Consolidated Clinical Trial Protocol

Explorative trial evaluating the efficacy, tolerability and safety of LEO 43204 applied in a split-face (left/right) topical design in adults with moderate to severe acne

Phase 2a, single-centre, prospective, randomised, vehicle-controlled, double-blind, split-face (left/right) design trial

ICH GCP statement: The clinical trial will be conducted in compliance with the clinical trial protocol, GCP and the applicable regulatory requirement(s).

LEO Pharma A/S	Trial ID:	**EXP-1223**
	Date:	**15-Sep-2016**
	Version:	**5.0**

1 Clinical Trial Protocol Statement

1.1 Approval Statement LEO Pharma A/S

The following persons have approved this clinical trial protocol by using electronic signatures as presented on the last page of this document:

PPD

Biostatistics Lead, Global Clinical Operations

PPD

Head of Translational Medicine

1.2 Approval Statement International Coordinating Investigator

The international coordinating investigator approves the clinical trial protocol and consolidated clinical trial protocol(s) comprising any subsequent amendment(s) by manually signing the International Coordinating Investigator Clinical Trial Protocol Approval Form, which is a separate document adjoined to this document.

The following person has approved this clinical trial protocol:

Hala Koudsi, MD

International Coordinating Investigator

Table of Contents

2 Trial Identification

IND number: 118384

CT.gov number: NCT02575950

3 Introduction and Rationale

3.1 Acne Vulgaris Introduction

Acne vulgaris, commonly referred to as acne, is a very common chronic inflammatory skin disease affecting approximately 80- 90% (50 million) of adolescents and young adults in the United States (1, 2, 3). Increased production of sebum and colonization of the bacteria *Propionibacterium acnes* (*P. acnes*) in the sebaceous glands are key factors in the development of acne vulgaris. Retention of sebum results in formation of comedones which may become inflamed and develop into pustules or deep-seated nodules in more severe cases. Moderate to severe acne vulgaris can reduce the quality of life and self-esteem and result in disfiguring persistent scarring and dyspigmentation (4, 5). Current available topical and systemic treatment options for acne vulgaris often require therapy for 3 to 6 months and are often associated with some degree of local side effects during the treatment period (e.g., dryness, skin irritation, scaling). This often reduces compliance, and consequently leads to disease relapse and disappointing treatment outcomes.

3.2 Experience with Investigational Product

LEO 43204 gel is a novel ingenol derivative being developed for field treatment of actinic keratosis (AKs) on face, balding scalp and treatment areas of up to 250 cm^2 (40 in^2) on the chest. LEO 43204 gel is in phase 3 of its clinical development program.

Please refer to the Investigator's Brochure of 43204 gel in Actinic Keratosis Edition 4 or any updates hereof for all relevant non-clinical and clinical information. Refer to the Investigator’s Brochure Addendum for Acne Vulgaris for additional information pertaining to this exploratory trial.

3.3 Trial Rationale

There is an unmet medical need for safe acne vulgaris treatments of short duration with good efficacy and the ability to improve the patient’s disease related quality of life.

The clinical rationale for investigating the efficacy of LEO 43204 gel on acne vulgaris is based on two case reports indicating a beneficial effect of ingenol mebutate on acne vulgaris, and the hypothesis that the effect of ingenol mebutate gel on the sebaceous gland (6) may be

similar to the effects observed for photodynamic therapy (PDT) in combination with aminolaevulinic acid (ALA) in the treatment of acne vulgaris (7).

The first case indicating beneficial effects of ingenol mebutate involved a female employee at an ingenol mebutate manufacturing site suffering from acne. The employee accidentally became exposed to a large dose of dry-powder ingenol mebutate in the face. Following complete resolution of a severe facial skin response, the pre-existing acne vulgaris also cleared. In the second case, a female laboratory technician at an academic research laboratory was accidentally exposed in the face to an ingenol containing extract from the *E. peplus* plant. She also recovered completely from a severe skin response and later reported that her pre-existing acne vulgaris had cleared.

The scientific rationale for investigating LEO 43204 gel as a treatment for acne vulgaris is based on the observation that ingenol mebutate has a stronger local skin response (LSR) around the hair follicles (6), suggesting accentuated cell death and inflammation in the pilosebaceous unit (refer to the Investigator's Brochure of 43204 gel in Actinic Keratosis Edition 4 or any updates hereof for details on mode of action). This could reduce the size of the sebaceous gland and possibly have a beneficial effect on acne vulgaris similar to the effect of PDT with ALA (7).

In ALA-PDT the ALA serves as a precursor for the photosensitizer protoporphyrin IX. This molecule has significant phototoxic effects in the epidermis and pilosebaceous unit when irradiated with the appropriate wavelength of light (8, 9). Histologically, ALA-PDT therapy induces severe cell damage and cell death in the sebaceous gland epithelium resulting in a reduced gland size and sebum production (7). Studies have shown improvement of acne vulgaris disease severity for up to 20 weeks after therapy (7,10, 11). Clinically the ALA-PDT therapy is associated with transient erythema, crusting edema, temporary changes in pigmentation and pustular eruptions (11) similar to the local skin responses observed after treatment with ingenol mebutate.

Based on this, we hypothesize that the inflammation and local skin response induced by LEO 43204 gel may improve acne vulgaris by reducing 1) the size of the sebaceous glands, 2) the sebum production and 3) the colonisation of *P.acnes*.

The objective of this explorative trial is to evaluate efficacy, safety and tolerability of LEO 43204 gel in the treatment of moderate to severe acne vulgaris. Efficacy will be evaluated by an acne lesion count and investigator’s global assessment (IGA) of the treatment areas. In addition, the effects of LEO 43204 gel on inflammatory biomarkers, microbiome profile and cosmetic skin appearance will be investigated.

3.3.1 Dose Selection

LEO 43204 gel has not previously been administered to subjects between 18 and 35 years of age with acne vulgaris. Previous clinical trials with field treatment for actinic keratosis (AK) in the face included only subjects over 40 years of age and Fitzpatrick skin type I-III. These trials have shown good tolerability and safety of LEO 43204 gel 0.018% when used in a 3-day once daily dosing regimen (refer to Investigator's Brochure of LEO 43204 gel in Actinic Keratosis, Edition 4 or any updates hereof) and is currently under development for AK. In this clinical trial the same strength of LEO 43204 gel 0.018% is selected for once daily treatment for up to three consecutive days.

It is unknown whether the subjects with acne in this trial will have a different safety profile and LSR profile compared to the subjects investigated in the AK clinical trials. To ensure the safety of the subjects with acne vulgaris in this trial, additional safety measures (described in section 6.1 and section 12) have been adapted to ensure early detection of unexpected severe adverse events (AEs), LSRs and poor tolerability.

The safety and tolerability data will be reviewed by a Safety Review Committee (SRC) during the trial (section 12).

3.4 Ethical Consideration Statement

Subjects under the age of 18 or vulnerable subjects incapable of giving informed consent will not be enrolled in this clinical trial. Furthermore pregnant, breastfeeding women or women planning on becoming pregnant during the trial will not be enrolled. Women of child bearing potential have to agree to use a highly effective method of contraception to prevent pregnancy during the clinical trial and until end of trial. In addition, all female subjects of child bearing potential will have a pregnancy test performed before, during and at End of Trial to ensure that no pregnant women are exposed to LEO 43204 gel. Female partners of male subjects are not required to use contraception as described in section 7.3.6 of the Investigator's Brochure of LEO 43204 gel in Actinic Keratosis, Edition 4 or any updates hereof.

Only adult subjects with acne vulgaris who are otherwise healthy will be enrolled in this trial investigating efficacy and safety of LEO 43204 gel.

Prior to any trial activities subjects must have signed the informed consent form (refer to section 17.3). The informed consent will highlight that LSR and treatment related AEs (such as pruritus and pain) are common events. In addition, the subjects will be informed that both the acne vulgaris disease severity and skin appearance (including texture, pigmentation, scars)

may appear different when comparing the left and right side of the face after end of trial. This difference may persist for several months or longer.

As noted in section 3.3.1, all safety data on LEO 43204 gel stems from studies in subjects older than 40 years of age, with Fitzpatrick skin type I-III and the diagnosis of AK. In these subjects clinical findings following treatment are localised application site reactions (e.g., pruritus, pain, irritation) and local skin responses (LSRs), particularly erythema, oedema, flaking and scaling. These LSRs are transient and typically resolve without sequelae within 2-4 weeks of application. Furthermore, these local events do not have a tendency to become infected or cause scarring and generally do not cause pain beyond the first few days. No data involving young adults or individuals with pre-existing inflammation in the treatment area are available and it is thus unknown whether the LSRs will be different in this trial.

To limit the number of exposed subjects, this early phase explorative clinical trial is designed as a left/right comparison within-subject. This design requires fewer subjects to achieve statistical power to detect a difference between treatments than a trial with comparison of treatments between-subjects. The vehicle gel control serves as an external validity check of the trial results and shows what an agent-free therapy contributes in terms of efficacy and safety.

Moreover, to mitigate the risk of unexpected severe LSRs and AEs, the trial includes a small treatment escalation cohort with continuous safety review (refer to section 6.1), and 3 subsequently treated cohorts separated by interim analysis of safety and tolerability data by a Safety Review Committee (refer to section 12).

Subjects participating in this trial will be under the supervision of an experienced investigator during the course of the trial. The subject's safety will be monitored daily (Day 1 to Day 4) and closely during the follow up-period until 12 weeks after treatment.

Lastly only subjects with skin type I-III will be included due to lack of safety data from subjects with darker skin types and a potential higher risk of post-inflammatory hyperpigmentation.

There are no invasive procedures in this clinical trial.

All randomized subjects in Cohort 2, 3 and 4 will have biomarkers and microbiome samples collected by a tape-lifting procedure and standard bacterial swab, respectively (Appendix 2). This will be done at visit 2, 7, 8, 9 and 10. Both procedures may cause minor transient redness (less than 1 hour) and without long-term risks.

All subjects in cohort 3 and 4 will have photographs taken at screening for documentation of eligibility.

All randomized subjects in cohort 1, 2 and 3 will have digital photographs taken at Day 1 and all subsequent visits (Appendix 3). These are used for documentation.

The FDA guidance for developing drugs for acne vulgaris (12) recommends 12 weeks of treatment and 4 weeks of follow-up after end of treatment. These recommendations are not considered relevant for this trial in which the treatment period is only once daily for up to 3 days due to the mode of action of LEO 43204. The efficacy endpoints (total lesion count and investigator global assessment) are chosen in accordance with the FDA guideline, but evaluated at follow-up after end of treatment at Week 2, 4, 8 and 12. The primary endpoint at Week 12 is chosen based on the expectation of efficacy lasting several months.

In conclusion, it is considered safe and without unacceptable risks to test topical application of LEO 43204 gel, 0.018%, once daily, for one, two or three consecutive days on the cheeks in the face of adults (18 to 35 years inclusive) with Fitzpatrick skin types I-III to investigate whether LEO 43204 gel may be a new treatment strategy for acne vulgaris.

4 Trial Objectives

4.1 Primary Objective

To assess the efficacy of treatment with LEO 43204 gel and vehicle gel on acne vulgaris disease severity 12 weeks after end of treatment.

Treatment is defined as once daily application of LEO 43204 gel and vehicle gel for up to 3 days.

4.2 Secondary Objectives

To assess the safety and tolerability of treatment with LEO 43204 gel and vehicle gel 12 weeks after end of treatment.

4.3 Explorative Objectives

To evaluate the time course of clinical efficacy of LEO 43204 gel and vehicle gel and, based on this, define a time point for evaluation of the effect on expression of inflammatory biomarkers and skin microbiome.

To assess subject-reported outcomes using the acne-specific quality of life questionnaire (Acne-QoL, (13, 14)) and the treatment satisfaction questionnaire for medication (TSQM II, (15)).

To assess the effect of LEO 43204 gel and vehicle gel on subject-evaluated change in cosmetic skin appearance using a Subject Global Cosmetic Score questionnaire.

5 Trial Endpoints

5.1 Primary Endpoint

Total lesion count (inflammatory and non-inflammatory) in the treatment area for LEO 43204 gel and vehicle gel at Week 12.

5.2 Secondary Endpoints

- Inflammatory lesion count in the treatment area for LEO 43204 gel and vehicle gel at Week 12.
- Non-inflammatory lesion count in the treatment area for LEO 43204 gel and vehicle gel at Week 12.
- Investigator's Global Assessment of the treatment area for LEO 43204 gel and vehicle gel at Week 12.
- Composite and component LSR score at all visits
- Occurrence of unacceptable LSR scores or unacceptable safety and tolerability events at all visits (as described in section 12)

5.3 Exploratory Endpoints

- Total lesion count in the treatment area at Day 1 and Week 2, 4, 8 and 12 (time course).
- Inflammatory lesion count in the treatment area at Day 1 and Week 2, 4, 8 and 12 (time course).
- Non-inflammatory lesion count in the treatment area at Day 1 and Week 2, 4, 8 and 12 (time course).
- Investigator's Global Assessment of the treatment area at Day 1 and Week 2, 4, 8 and 12 (time course).

- Treatment success, i.e. at least a two grade improvement of IGA at week 12 compared to baseline
- Inflammatory cytokine expression at time points defined after evaluation of the clinical data.
- Microbiome profile at time points defined after evaluation of the clinical data.
- Subject evaluation of Acne-QoL at screening and Day 1 and Week 12.
- Subject evaluation of TSQM II at Week 12.
- Subject Global Cosmetic Score at Week 12 (Appendix 5).

6 Trial Design

6.1 Overall Trial Design

This is an exploratory clinical (phase 2a), single-centre, prospective, randomised, vehicle-controlled, double-blinded, intra-individual comparison, split-face model (left/right design) trial. Subjects with moderate to severe acne vulgaris will be treated with LEO 43204 gel 0.018% and vehicle gel (i.e. the Investigational Products (IPs)). The IPs are administered as a thin wet layer to each treatment area (TA) on the left (TA_{left}) and right (TA_{right}) cheeks of the face, each area corresponding to approximately 36 cm^2 (refer to section 10.2.1). Assessments during the trial are outlined in section 8.1.

The subjects will be enrolled sequentially into 4 cohorts (n=40 total).

Progression from one cohort to the next will be decided after a review of LSRs, safety and tolerability by the Safety Review Committee after Week 2 (Visit 7).

Handling of LSRs, safety or tolerability deemed unacceptable is described in section 12.

Cohort 1 (n=3): Treatment escalation with once daily application of IPs for one, two and three days respectively for each of the first three subjects.

Subjects will enter treatment sequentially such that the second and third subjects only are exposed after a safety evaluation of the preceding subject is done. The first subject will be dosed for one day only, the second subject up to two days and the third subject up to three days.

The safety evaluation that allows the next subject to be dosed consists of the maximal LSR score from evaluations at days 1, 2, 3, 4, 8 and week 2 or until considerable reduction of LSR score and any treatment related AEs has been observed.

For subjects two and three, the second and third treatment day depends on the following criteria:

- The subject not reporting intolerable response to treatment.
- The investigator not evaluating LSRs or treatment-related AEs to be unacceptable.
- The LSR scores not exceeding predefined criteria (see Table 1, section 6.1).

Subjects not receiving the optional treatment on Day 2 and/or Day 3 due to severe LSRs or treatment related AEs will remain in the trial and attend the scheduled follow up visits.

Cohort 2 (n=6): Once daily treatment for three days with the second and third day optional dependent on predefined criteria (see 'Treatment Phase' below) Two subjects may initiate treatment per week. The subjects will follow the same scheduled visits as in cohort 1.

Cohort 3 (n=6): Once daily treatment for three days with the second and third day optional dependent on predefined criteria (see 'Treatment Phase' below). Subjects may be enrolled without restrictions to the number of subjects per week. The subjects will follow the same scheduled visits as in cohort 1.

Cohort 4 (n=25): Once daily treatment for three days with the second and third day optional dependent on predefined criteria (see 'Treatment Phase' below). Subjects may be enrolled without restrictions to the number of subjects per week. The visit on Day 8 will be conducted as a phone call visit.

The trial consists of the following phases:

Screening Phase (Day -28 to Day -1)

Following careful information about the protocol, LSRs and other risks, the subjects willing to participate in this clinical trial must sign the trial specific informed consent. Screening and Day 1 may be combined.

At the screening visit, the diagnosis of acne vulgaris will be confirmed by the (sub)investigator and the overall disease severity will be assessed using the IGA of the full face (Table 4 in section 8.15).

Two symmetrically located TAs on the left (TA_{left}) and right (TA_{right}) cheeks of the face will be identified by the (sub)investigator and documented on individual transparent film(s) using a three-point landmark technique as (described in Appendix 10). The (sub)investigator will assess disease severity in TA_{left} and TA_{right} by the IGA scale and lesion counts. In addition, the symmetry of the total lesion count when comparing TA_{left} and TA_{right} will be assessed (refer to criteria 4 in section 7.2).

The subject's eligibility for the trial will be checked according to inclusion and exclusion criteria.

If a subject is ineligible due only to current or recent use of prohibited therapies, he/she may be re-screened after a washout period. A decision to stop an ongoing therapy should always be discussed and approved by the (sub)investigator.

If the subject is eligible, assessments listed in section 8.1 will be performed and recorded in the eCRF. Females will have a urine pregnancy test performed.

Pre-treatment Phase (Day 1)

If the Day 1 (Visit 2) is not combined with the Screening (Visit 1), eligibility must be confirmed by review of inclusion and exclusion criteria prior to randomization. Following randomization, the subject must complete the AcneQoL questionnaire before any other assessments are undertaken in addition to safety assessments.

Women of childbearing potential must have a urine pregnancy test performed.

In Cohort 2, 3 and 4, non-invasive samples from the skin will be taken for evaluation of inflammatory markers, skin microbiome profile (For details see Appendix 2 and Appendix 4).

Subjects in Cohort 1, 2 and 3 will be photographed at all site visits from Day 1 and onwards for documentation of physical appearance (Appendix 3). Photographs will be taken at screening for Cohort 3 and 4 for documentation of eligibility.

Each subject will be left/right randomised to receive active treatment on TA_{left} or TA_{right}. The other side will be treated with vehicle gel.

Treatment Phase (Day 1, 2 and 3)

During the treatment phase, trial visits will be performed on Day 1, Day 2 and Day 3.

The individual transparent film(s) will be used to locate the TAs.

LSR scores for the TAs will be recorded and any new or on-going AEs, and changes in medication will be recorded.

Criteria for treatment on Day 2 and Day 3:

- The subject not reporting intolerable response to treatment.
- The (sub)investigator not evaluating LSRs or treatment-related AEs to be unacceptable.
- The LSR scores not exceeding predefined criteria (see Table 1).

Table 1. LSR score criteria for not administering second or third treatment.

LSR component(s)	Score on Day 2 and/or 3
Erosion/ulceration	≥2
Vesiculation/pustulation	≥3
Any LSR component	=4
Flaking/scaling + crusting	≥5 (sum)
Flaking/scaling + crusting + vesiculation/pustulation	≥6 (sum)

The reason not to treat is recorded in the eCRF. Subjects will remain in the trial and attend the follow-up visits according to the protocol.

The IPs are to be applied to the TAs by the site staff as per the randomization schedule at all three treatment visits (Visit 2, 3 and 4). Subjects will be carefully instructed in how long the IP must remain on the skin and how it can be washed off. Moreover, the subjects will be reminded about the precautions regarding accidental transfer of the IP to eyes and other areas (refer to section 10.3.2).

Post-treatment assessment (Day 2, 3, 4 and 8)

If the subject is not treated on Day 2 or Day 3, trial procedures will follow the trial schedule as described in Section 8.1. LSR scores for the TAs will be recorded and any new or ongoing AEs, and changes in medication will be recorded in the eCRF.

On Day 8 subjects in cohort 1, 2 and 3 will have a site visit, while subjects in cohort 4 will be contacted by phone to inquire about tolerability (i.e. subjective evaluation), AEs and concomitant medication. Should the subjects in cohort 4 express worsening of LSR or

treatment related AEs at Day 8, it will be decided by the (sub)investigator whether an unscheduled trial site visit for evaluation is required.

Post-treatment assessment (Week 2, 4, 8 and 12)

At Week 12 the subject must complete the Acne QoL (Appendix 11), TSQM II (Appendix 12) and the Subject Global Cosmetic Score (Appendix 5) before any other assessments are undertaken.

The individual transparent film(s) will be used to locate each TA for assessments. Clinical assessment of TA_{left} and TA_{right} including IGA scoring, inflammatory and non-inflammatory lesion counts, LSR will be recorded in the eCRF. For biomarker assessments and microbiome analyses, tape-lifts and swabs from TA_{left} and TA_{right} will be taken at Week 2, 4, 8 and 12 after all other assessments have been completed (Appendix 2 and Appendix 4).

Concomitant medication, new and ongoing AEs will be reported at these visits.

Trial periods:

Screening phase: 1 Week (Day -28 to -1)

Treatment phase: 3 days

Post treatment assessment: 12 Weeks

Planned date of enrolment of first subject: Q2-2016
Planned date of completion of last subject: Q4-2016

6.2 Sample Size

A total of 40 subjects (male and female) will be randomised. Subjects withdrawn after randomization will not be replaced.

The expected statistical properties of the primary endpoint are described in section 11.3.4.

6.3 Randomisation

Subjects will be randomised to either treatment with LEO 43204 gel 0.018% on the treatment area on the left cheek of the face, TA_{left}, and vehicle gel on the treatment area on the right cheek of the face, TA_{right}, or vice versa in a 1:1 ratio.

6.4 Blinding

All staff involved in the conduct of the trial and all subjects should remain blinded to treatment allocation for the entire duration of the trial.

The packaging and labeling of the investigational products must contain no evidence of the allocated treatment. It is not considered possible to differentiate between the investigational products solely by sensory evaluation. Consequently, it is expected that the subjects and the site staff remain unaware of the individual treatment assignments during the conduct of the clinical trial.

7 Trial Population and Withdrawal

7.1 Subject Eligibility

The (sub)investigator should only enroll subjects who meet all eligibility criteria, who are not put at undue risk by participating in the trial, and can be expected to comply with the protocol.

The subject's eligibility for the clinical trial must be checked according to the inclusion and exclusion criteria at the screening visit and at Day 1 as specified in "Schedule of Trial Procedures" in Section 8.1.

Randomisation (Day 1, Visit 2) should be performed within 28 days after the Screening Visit (Visit 1). Re-screening is allowed if the visit window cannot be complied with for practical reasons or if required due to recent or current use of prohibited therapy (refer to section 6.1, screening phase). Re-sampling or re-screening is not allowed if the subject has failed eligibility according to inclusion or exclusion criteria (except prohibited therapy).

Any implementation of national requirements/law for the subject's participation in the clinical trial must be ensured and described in the submission documentation to authorities/ethics committees, as applicable.

7.2 Inclusion Criteria

1. Following verbal and written information about the trial, the subject has to provide signed and dated informed consent before any trial-related activities are carried out
2. Subjects should be diagnosed with acne vulgaris of the face.
3. Acne vulgaris disease severity in the full face and in the TA should be scored as moderate to severe (grade 3-4) according to the Investigator's Global Assessment (IGA) Scale (Table 4, section 8.15).

4. Disease severity and total lesion count should be similar in both TAs (with a maximal 2 fold difference in total lesion count).
5. Fitzpatrick skin types I-III (Table 2, section 8.3)
6. Age 18 to 35 years inclusive.
7. Male or female subjects who are otherwise in overall good health including well-controlled diseases (e.g. hypertension, diabetes and thyroid disease) as determined by medical history, physical examination, vital signs (blood pressure, heart rate).
8. Female subjects:

    - of non-childbearing potential, i.e. have a confirmed clinical history of sterility (e.g. the subject is without a uterus or has tubal litigation)

      OR

    - of child-bearing potential* provided there is a confirmed negative pregnancy test prior to trial treatment to rule out pregnancy AND willing to use effective contraception at trial entry and until completion of the trial.

      *Female subjects are considered of child-bearing potential unless they have had a hysterectomy or have undergone tubal ligation.

    Effective contraception is defined as follows:

    - Abstinence (when this is in line with the preferred and usual life style of the subject).
    - Vasectomised partner (given that the subject is monogamous).
    - An intrauterine device.
    - Double barrier method defined as two distinct methods (two actual barrier methods).
    - Hormonal contraceptive (oral hormonal birth control, oestrogenic vaginal ring, percutaneous contraceptive patches, implants and injectables) for at least one menstrual cycle prior to enrolment.
9. Able to communicate with the (sub)investigator and understand and comply with the requirements of the trial.

7.3 Exclusion Criteria

1. Subjects with nodulocystic acne, acne conglobata, acne fulminans, secondary acne (e.g. chlor-acne, drug-induced acne).

2. Subjects with previous history of keloid formation or post-inflammatory hyperpigmentation.
3. Fitzpatrick skin types IV-VI.
4. Subjects in whom the (sub)investigator would recommend systemic therapy to prevent risk of scarring due to current disease severity of acne vulgaris.
5. Subjects with excessive facial hair, facial skin disorders or skin reactions that may interfere with trial assessments (including but not limited to AK, eczema, psoriasis, seborrheic dermatitis, rosacea, acute or recent sunburn).
6. Subjects with a clinical diagnosis, history or evidence of any medical condition that would expose the subject to an undue risk of severe AE or interfere with assessments of safety and efficacy during the course of the trial, as determined by the investigator's clinical judgment.
7. Supine BP at Visit 1 (screening) > 140/90 mmHg or < 90/50 mmHg and/or heart rate at Visit 1(screening) > 100 beats per minute (bpm) or < 50 bpm after up to 15 min of rest.
8. Subjects with Herpes simplex (type 1 and/or type 2) with recurrent outbreaks (6 or more outbreaks per year), or a recent (within 2 months) or current outbreak.
9. Subjects known to be infected with Human Immunodeficiency Virus (HIV).
10. Subjects with any haematological malignancies.
11. Use of cosmetic or therapeutic products and procedures which could interfere with the assessments of the treatment areas.
12. Known sensitivity or allergy to any of the ingredients in the vehicle gel or IP.
13. Subjects who have been treated with ingenol mebutate gel in the face within the last 12 months.
14. Change of use of hormonal oral contraceptives within the last 6 months prior to the randomisation.
15. Subjects who are known or, in the opinion of the (sub)investigator, are unlikely to comply with the Clinical Trial Protocol (e.g. due to alcoholism, drug abuse or psychotic state) or who are impossible to contact in case of emergency.
16. Current participation in any other interventional clinical trial or previously enrolled in an interventional clinical trial, which in the opinion of the (sub)investigator may interfere with the interpretation of the trial results.
17. Close affiliation with the (sub)investigator (e.g. a close relative) or a persons working at the trial sites or as an employee of the sponsor.
18. Female subjects who are pregnant, of child-bearing potential and who wish to become pregnant during the trial, or who are breast feeding.

Prohibited Therapies and/or Medications within 6 months prior to Day 1 (Visit 2).

19. Treatment with systemic retinoids
20. Cosmetic or therapeutic procedures within 2 cm from the treatment area including ablative or non-ablative laser therapy, intense pulsed light therapy, PDT, dermabrasion, medium or greater depth chemical peel, or subjects who intend to have such procedures done within the first 6 months after Day 1.

Prohibited Therapies and/or Medications within 1 month prior to Day 1 (Visit 2).

21. Treatment of the face with topical retinoids.
22. Treatment with systemic antibiotics.
23. Treatment in the face with ultraviolet light A or ultraviolet light B or intensive solar exposure.
24. Treatment in the face with light chemical peel.
25. Treatment with any non-marketed substance (i.e. an agent which has not yet been made available for clinical use following registration).
26. Treatment with systemic medications that suppress the immune system (e.g. cyclosporine, prednisolone). Note: inhaled, nasal, intra-articular, ophthalmic and intra-auricular corticosteroids are permitted.

Prohibited Therapies and/or Medications within 2 weeks prior to Day 1 (Visit 2).

27. Treatment within 5 cm from the treatment area with topical drugs or cosmetics containing benzoyl peroxide, antibiotics, keratolytic agents such as alpha- and beta-hydroxy acids, including glycolic acid, lactic acid and other fruit acids, salicylic acid, urea, soaps containing antibacterial agents such as skin fresheners/astringents or aftershave products)
28. Treatment in the face within 5 cm from the treatment area with any other topical treatment that in the opinion of the (sub)investigator may influence the subject's acne vulgaris status (e.g. topical steroids, calcineurine inhibitors, metronidazole, permethrin, artificial tanners).
29. Treatment in the face within 5 cm from the treatment area with electrolysis, waxing or depilatories.

    Note: non-medicated/non-irritant lotions/creams/sunscreens are acceptable on the treatment area until within 3 days of Visit 2/Day 1.

7.4 Subject Enrolment Log

As a minimum, subjects who have signed the informed consent form, but who are not necessarily randomised in the trial/treatment assigned, should be registered on the log.

7.5 Subject Identification List

The (sub)investigator must maintain a list of all subjects randomised/treatment assigned at the trial site including each subject's identity, date of enrolment and corresponding subject ID so that any subject may be identified if required for any reason. The list is kept by the investigator and must not be copied or retained by LEO.

At the screening Visit, each subject must be assigned a unique subject ID to protect the subject's identity and which will be used in lieu of the subject's name when the (sub)investigator reports trial-related data.

The subject ID is distinct from the randomisation code number.

7.6 Restrictions during Trial

Prohibited medication and procedures prior to trial entry are detailed in the Exclusion Criteria; see Section 7.3 for details. Any medication and procedures during the trial must be recorded along with the indication.

Make-up and sunscreens are not allowed in the TAs from 3 days prior to Day 1 and until 15 days after last IP application. Moreover, make-up and sunscreens are not allowed from the evening before follow up visits at Week 4, 8 and 12 until after the assessments.

Non-medicated and non-irritant emollients, lotions, creams, gels or foams are not allowed in the TAs from 3 days prior to Day 1 and during treatment days and 3 days before trial visits. Note: Subjects should wash treatment areas with a mild soap before starting use of emollients, lotions, creams again. Eye make-up within peri-orbital area and lipstick is allowed from 1 day after last treatment.

Subjects may be advised to use icepacks and cooling fans to attenuate burning sensation and pain. From experience, weak analgesics with or without antihistamine are also useful in treating the pain. In the case of periorbital oedema, a light and cold compression may be useful. In case of sleeping disorders due to pain, mild sedatives can be used.

Icepacks and cooling fans will not be considered a medical intervention, but should be recorded in the eCRF as a concomitant medication.

Use of concomitant treatment and indication must be recorded in the subject’s medical record and the eCRF (treatment/drug name, dose, and dates of start and stop).

Subjects should not undergo any elective medical procedure without prior consultation with the (sub)investigator. Elective procedures (e.g. minor day-surgery, dental surgery, etc.) that

might require hospitalisation or anesthesia should be deferred during the first 15 days after first IP administration.

7.7 Withdrawal Criteria

Subjects **may** withdraw from the trial for any of the following reasons:

1. Unacceptable treatment efficacy: the (sub)investigator is free to withdraw the subject at any time based on a medical judgment.
2. Unacceptable AEs or LSRs: any AEe or LRS that the (sub)investigator or the subject considers unacceptable.
3. Exclusion criteria: any exclusion criteria which emerge/become apparent during the subject's participation in the clinical trial.
4. Voluntary withdrawal: subjects are free to withdraw from the clinical trial at any time and for any reason.
5. Subjects must withdraw from the trial for any of the following reasons:
    a. Subject becomes pregnant during the trial.
    b. Subject with positive pregnancy test at screening and/or Day 1 will be excluded and complete End of Trial Form. Subjects with positive pregnancy test at visits after treatment (Week 2, 4, 8, or 12) may remain in trial for follow up.

Reason(s) for withdrawal must be recorded in the eCRF and medical records.

Subjects who are discovered, after enrolment/randomisation, not to have fulfilled all in-/exclusion criteria at the time of enrolment should discontinue treatment unless the (sub)investigator, based on clinical and ethical evaluation, finds discontinuation inappropriate.

Subjects who discontinue treatment after at least one treatment should remain in the trial for follow-up assessments. AEs should be followed up in all subjects as described in section 9.5

Subjects withdrawn will not be substituted.

8 Trial Schedule and Assessments

8.1 Schedule of Trial Procedures

	Screening Visit (SV) Day 0	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 8**	**Week 2**	**Week 4**	**Week 8**	**Week 12**
Visit number	**1**	**2***	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Visit window	Day -28 to Day 1						±3 Days	±3 Days	±5 Days	±1 Week
Informed consent	x									
In-/exclusion criteria[1)]	x	x								
Subject demographics	x									
Subject height and weight	x									
Identification of Treatment Areas (TA)	x	x	x	x	x	x	x	x	x	x
Medical history and concurrent diagnosis	x									
Acne Treatment History	x									
Concomitant medication	x	x	x	x	x	x	x	x	x	x
Abbreviated physical examination	x									x
Vital signs	x									x
Urine pregnancy test	x	x[1)]					x	x	x	x
Clinical assessments of full face IGA	x									
Clinical assessments of TA_{left} and TA_{right} for IGA and lesion count	x	x					x	x	x	x
Photos (cohort 1,2 and 3)		x	x	x	x	x	x	x	x	x
Photos (only cohort 3 and 4)	x									
Subject questionnaire AcneQoL		x								x
Subject questionnaire TSQM II										x
Subjects Global Cosmetic Score										x
Tape lift for inflammatory biomarker analysis [4)]		x					x	x	x	x

Swab for microbiome collection [4)]		x					x	x	x	x
Randomisation		x								
Administration of trial medication by site staff		x	x**	x**						
LSR evaluation		x	x	x	x	x[2)]	x	x	x	x
Adverse Events		x	x	x	x	x	x	x	x	x
Phone Call						x[3)]				
End of Trial Form										x

1) For women of child-bearing potential a urine pregnancy test must be performed, prior to treatment.

2) Not applicable for cohort 4

3) Only applicable for cohort 4

4) Not applicable for cohort 1

* Can be performed the same day as Screening

** Treatment on Day 2 and/or 3 is optional as described in section 6.1.

8.2 Subject Eligibility

Refer to Sections 7.2 and 7.3.

8.3 Demographics

Subject demographics will be recorded at the Day 0 (Screening). The following will be recorded in the eCRF:

- Date of birth
- Sex
- Race: American Indian or Alaska Native; Asian, Black or African American; Native Hawaiian or Other Pacific Islander; White; Other
- Ethnic origin (self-reported by the subject): Hispanic or Latino, not Hispanic or Latino
- Fitzpatrick skin type (see Table 2)

Table 2: Fitzpatrick skin type

Number	Description
I	Always burns easily, never tans
II	Always burns easily, tans minimally
III	Burns moderately, tans gradually (light brown)
IV	Burns minimally, always tans well (moderate brown)
V	Rarely burns, tans very well (moderate brown)
VI	Never burns, deeply pigmented

8.4 Height and Weight

The subject's height must be measured or self-reported (cm or inches) and weight must be determined or self-reported (kg or pound) at Visit 1.

8.5 Vital Signs

Blood pressure and heart rate must be assessed after approximately 5 to 15 minutes in a supine position at visits indicated in Section 8.1.

If an abnormal vital sign at Visit 1 (screening) is considered to be clinically significant by the (sub)investigator, it will be up to the (sub)investigator´s discretion if the subject should be enrolled into the trial. Abnormal findings of clinical relevance at Visit 1 (screening) will be documented as medical history in the eCRF. If an abnormal vital sign recorded at any other visit than Visit 1 (screening) is considered to be clinically significant by the (sub)investigator, it will be reported as an AE.

8.6 Physical Examination

An abbreviated physical examination including general appearance, regional lymph nodes and dermatologic examination of the skin must be performed at visits indicated in Section 8.1

If an abnormal physical examination at Visit 1(screening) is considered by the (sub)investigator to be clinically significant, it will be up to the (sub)investigator´s discretion if the subject should be enrolled into the trial. Abnormal findings of clinical relevance in the physical examination at the Screening Visit will be documented as medical history in the eCRF. If an abnormal physical examination at Visit 10 is considered by the (sub)investigator to be clinically significant, it will be reported as an AE.

8.7 Medical History

Relevant medical and surgical history must be recorded at the Screening Visit 1. This includes previous skin disease within the treatment areas.

8.8 Acne vulgaris specific medical history

Specified relevant medical history pertaining to acne vulgaris should be recorded as detailed in Table 3.

Table 3: Specified medical history for acne vulgaris

Detailed history	eCRF recording
Debut	Age at onset
Characteristics at debuted (yes/no)	Early and more severe sebum production Early onset relative to menarche Mild facial comedones
Current disease characteristics (yes/no)	Persistent refractory disease Responding to standard therapies but relapsing Acne scarring Acne on trunk Hyperseborrheia
Family history (yes/no)	Moderate to severe acne in one parent Moderate to severe acne in one sibling
Previous acne vulgaris therapy (yes/no) * used more than 1 month	Systemic retinoids * Systemic antibiotics* Systemic hormone therapy for acne control * Topical retinoid monotherapy * Topical retinoid combination therapy * Other topical combination therapies * Topical benzoyl peroxide * Azealic acid * PDT Chemical peels Other light based therapies (specify) Other topical therapies (specify)

8.9 Concomitant Medication

Concomitant medication is defined as any medication used by a subject during the clinical trial apart from the investigational product. Concomitant medication including diagnoses must be recorded in the medical record and the eCRF at visits specified in section 8.1.

8.10 Pregnancy Test

A urine pregnancy test must be performed at the trial site in female subjects of child-bearing potential at visits specified in section 8.1.

8.11 Laboratory Assessments

8.11.1 Urine collection for pregnancy test

Qualitative urine pregnancy test (dip-stick) of human chorionic gonadotropin (HCG) must be performed as scheduled in section 8.1. The test will be performed locally.

8.11.2 Microbiome and Biomarker

Collection is described in Appendix 2 and Appendix 3. Handling and shipment instructions for the samples are provided in a separate laboratory manual.

8.12 Adverse Events

AEs must be assessed and recorded as specified in section 9.

8.13 Other Safety Assessments

Local Skin Responses (LSRs)

Assessment of local skin responses in the treatment areas using the LSR Grading Scale will be performed at Day 1 prior to first IP application and at all subsequent visits as indicated in section 8.1.

Local skin responses are defined as erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation and erosion/ulceration. The presence/absence and grade of each LSR will be recorded using the LSR Grading Scale shown in Appendix 6. This grading scale will also be provided as hard copy to the site. Any local skin responses identified within the treatment area which do not match the criteria in the LSR Grading Scale should be reported as AEs.

8.14 Subject Reported Outcomes

The subject must complete Acne-QoL at Visit 2 (Day 1) and Visit 10 (Week 12, End of Trial).

The subject must complete TSQM II and Subject Global Cosmetic Score at Visit 10 (Week 12, End of Trial).

Subject-reported outcome measures should be completed prior to any other assessments at the respective trial visits in the following order: Acne QoL, TSMQ II and Subject Global Cosmetic Score. The subjects should be encouraged to answer all questions in the questionnaires.

8.15 Investigator Assessments

The investigator assessments will be conducted by an experienced and qualified dermatologist. All assessments of each subject at the site should preferably be performed by the same dermatologist. At Visit 1, identification of the treatment area should be documented on an individual transparent film using three-point landmark technique (refer to Appendix 10

for details). At all subsequent visits, the transparent film should be used to locate the treatment area for further treatment or assessments of the treated skin.

The following clinical assessments must be made at visits as specified in section 8.1:

1. IGA of the full face (see Table 4 for grading) at Screening to determine acne vulgaris severity for inclusion to the trial at Screening.
2. IGA and non-inflammatory lesion count (open and closed comedones), and inflammatory lesion count (erythematous papules and pustules) in TA_{left} and TA_{right} at Screening and Day 1, Week 2, 4, 8, and 12.
3. LSR assessments (see 8.13) in TA_{left} and TA_{right} using the LSR Grading Scale at Day 1 prior to IP application, and on all subsequent site visits.
4. Skin photography at Day 1, prior to treatment, and on all subsequent site visits (only for cohort 1, 2, and 3).
5. Skin photography at screening for cohort 3 and 4
6. All other skin findings than LSRs and acne will be reported as medical history at Screening or as AEs at subsequent visits.
7. Biomarker and microbiome samplings in Cohort 2, 3 and 4 at Day 1 and at Week 2, 4, 8 and 12. See Appendix 2 and Appendix 4. Samples will be stored for later analysis.

Table 4. Investigator's Global Assessment Scale for Acne Vulgaris*

Grade	Description
0	Clear skin with no inflammatory and non-inflammatory lesions
1	Almost clear; rare non-inflammatory lesions with no more than one small inflammatory lesion
2	Mild severity; greater than Grade 1; some non-inflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions)
3	Moderate severity; greater than Grade 2; up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesions
4	Severe; greater than Grade 3; up to many non-inflammatory and inflammatory lesions, but no more than a few nodular lesions

*The same scale will be used for full face and TA evaluation of IGA.

8.16 Dispensing of IP

Not applicable as this is an investigator applied IP.

8.17 Return of IP and Compliance

Refer to Sections 10.7.1 and 10.7.3.

8.18 End of Trial Form

The End of Trial Form must be completed for all subjects who have signed informed consent. This includes e.g. date of last dose, last attended scheduled visit number, primary reason for withdrawal, etc.

9 Adverse Events

- AEs and serious AE (SAEs) are defined in Appendix 7.
- Classification of adverse events in terms of severity, causality and outcome are defined in Appendix 8.

9.1 Collection of Adverse Events

AEs must be collected from the time of first trial-related activity after the signing of the informed consent form until last visit at Week 12.

Abnormal findings observed at the screening visit should be recorded as diagnoses in the Concomitant Medication page if medication is currently being taken for the condition. If not, it will be documented as medical history in the eCRF.

AEs must be assessed by medically qualified personnel. A qualified and experienced dermatologist must conduct all dermatologic examinations, LSR and AE evaluations of the treatment areas.

For AEs recorded on the day starting treatment, it should be specified whether the AE started prior to or after first application of IP.

At all visits, the subject will be asked a non-leading question by the (sub)investigator about AEs, for example: “How have you felt since I saw you last?”. No specific symptoms should be asked for. It is important that the (sub)investigator also observes the subject for any changes not reported by the subject and records these changes.

9.1.1 Local Skin Responses

Local Skin Responses which match the criteria in the LSR Grading Scale are to be reported on the Local Skin Response sections in the eCRF and not as AEs in the eCRF even if they require treatment. Skin responses other than those identified in the LSR scale must be recorded appropriately as AEs.

Any LSRs classified as a SAE must be added to the AE form and in addition be reported to LEO on the SAE Form (according to "Investigator Reporting Responsibilities", section 9.4.1)

Any treatment for a LSR must be recorded on the concomitant medication page of the eCRF with the most important LSR (e.g. swelling should be reported as swelling-LSR).

9.2 Reporting of Adverse Events in the eCRF

AEs reported by the subject or observed by the (sub)investigator must be recorded on the adverse event form of the eCRF and should be described in the following manner:

The *AE term* will be in precise English medical terminology (i.e. not necessarily the exact words used by the subject). Whenever possible, a specific diagnosis should be stated (e.g. allergic contact dermatitis).

For AEs, the location must be part of the adverse event description and may be described as "in the treatment areas", "outside the treatment areas" or "not applicable". For adverse events in treatment areas the lateral side needs to be specified also.

The *duration* of the AE must be reported as the start date and stop date of the event. In addition, it must be recorded whether the AE started prior to start of trial medication.

AEs must be classified in terms of severity, causality and outcome according to the definitions in Appendix 8.

9.2.1 Actions Taken as a Consequence of an AE

Action taken with trial treatment: Any action taken with trial medication as a consequence of the AE must be recorded (dose not changed, dose reduced, dose increased, drug interrupted, drug withdrawn, not applicable, unknown).

Other action taken: Any other action taken as a result of the AE must be recorded (none, concomitant medication, concurrent procedure).

Withdrawn due to AE: It must be recorded whether the AE leads to withdrawal from the trial.

9.3 Other Events to be Reported

9.3.1 Pregnancy

Any pregnancy occurring during the clinical trial must be reported to LEO within 24 hours of first knowledge using the (paper) Pregnancy Form (Part I). All such pregnancies must be

followed up until delivery or termination and final outcome must be reported on the (paper) Pregnancy Form (Part II) within 24 hours of first knowledge.

The completed Pregnancy Forms must be faxed or scanned and e-mailed to Global Pharmacovigilance, LEO (see section 9.4.1 for contact details).

Please also confer with section 7.7, Withdrawal Criteria.

9.3.2 Overdose

Overdose refers to the administration of a quantity of a medicinal product given per administration or per day which is above the protocol defined dosage.

The term overdose must be documented on the adverse event form of the eCRF book. In addition, AEs originating from overdose must be documented on a separate line.

9.3.3 Medication Error

Medication error refers to any unintentional error in the dispensing or administration of a medicinal product while in the control of the (sub)investigator or subject. Broadly, medication errors fall into four categories: wrong medication, wrong dose (including strength, form, concentration, amount), wrong route of administration or wrong subject.

The medication error must be documented on the adverse event form of the eCRF book. In addition, AEs originating from a medication error must be documented on a separate line specifying the category of error (see definitions above).

9.3.4 Misuse

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

The term misuse must be documented on the adverse event form of the eCRF book. In addition AEs originating from misuse must be documented on a separate line.

9.3.5 Abuse

Abuse relates to the sporadic or persistent, intentional excessive use of an IP which is accompanied by harmful physical or psychological effects.

The term abuse must be documented on the adverse event form of the eCRF book. In addition, AEs originating from abuse must be documented on a separate line.

9.3.6 Aggravation of Condition

Any clinically significant aggravation/exacerbation/worsening of any medical condition(s), compared to baseline, must be reported as an AE.

9.3.7 Lack of Efficacy

Not applicable

9.3.8 Adverse Events of Special Interest

In the clinical trials investigating LEO 43204 gel for AK in subjects with sun-damaged skin, there is a special interest for adverse events regarding development of keratoacanthoma (KA) or squamous cell carcinoma (SCC). Moreover, KA can be difficult to distinguish clinically and histologically from SCC. Sun-damaged skin is also prone to development of KA as a response to local irritation and/or inflammation. The subjects in this trial are not expected to have sun-damaged skin due to younger age and are thus considered to have a very low risk of developing KA or SCC.

To ensure that all information relevant for surveillance is collected, SCCs and KAs in the treatment area are considered adverse events of special interest (AESI).

For SCCs and KAs in the treatment area, the relevant information will be collected in the eCRF. In addition, histology report should be faxed or emailed to Global Pharmacovigilance, once available, using the following fax number or email address:

Fax number: +45 7226 3287

Email address: drug.safety@leo-pharma.com

SCCs and KAs in the treatment area that meet the criteria for being serious should be reported as SAEs (please refer to section 9.4.1 for reporting details).

The pathology slides that have been used for the initial diagnosis of SCC or KA will be sent for central pathology review. Central pathology reports will be distributed to the investigator. If there are any discrepancies between the local pathology report and the central pathology report, there should not be any changes in the eCRF. For the central pathology review, the local pathology laboratory will send the relevant histology slides to the investigator who will forward the slides to the pathologist doing the central reading. Only if the original slides cannot be sent is it acceptable to use new slides made from the tissue block.

9.4 Additional Reporting Requirements for Serious Adverse Events

9.4.1 Investigator Reporting Responsibilities

Any Serious Adverse Event (SAE) must be reported to LEO on the (paper) Serious Adverse Event Form – Clinical Trials within 24 hours of first knowledge. This report should contain an assessment of available information on seriousness, severity, causal relationship to the IP, comparator or trial procedure, the action taken, the outcome to date, and a narrative description of the course of the event.

Any LSR classified as a SAE must be added to the adverse event form in the eCRF and in addition reported to LEO on the SAE form.

The completed SAE form must be faxed or scanned and e-mailed to Global Pharmacovigilance, LEO using the following fax number or e-mail address:

Fax number: +45 7226 3287 (for Global Pharmacovigilance)

E-mail address: drug.safety@leo-pharma.com (for Global Pharmacovigilance)

It may be relevant for the (sub)investigator to enclose other information with the SAE form, such as reports of diagnostic procedures, hospital records, autopsy reports, etc.

Additionally, Global Pharmacovigilance, LEO may request further information in order to fully assess the SAE. The (sub)investigator must forward such information to Global Pharmacovigilance, LEO upon request by fax or e-mail (see contact details above).

The investigator must notify the local IRB(s)/IEC(s) of SAEs as required by current applicable legislation for the concerned country.

SAEs occurring after the completion of the clinical trial including any protocol required post-treatment follow-up period should not be routinely sought or collected. However, such events should be reported to Global Pharmacovigilance, LEO (drug.safety@leo-pharma.com) if the (sub)investigator becomes aware of them.

9.4.2 LEO Reporting Responsibilities

Global Pharmacovigilance, LEO is responsible for assessing whether or not a SAE is expected. The relevant reference document for this clinical trial is:

For the IP, the Investigator's Brochure, LEO 43204 gel, Field Therapy, Edition No. 4 including Addendum of LEO 43204 gel in Acne Vulgaris (Exploratory Edition No. 1) and subsequent updates hereof must be used.

Global Pharmacovigilance, LEO will notify the regulatory authorities and concerned investigators of SAEs according to the current applicable legislation for the concerned country.

The IRB(s)/IEC(s) will be notified of SAEs according to the current applicable legislation for the concerned country.

For the US, all SAEs which are assessed as causally related to the IP by LEO (Guidance for Industry and Investigators – Safety Reporting Requirements for INDs and BA/BE Studies) and which are unexpected (Serious and Unexpected Suspected Adverse Reactions (IND safety report)) are subject to expedited reporting to regulatory authorities and IRB(s)/IEC(s) according to current applicable legislation in the concerned country. Investigators will be notified of these on an ongoing basis.

9.5 Follow-up for Final Outcome of Adverse Events

During the trial, the investigator should follow up for final outcome on all AEs (including SAEs). Once a subject has completed the clinical trial, LSRs as well as AEs classified as possibly or probably related to the IP that are deemed clinically significant should be followed for 2 months or until final outcome is determined, whichever comes first.

SAEs must be followed up until a final outcome has been established, i.e. the follow-up may continue beyond the end of the clinical trial.

10 Investigational Product(s)

10.1 Investigational Product Description

Finished product (brand) name (if available)/name investigational product	LEO 43204, 0.018%
Formulation	Gel
Active ingredient name/concentration	LEO 43204, 0.018% w/w
Excipients	CCI [redacted]
Pack size(s)	1 g laminate tubes each containing 0.67g
Manufacturer's name of bulk medication (IP)	LEO Pharma 55 Industriparken 2750 Ballerup Denmark Or LEO Laboratories LTD. 285 Cashel Road Dublin 12 Ireland
Certifier's name of bulk medication (IP)	LEO Pharma A/S
Supplier's name	LEO Pharma A/S,
Manufacturer's name of subject treatment packages	CCI [redacted]
Certifier's name of subject treatment packages	LEO Pharma A/S
Finished product (brand) name (if available)/name investigational product	Vehicle gel
Formulation	Gel
Active ingredient name/concentration	Not applicable
Excipients	CCI [redacted]
Pack size(s)	1 g laminate tubes each containing 0.67g

Manufacturer's name of bulk medication (IP)	LEO Pharma 55 Industriparken 2750 Ballerup Denmark Or LEO Laboratories LTD. 285 Cashel Road Dublin 12 Ireland
Certifier's name of bulk medication (IP)	LEO Pharma A/S
Supplier's name	LEO Pharma A/S,
Manufacturer's name of subject treatment packages	CCI [redacted]
Certifier's name of subject treatment packages	LEO Pharma A/S

10.2 Administration of Investigational Products

Route of administration	Topical administration
Application range	Left and right cheek treatment areas (TA_{left} and TA_{right}) corresponding to approximately 36 cm^2 each.
Application frequency	Once daily for up to three consecutive days
Daily maximum	Approximately 1/3 of a tube per TA applied by the trial staff as a thin wet layer.
Time of day for application	No specific requirements
Relation of time of application to dietary intake	No specific requirements

The IP will be applied to the treatment areas at the clinic by the trial site staff .

10.2.1 Trial Medication Application

At each application, a thin wet layer of trial medication should be applied evenly within the identified TA of approximately 36 cm^2 by the trial site staff. The required total amount of IP to produce a thin wet layer is approximately 1/3 of a squeezed tube and equal to a pea-sized drop. The trial staff will be trained to dispense the correct amount of IP. Prior to application, the location of the TA is identified using a transparent film and a three-point landmark technique (Appendix 10).

Trial medication should be applied according to the following procedure:

1. Using standard hospital gloves, remove the cap from the unit dose tube. Squeeze a pea-sized drop of IP from tube onto the index finger.

2. Spread the trial medication evenly over the assigned treatment areas such that a thin wet layer of IP is applied.
3. Recap the tube and store for drug account (refer to section 10.7).
4. Dispose of gloves and wash hands with soap and water.
5. Allow the trial medication to dry for at least 15 minutes following application.

General treatment guidance:

- Subjects should not shave or trim the treatment areas during the treatment days.
- Subjects should not wash the treatment areas on the treatment days prior to IP application.
- Subjects must avoid washing the treatment areas or engaging in activities that cause excessive sweating for at least 6 hours following IP application.
- When subjects resume their normal washing routine, they should wash the treatment areas gently using a mild soap.
- Subjects should avoid use of non-medicated/non-irritant salves/emollients on the treatment areas during treatment days and within 3 days prior to the first treatment day.
- Subjects should avoid use of make-up and sunscreens on the treatment areas from 3 days prior to first treatment day and 15 days after last IP application. Note: Eye-make-up within peri-orbital area and lipstick is allowed.
- Subjects should be advised not to allow other persons (including children) and pets to come into contact with the treatment areas for a period of 6 hours following application.
- Subjects should avoid contact of IP with eyes.
- Subjects should avoid excessive sun exposure (e.g. sunbathing, tanning booths) of the treated area.

10.3 Precautions/Over dosage

10.3.1 Skin exposure

The most common LSRs reported in the AK studies with LEO 43204 gel are erythema, flaking/scaling, and crusting. Less common LSRs include swelling/oedema, vesiculation/pustulation, and erosion/ ulceration. Completed clinical trials have shown LSRs to be transient and normally resolved within two weeks (please refer to the Investigator's Brochure of LEO 43204 gel in Actinic Keratosis Edition 4 or any updates hereof for further details).

In a low percentage of subjects treated on face or scalp, swelling around the eyes or on the eyelids may develop to a point where it may be considered clinical significant. In such cases these AEs should be recorded as peri-orbital oedema or eyelid edema. Treatment is usually straightforward with cold compress on the eye(s) with the subject resting in supine position for a few hours.

The mean maximum composite LSR score in Part 2 of LP0084-1013 (face) for the doses of LEO 43204 gel that will be used in the current trial was 8.9 for face. Using the same doses for 3 consecutive days (LP0084-1148), mean maximum composite scores were 10.6 for face. Peak value in the LP0084-1013 trial (face) was at Day 3. At Day 15, mean maximum composite LSR score was either at baseline value or close to baseline value in almost all subjects treated on face (refer to the Investigator's Brochure of 43204 gel in Actinic Keratosis Edition 4 or any updates hereof).

Investigators conducting clinical trials with LEO 43204 gel should ensure that investigational site staff is trained in the protocol-specified application procedure(s) and follow appropriate precautions. Investigators must monitor their subjects for the emergence and resolution of LSRs and AEs

10.3.2 Ocular Exposure

If accidental eye exposure occurs, the eye should be irrigated immediately and extensively with water. The subject should immediately seek medical attention by contacting the investigator or other medically qualified healthcare professional (e.g., in an Emergency Room) for assessment and treatment. All treatments are to be administered at the discretion of the healthcare professional (in emergency room, ophthalmologist, and/or the investigator). Treatment with topical cycloplegic and topical ophthalmic antibiotics is recommended. Topical anti-inflammatory agents and eye pads may also be useful for subject comfort. The subject should be monitored closely in the first few days following exposure to check for secondary infection and to assess visual acuity. Subjects should be warned that vision might worsen before improvement occurs.

Any suspected ocular exposure should be documented and brought to the attention of the monitor

10.3.3 Other Exposure

LEO 43204 gel must not be ingested. If accidental ingestion occurs the subject should drink plenty of water.

10.4 Packaging of Investigational Products

The IP will be packaged in individually numbered kits. Each kit contains 2 unit-dose tubes.

Each unit-dose tube will contain LEO 43204 gel or vehicle gel to be handled in the hospital clinic up to three consecutive days.

The label on the tubes will be colored (e.g. red and green) to instruct the site personnel on which site (left or right) the product should be applied.

The labeling of trial products must be in accordance with Annex 13, local regulations and trial requirements.

10.5 Storage of Investigational Products

All LEO supplied drugs must be stored in a secure and restricted area under the conditions specified on the label and remain in the original container until dispensed.

The IP must be stored in a refrigerator between [redacted]°C and [redacted]°C ([redacted]°F to [redacted]°F). The refrigerator temperature must be monitored continuously and recorded. Do not freeze.

10.6 Treatment Assignment

Subjects who have been found to comply with all the inclusion criteria and not to violate any of the exclusion criteria will be randomised to receive treatment with LEO 43204 gel and vehicle gel to the treatment areas identified on three consecutive days.

10.6.1 Randomisation Code List

The randomisation files must be kept during the clinical trial in a secure area on the database server at LEO inaccessible to staff involved with the conduct and administration of the clinical trial until the clinical trial is unblinded.

10.7 Drug Accountability and Compliance Checks

10.7.1 Drug Accountability

The investigator is fully responsible for the investigational products at the trial site and for maintaining adequate control of the investigational products and for documenting all transactions with them.

An inventory must be kept of the investigational product given to each subject randomised in the trial. This inventory must be available for inspection during monitoring visits and will be checked by the monitor to ensure correct dispensing of the investigational product.

All investigational products supplied by the Contract Manufacturing Organisation (CMO) on behalf of LEO must be returned to the CMO. Prior to their return, they must be fully accounted for by the monitor with the help of the person responsible for dispensing the investigational products. Accountability must be documented by using drug accountability forms.

Investigational products may be returned from the trial site directly to the CMO responsible for the running of the clinical trial.

10.7.2 Trial Product Destruction

Used and unused trial products will be destroyed by the CMO according to LEO procedures.

10.7.3 Treatment Compliance

Treatment is performed at the clinic according to the protocol by the trial site staff.

10.8 Emergency Unblinding of Individual Subject Treatment

While the safety of a subject always comes first, it is still important to seriously consider if unblinding is necessary to ensure subject's safety. This section describes the procedures for unblinding a subject. An emergency unblinding request can be made by the (sub)investigators, other health care professionals or authorized LEO personnel.

Provisions are in place for 24 hour emergency unblinding of individual subject treatment. If emergency unblinding is required, the individual subject's treatment assignment can be obtained via the IWRS. Requester without access to IWRS (Health Care Professionals), can contact the investigator or LEO for emergency unblinding.

11 Statistical Methods

11.1 Determination of Sample Size

With a sample size of 38 subjects the power of observing a difference between active and vehicle gel will be 84% in a trial with intraindividual comparisons, using a paired two-sided t-test on a 5% level, assuming an approximate total lesion count of 36 at baseline and reductions at end of trial from baseline around 7.3 (20%) and 12.4 (34%) for vehicle gel and active respectively, and a standard deviation of the difference between treatments at end of treatment up to 10.4.

The assumptions on sample size are that all but the two first subjects of the 40 subjects randomised are included in the efficacy analyses, and the assumptions on efficacy rely on experiences from a previous trial conducted by LEO in subjects suffering from acne vulgaris

(LP0045-01), together with an expected reduction in standard deviation of the primary endpoint of at least 20% due to the intraindividual comparisons.

11.2 Definition of Trial Analysis Sets

All subjects enrolled in the trial (i.e. subjects for whom informed consent has been obtained and who have been registered in the clinical trial) will be accounted for in the clinical trial report.

All subjects randomised except the first two subjects with a reduced exposure are included in the full analysis set and will be analysed for efficacy. The size of the full analysis set will then be 38 subjects Exclusions from the full analysis set can be considered in special cases as described in ICH E9, section 5.2.1. Full Analysis Set. If it is decided to exclude a randomised subject from the full analysis set, a justification addressing ICH E9 will be given.

A per protocol analysis set will be defined by excluding subjects from the full analysis set based on the review of protocol deviations before the unblinding of the trial. If it is decided to exclude a subject from the per protocol analysis set, a justification will be given.

A safety analysis set will be defined by excluding subjects from the full analysis set who either received no treatment with investigational product and/or for whom no post-baseline safety evaluations are available.

The decisions regarding inclusion/exclusion of subjects and/or subject data from the trial analysis sets will be documented in the statistical analysis plan update before breaking the randomisation code.

11.3 Statistical Analysis

11.3.1 Disposition of Subjects

The reasons for leaving the trial will be presented for all randomised subjects by last visit attended.

11.3.2 Demographics and other Baseline Characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for the safety analysis set.

Demographics include age, sex, race, ethnicity and skin type. Other baseline characteristics include height, weight, BMI and, duration of acne vulgaris, concurrent diagnoses, concomitant medication, previous treatments for acne vulgaris.

11.3.3 Exposure and Treatment Compliance

Descriptive statistics on treatment duration will be provided for the safety analysis set.

11.3.4 Analysis of Primary Endpoints

11.3.4.1 Total lesion count

The evaluation of the treatment effect on total lesion count (inflammatory and non-inflammatory) lesions at Week 12 (primary endpoint) will be performed within the framework of an ANCOVA model with treatment as fixed effect, baseline total lesion count as covariate and subject as random effect.

Comparison between active and vehicle gel will be done by means of a t-test on the estimated treatment contrast in the model. Estimated difference, 95% confidence limit and test probability will together with least square means and their 95% confidence limits be presented from the model.

A sensitivity analysis investigating potential effect of lateral side of lesion will be performed by adding this effect to the above model.

11.3.5 Analysis of Secondary Endpoints

11.3.5.1 Lesion counts

Descriptive statistics will be provided for inflammatory, non-inflammatory and their sum by treatment and visit.

Descriptive statistics will include means, standard deviations, median and ranges. Furthermore mean curves over time will be made.

11.3.5.2 Investigator's Global Assessment

Descriptive statistics will be provided for the investigator's global assessment of disease severity in the treatment area, presented by treatment and visit.

Descriptive statistics will show frequencies for each score.

11.3.6 Analysis of Exploratory Endpoints

11.3.6.1 Lesion counts by clinical evaluation.

Descriptive statistics will be provided for inflammatory, non-inflammatory and their sum by treatment and visit for data obtained by clinical assessment.

Descriptive statistics will include means, standard deviations, median and ranges. Furthermore mean curves over time will be made.

11.3.6.2 Treatment success according to IGA

Rates of treatment success, defined as at least a two grade improvement in IGA at week 12 compared to baseline, will be compared between treatments using Fisher's exact test.

11.3.6.3 Inflammatory cytokine expression

Descriptive statistics will be presented showing means, standard deviations medians and ranges by treatment and time point. The results will also be shown as box-plots.

If applicable data will be log transformed before deriving descriptive statistics.

11.3.6.4 Microbiome profile

The analysis of data relating to the microbiome will be specified in a separate analysis plan, and the reporting will be done separately.

11.3.6.5 Subject evaluation of Acne QoL

Descriptive statistics will be provided for the subject's evaluation of Acne QoL at Day 1 and Week 12 for the total and each of the four domains contained within the questionnaire (self-perception, role-social, role-emotional and acne symptoms).

11.3.6.6 Subject evaluation of TSQM II

Descriptive statistics will be provided for the subject's evaluation of TSQM II at Week 12 for the total and each of the four domains contained within the questionnaire (effectiveness, side effects, convenience and global satisfaction).

11.3.6.7 Subject Global Cosmetic Score

Descriptive statistics will be presented for the Subject's Global Cosmetic Score at Week 12 showing means, standard deviations medians and ranges by treatment.

11.3.7 Analysis of Safety

The analysis of safety will be based on the safety analysis set.

11.3.8 Adverse Events

Treatment emergent adverse events, i.e. with an onset or intensifying after treatment start will be coded according to MedDRA v19.0 summarised by the following tables showing event counts, incidences and incident rates:

- An overall summary showing statistics for all AEs, serious AE's, AE's with actions taken, AE's stratified by severity, related AE's by treatment, cutaneous AE's by treatment
- AE by system organ class and preferred term
- AE's by system organ class and preferred term stratified by disease severity
- Related AE's by system organ class and preferred term by treatment
- Cutaneous AE's by system organ class and preferred term by treatment
- Serious adverse events will be evaluated separately and a narrative for each will be given.
- AEs leading to withdrawal from trial or discontinuation of investigational product will be listed.

11.3.9 Other Specific Safety Assessments

11.3.9.1 Composite and component LSR score

The incidence and grade of LSRs will be summarised by treatment and time point. LSR grades will be summarised by descriptive statistics including mean, standard deviation, median and range as well as frequency counts by treatment for each of the six individual LSRs: erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration. LSRs leading to withdrawal from trial and/or withdrawal of IP will be tabulated.

A composite (sum) score will be obtained by summing the six individual component LSR scores (range 0-24) at each visit (Visit 2 to 10). The composite score and change from baseline will be summarised by treatment group at each visit using descriptive statistics. The maximum composite LSR score across visits and the visits of occurrence of the maximum composite LSR score will be tabulated by treatment. After the maximum is attained, the first visit where the composite LSR score is less than or equal to the composite score at baseline will be tabulated by treatment group.

11.3.9.2 Vital Signs and Physical Findings

Observed values and changes from baseline in vital signs blood pressure, heart rate, will be summarised as mean, standard deviation (SD), median, minimum and maximum values.

Clinically relevant physical findings will be reported as medical history or AEs as applicable.

11.3.9.3 Clinical Laboratory Evaluation

Not applicable

11.3.10 Interim Analysis

After Week 2 (Visit 7) for specified number of subjects (refer to section 6.1) along the course of the trial analyses of blinded data will be performed evaluating the safety profile and the LSRs (refer to section 12).

The analyses will include:

- List of adverse event, using investigators term
- Number of subjects with:

  One of the following scores on the LSR scale at any time:

  - Grade 4 crusting
  - Grade 4 erosion / ulceration
  - Grade 4 vesiculation / pustulation extending significantly outside the treatment area

  Or two or more of the following scores on the LSR scale at any time:

  - Grade 4 erythema
  - Grade 3 crusting
  - Grade 4 swelling extending significantly outside the treatment area
  - Grade 3 erosion / ulceration
  - Grade 3 vesiculation / pustulation

- Descriptive statistics of composite and components of LSRs by visit and lateral side
- Plots of mean and individual profiles of composite LSRs by visit and lateral side
- Descriptive statistics of maximum of right and left side composite and component LSRs by visit

- Plots of mean and individual profiles of maximum of right and left side composite LSRs by visit

- List of individual component LSRs

11.3.11 General Principles

All significance tests will be two-sided using the 5% significance level. All confidence intervals will be presented with 95% degree of confidence.

An observed cases approach will be used for tabulations of data by visit (i.e. involving only those subjects who attended each specific visit).

Categorical data will be summarised using the number and percentage of subjects in each category. Continuous data will be summarised using the mean, median, standard deviation (SD), minimum and maximum values.

Any changes from the statistical analysis planned in this clinical trial protocol will be described and justified in a protocol amendment or the statistical analysis plan update and/or in the clinical trial report dependent on the type of deviation.

11.3.12 Handling of Missing Values

Subjects with missing counts of inflammatory and non-inflammatory lesions at visits 7, 8 and 9 (weeks 2, 4 and 8) will be excluded from the analyses based on FAS and PP for these time points, and missing lesion counts will therefore not be imputed for these subjects. For subjects with missing lesion counts at visit 10 (week 12), the missing lesion counts of visit 10 will be imputed and the endpoints will be derived afterwards from the imputed values.

A multiple imputation method will be used to handle missing data. The imputation method relies on the assumption that the missing data are missing at random (MAR), i.e. the probability that an observation is missing can depend on observed data but is unrelated to the data not observed. All imputations will be performed by lesion type and treatment group.

Imputation of missing values for subjects with a monotone missing data pattern (i.e. there exist a time point for the subject where all observations before the time point are present and all later observations are missing) will be based on the full observed dataset excluding subjects with a non-monotone missing data pattern. The missing values for lesion counts at visit 10 will be imputed sequentially from a linear regression model with lesion counts at previous visits as covariates and treatment compliance (as identified by means of protocol deviations) as factor.

For subjects with a non-monotone missing data pattern, the lesion counts at visit 10 will be imputed using data from subjects without a non-monotone missing data pattern based on the Markov Chain Monte Carlo (MCMC) method including compliance effect, and lesion counts at previous visits 7, 8 and 9 as continuous variables. In case of non-convergence the compliance effect will be excluded from the imputation model. The imputed values at visit 10 will be rounded to the nearest non-negative integer.

Table 5 shows seed and numbers of imputations used for the multiple imputations

Sensitivity analyses of the method of handling missing data will be performed for the analyses of the imputed endpoints: last observation carried forward (LOCF) and an observed cases approach.

Table 5 Parameters defining imputation of lesion counts

Assessment	Seeds for Imputation for subjects with monotone pattern of missing data	Seeds for Imputation for subjects with non-monotone pattern of missing data	Number of imputations
Inflammatory lesions	255951	897661	100
Non-inflammatory lesions	477345	657616	100

12 Trial Committees

The Safety Review Committee will comprise the following members:

- The International Coordinating Investigator
- Sponsor’s medical expert
- Sponsor’s Head of Translational Medicine
- Sponsor’s pharmacovigilance expert
- Sponsor’s Statistician
- The ICTM

Primary functions of the Committee:

- Operate to written procedures defined by the Safety Review Committee Charter for the trial.
- Document decision in the meeting minutes.

- Convene to review safety and tolerability after the last subject in cohort 1, 2 and 3 has completed the Week 2 follow-up visit (Visit 7).
- Decide whether quality of data is sufficient and whether unacceptable LSRs, safety or tolerability events have occurred necessitating termination of the clinical trial.

Prior to dosing of the first subject, the Safety Review Committee Charter will be finalised detailing the evaluation procedure and processes for immediate communication between sites.

Unacceptable LSR scores, safety and tolerability events:

Unacceptable safety and tolerability events in an individual subject are defined as 1) clinically relevant signs or symptoms observed, which in the opinion of the investigator are deemed unacceptable or 2) one or more of the following LSRs:

- Grade 4 crusting
- Grade 4 erosion / ulceration
- Grade 4 vesiculation / pustulation extending significantly outside the treatment area

Or two or more of the following:

- Grade 4 erythema
- Grade 3 crusting
- Grade 4 swelling extending significantly outside the treatment area
- Grade 3 erosion / ulceration
- Grade 3 vesiculation / pustulation

Criteria for terminating the trial:

The trial will be terminated if the perception of the benefit/risk ratio (judged from clinical symptoms, signs and/or (S)AEs) becomes unfavorable for the continuation of the trial.

- Any decision regarding premature termination of the entire trial will be made after mutual agreement between the Investigator and the sponsor.
- The sponsor reserves the right to cancel the trial at any time
- Due to the design of the trial, there are no statistical criteria for trial termination.
- The cumulative frequencies of subjects with unacceptable LSRs, safety and tolerability events (as defined above) that will strongly support the decision for trial termination are:

- 2 out of 3 subjects with unacceptable LSRs, safety and tolerability events after Cohort 1
- 3 out of 9 subjects with unacceptable LSRs, safety and tolerability events after Cohort 2 (cumulative)
- 5 out of 15 subjects with unacceptable LSRs, safety and tolerability events after Cohort 3 (cumulative)

13 Electronic Case Report Forms and Data Handling

13.1 Electronic Case Report Forms (eCRFs)

Data will be collected by means of Electronic Data Capture (EDC). The investigator or staff authorised by the investigator must enter subject data into electronic CRFs. Data recorded in the electronic CRFs must be accessible to site staff through a secure internet connection immediately after entry. The eCRFs must be maintained in an up-to-date condition at all times.

The investigator must electronically sign all CRFs used. This signature information (including date of signature) will be kept in the audit trail and cannot be altered. Any correction(s) made by the investigator or authorised site staff to the eCRF after original entry will be documented in the audit trail. Changes to data, already approved, will require the re-signature of the investigator. The person making the change and the date, time and reason for the change will be identified in the audit trail.

For archiving purposes, each investigator must be supplied with a copy of the eCRFs for all subjects enrolled at the trial site via an electronic medium at completion of the trial and before access to the eCRF is revoked. Audit trail information must be included. eCRFs must be available for inspection by authorised representatives from LEO (e.g. audit by the quality assurance department), from regulatory authorities and/or IEC/IRBs.

13.2 Data Handling

Subject data should be entered into the eCRF as soon as possible after the visit in accordance with the time requirements described in the Clinical Trial Agreement with the site. 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, whether generated by the system or by a user, will be in an electronic format. This systematic validation will ensure that a clean and consistent database is provided prior to the statistical analysis being performed.

13.3 Source Data

For all data recorded, the source document must be defined in a source document agreement at each trial site. There must only be one source defined at any time for any data elements.

The trial monitor will check the eCRFs for accuracy and completeness by verifying data recorded in the eCRF against source data to ensure such records are consistent.

Source data should as a general rule be recorded in the subject's medical record or other defined document normally used at the trial site. Source data not normally collected as a routine part of the clinical practice at the site may be entered on a worksheet. Clinical assessments/safety evaluations must be signed by medically qualified (sub)investigators.

- If the worksheet does not become part of the subject's medical record, the following should as a minimum be added to the subject's medical record:
- Date(s) of conducting the informed consent process (date of enrolment) including date of provision of subject information
- Subject ID
- Randomisation code number (if applicable)
- The fact that the subject is participating in a clinical trial in acne including treatment arms of LEO 43204 gel and vehicle gel once daily for up to three consecutive days
- Other relevant medical information

13.4 Trial Monitoring

During the course of the trial, the monitor will visit the trial site to ensure that the protocol and GCP are adhered to, that all issues have been recorded to perform source data verification, and to monitor drug accountability.

The first monitoring visit should be performed as soon as possible after First Subject First Visit (FSFV) and no later than 4 weeks after.

The monitoring visit intervals will depend on the trial site's recruitment rate, the compliance of the trial site with the protocol and GCP.

In order to perform their role effectively, monitors and persons involved in quality assurance and inspections will need direct access to source data, e.g. medical records, laboratory reports, appointment books, etc. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition, relevant

site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).

14 Handling of an Urgent Safety Measure

An Urgent Safety Measure is a measure taken to implement an action/protocol deviation under an emergency. This is defined within the EU Directive as *"...the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the subjects, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard.*" (Article 10(b) of Directive 2001/20/EC).

If the investigator becomes aware of information that necessitates an immediate change in the clinical trial procedure or a temporary halt to the clinical trial in order to protect clinical trial subjects from any immediate hazard to their health and safety, the investigator can do so without prior approval from LEO, regulatory authority(ies) or IRB(s)/IEC(s).

The investigator must immediately inform LEO - by contacting the ICTM or medical expert - of this change in the clinical trial procedure or of the temporary halt providing full details of the information and the decision making process leading to the implementation of the urgent safety measure.

LEO must act immediately upon receipt of the urgent safety measure notification in accordance with the internal procedures.

15 Quality Assurance/Audit

The clinical trial will be subject to audits conducted by LEO or inspections from domestic or foreign regulatory authorities or from IRBs/IECs. Audits and inspections may take place during or after the trial. The investigator and the site staff as well as LEO staff have an obligation to cooperate and assist in audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial site relevant to the clinical trial. This includes permission to examine, verify and reproduce any records and reports that are important to the evaluation of the trial.

If the trial site is contacted for an inspection by competent authorities, LEO must be notified immediately.

16 Completion of Trial

16.1 Trial Completion Procedures

Trial enrolment will be stopped at the trial site when the total requested number of subjects for the clinical trial has been obtained.

Upon completion of the clinical trial, LEO must undertake arrangements for the collection and disposal of any unused trial material that the investigator is not required to keep in his/her files.

16.1.1 Criteria for Premature Termination of the Trial and/or Trial Site

LEO, the investigator, the IRB/IECs or competent authorities may decide to stop the trial, part of the trial or a trial site at any time, but agreement on procedures to be followed must be obtained.

If a trial is suspended or prematurely terminated, the investigator must inform the subjects promptly and ensure appropriate therapy and follow-up. As specified by applicable regulatory requirements, the investigator or LEO must promptly inform IRB/IECs and provide a detailed written explanation. Relevant competent authorities must be informed.

The trial must be terminated if the perception of the benefit/risk ratio (judged from clinical signs and symptoms, (S)AEs and/or remarkable safety laboratory changes) becomes unfavorable for the continuation of the trial.

16.2 Provision for Subject Care Following Trial Completion

After the completion of the trial, the subjects will be treated at the investigator's discretion or referred to other physician(s) according to standard practice.

16.3 Archiving of Trial Documents

The investigator at each trial site must make arrangements to store the essential trial documents including the Investigator Trial File (ICH E6, Guideline for Good Clinical Practice) until LEO informs the investigator that the documents are no longer to be retained or longer if required by local regulations.

In addition, the investigator is responsible for the archiving of all relevant source documents so that the trial data can be compared against source data after the completion of the trial (e.g. in case of an inspection from regulatory authorities).

The investigator is required to ensure the continued storage of the documents even if the investigator leaves the clinic/practice or retires before the end of the required storage period.

The destruction process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

17 Ethics and Regulatory Authorities

17.1 Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and Regulatory Authorities

Written approval or favourable opinion must be obtained from relevant IRB/IECs prior to the enrolment of subjects.

Any amendments to the approved clinical trial must be approved by/receive favorable opinion from relevant IRBs/IECs and regulatory authorities as required prior to the implementation.

The appropriate regulatory authority(ies) must be notified of/approve the clinical trial, as required.

17.2 Ethical Conduct of the Trial

This clinical trial must be conducted in accordance with the principles of the revision current at the start of the trial of the World Medical Association (WMA), Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects.

17.3 Subject Information and Informed Consent

All subjects shall receive written and verbal information concerning the clinical trial. This information will emphasise that participation in the clinical trial is voluntary and that the subject may withdraw from the clinical trial at any time and for any reason. All subjects will be given an opportunity to ask questions and will be given sufficient time to consider before consenting.

The subject’s signed and dated informed consent to participate in the clinical trial must be obtained prior to any clinical trial related procedure being carried out in accordance with ICH GCP (4.8) and all applicable laws and regulations.

17.4 Processing of Personal Data

This protocol specifies the personal data on trial subjects (e.g. age, gender, health condition, height, medical history, test results, etc.) which shall be collected as part of the trial and processed during and after trial completion.

Personal data collected as part of the clinical trial will be transferred to/from the institution/investigator and LEO.

Processing of personal data on behalf of LEO requires a written agreement between LEO and the relevant party which covers collection, processing and transfer of personal data in the clinical trial. In certain cases an agreement on transfer of personal data may also be required.

Investigators and LEO must ensure that collection, processing and transfer of personal data are in compliance with national legislation on data protection and privacy.

The investigator/institution may be considered as data controller when they wish to use personal data collected in the clinical trial for their own purpose such as publication of clinical trial results.

Subjects must be asked to consent to the collection, processing and transfer of their personal data to EU and non-EU countries for the purpose of conducting the clinical trial, research and development of new or existing products/services, improving existing products/services, applying for marketing authorisations for products/services, marketing of products/services and other related activities.

If required, LEO has obtained the necessary authorisations for the processing by LEO of personal data collected in the trial.

18 Insurance

LEO has taken out relevant insurances covering the subjects in the present clinical trial in accordance with applicable laws and regulations.

19 Use of Information

This clinical trial protocol as well as all other information, data and results relating to this clinical trial and/or to the investigational product(s) is confidential information of LEO and shall not be used by the investigator for purposes other than this clinical trial.

The investigator agrees that LEO may use any and all information, data and results from this clinical trial in connection with the development of the investigational product(s) and, therefore, may disclose and/or transfer information, data and/or results to other investigators, regulatory authorities and/or commercial partners.

20 Publication

Basic information of this clinical trial will be posted on the website: www.clinicaltrials.gov before the first subject enters into the clinical trial (16, 17).

Results will be made available on LEO's web site according to LEO's position on access to clinical trial information.

After the clinical trial has been completed or terminated and all data have been received, defined as database lock of the clinical trial, the investigator shall have the right to publish the results from the clinical trial generated by the investigator, subject to the following notice requirements.

Prior to submitting or presenting a manuscript relating to the clinical trial to a publisher, reviewer or other outside person, the investigator shall provide to LEO a copy of all such manuscripts, and LEO shall have rights to review and comment. Upon the request of LEO, the investigator shall remove any confidential information (other than results generated by the investigator) prior to submitting or presenting the manuscripts. The investigator shall, upon the request of LEO, delay the publication or presentation to allow LEO to protect its inventions and other intellectual property rights described in any such manuscripts. In case the first multi-centre publication is still ongoing and has not been made public at the time of notification, LEO and the Writing Committee may also delay the publication or presentation if the manuscript is deemed to harm the ongoing multi-centre publication.

In case of publications made by the investigator after the first multi-centre publication has been published, the above-mentioned requirements must be followed.

LEO also subscribes to the joint position of the innovative pharmaceutical industry (18) for public disclosure of clinical trial results in a free, publicly accessible database, regardless of outcome.

21 Responsibilities

The International Coordinating Investigator is responsible for the approval of the (Consolidated) Clinical Trial Protocol, Clinical Trial Protocol Amendment(s) and the Clinical Trial Report as agreed to in an international coordinating investigator agreement.

22 List of Abbreviations

AESI	Adverse Events of Special Interest
ADR	Adverse Drug Reaction
AE	Adverse Event
AK	Actinic keratosis
ALA	Aminolaevulinic acid
AV	Acne vulgaris
CDMS	Clinical Data Management System
CMO	Contract Manufacturing Organisation
eCRF	Electronic Case Report Form
CRO	Contract Research Organisation
EDC	Electronic Data Capture
GCP	Good Clinical Practice
GPV	Global Pharmacovigilance
ICH	International Conference on Harmonisation
ICTM	International Clinical Trial Manager
IEC	Independent Ethics Committee
IGA	Investigator Global Assessment
IP	Investigational Product
IPL	Intense pulsed light
IRB	Institutional Review Board
KA	Keratoacanthoma
LSR	Local Skin Response
NLCRA	National Lead Clinical Research Associate
PDT	Photodynamic therapy
QoL	Quality of Life
SRC	Safety Review Committee
SAE	Serious Adverse Event
SCC	Squamous Cell Carcinoma
SOP	Standard Operating Procedure

SUSAR	Suspected Unexpected Serious Adverse Reaction
TA	Treatment area
TSQM	Treatment Satisfaction Questionnaire
VPN	Virtual Private Network
WMA	World Medical Association

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24 List of Appendices

25 Appendix 1: Protocol Summary

Name of finished/ investigational product	LEO 43204 gel 0.018%
Name of active substance	LEO 43204
Title of trial/trial ID/	Explorative trial evaluating the efficacy, tolerability and safety of LEO 43204 applied in a split-face (left/right) topical design in adults with moderate to severe acne / EXP-1223
International Coordinating Investigator	Hala Koudsi, M.D.
Sponsor's name/ address	LEO Pharma A/S, Industriparken 55, 2750 Ballerup, Denmark
Estimated number of trial sites and distribution	Single site in USA
Trial period	Planned date of enrolment of first subject: Q2-2016 Planned date of completion of last subject: Q4-2016
Main objective(s)	To assess the efficacy of treatment with LEO 43204 gel and vehicle gel on acne vulgaris disease severity 12 weeks after end of treatment. Treatment is defined as once daily application of LEO 43204 gel and vehicle gel for up to 3 days
Methodology	Phase 2a, Single centre, prospective, randomised, vehicle-controlled, double-blinded, split-face (left/right) design trial
Number of subjects to be enrolled	Planned to enroll 40 subjects Planned to complete 30 subjects
Main criteria for inclusion	• Subjects should be diagnosed with moderate to severe acne vulgaris of the face. • Fitzpatrick skin types I-III (due to lack of safety data for the investigational product in darker skin types) • Lesions should be relatively symmetrical in appearance on both sides of the face (asymmetrical disposition of acne lesions defined as: the number of acne lesions on any hemiface is greater than twice the number on the other hemiface for either inflammatory or non-inflammatory lesions). • Male or female aged 18 to 35 years inclusive.

Main criteria for exclusion	• Subjects with nodulocystic acne, acne conglobata, acne fulminans, secondary acne (e.g. chlor-acne, drug-induced acne). • Fitzpatrick skin types IV-VI Subjects in whom the investigator would recommend systemic therapy to prevent risk of scarring due to current disease severity of acne vulgaris. • Subjects with excessive facial hair, facial skin disorders or skin reactions that may interfere with trial assessments (including but not limited to, actinic keratosis, eczema, psoriasis, seborrheic dermatitis, rosacea, acute or recent sunburn). • Known sensitivity or allergy to any of the ingredients in the vehicle gel or IP. • Current participation in any other interventional clinical trial orpreviously enrolled in an interventional clinical trial which in the opinion of the investigator may interfere with the interpretation of the trial results. • Female subjects who are pregnant, of child-bearing potential and who wish to become pregnant during the trial, or who are breast feeding. Prohibited Therapies and/or Medications within 6 Month prior to Day 1 (Visit 2). 1. Treatment with systemic retinoids Prohibited Therapies and/or Medications within 1 month prior to Day 1 (Visit 2). 2. Treatment of the face with topical retinoids 3. Treatment with systemic antibiotics 4. Treatment in the face with ultraviolet light A (UVA) or ultraviolet light B (UVB) or intensive solar exposure. 5. Treatment in the face with light chemical peel 6. Treatment with systemic medications that suppress the immune system (e.g. cyclosporine, prednisolone). Prohibited Therapies and/or Medications within 2 weeks prior to Day 1 (Visit 2). 7. Treatment within 5 cm from the treatment area with topical drugs

	or cosmetics containing benzoyl peroxide, antibiotics, keratinolytic agents such as alpha- and beta- hydroxy acids, including glycolic acid, lactic acid and other fruit acids, salicylic acid, urea, soaps containing antibacterial agents such as skin fresheners/astringents or aftershave products)
Investigational product(s)	LEO 43204 gel 0.018%. Each visit kit should contain 1 tube with active gel and 1 tube with vehicle gel, to be handled in the hospital clinic on Day 1, Day 2 and Day 3, respectively. The label on the tubes will be colored as green to be applied on the right side of the face and red to be applied on the left side of the face.
Investigational reference product(s)	Vehicle gel. Each kit will be generic and the site personnel will add the randomisation number when assigned to the subject. Each kit contains 2 unit-dose tubes for topical administration
Duration of treatment	Treatment for up to 3 consecutive days with a follow-up period of 12 Weeks
Main assessments	Acne lesion (non-inflammatory and inflammatory lesions) counts in treatment areas Investigator Global Assessment of acne severity in treatment areas Tolerability, safety and Local Skin Responses Acne related quality of life and treatment satisfaction questionnaires
Primary endpoint	Count of total (inflammatory and non-inflammatory) lesions in the treatment area at Week 12.
Secondary endpoint(s)	Count of inflammatory lesions in the treatment area at Week 12. Count of non-inflammatory lesions in the treatment area at Week 12. Investigator's Global Assessment of the treatment area at Week 12.
Statistical methods	Lesion count will be analysed by a ANCOVA model with treatment, site and baseline count of total lesions as fixed effects and subject as random effect. Comparison between active and vehicle gel will be done by means of a t-test on the estimated treatment contrast in the model. Investigator Global Assessment will be analysed by descriptive statistics of disease severity by treatment and at Week 12. Desriptive statistics will show frequencies for each score.

For submission to IEC/IRBs and/or regulatory authorities, attach schedule of trial procedures (Section 8.1)

26 Appendix 2: Tape lifting procedure and biomarker analyses

Tape lifting procedure:

Skin contents will be collected from the subjects as described in 8.1Schedule of Trial Procedures for inflammatory marker analysis, using D-squame Stripping Discs (CuDerm, Dallas, TX). Apply the tape strip to the treatment area, smooth side down, pressing down to ensure good contact with skin. Slowly and carefully peel off starting at edges, pulling toward center and place the strip immediately in an Eppendorf tube for storage until analysis. For further details refer to the Lab Manual.

Biomarker analyses

Expression of inflammatory mediators such as, but not limited to, IL-1, IL-6, IL-8, IL-10 and TNF-α will be analyzed from tape strips sampled from the treatment areas. We hypothesize that treatment with ingenol mebutate may modulate the levels of pro-inflammatory mediators, including IL-1, TNF-α and IL-8. Recently, a non-invasive method of detecting changes in cytokine expression in skin has been demonstrated (19). Using a similar technique, we will compare the changes in expression of inflammatory mediators before and after topical application of LEO 43204 gel or vehicle gel as one of the exploratory endpoints. Skin samples will be collected using a tape stripping method as described previously in a psoriasis trial (20). Samples will be used to isolate RNA and mRNA expression of inflammatory mediators will be determined by real-time PCR using the Fluidigm Platform at AROS Applied Biotechnology A/S, Denmark For details, see Lab Manual.

27 Appendix 3: Skin photography

Using a standard digital camera three photographs (left side, frontal, right side) will be taken of the face .Exposure and distance will be controlled to provide optimal images. The site staff will be trained in using the camera.

Images should be obtained prior to samplings for biomarkers and microbiome analyses.

Images will be uploaded from the clinical site to Canfield Scientific, Inc. (253 Passaic Avenue, Fairfield, NJ) for quality control and de-identification.

28 Appendix 4: Microbiome collection and profile analysis

Microbiome collection

Skin contents for microbiome analyses will be collected from the subjects as described in 8.1Schedule of Trial Procedures. The collection swab (CatchAll®Sample Collection Swab, Epicenter) is moistened and the treatment area is swabbed for 30s rubbing the swab back and forth about 50 times applying firm pressure. The swab is then stored until microbiome analysis. Details on collection and storage are described in the Lab Manual.

Microbiome profile analysisDNA will be extracted using the MoBio UltraClean Microbial DNA isolation kit. Microbial sequencing will be performed on the Illumina MiSeq next generation sequencing platform at the UCLA Sequencing and Genotyping Core Laboratory as per protocol, refer to the Lab Manual.

29 Appendix 5: Subject Global Cosmetic Score

Subject Self-assessment Questionnaire for Global Cosmetic Score

In each row below, please check the box that most closely matches your judgement of how your skin looks and feels today compared to before you were treated with the trial drug in this clinical trial.

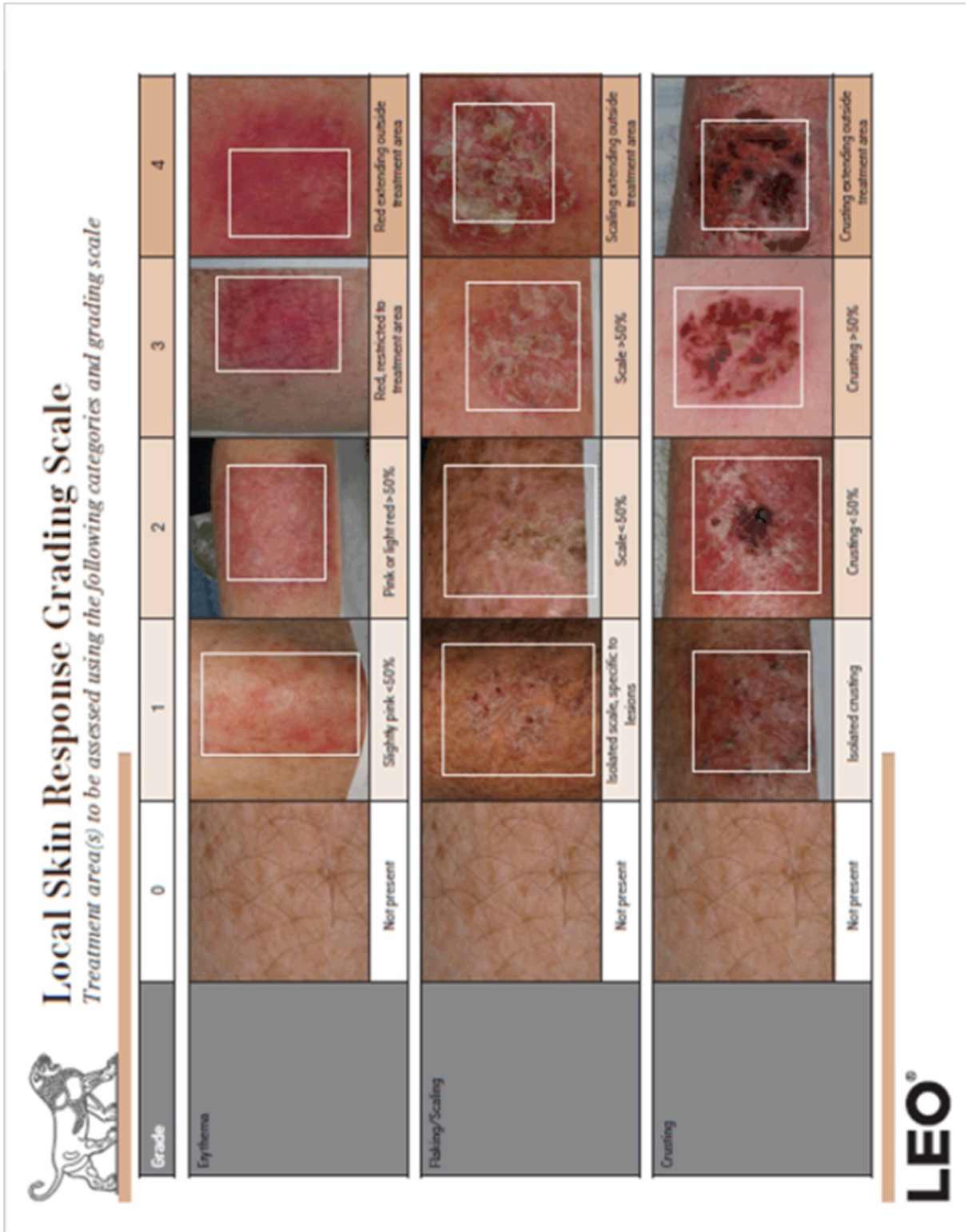
Right side

	Much worsened	Somewhat worsened	No change	Somewhat improved	Much improved
Overall appearance of the treatment areas					
Overall feel of the treatment areas					

Left side

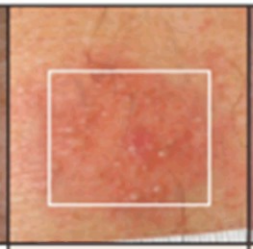
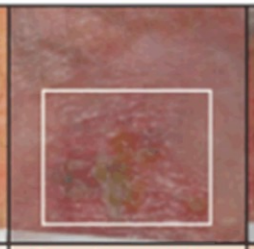
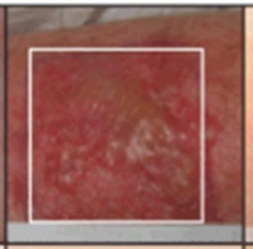
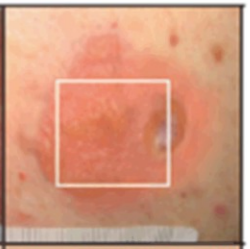
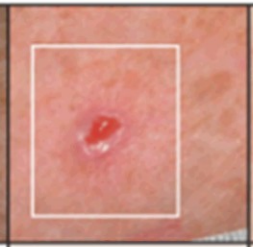
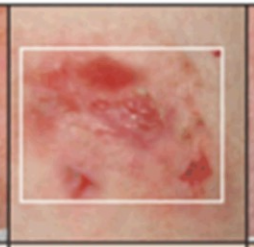
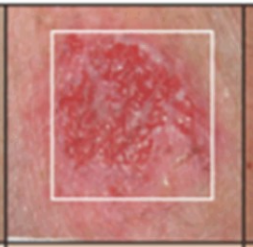
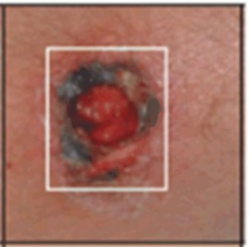
	Much worsened	Somewhat worsened	No change	Somewhat improved	Much improved
Overall appearance of the treatment areas					
Overall feel of the treatment areas					

30 Appendix 6: Local Skin Response Grading Scale



Local Skin Response Grading Scale

Treatment area(s) to be assessed using the following categories and grading scale

Grade	0	1	2	3	4
Swelling	Not present	Slight, lesion specific oedema	Palpable oedema extending beyond individual lesions	Confluent and/or visible oedema	Marked swelling extending outside treatment area
Vesiculation/ Pustulation					
	Not present	Vesicles only	Transudate or pustules, with or without vesicles <50%	Transudate or pustules, with or without vesicles >50%	Transudate or pustules, with or without vesicles extending outside treatment area
Erosion/ Ulceration					
	Not present	Lesion specific erosion	Erosion extending beyond individual lesions	Erosion >50%	Black eschar or ulceration

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31 Appendix 7: Definitions of Adverse Events and Serious Adverse Events

31.1 Adverse Event Definition

An adverse event is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable 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. (ICH Harmonized Tripartite Guideline for Good Clinical Practice, E6 (R1)).

This definition includes:

- accidental injuries, events related to trial procedures, reasons for any unfavourable and unplanned change in medication (drug and/or dose), clinically significant worsening of pre-existing conditions, or reasons for admission to hospital or surgical procedures unless these were planned before enrolment. It also includes AEs commonly observed and AEs anticipated based on the pharmacological effect of the investigational product. In addition, any laboratory abnormality assessed as clinically significant by the (sub)investigator must be recorded as an AE.

31.2 Serious Adverse Event Definition

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

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation. Planned hospitalisation or planned prolonged hospitalisation do not fulfill the criteria for being an SAE but should be documented in the subject’s medical record.
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

or

- is a medically important condition. Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples are intensive treatment in an emergency room or at home for allergic broncospasm, blood dyscrasias and convulsions that do not result in hospitalization, development of drug dependency or drug abuse.

32 Appendix 8: Classification of Adverse Events

32.1 Severity

The *severity* of the AE should be described in terms of mild, moderate or severe according to the (sub)investigator's clinical judgement.

Mild	An adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	An adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	An adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

If the severity of an AE worsens, a new AE should be recorded.

32.2 Causality

The *causal relation* of the AE to the use of the investigational product should be described in terms of probable, possible or not related according to the following:

Probably related	Follows a reasonable temporal sequence from administration of the investigational product. Could not be reasonably explained by the subject's clinical state, environmental or toxic factors or other therapies administered to the subject. Follows a known pattern of response to the investigational product. Disappears or decreases on cessation or reduction in dose of the investigational product. Reappears or worsens upon re-challenge.
Possibly related	Follows a reasonable temporal sequence from the administration of the investigational product. Could also be reasonably explained by the subject's clinical state, environmental or toxic factors or other therapies administered to the subject. Follows a known pattern of response to the investigational product.
Not related	Does not follow a reasonable temporal sequence from administration of the investigational product. Is better explained by other factors like the subject's clinical state, environmental or toxic factors or other therapies administered to the subject. Does not reappear or worsen upon re-challenge. Does not follow a known pattern of response to the investigational product.

32.3 Outcome

The *outcome* of the event should be classified and handled as follows:

Recovered/ resolved	The event has stopped. The stop date of the event must be recorded.
Recovering/ resolving	The subject is clearly recovering from an event. The event is not yet completely resolved.
Not recovered/ not resolved	Event is still ongoing.
Recovered with sequelae	The event has reached a state where no further changes are expected and the residual symptoms are assumed to persist. An example is hemiparesis after stroke. The stop date of the event must be recorded. In case of a SAE, the sequelae should be specified.
Fatal	The subject has died as a consequence of the event. Date of death is recorded as stop date for the AE.
Unknown	Unknown to (sub)investigator, e.g. subject lost to follow-up.

33 Appendix 9: Contact list of LEO, protocol authors, vendors, trial committees and coordinating investigators

Contact details for the international clinical trial manager (ICTM), national lead CRA (NLCRA), medical expert and safety scientist/safety physician are provided to participating trial sites outside the protocol on a list of LEO representatives which is included in clinical trial applications.

Sponsor

LEO Pharma A/S (referred to as 'LEO' in this clinical trial protocol) is the sponsor of the clinical trial:

LEO Pharma A/S
Industriparken 55
DK-Ballerup

Protocol Author(s)

Hala Koudsi, MD, International Coordinating Investigator

PPD, MD, Ph.D, UCLA

PPD, ICTM, LEO Pharma A/S

PPD, MD, Senior Scientist, LEO Pharma A/S

PPD, Senior Scientist, LEO Pharma A/S

PPD, Biostatistician, LEO Pharma A/S

PPD, MSc Pharm., PV Advisor, LEO Pharma A/S

PPD, Medical Writer, LEO Pharma A/S

Trial Committees

Safety Review Committee members

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PPD , ICTM, LEO Pharma A/S, Industriparken 55, 2750 Ballerup, Denmark, Tel.: +45 PPD , email: PPD @leo-pharma.com

Contract Research Organisations (CROs)/vendors

PPD , PPD , PPD , PPD , PPD will be responsible for providing a portal to upload, de-identify and store digital photographs of treatment areas in the faces of the trial subjects , as agreed to in a Service Agreement/Contract

PPD PPD , PPD , PPD , PPD PPD will be responsible for providing electronic data capture and IWRS services as agreed to in a Service Agreement/Contract.

PPD PPD PPD PPD PPD PPD PPD will be responsible for analyzing of the Microbiome

PPD , PPD , PPD , PPD PPD PPD will be responsible for analyzing of the Biomarkers

34 Appendix 10: Identifying and Documenting the Treatment Area

Identifying and Documenting the Treatment Area

On each cheek of enrolled subjects representative areas of approximately 36 cm^2 (6cm ×6 cm) are selected as treatment areas by the investigator.

These TAs area will be documented using a '3-point landmark technique' on the study transparencies.

Instructions are provided below. Transparencies and markers will be provided to the trial sites.

Three point landmark technique for each study transparency:

1. Complete information on the transparency using a permanent marker.
2. Place the transparency over the treatment area and cut a hole for the nose.
3. Map and label at least 3 anatomical landmarks on the transparency which are in the vicinity of the treatment area. These landmarks should not change during the trial (e.g., scars, moles, birthmarks, bony landmarks, etc.)
4. Mark the outline of the treatment area on the provided transparency.
5. Use the transparency to re-locate the treatment area for subsequent trial visits. When realigning the transparency, use the documented anatomical landmarks to accurately duplicate transparency placement.
6. Retain the transparency as part of the subject's source documents.

35 Appendix 11: Acne QoL

Acne-Specific Quality of Life Questionnaire (Acne-QoL)

(Please check one box for each question)

1 In the past WEEK, how unattractive did you feel because of your facial acne?

extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

2 In the past WEEK, how embarrassed did you feel because of your facial acne?

extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

3. In the past WEEK, how self-conscious (uneasy about oneself) did you feel about your facial acne?

Extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

4 In the past WEEK, how upset were you about having facial

extremely ☐ very much ☐ quite a bit ☐ somewhat ☐ a good bit ☐ a little bit ☐ not at all ☐

5. In the past WEEK, how annoyed did you feel at having to spend time every day cleaning and treating your face because of your facial acne?

extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

6. In the past WEEK, how dissatisfied with your self-appearance did you feel because of your facial acne?

extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

7. In the past WEEK, how concerned or worried were you about not looking your best because of your facial acne?

extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

8. In the past WEEK, how concerned or worried were you that your acne medication/products were working fast enough in clearing up the acne on your face?

extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

9. In the past WEEK, how bothered did you feel about the need to always have medication or cover-up available for the acne on your face?

extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

10. In the past WEEK, how much was your self-confidence (sure of yourself) <u>negatively</u> affected because of your facial acne?

extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

11. In the past WEEK, how concerned or worried were you about meeting new people because of your facial acne?

extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

12. In the past WEEK, how concerned or worried were you about going out in public because of your facial acne?

extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

13. In the past WEEK, how much was socializing with people a problem for you because of your facial acne?

extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

14. In the past WEEK, how much was interacting with the opposite sex (or same sex if gay or lesbian) a problem for you because of your facial acne?

extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

15. In the past WEEK, how many bumps did you have on your face?

Extensive ☐ A whole lot ☐ A lot ☐ A moderate amount ☐ Some ☐ Very Few ☐ No ☐

16. In the past WEEK, how many bumps full of pus did you have on your face?

Extensive ☐ A whole lot ☐ A lot ☐ A moderate ☐ Some amount ☐ Very Few ☐ None ☐

17. In the past WEEK, how much scabbing from your facial acne did you have?

Extensive ☐ A whole lot ☐ A lot ☐ A moderate ☐ Some amount ☐ Very Few ☐ None ☐

18. In the past WEEK, how concerned or worried were you about scarring from your facial acne?

extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

19. In the past WEEK, how oily was your facial skin?

extremely ☐ very much ☐ quite a bit ☐ a good bit ☐ somewhat ☐ a little bit ☐ not at all ☐

36Appendix 12: TSQM II

A derived score for each of the four dimensions of the TSQM (effectiveness, side effects, convenience, global satisfaction) will be calculated for each subject. For each of the TSQM dimensions the derived score will be summarised using the mean, SD, median, minimum and maximum values at week 12 for each treatment group.

TSQM (Version II): Treatment Satisfaction Questionnaire for Medication

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat the condition?
    1. Extremely Dissatisfied
    2. Very Dissatisfied
    3. Dissatisfied
    4. Somewhat Satisfied
    5. Satisfied
    6. Very Satisfied
    7. Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves symptoms?
    1. Extremely Dissatisfied
    2. Very Dissatisfied
    3. Dissatisfied
    4. Somewhat Satisfied
    5. Satisfied
    6. Very Satisfied
    7. Extremely Satisfied

3. As a result of taking this medication, do you experience any side effects at all?
    1. Yes
    2. No

4. How dissatisfied are you by side effects that interfere with your physical health and ability to function (e.g., strength, energy levels)?

1. Extremely Dissatisfied
2. Very Dissatisfied
3. Somewhat Dissatisfied
4. Slightly Dissatisfied
5. Not at all Dissatisfied

5. How dissatisfied are you by side effects that interfere with your mental function (e.g., ability to think clearly, stay awake)?

1. Extremely Dissatisfied
2. Very Dissatisfied
3. Somewhat Dissatisfied
4. Slightly Dissatisfied
5. Not at all Dissatisfied

6. How dissatisfied are you by side effects that interfere with your mood or emotions (e.g., anxiety/fear, sadness, irritation/anger)?

1. Extremely Dissatisfied
2. Very Dissatisfied
3. Somewhat Dissatisfied
4. Slightly Dissatisfied
5. Not at all Dissatisfied

7. How satisfied or dissatisfied are you with how easy the medication is to use?

1. Extremely Dissatisfied
2. Very Dissatisfied
3. Dissatisfied
4. Somewhat Satisfied
5. Satisfied
6. Very Satisfied
7. Extremely Satisfied

8. How satisfied or dissatisfied are you with how easy it is to plan when you will use the medication each time?

1. Extremely Dissatisfied
2. Very Dissatisfied
3. Dissatisfied
4. Somewhat Satisfied
5. Satisfied
6. Very Satisfied
7. Extremely Satisfied

9. How satisfied or dissatisfied are you by how often you are expected to use/take the medication?

1. Extremely Dissatisfied
2. Very Dissatisfied
3. Dissatisfied
4. Somewhat Satisfied
5. Satisfied
6. Very Satisfied
7. Extremely Satisfied

10. How satisfied are you that the good things about this medication outweigh the bad things?

1. Extremely Dissatisfied
2. Very Dissatisfied
3. Dissatisfied
4. Somewhat Satisfied
5. Satisfied
6. Very Satisfied
7. Extremely Satisfied

11. Taking all things into account, how satisfied or dissatisfied are you with this medication?
    1. Extremely Dissatisfied
    2. Very Dissatisfied
    3. Dissatisfied
    4. Somewhat Satisfied
    5. Satisfied
    6. Very Satisfied
    7. Extremely Satisfied

EXP-1223 Consolidated Clinical Trial Protocol 5 15-Sep-2016 - English

ELECTRONIC SIGNATURES

Electronic signature made within eDoc LEO by LEO Pharma A/S employees or employees of any LEO Pharma A/S affiliate located anywhere in the world, are to be considered to be legally binding equivalent of traditional handwritten signatures.

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Head of Tranlsational Medicine Approval	15-Sep-2016 16:04 GMT+02
PPD	Biostatistics Lead, Biostatistical Approval	18-Sep-2016 22:26 GMT+02