 of 16 April 2014 on clinical trials on medicinal products for human use (CTR), the Sponsor will collect and report any SUSARs to the Competent Authority/ies (via Eudravigilance for EU Countries). In addition, the Sponsor will inform the relevant Institutional Review Boards (IRBs) or Independent Ethics Committees (IECs) of SUSARs in accordance with local regulatory requirements and ICH GCP, unless locally this is an obligation of the Investigator.

The Sponsor shall ensure that all relevant information about suspected unexpected serious adverse reactions (SUSAR) that are fatal or life-threatening is recorded and reported as soon as possible to the competent authorities in the modalities required by the local regulations, and in any case no later than seven days after knowledge by the Sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

All other SUSARs shall be reported to the competent authorities concerned and to the ethics committee concerned as soon as possible but within a maximum of fifteen days of first knowledge by the Sponsor accordingly.

The PV-Sponsor shall also inform all investigators.

7.4. Urgent safety measures and other relevant safety reporting

Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator will take appropriate urgent safety measures to protect the patients. In addition the sponsor will notify the CAs according to modalities required by local regulations. That notification will be made without undue delay but no later than 7 days from the date the measures have been taken.

7.5. Emergency procedures

Randomization will be supported by an interactive web response system (IWRS) to ensure study medication assignment according to stratification.

The sites will have access to the interactive web response system (IWRS) and will receive instructions how to use the system. Neither the patient nor the investigational staff will know which IMP a patient will be receiving. Where safety reasons may be warranted, and for those study members with appropriate access rights (including all study investigators) unblinding of a patients' treatment allocation will be possible via the IWRS.

7.6. Unblinding

- Unblinding by the request of the investigator should occur only in the event of an AE or SAE for which it is necessary to know the treatment to determine an appropriate course of therapy for the patient. The investigator may only request that the code is opened in the case of an emergency and when the identity of the study medication is crucial for emergency treatment
- The trial blind should not be broken except in case of a medical emergency (where knowledge of the IMP received would affect the treatment of the emergency) or regulatory requirement (e.g., for SUSAR)
- The unblinding of a patient treatment allocation is possible via the IWRS module, it must be performed only when serious safety reasons may be warranted, and only Investigators (Principal Investigator and his/her delegate) can perform this procedure
- If the blind is broken, the date, time, person who broke the blind and the reason must be recorded in the patient's eCRF, and any associated AE report
- If unblinding occurs, the patient must be discontinued from the trial.

7.7. Pregnancies

Pregnancies occurring during a patient's participation in a clinical trial, although not typically considered a SAE, must be notified to the Sponsor-PV within the same timelines as a SAE (within 24 hours after being made aware of the pregnancy) on a pregnancy notification form. The pregnant trial patient should be withdrawn immediately from the trial.

Pregnancy should be emailed/faxed to Sponsor-PV:

QPPV: [redacted] (business hours)

Email: [redacted]

Mobile: [redacted]

FaxToMail: [redacted]

Any pregnancy that occurs in a trial patient should be followed up until outcome. If relevant, the development of the newborn has to be monitored for an appropriate time post-delivery, but only if written consent of parents (or only one parent depending on local regulations) is provided.

8. Discontinuation criteria

8.1. Premature termination of the trial

The sponsor is under obligation to monitor the progress of the clinical trial with regard to safety-relevant developments and, if necessary, initiate the premature termination of the clinical trial. The sponsor will be supported in this responsibility by the DSMB, with particular attention for children. The clinical trial must be terminated prematurely if:

– the benefit-to-risk ratio for the patients changes markedly

– the sponsor or the DSMB considers that the termination of the trial is necessary

– indications arise that the trial patients' safety is no longer guaranteed

– an insufficient recruitment rate makes a successful conclusion of the clinical trial unrealizable/no longer feasible

– the responsible Competent Authority (CA) revokes its approval.

The Sponsor reserves the right to discontinue the trial at any time for clinical or administrative reasons.

If the trial is prematurely terminated or suspended for any reason, the investigator has to notify the patients and to assure appropriate follow-up.

The Sponsor will promptly inform the investigators/institutions, and the regulatory authorities and EC of the termination or suspension and the reason(s) for the termination or suspension by the modalities and timelines according to applicable regulations.

8.2. Premature termination of the trial at one of the trial sites

Both the investigator and the sponsor have the right to terminate the trial at one of the sites.

The clinical trial can be terminated prematurely at his site by the investigator if, for instance unforeseeable circumstances have arisen at the trial site which preclude the continuation of the clinical trial, the investigator considers that the resources for continuation are no longer available, the investigator considers that the continuation of the trial is no longer ethically or medically justifiable.

The sponsor can initiate the exclusion of a site from further participation if, for instance, patient recruitment is inadequate, serious problems arise with regard to the quality of the collected data which cannot be resolved.

Premature termination at one of the trial sites does not automatically mean a termination of the trial for already enrolled trial patients. A separate decision on further treatment must be made for each patient, depending on the overall situation. Adequate further treatment and follow-up of already enrolled trial patients must be ensured. The documentation of already enrolled trial patients will be reviewed for completeness and plausibility. Queries may be raised for further clarification before the site is closed. These queries must be answered properly by the site. The CA(s) and IEC(s) must be duly notified of the site´s closure, including reasons, within the specified period, according to applicable regulations. The trial site concerned will be closed in stages by the CRA when a decision has been made on the further treatment of the patients concerned.

8.3. Discontinuation of trial treatment or trial participation for individual patients

8.3.1 Premature discontinuation of trial treatment

The trial patient can have his/her trial treatment terminated prematurely at any time, without having to give reasons.

Patients will be withdrawn from the treatment if their safety or well-being is at risk. Discontinuation will be made at the discretion of the investigator/Sponsor/DSMB or at the patient's request.

The investigator should contact the Sponsor to discuss the withdrawal of a patient who fulfils the discontinuation criteria, prior to discontinuing a patient from the study, unless in those circumstances where the investigator considers that the patient is at immediate clinical risk.

A patient must be discontinued under the following circumstances:

- Withdrawal of consent
- IMP permanent discontinuation for any reason in one or both treated areas
- Pregnancy
- An AE, including intercurrent illness for which the patient desires to discontinue treatment or the investigator determines that it is in the best interest of the patient to be discontinued
- In case of unexpected laboratory out-of-range values in the blood samples collected at screening, which in the Investigator's opinion may pose the patient at increased risk during participation to the clinical trial the patient will be contacted to discontinue the treatment and will be withdrawn from the study.
- Serious concomitant symptoms (e.g., extensive blisters or erosions) in the facial area as well as a local or generalized allergic reaction to the IMP or procedures
- Lost to follow-up.

A patient may be required to discontinue from the trial at any time for the following reasons:

- The patient's treated and not treated acne worsens and requires alternative or supplemental medication during the trial.
- Occurrence of another dermatosis requiring treatment that interferes with the inclusion criteria
- Subsequent disclosure that the inclusion and exclusion criteria were not fulfilled when the patient was enrolled in the trial if the safety and well-being of the patient might be influenced
- At the discretion of the investigator
- Non-compliant use of IMP or protocol requirements
- Treatment code is broken.

In the case trial treatment of a patient has been stopped prematurely, ETV procedures should be conducted as far as possible. The DSMB will be informed accordingly, and all the relevant information provided.

8.3.2 Premature termination of trial participation

Every patient has the right to refuse further participation in the trial at any point in time and without giving reasons. Nonetheless, efforts should be made to find out the cause and to document it in the eCRF.

In the case trial participation of a patient was stopped prematurely, the documentation should be completed as far as possible under these circumstances, e.g. a final examination and documentation according to the protocol (if possible), a documentation of the premature trial termination on the CRF and in the medical record, giving reasons, appropriate further treatment and follow-up outside the trial should be ensured; inform general practitioner of the termination, if necessary (provided that the patient agrees). The DSMB will be informed accordingly, and all the relevant information provided.

8.4 Arrangements for patients after their participation in the clinical trial ended

A separate open-label long-term extension study is planned. Patients completing the treatment-phase of this trial will be offered the opportunity to participate in this follow-on study (A long-term safety and efficacy study of N-Acetyl-GED-0507-34-LEVO [redacted]%, in patients with acne vulgaris (GEDACNE-LT; EU CT Number: 2023-510342-24-00). Patients will be allowed to join the long-term study until the long-term study enrollment target of 400 patients is reached. In this open label study, all patients will apply the active medication (NAC-GED-0507-34-LEVO gel [redacted]%) OD for up to 9 additional months of treatment (for a total of up to 12 months).

All the patients who will not join the long-term study, once completed or discontinued the present study, will be treated according to the Standard of Care, as per Investigator's judgment.

8.5 Definition of end of trial

The end of the trial is defined as the last visit of the last patient completing the trial (including follow-up visit, for patients who do not roll-over to GEDACNE-LT).

9. Electronic case report form (eCRF), documentation and archiving

- The eCRFs will be provided by [redacted] and will be used for data processing.
- All trial paper documents, in particular the source documents, must be continually filled out. Possible necessary corrections will be made in such a way that the entries to be corrected remain legible. The correction will be initialed and dated. If necessary, a comparison between originals and copies or duplicates will be carried out.
- The documentation (patient's records, investigator site file) will be kept in such a way (patient's records, investigator site file), that it is possible to easily reconstruct the course of the trial at a later date (in accordance with the details given in the clinical trial protocol). All data will be recorded in the eCRF as required by the site staff with appropriate principles.
- Trial data include all findings, measurements, other individual data, [redacted] measuring strips, summaries, etc. in written/paper form. All data stored in electronic data retrieval systems during the trial are to be made available for archiving purposes in hard copies initialed and dated by those trial staff responsible and filed with the patient's records. [redacted] are to be stored on electronic data media for archiving purposes. At the end of the trial the patient data in PDF files will be generated from the eCRF and will be provided to the site for archiving. Other electronic data are not considered originals, but may be archived in addition to the trial documentation.
- Following the specific patient information, consent forms will be signed by the patient and the physician responsible for supplying information and kept in the investigator file. The patient will be given a signed copy of the consent form.
- The use of IMP will be documented by a designated member of the trial staff.
- Electronic data media are to be clearly marked with the trial number/data type/date/hard- and software information (readability).
- All trial documents drawn up or available in paper form (e.g., raw data on data forms, source documents, informal papers, printouts, etc.) are to be uniformly labelled with the trial number/patient number/data type/measurement time point and date/initials of the staff member.
- Any changes from the clinical trial protocol in trial planning or execution after submission of the final version of the clinical trial protocol that have ethical or medical implications are to be documented as a "Substantial amendment to clinical trial protocol," including cause, content, grounds, consequences, date and the signature of the Sponsor and investigator. Such an amendment must be submitted to the appropriate ethics committee(s)/competent authority(ies) for approval. All staff involved in the trial will be informed by the clinical trial manager and investigator. Changes in the clinical trial protocol are only allowed after prior consultation with the person in

charge of the trial at the Sponsor (clinical trial manager). Changes without ethical or medical implications are to be documented as non-substantial amendments or file notes including date and signature of the Sponsor and the responsible person.

- After the conclusion of the trial, the original trial documents (TMF, patient data in PDF files from the eCRF) are to be submitted to the Sponsor according to the agreements made. The investigator file will be archived by the trial site.
- The trial documents will be archived according to applicable law at that time. Currently the statutory period for archiving the documents after conclusion of the trial is at least **25** years, according to EU Regulation 536/2014. According to EU Clinical Trial Regulation (CTR) 536/2014, the statutory period for archiving the records after the conclusion of a trial is at least 25 years.

10. Statutory regulations and GCP

Planning and execution of this clinical trial are patient to globally accepted standards of good clinical practice (as defined in the ICH E6 guideline for good clinical practice, January 1997, the integrated addendum E6(R2), June 2017 and any updates), in agreement with the Declaration of Helsinki and in keeping with CTR (EU) Regulation 536/2014 and local regulations.

10.1 Ethics committee/competent authorities

Before the start of the trial, the clinical trial protocol, informed consent document, and other appropriate documents will be submitted to the appropriate ethics committee/s (EC) and competent authority/ies (CA) according to applicable regulations. The trial must not start before approval has been granted by the EC/CA.

10.2 Insurance

Insurance policy will be provided for each country participating in the study in accordance with local regulations.

Injuries to health and deteriorations of illnesses already in existence which would have occurred or continued to exist even if the patient had not taken part in the clinical trial are excluded from this.

The insurance cover is jeopardized if the patient fails to report immediately to the investigator or responsible physician any injury to health which might have resulted from participation in the clinical trial, or if he/she undergoes any other medical treatment without their consent before the clinical trial has been completely finished - insofar as the individual patient is concerned.

Any injury to health which might have occurred as a result of participation in the clinical trial must be reported by the patient to the Investigator without delay.

10.3 Patient instruction and consent forms

Protection of trial patients and informed consent will follow the rules outlined in CTR (EU) 536/2014, Chapter V. Before enrollment in the clinical trial, the patient and his/her parents/guardian(s) (or only one parent depending on local regulations) will be informed that participation in the clinical trial is voluntary and that he/she may withdraw from the clinical trial at any time without having to give reasons and without penalty or loss of benefits to which the patient is otherwise entitled. Every patient/parents/guardian(s) (or only one parent depending on local regulations) will receive a complete and comprehensive explanation of the significance, nature, extent and possible risks of the trial as well as information on the treatment choices available. Moreover, they will be instructed to contact the study investigators in the circumstances they experience worsening of acne symptoms or any other health issue. To this end, a detailed patient information sheet will be available. In addition, a physician will carry out an oral information session during which the patients and his/her parents/guardian(s) (or only one parent depending on local regulations) will be given sufficient time and opportunity to clarify remaining questions. Two identical forms for written informed consent will be given to the patients for signature. One copy of the signed forms will be archived in the investigator file and the other retained by the patient. The investigator will acknowledge instruction of every patient in accordance with the clinical trial protocol and the existence of a signed consent form.

Both parents/guardian(s) (or only one parent depending on local regulations) will be required to sign informed consent for patients < 18 years (or different age based on local regulations) at the Screening visit. A discussion sheet/assent form is available for children/ adolescent according to their grade of comprehension.

In the case of substantial amendments, the patient and his/her parents (or only one parent depending on local regulations) must be informed with an appropriate revised patient information/consent form. Changed trial procedures can only be carried out if they have been approved by the CA and the leading IEC, and if the patient and his/her parents (or only one parent depending on local regulations) has been appropriately informed and has given their written consent.

Women of childbearing potential should be informed that taking the IMP may involve unknown risks to the fetus if pregnancy were to occur during the trial and agree that in order to participate in the trial they must adhere to the contraception requirement for the duration of the trial. Contraception needs to be classified as “acceptable effective” such as progestogen-only hormonal contraception or condom (see recommendations related to contraception and pregnancy testing in clinical trials, CTCG – See **appendix C**). Sexual abstinence is considered a highly effective method, as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated by the investigator on the basis of patient’s age and usual lifestyle.

10.4 Patient’s reimbursement

No patient’s reimbursement is planned. According to country requirements, patients’ travel costs can be reimbursed.

10.5 Data protection

During the clinical trial medical and personal information (like age, gender) will be collected at the site and documented in the personal file or electronically saved. In addition, important data for the clinical trial will be saved pseudonymized, transferred, and evaluated.

The collected and saved data during the clinical trial will be held for inspection by the supervisory authority or by people charged by the Sponsor who check that the trial is done properly. If needed, the related data will be shared pseudonymized to:

- The Sponsor or Sponsor-appointed party for the purpose of scientific analysis
- The applicant and the authority responsible for marketing authorization, in case that application for marketing authorization is requested
- Sponsor and the responsible competent authority, which will also forward the data to the European database, in case of AEs relate to the IMP
- Parties in Europe and in non-European foreign countries which are affiliates of the Sponsor and as well forwarded to the responsible authorities in charge of marketing authorization by the latter.

Personal and medical data collected during the trial may be moved, stored and used in the European Union (EU) or another country where the Sponsor or those working with the Sponsor are located. Data – including trial results – might be published in Scientific Journals, Conference abstract, etc.

Data protection will be performed in accordance with the new EU regulation (General Data Protection Regulation [GDPR] (EU) 2016/679).

10.6 Data safety and monitoring board (DSMB)

A Data Safety Monitoring Board will be established to undertake periodic risk-benefit assessments during the clinical trial; the composition, functions and activity of the DSMB will be regulated by a specific written charter which will be finalized before the establishment of the DSMB which will be active before the start of recruitment.

10.7 Quality control (Trial monitoring)

Quality management procedures will be applied to all steps of the trial e.g., planning, conduct, analysis and reporting.

In each country, local clinical research associates (CRAs) will monitor the trial progress according to the Monitoring Plan during the conduct of the trial until the last case report forms have been completed and all queries have been resolved.

The trial and site activities will be monitored according to the ICH-GCP guidelines for:

- Protocol adherence (trial follows the currently approved protocol and any other study agreements)

- Quality of data (data are authentic, accurate, and complete)
- Drug accountability
- Protection of safety and rights of patients
- Compliance with regulatory requirements (trial is conducted in accordance with GCP, and all applicable regulatory requirements)
- Adequacy of the facilities (unchanged high qualification of the site and site staff).

The investigators and the head of the medical institutions (where applicable) agree to allow the monitor direct access to all relevant documents.

10.8 Quality assurance

Investigators will be trained on the dermatological scoring systems used in this study during the investigator meeting; where Investigators will not be able to attend, they will be required to attend a 'webinar' training. A final test will be performed by the investigators to assess if the training was conducted successfully; only the investigator reaching the prefixed minimum score will be allowed to conduct the dermatological evaluations (otherwise, re-trainings and re-test should be conducted). As part of the Investigator meeting, training will also be undertaken on GCP requirements, SAE reporting, e-CRF completion, IWRS.

To ensure compliance with GCP and all applicable regulatory requirements Sponsor may conduct a quality assurance assessment and/or audit of the site records at any time during and/or after completion of the trial.

Independent of any Sponsor audit the regulatory agencies may conduct a regulatory inspection at any time during and/or after completion of the trial.

In the event of an assessment, audit or inspection, the investigators (and institutions) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the trial, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.9 Risk management

According to ICH-GCP risk management has to be applied to all processes of a clinical trial/investigation. This trial's risk is performed by general risk evaluation and individual risk evaluation using a risk register. Procedural risks and risks due to IMP are described in Section 0. A monitoring plan describes the on-site monitoring activities.

A risk register and analysis log are kept and updated in an ongoing manner. Among others, risks related to the primary endpoint and SAEs have been identified and assessed for likelihood and impact in this trial.

Mitigations are described in detail in the risk register and analysis log. Patient compliance is reviewed on a regular basis as described in Section 5.4.88. SAE reporting follows the procedures described in Section 0.

10.10 Handling of investigational products

The investigators or their representatives confirm receipt of the IMPs in writing and will only use them within the framework of this clinical trial and in accordance with the existing clinical trial protocol. IMP will only be supplied to patients that have signed ICF and who are eligible to participate in the trial.

Delivery, consumption and return must be completely documented.

At the end of the trial, all containers opened, together with remaining contents and unopened containers will be returned to by the patients to the sites. A written explanation must be provided for any missing containers/IMP. The IMPs will be stored in a safe place according to the manufacturer's instructions for storage.

Deviations in storage requirements should be reported to the responsible CRAs, and to the Sponsor and may require that the IMP is quarantined during the deviation's review.

10.11 Confidentiality, use of information and publication

All information related to this trial that is supplied by the Sponsor and not previously published is considered confidential information. This information includes but is not limited to data, materials (protocol, eCRFs), equipment, experience (whether of a scientific, technical, engineering, operational, or commercial nature), designs, specifications, know-how, product uses, processes, formulae, costs, financial data, marketing plans and direct selling systems, customer lists, and technical and commercial information relating to customers or business projections used by the Sponsor in its business. Any data, inventions, or discoveries collected or developed as a result of this trial are considered confidential. This confidential information shall remain the sole property of the Sponsor, shall not be disclosed to any unauthorized person or used in any unauthorized manner without written consent of the Sponsor, and shall not be used except in the performance of the trial.

The information developed during the course of this trial is also considered confidential and will be used by the Sponsor in the development of the study medication. The information may be disclosed as deemed necessary by the Sponsor. To allow the use of the information derived from this trial, the investigator is obliged to provide the Sponsor with complete test results and all data developed in the trial. The information obtained during this trial may be made available to other investigators who are conducting similar trials.

The investigator shall not make any publication related to this trial without the express written permission of the Sponsor. If the investigator wants to publish or present the results of this trial, he or she agrees to provide the Sponsor with an abstract, manuscript, and/or presentation for review 60 days prior to submission for publication or presentation. The Sponsor retains the right to delete confidential information and to object to suggested publication/presentation and/or its timing (at the Sponsor's sole discretion).

10.12 Responsibilities of the Sponsor/CRO

The specific responsibilities of the CRO are detailed in the relevant study agreement. In general responsibilities of the Sponsor/CRO include:

- select qualified Investigators
- provide each Investigator with an Investigator's Brochure which is updated annually or when significant information becomes available
- submit notification/application to the relevant authorities when appropriate
- prepare and submit to the IEC/AC all the pertinent documentation needed according to current regulation
- implement and maintain quality assurance and quality control system with written SOPs to ensure the trials are conducted and data are generated, documented (recorded), and reported in compliance with the CTP, GCPs, and the applicable regulatory requirement(s)
- promptly act in case of non-compliance by an Investigator or by members of the Sponsor’s staff
- provide audit certificate when required by applicable law or regulation
- ensure that the investigational product and placebo, is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP, is coded and labelled in a manner that protects blinding, if applicable, and labelling complies with applicable regulatory requirement(s)
- supply the Investigator(s)/institution(s) with the investigational product(s)
- appoint appropriately trained Monitor(s)
- report all SAE promptly in accordance with local or international regulations and take appropriate measures necessary to safeguard trial patients
- promptly report to IEC and to Regulatory Authorities all adverse drug reactions (ADRs) that are both serious and unexpected, according to current regulations
- promptly notify all concerned Investigator(s)/institution(s) and the regulatory authority(ies) of findings that could affect adversely the safety of patients, impact the conduct of the trial, or alter the IEC favorable opinion to continue the trial
- whether the trial is completed or prematurely terminated, prepare or ensure preparation of a comprehensive final report for regulatory purposes
- prepare safety up-dates, if required; long-term trials may require an annual report to authorities
- secure agreement from all involved parties to ensure direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by domestic and foreign regulatory authorities

- provide adequate treatment/compensation for patients in the event of trial-related injury in accordance with the applicable regulatory requirements
- provide indemnity for the Investigator in accordance with this CTP
- terminate Investigator's/institution's participation in case of non-compliance
- promptly inform the Investigators/Institutions, the regulatory authority(ies) and the independent ethics committee (IEC) of premature termination or suspension of a trial and the reason (s) for the termination or suspension
- designate appropriately qualified medical personnel who will be readily available to advise on trial related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose
- Notify serious breaches to Competent Authorities without undue delay and at the latest within 7 calendar days of the sponsor becoming aware of the serious breach.

10.13 Responsibilities of the Clinical Trial Monitor

The Monitor is the principal communication link between the Sponsor/CRO and the Investigator. Responsibilities of the Clinical Trial Monitor include:

- explain, interpret and assure the Investigator(s) understanding of all applicable Sponsor's SOPs and regulations concerning the clinical evaluation of an IMP, and assure an understanding of the CTP, the reporting requirements, responsibilities and validity of data
- work according to predetermined SOPs, visit the Investigator periodically to verify adherence to the CTP and assure that all data are correctly and completely recorded. In order to perform his/her role effectively, the Monitor must be given access to primary patient data which support data on the CRF for the study, i.e., hospital and general practice charts, appointment books, original laboratory records, etc.
- ensure that the trial site has adequate space, facilities, equipment, staff and that an adequate number of trial patients is likely to be available for the duration of the trial
- ensure that all staff assisting the investigator in the trial have been adequately informed about details of the trial verifying that the investigator follows the approved CTP and approved amendment(s), if any, and that they are performing the specified trial functions in accordance with CTP and any other written agreement between the Sponsor/CRO and the Investigator/Institution, and have not delegated these functions to unauthorized individuals
- ensure that Informed Consent has been obtained and recorded from all the patients prior to their participation to the trial
- provide communication between the Investigator and Sponsor/CRO promptly and at any time

- aid the Investigator and at the same time the Sponsor/CRO, in the maintenance of complete, legible, well-organized and easily retrievable data
- inform the Investigator of any CRF entry error, omission or illegibility. The monitor should also ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialed by the Investigator
- check that the storage, dispensing, administering, returning of IMPs are safe, handled in accordance with local regulations as well as study requirements and Sponsor/CRO SOP. All those activities have to be adequately documented
- assist the Investigator in any notification/application procedure
- assist the Investigator in reporting the trial data and results to the Sponsor/CRO
- submit to the Sponsor/CRO a written monitoring report of site visits and written documentation of all relevant telephone calls, letters and other contacts with the Investigator
- verify that the Investigator is maintaining the essential documents (Investigator's file).

10.14 Responsibilities of the Investigator

Responsibilities of the Investigator include:

- be thoroughly familiar with the properties of the IMP(s) as described in the IB
- ensure a network of proper interaction with other department of the institution in order to guarantee the safety of the patients and the effectiveness of the study
- ensure that he/she has sufficient time to conduct and complete the trial, has adequate staff and appropriate facilities and that other trials do not divert essential patients or facilities away from the trial in hand
- provide retrospective data on numbers of patients who satisfied the proposed entrance criteria during preceding time periods, in order to assure an adequate recruitment rate for the trial
- submit an up-to-date curriculum vitae and other credentials to the Sponsor/CRO and, where required, to relevant authorities
- agree and sign the CTP with the Sponsor confirming that he/she will work according to the CTP and GCPs and accepting the role of the Monitor and the need for control procedures
- nominate (if appropriate) a local study coordinator or co-Investigator(s) to assist in the management of the trial
- follow the submission of notification/application to relevant bodies including local hospital management jointly with the Sponsor/CRO where appropriate

- provide information to all staff members involved with the trial
- fully inform trial patients about the Clinical Trial and obtain their informed consent
- certify that all IMP(s) have been correctly delivered, stored, and safely handled, and that reconciliation of stock can be justified. Account must be given of any discrepancies. Certificates of delivery and returns must be signed
- follow the trial's randomization code procedure if applicable
- collect, record, and report data properly
- notify the Sponsor/CRO immediately in the case of SAE and take appropriate measures to safeguard patients
- promptly report to the Sponsor changes increasing the risk to patients and /or affecting significantly the conduct of the trial and new information that may affect adversely the safety of the patients or the conduct of the trial
- agree with and sign the Final Report of the trial, if requested
- ensure that the confidentiality of all information about patients is respected by all persons involved as well as the information supplied by the Sponsor
- make all data available for direct access to the Sponsor/CRO personnel (e.g. Monitor, auditor), IEC or relevant Authorities for validation/audit/review/inspection purposes
- ensure that medical records are clearly marked to show that the patient is participating in a Clinical Trial
- inform the family doctor, with patient’s consent, about patient’s participation in the trial
- provide a list of appropriately qualified persons (Study Personnel Form) to whom the Investigator has delegated some duties relevant to the conduct of the trial, together with their signatures and initials
- immediately report any events that might meet the definition of a serious breach to the contact point designated by the sponsor.

11. Literature

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12. Appendix A

Appendix A

Trial flow chart

ACTIVITIES[15]	Screening[1]	Baseline/ First Dose	Phone Contact (for 9 to < 12 years old)[9]	Treatment and Evaluations		Phone Contact (for 9 to < 12 years old)[9]	End of Treatment (EoT)[12]	Follow-up or ETV after EoT (Phone contact)[13]	ETV (WithDrawal)
Visit – Week	V1	V2	T2/Wk2	V3/Wk4	V4/Wk8	T10/Wk10	V5/Wk12	V6/Wk14	
	Day -14/1	Day 1	Day 15 (±2)	Day 29 (±2)	Day 57 (±2)	Day 71 (±2)	Day 85 (+3)	Day99(+2)	ANY TIMES
Informed consent / Informed assent signature (if applicable)	X								
Demography	X								
Medical history	X								
Physical examination	X	X[5]		X	X		X		X
Prior medications	X								
Vital signs	X	X[5]		X	X		X		X
Body weight and height	X	X[5]					X[18]		
Blood pregnancy test, if applicable[2]	X						X		X
Laboratory tests[3]	X						X	X[3]	X
Lesion count, separately for inflammatory and non- inflammatory lesions	X	X[5]		X	X		X		X
Investigator's Global Assessment (IGA) -FACE	X	X[5]		X	X		X		X
Physician Global Assessment (PGA) – TRUNK[14]	X	X[5]		X[14]	X[14]		X[14]		X[14]
Eligibility evaluation	X	X[5]							
Assessment of local tolerability- Application site signs/symptoms		X[16]	X	X	X	X	X		X
Assessment of overall application site irritation		X[17]					X		X
Enrollment and randomization		X							
Study medication supply delivery[4]		X			X				
Study medication application at site [6]		X							
Study medication supply return and accountability					X		X		X
Diary dispensing		X		X	X				
Diary return				X	X		X		X
Adverse events monitoring[7]	X	X	X	X	X	X	X	X	X
Concomitant medication intake monitoring	X	X	X	X	X	X	X	X	X
Patient's compliance assessment by diary check (or questions during phone contact)			X	X	X	X	X		X
DLQI or C-DLQI[8]		X					X		X
[redacted]		X					X		X
[redacted]		X					X		X

1. *Screening procedure should be completed within 14 days*
2. *All sexually active women of childbearing potential. For pre-menstrual patients re-confirm pre-menses status at every visit and in case of status change collect information on contraceptive method and perform a UPT. Additional UPTs may be performed at the Investigator's discretion. For the ones who begin menses after the Screening visit, pregnancy tests will be performed at the visit where there was a change in status and according to the schedule for females of childbearing potential. Additional pregnancy tests may be performed at the Investigator's discretion*
3. *Safety tests will be conducted at screening and EoT: CBC/diff, glycemia, [redacted] transaminases, cholesterol, triglycerides, [redacted]. If clinically significant abnormal values are detected at EoT visit, patient will be asked to visit the site at V6 to repeat the test*
4. *At Visits 2 and 4, the patients will be given a patient's box with the study medication supply for the daily applications at home*
5. *These assessments are performed also at V2, and considered as baseline assessments, only if screening (V1) is performed > 3 days before V2, Day 1. If V1 is performed ≤ 3 days before V2 the assessments will not be repeated at V2 and will be considered as baseline assessments. Assessment of local tolerability has to be performed before IMP application. Height not to be measured at V2.*
6. *The first dose will be applied by the patient under supervision of study staff at the clinical site. The following doses will be self-applied OD by the patient at home according to the instructions received at the clinical site. The last IMP dose will be applied by the patient the day before the EoT visit*
7. *AEs monitored starting at the screening visit, immediately after informed consent, up to the final visit/EoT*
8. *Dermatology Life Quality Index (DLQI) (age 17 and older) / Children's Dermatology Life Quality Index (C-DLQI) (for 16 years and younger). If the patient completed a C-DLQI at the Baseline visit, a C-DLQI should be completed at the Week 12/ET Visit, regardless of the patient's age at the Week 12/ET visit. Questionnaires must be completed prior to any Investigator assessments to not impact the patient's answers to the quality of life*
9. *For patients aged 9 to < 12 only, a phone contact will be kept at Wk2 and Wk10 (with the presence of parents/guardian(s) who gave consent or only one parent depending on local regulations), to check concomitant medications/therapies and AEs and assessment of local tolerability by local signs/symptoms (the patient will also be questioned if he/she experienced any of them in the last 24 hours). Patient will also be questioned on compliance to study medication. The outcome of the contact is entered in the eCRF*
10. [redacted].
11. [redacted]
12. *Patients who complete 12 weeks of treatment will be eligible to continue treatment with NAC-GED-0507-34-Levo [redacted]% gel in a separate open-label long-term study (GEDACNE-LT)*
13. *V6 will not be performed for patients who continue the open-label long-term treatment with NAC- GED-0507-34-Levo [redacted]% gel in GEDACNE-LT study*
14. *After baseline visit, the PGA will be evaluated only if the trunk is treated (PGA score should be 2 or 3 at screening/baseline visit as per inclusion criteria).*
15. *All study visits for school age children should be planned outside of school hours*
16. *At baseline, the presence or absence of signs/symptoms in the past 14 days will be also collected*
17. *Presence or absence of overall application site irritation at the baseline visit will be collected.*
18. *Height to be measured for minors only*

EoT = End of treatment
ETV = Early termination visit (WithDrawal)

13. Appendix B

Appendix B

Investigator statement template

Investigator signature

Title	A phase III study to assess efficacy and safety of N-Acetyl-GED-0507-34-LEVO gel [redacted]%, applied once daily for 12 weeks in patients with acne vulgaris (GEDACNE-1)
Protocol no:	NAC-GED-0507-ACN-01-23-A
Protocol version:	Final V2.0 (UK only)
Protocol date:	24JAN2025

I confirm with my signature

- that I agree to conduct the trial in accordance with regulations as laid down in this clinical trial protocol/amendment, in the currently valid revision of the Declaration of Helsinki and in the ICH-GCP guideline and applicable national laws and regulations. Changes to this protocol require written agreement of both investigator and Sponsor
- that I have acquainted myself with the results of the pharmacological and toxicological trials of the investigational product and the results of other trials as described in the investigator's brochure, or other appropriate information.

I agree:

- to provide direct access to source data/documents (source document verification)
- to permit trial-related monitoring, audits, ethics committees (ECs), and regulatory inspections
- to use the trial material, including medication only as specified in this protocol
- to report to the Sponsor's Pharmacovigilance (PV) department any serious adverse event (SAE), whether considered treatment related or not.

.....
location, date

.....
signature

14. Appendix C

Appendix C

Women of childbearing potential definition and birth control method definition

Women of Childbearing Potential and Birth control method definition

According to Recommendations related to contraception and pregnancy testing in clinical trials (CTCG, March, 2024), a woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.

Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Definitions of *"acceptable"* and *"highly effective"* birth control methods are schemed below:

Acceptable birth control methods (with a failure rate of more than 1% per year):
• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action. • Male or female condom with or without spermicide. • Cap, diaphragm or sponge with spermicide. Combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier method).
Highly Effective birth control methods that result in a failure rate of less than 1% per year
• Hormonal contraception that stops ovulation (oral, intravaginal, through the skin, injectable, implantable) • Intrauterine hormone-releasing or copper intrauterine device • Bilateral tubal occlusion • Monogamous relationship with a vasectomized partner (the partner must have received medical confirmation that the procedure was successful) • Abstinence or absence of sexual intercourse with men (when this is in line with the preferred and usual lifestyle of the participants)

15. Appendix D

Appendix D

Unblinding procedures

Unblinding procedures

Unblinding by the request of the investigator should occur only in the event of an AE or SAE for which it is necessary to know the treatment to determine an appropriate course of therapy for the patient. The investigator may only request that the code is opened in the case of an emergency and when the identity of the study medication is crucial for emergency treatment.

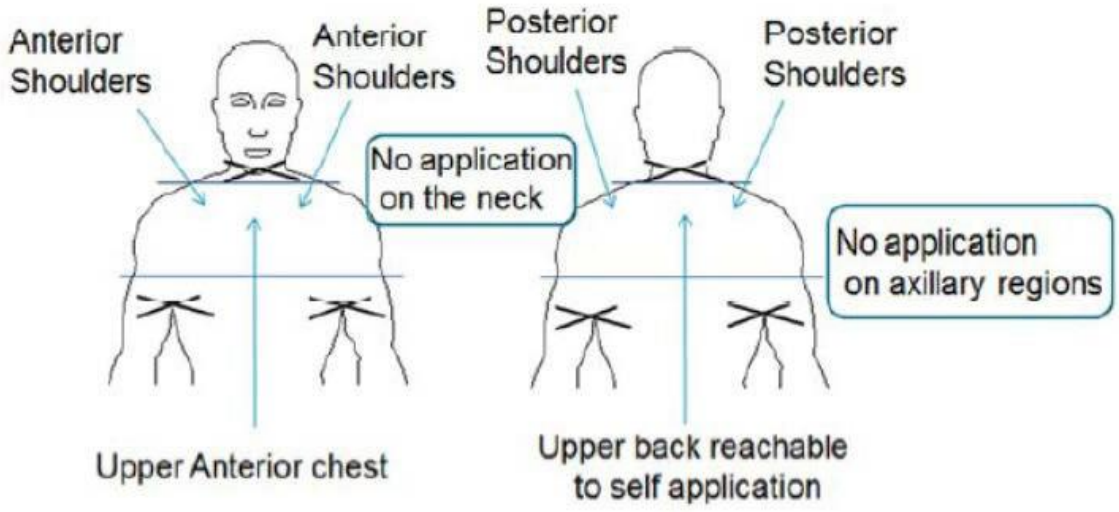
The trial blind should not be broken except in case of a medical emergency (where knowledge of the IMP received would affect the treatment of the emergency) or regulatory requirement (e.g., for SUSAR).

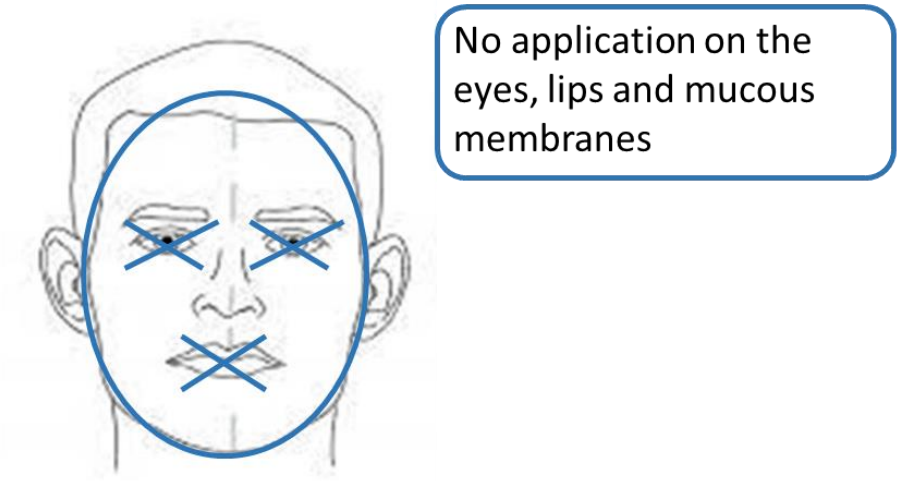
If unblinding occurs, the patient must be discontinued from the trial.

16. Appendix E

Appendix E

IMP Application


Anterior Shoulders
Anterior Shoulders
Posterior Shoulders
Posterior Shoulders
No application on the neck
No application on axillary regions
Upper Anterior chest
Upper back reachable to self application


No application on the eyes, lips and mucous membranes

17. Appendix F

Appendix F

DLQI and c-DLQI

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date:
Name: Score:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	❒ ❒	Not relevant ❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒

Please check you have answered EVERY question. Thank you.

CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX

Hospital No
Name: Diagnosis: CDLQI
Age: SCORE:
Address: Date:

The aim of this questionnaire is to measure how much your skin problem has affected you OVER THE LAST WEEK. Please tick ✓ one box for each question.

1.	Over the last week, how **itchy**, **"scratchy"**, **sore** or **painful** has your skin been?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
2.	Over the last week, how **embarrassed** or **self conscious**, **upset** or **sad** have you been because of your skin?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
3.	Over the last week, how much has your skin affected your **friendships**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
4.	Over the last week, how much have you changed or worn **different** or **special clothes/shoes** because of your skin?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
5.	Over the last week, how much has your skin trouble affected **going out**, **playing**, or **doing hobbies**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
6.	Over the last week, how much have you avoided **swimming** or **other sports** because of your skin trouble?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
7.	Last week, was it **school time?** **OR** was it **holiday time?**	**If school time**: Over the last week, how much did your skin problem affect your **school work**? **If holiday time**: How much over the last week, has your skin problem interfered with your enjoyment of the **holiday**?	Prevented school ☐ Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐ Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐
8.	Over the last week, how much trouble have you had because of your skin with other people **calling you names**, **teasing**, **bullying**, **asking questions** or **avoiding you**?		Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐
9.	Over the last week, how much has your **sleep** been affected by your skin problem?		Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been?		Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐

Please check that you have answered EVERY question. Thank you.

18. Appendix G

Appendix G

FITZPATRICK SKIN TYPE

FITZPATRICK SKIN TYPE

Type	Features of unexposed skin	Tanning and burning
1	very pale white skin, often with green or blue eyes and fair or red hair	burns without tanning
2	white skin, often with blue eyes	burns and does not tan easily
3	fair skin with brown eyes and brown hair	burns first then tans
4	light brown skin, dark eyes, and dark hair	burns a little and tans easily
5	brown skin, dark eyes, and dark hair	easily tans to a darker color and rarely burns
6	dark brown or black skin, dark eyes, and dark hair	never burns but tans darker