

# Clinical Trial Protocol

## Picato for the Treatment of Molluscum Contagiosum in Immunocompromised Patients

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

Sponsor:	Center for Clinical Studies
Collaborator	LEO Pharma
Trial ID:	IIS-PICATO-1386
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## **1 Clinical Trial Protocol Statement**

### **1.1 Approval Statement Center for Clinical Studies**

The following persons have approved this clinical trial protocol by printing his/her name below:

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Director of Clinical Research and Principal Investigator

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Sub-Investigator

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## 2 Trial Identification:

ClinicalTrials.gov number: Application pending

## 3 Introduction and Rationale

### 3.1 Molluscum Contagiosum

Molluscum contagiosum (MC) is a common skin infection in children caused by a poxvirus that is transmitted through direct skin-to-skin contact, fomites, or autoinoculation (1). In adults, it is less common and often sexually transmitted, with a greater predisposition for immunocompromised patients (2). MC is characterized by asymptomatic, discrete, smooth, flesh-colored, dome-shaped papules with central umbilication (3). In immunocompetent adults, lesions are usually confined to the genital area and adjacent regions of the skin (1). In patients with immunocompromised conditions, lesions can be widespread and even disfiguring (1,2,4,5). MC in immunocompromised patients are often resistant to conventional treatment used to treat those in immunocompetent patients (5). There is an unmet need for improved therapies for treatment of MC in immunocompromised patients.

### 3.2 Experience with Investigational Product

Ingenol mebutate (Picato, LEO Pharma), a macrocyclic diterpene ester, is the active agent in the sap of the plant *Euphorbia peplus*, which is known for its therapeutic effects in common skin lesions, including cancerous lesions (6). Preclinical studies have demonstrated that ingenol mebutate has a dual mechanism of action: rapid lesion necrosis and specific neutrophil-mediated, antibody-dependent cellular cytotoxicity (7,8). Picato was originally licensed as a field therapy for actinic keratosis (6). It has also been reported to be effective against anogenital warts and MC in immunocompetent patients (9,10). Picato gel is available in two strengths, 0.015% once daily for the face and scalp and 0.05% once daily for the trunk and extremities. The safety of all doses studied so far has been with an acceptable benefit-risk profile and no major safety concerns have been identified. Possible risks associated with use of Picato gel are summarized in Section 10.3.

### 3.3 Trial Rationale

The purpose of this trial is to provide evidence of the efficacy and safety of Picato gel in the treatment of subjects with MC in the setting of immunocompromised status. The trial duration is 24 weeks.

The primary efficacy endpoint is complete clearance of MCs in the treatment area at Week 4, with a secondary efficacy endpoint of partial clearance in the treatment area at Week 4. Assessment of long-term efficacy will be based on the percentage of subjects who sustain complete clearance of MCs in the treatment area at Week 24 and the percentage of subjects who clear MCs outside of the treatment area at Week 24.

Safety and tolerability endpoints will include development of local skin reactions (LSRs) including erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration, patient's global satisfaction as measured by Treatment Satisfaction Questionnaire of Medication (TSQM) v.9, and health-related quality of life (HQoL) as measured by EQ-5D-5L questionnaire.

For evaluation of safety, all subjects will be followed for AEs and Serious Adverse Events (SAEs) occurring in the treatment area from the signing of the informed consent form through completion of the study.

### 3.4 Justification for Dose

The selected dose for this trial is topically administered Picato 0.05% gel. The Picato gel 0.05% dose was chosen based on principal investigator's extensive clinical experience in treating immunocompromised patients with MC using the higher concentration. For subjects who cannot tolerate Picato 0.05% gel as judged by the sub(investigator), the lower concentration of 0.015% will be used.

### 3.5 Ethical Considerations

No children or other vulnerable subjects incapable of giving informed consent will be enrolled in this clinical trial. Furthermore, women who are pregnant, breastfeeding, or trying to become pregnant will not be enrolled in this clinical trial. Women of child-bearing potential have to agree to use an effective method of contraception to prevent pregnancy during the clinical trial. In addition, all female subjects of child-bearing potential will have a pregnancy test performed before, during and at End of Treatment to ensure that no fetuses are exposed to the IMP.

Altogether, the risks associated with participating in this clinical trial are considered very low and outweighed by the benefit of a potential future treatment option for MC in immunocompromised patients.

In accordance with the current version of the International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines, qualified medical personnel employed by LEO Pharma A/S and Center for Clinical Studies will be readily available to advise on trial-related medical questions.

In conclusion, the trial design chosen for this efficacy and safety trial on Picato is regarded as ethically justified and adherent with ethical requirements.

## 4 Trial Objectives

### 4.1 Primary Objective

- To evaluate the efficacy of Picato gel (0.05% and/or 0.015%) in MC in immunocompromised patients when applied topically once nightly for three consecutive nights

### 4.2 Secondary Objectives

- To evaluate the efficacy of Picato gel (0.05% and/or 0.015%) on patient's global satisfaction and health-related quality of life
- To evaluate the safety and tolerability of Picato gel (0.05% and/or 0.015%) in MC in immunocompromised patients when applied topically once nightly for three consecutive nights
- To evaluate the long-term efficacy of Picato gel (0.05% and/or 0.015%) in MC in immunocompromised patients over a 24-week period

## 5 Trial Endpoints

### 5.1 Primary Endpoint

- Complete clearance at Week 4, defined as no clinically visible MCs in the treatment area

### 5.2 Secondary Endpoints

- Partial clearance at Week 4, defined as at least 50% reduction in the number of clinically visible MCs in the treatment area

- Percentage of subjects who sustain complete clearance of MCs in the treatment area at Week 24
- Percentage of subjects who clear MCs outside of the treatment area at Week 24

### 5.3 Other Endpoints

#### Patient reported outcomes

- TSQM v.9, Global Satisfaction
- EQ-5D-5L, Index and Health Status

## 6 Trial Design

### 6.1 Overall Trial Design

This is a case series in subjects with MC in the setting of immunocompromised status.

Subjects will attend a screening visit where they will be assessed for eligibility. Eligible subjects will complete the baseline visit on the same day as the screening visit. There will be no washout period in this trial. Eligible subjects will be assigned Picato 0.05% gel at Visit 1. Two boxes, each containing 2 tubes of Picato 0.05% gel, will be dispensed to each subject at Visit 1. Subjects should use a new tube for each treatment day.

All subjects will apply gel using a cotton swab for 3 consecutive nights at home (Day 0, Day 1, Day 2). Subjects will be followed for 4 weeks after the first application of IP at Day 0 (3-day treatment period including 4-week follow-up period).

Subjects who have not achieved complete clearance in the treatment area at Week 4 will receive a second course of treatment for 3 consecutive nights (Day 28, Day 29, Day 30). These subjects will be followed for another 4 weeks after the first application of the second course of IP at Day 28 (3-day treatment period including 4-week follow-up period).

Subjects who have not achieved complete clearance in the treatment area at Week 8 will receive a third course of treatment for 3 consecutive nights (Day 56, Day 57, Day 58). These subjects will be followed for another 4 weeks after the first application of the third course of IP at Day 56 (3-day treatment period including 4-week follow-up period).

Residual erythema may be present and will not be considered lesions. All subjects will have follow-up visits at Week 16, Week 20, and Week 24 from the first application of IP.

The number of MCs within the treatment area and outside of the treatment area will be counted at every visit. The treatment area may be one contiguous area or up to two non-contiguous areas. The total treatment area should not exceed 100 cm<sup>2</sup>. Picato gel should be applied at least 2 hours before sleeping and be allowed to dry for at least 15 minutes after application. For subjects who cannot tolerate Picato 0.05% gel as judged by the sub(investigator), the lower concentration of 0.015% will be used. The treatment area will be identified and tracked with a transparency, which will capture both anatomical landmarks and the treatment area, to orient the patient and investigator to the treatment area over time.

### 6.2 Sample size

In total 10 subjects will be enrolled in the trial and all subjects will received Picato gel in either 0.05% or 0.015% concentration depending on subject's tolerability.

## 7 Trial Population and Withdrawal

### 7.1 Subject Eligibility

The (sub)investigator should only enroll subjects who meet all eligibility criteria, 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 visits specified in the "Schedule of Trial Procedures" (see Section 8.1)

Re-screening is allowed if the visit window cannot be complied with for practical reasons. Re-sampling or re-screening is not allowed if the subject has failed one of the inclusion or exclusion criteria.

### 7.2 Inclusion Criteria

1. Signed and dated informed consent has been obtained.
2. Male or non-pregnant female at least 18 years of age.
3. Subject must have an immunocompromised condition due to use of immunosuppressive therapies for cancer or autoimmune disease treatment or prevention of organ transplant rejection or due to an inherited condition that affects the immune system.
4. Subject has at least 10 clinically typical, visible and discrete MCs within a treatment area on either the face and/or trunk. Treatment area is defined as either:
  - One contiguous treatment area of at most 100 cm<sup>2</sup>
  - Two non-contiguous treatment areas totaling at most 100 cm<sup>2</sup>
5. Subject must be willing to forego any other treatments of MC on the face and/or trunk, including tanning bed use and excessive sun exposure, throughout the duration of the trial.
6. Subject is willing and able to participate in the study as an outpatient, making frequent visits to the study center during the treatment and follow-up periods, and to comply with all study requirements.
7. Female subjects of childbearing potential\* must have a negative urine pregnancy test prior to trial treatment.

\* A female is defined as not being of child-bearing potential if she is postmenopausal (at least 12 months with no menses without an alternative medical cause prior to screening) or surgically sterile (hysterectomy, bilateral salpingectomy or bilateral oophorectomy).

8. Female subjects of childbearing potential must be willing to use effective contraception at trial entry and until the last follow-up visit at Week 24.

Effective contraception is defined as follows:

- Abstinence (when this is in line with the preferred and usual life style of the subject).
- Vasectomized partner (given that the subject is monogamous).
- An intrauterine device.
- Double barrier method defined as condom in combination with diaphragm
- Hormonal contraceptive (oral hormonal birth control, estrogenic vaginal ring, percutaneous contraceptive patches, implants and injectables) for at least one menstrual cycle prior to enrollment.

### 7.3 Exclusion Criteria

1. Location of the treatment area
  - on the periorbital skin
  - within 5 cm of an incompletely healed wound
  - within 10 cm of a suspected basal cell carcinoma (BCC) or squamous cell carcinoma (SCC).
2. Previous participation in an ingenol mebutate trial.
3. Treatment with ingenol mebutate gel in the treatment area within 6 months or outside of the treatment area within 30 days prior to study treatment initiation.
4. Receipt of the following within 90 days prior to study treatment initiation:
  - interferons or interferon inducers
  - any dermatologic procedures or surgeries within the treatment area
5. Receipt of any topical prescription medications in the treatment area within 30 days prior to study treatment initiation.
6. Lesions in the treatment area have atypical clinical appearance (e.g. giant lesions greater than 5 mm, eczematous lesions, or folliculocentric lesions).
7. Active dermatologic conditions that may confound the diagnosis of MC or would interfere with assessment of treatment, such as scabies, cutaneous lymphoma, or psoriasis.
8. Clinical diagnosis/history or evidence of any medical condition that would expose a subject to an undue risk of a severe AE or interfere with assessments of safety and efficacy during the course of the trial, as determined by the (sub)investigator's clinical judgment.
9. Known history of infection with Human Immunodeficiency Virus (HIV).
10. History of melanoma.
11. History of chronic alcohol or drug abuse within 12 months prior to screening, or any condition associated with poor compliance as judged by the (sub)investigator.
12. Known or suspected allergy or reaction to any component of the IMP formulation.
13. Patients who have experienced a clinically important medical event within 90 days prior to study treatment initiation (e.g., stroke, myocardial infarction, etc).
14. Pregnant, breastfeeding, or lactating women.
15. Participation in any another interventional clinical trial within 30 days prior to study treatment initiation.

### 7.4 Subject Screening Log

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

### 7.5 Subject Identification List

The (sub)investigator must maintain a list of all subjects enrolled in the trial site including each subject's identity, date of enrollment 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 Visit 1 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.

## 7.6 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 judgement.
2. *Unacceptable AEs/LSRs*: any AEs or LSRs 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. If applicable, the subject's legal representative can withdraw the subject from the trial.
5. *Other reasons*: other reasons than stated above which require the subject to (be) withdraw(n) should be specified.
6. *Lost to follow-up*.
7. *Death*.

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

Subjects who discontinue treatment for any reason should remain in the trial until Week 24. All subjects should as a minimum be asked to complete the final efficacy assessment that correlates with their treatment course (Week 4, Week 8 or Week 12) and the final visit at Week 24. For subjects withdrawn from treatment or trial, AEs should be followed up as described in Section 9. Subjects withdrawn can be substituted.

Reason(s) for discontinuation from IMP and withdrawal from the trial must be recorded in the medical records (lack of efficacy, AE, withdrawal by subject, lost to follow-up, death, other).

### Lost to follow-up

A subject will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and if the trial site is not able to get in contact with the subject.

The following actions must be taken if a subject fails to return to the trial site for a required visit:

- The trial site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the trial.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, they will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.

## **8 Trial Schedule and Assessments**

### **8.1 Schedule of Trial Procedures**

**Panel 1 Schedule of trial procedures: first course of treatment and follow-up period**

	Screening/Baseline <sup>1</sup>	First course of treatment				Follow-up period			
Visit Number	1	2	3	4	5	14	15	16	Unscheduled/ Early Term <sup>9</sup>
Week	0	1	2	3	4	16	20	24	N/A
Day	0	7	14	21	28	112	140	168	N/A
Visit Window	N/A	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	N/A
Informed consent	X								
Inclusion/Exclusion	X								
Demographics	X								
Medical history	X								
Medication history	X								
Vital signs	X								
Height and weight	X								
Physical examination <sup>2</sup>	X				X				X
Urine pregnancy test <sup>3</sup>	X	X	X	X	X	X	X	X	X
Dermatological Assessment (Diagnosis)	X								
Identification of treatment area	X								
MC lesion count	X	X	X	X	X	X	X	X	X
LSR assessment	X	X	X	X	X	X	X	X	X
Adverse event(s)	X	X	X	X	X	X	X	X	X
Concomitant medications/procedures <sup>4</sup>	X	X	X	X	X	X	X	X	X
PROs and Questionnaires <sup>5</sup>	X	X	X	X	X	X	X	X	X
Subject instruction/Diary review	X	X	X	X	X	X	X	X	X
Dispense medication/diary	X				X <sup>6</sup>				
Collect medication/diary		X							
Assess subject compliance		X	X	X	X	X	X	X	X

**Panel 2 Schedule of trial procedures: second and third course of treatment**

	Second course of treatment <sup>7</sup>				Third course of treatment <sup>8</sup>			
Visit Number	6	7	8	9	10	11	12	13
Week	5	6	7	8	9	10	11	12
Day	35	42	49	56	63	70	77	84
Visit Window	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days
Informed consent								
Inclusion/Exclusion								
Demographics								
Medical history								
Medication history								
Vital signs								
Height and weight								
Physical examination <sup>2</sup>					X			X
Urine pregnancy test <sup>3</sup>	X	X	X	X	X	X	X	X
Dermatological Assessment (Diagnosis)								
MC lesion count	X	X	X	X	X	X	X	X
LSR assessment	X	X	X	X	X	X	X	X
Adverse event(s)	X	X	X	X	X	X	X	X
Concomitant medications/procedures <sup>4</sup>	X	X	X	X	X	X	X	X
PROs and Questionnaires <sup>5</sup>					X			X
Subject instruction/Diary review	X	X	X	X	X	X	X	X
Dispense medication/diary				X <sup>6</sup>				
Collect medication/diary	X				X			
Assess subject compliance	X	X	X	X	X	X	X	X

- 1) Screening and baseline visit will be done on the same day. There will be no washout period.
- 2) Abbreviated physical examination including general appearance, regional lymph nodes and dermatologic examination of the skin.
- 3) Only female subjects of child-bearing potential.

- 4) At Visit 1, procedures should be recorded as Medical/Surgical History.
- 5) Patient reported outcomes (PROs) and questionnaires include EQ-5D-5L and TSQM v.9.
- 6) Additional IP will be dispensed at Week 4 and/or Week 8 for subjects who have incomplete clearance of MC in the treatment area.
- 7) A second course of treatment is warranted only for subjects who have incomplete clearance MC in the treatment area at Week 4.
- 8) A third course of treatment is warranted only for subjects who have incomplete clearance MC in the treatment area at Week 8.
- 9) For unscheduled visits, only assessments that require follow-up will be conducted.

## 8.2 Subject Eligibility

Refer to Sections 7.2 and 7.3.

## 8.3 Demographics

Subject demographics will be recorded at Visit 1. The following will be recorded:

- 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

## 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 Medical/Surgical History

Medical history must be recorded at Visit 1:

- Skin disease history
- MC treatment history
- Other medical/surgical history within the previous 12 months

It must be recorded if the skin disease or the MC treatment was within the treatment area.

## 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.

## 8.7 Vital Signs

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

## 8.8 Pregnancy Test

In female subjects of child-bearing potential a urine pregnancy test must be performed at the trial site at visits indicated in Section 8.1.

## 8.9 Dermatological Assessments (Diagnosis)

Assessment and diagnosis of molluscum contagiosum must be confirmed by the sub(investigator) prior to study treatment initiation.

## 8.10 Concomitant Medications and Procedures

Concomitant medication is defined as any medication used by a subject during the clinical trial apart from the IP.

Use of concomitant medication must be recorded in the subject's medical record (treatment/drug name, total daily dose, indication and dates of start and stop) at visits indicated in Section 8.1. For topical treatment it must be recorded if the treatment is within 5 cm (appr. 2 inches) of the treatment area.

Procedures including body location, diagnosis, start/stop date must be recorded at visits indicated in Section 8.1. It must also be recorded if the procedure is inside the treatment area. Procedures reported by the subject at Visit 1, should be recorded as medical/surgical history.

### **8.11 Adverse Events**

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

### **8.12 Other Safety Assessments**

Local Skin Reactions (LSRs) Assessment of local skin reaction in the treatment area using the LSR Grading Scale will be performed as specified in Section 8.1. Local skin reactions 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 2: Local Skin Reaction Grading Scale. 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.

### **8.13 Patient Reported Outcomes**

The subject must make self-assessments at visits specified in the schedule of trial procedures (Section 8.1). Patient reported outcome measures should be completed prior to other assessments on the day of completion of the questionnaire. The subjects should be encouraged to answer all questions in the questionnaire.

#### EQ-5D-5L

EQ-5D-5L is a standardized generic measure of health related quality of life (11). The questionnaire asks about overall health today in 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The health profiles are associated with utilities that are often derived from the general population and that can be used to calculate Quality-Adjusted-Life-Years.

#### Treatment Satisfaction Questionnaire for Medication (TSQM)

TSQM v.9 is a generic questionnaire measuring subjects' satisfaction with the treatment (12). The questionnaire will ask questions relating to effectiveness, side effects, convenience and overall satisfaction.

### **8.14 Investigator Assessments**

#### Identification of the treatment area

At Visit 1, identification of the treatment area should be documented on a study transparency using three-point landmark technique (See Appendix 1: Identifying and Documenting the Treatment Area). The treatment area must be one contiguous area or two non-contiguous areas up to a maximum size of 100 cm<sup>2</sup>. At all subsequent visits, the transparency should be used to re-identify the treatment area for assessment of the treated skin.

#### MC count in the treatment area

The number of clinically typical and visible MCs present in the treatment area will be counted at Visit 1 (baseline MC count) and at subsequent visits as specified in the schedule of trial procedures (Section 8.1).

### **8.15 IP Dosing Diary and Subject Instruction**

Subject will be required to maintain an IP dosing diary to record the date and time of IP application. Subject will be provided with a Patient Safety and Study Instruction Sheet at baseline.

### **8.16 Dispensing and Returning of IP**

Refer to Section 10.6.

## **9 Adverse Events**

- AEs and SAEs are defined in Appendix 3: Definitions of Adverse Events and Serious Adverse Events.
- Classification of AEs in terms of severity, causality and outcome are defined in Appendix 4: Classification of Adverse Events.

### **9.1 Collection of Adverse Events**

All AEs and SAEs must be collected from the signing of the informed consent form and until the last follow-up visit at Week 24.

Abnormal findings observed at screening do not constitute AEs, but must be recorded in medical history.

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

AEs must be assessed by medically qualified personnel. A qualified physician must conduct all dermatologic examinations, LSR and AE evaluation of the treatment area.

At all visits, the subject will be asked a non-leading question by the (sub)investigator such as: “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.

### **9.2 Reporting of Adverse Events**

AEs reported by the subject or observed by the (sub)investigator must be recorded on the AE form 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 AE description and may be described as “in the treatment area”, “outside the treatment area” or “non-cutaneous”.

The duration of the AE must be reported by 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 4: Classification of Adverse Events.

### **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 Additional Reporting Requirements for Serious Adverse Events**

Any SAE must be reported to LEO on the (paper) SAE 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 or trial procedure, the action taken, the outcome to date, and a narrative description of the course of the event.

Any LSR classified as an SAE must be added to the AE form and in addition reported to LEO on the SAE form.

The completed SAE form must be scanned and e-mailed to the local safety contact person of LEO Entity using the following e-mail address [usdrugsafety@leo-pharma.com](mailto:usdrugsafety@leo-pharma.com) stating the following reference in the e-mail subject field: “PV report – IIS-PICATO-1386”.

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

The investigator must notify the local Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) of SAEs as required by current applicable legislation for the concerned country, however no later than fifteen (15) days after becoming aware of the case.

In addition, the Sponsor shall forward to the LEO local safety contact person any received customer complaints related to any LEO produce, and ensure that all Adverse Events and customer complaints are described in the Final Report.

Causally related 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 LEO ([usdrugsafety@leo-pharma.com](mailto:usdrugsafety@leo-pharma.com)) if the (sub)investigator becomes aware of them.

### **9.4 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 has been established, 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 Products**

### **10.1 Instructions to be Followed by Study Staff**

The following guidelines should be followed by the study staff when instructing the subjects on how to apply trial medication:

1. Ensure the subject follows the trial medication application guidance provided (see Section 10.2).
2. Ensure the treatment area has been marked on the study transparency with a permanent ink marker using the three-point landmark technique (see Appendix 1: Identifying and Documenting the Treatment Area).
3. Ensure that the treatment area has been sufficiently marked on the skin to assist with identification of the treatment area for subsequent applications.
4. Ensure the subject understands that a cotton swab should be used to apply trial medication and hands should be washed immediately after application. Contact with skin other than the treatment area must be avoided.
5. Ensure the subject understands that the trial medication must be stored in the refrigerator at home.
6. Ensure the subject is instructed to return all dispensed tubes to the site at Visit 2, 6 and/or 10 (Week 1, 5 and/or 9).
7. Ensure that the subject is provided with a Patient Safety and Study Instruction Sheet.

### **10.2 Trial Medication Application**

During each application (once nightly for 3 consecutive nights) a thin and wet layer of trial medication should be applied evenly on the treatment area.

Face: Exclude the nares, periorbital and perioral regions. For subjects with a beard, the amount applied should be reduced proportionally to the size of the beard.

Trunk: Include the buttock and genital regions. Exclude the neck.

Trial medication should not be applied in the beard. Subjects with sparse hair in the treatment area can be enrolled as long as the LSR and MC assessments are not compromised as judged by the (sub)investigator. For subjects with a beard, IP should be applied up to the line of the beard.

The forehead should be defined by the previous hairline and the lower part of the face should be defined by the jawline and the tip of the chin, respectively. The perioral region should be defined by the margins of the lips, and the periorbital region should be defined by the top of the eyebrows and the top of the

cheekbones, respectively. Trial medication should be applied to the nose from its upper part downwards, excluding the nares.

The following general treatment guidance should be noted:

- Subjects should not shave the treatment area during the treatment days.
- Trial medication should not be applied immediately after taking a shower and should be applied at least two hours before bedtime
- Subjects must avoid washing the treatment area 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 area gently using a mild soap.
- Subjects should avoid use of non-medicated/non-irritant salves/emollients on the treatment area during treatment days. Subjects should wash the treatment area using a mild soap before starting use of salves/emollients.
- Subjects should avoid use of make-up and sunscreens on the treatment area until 15 days after last IP application. Note: Eye-make-up within the periorbital area and lipstick is allowed.
- Subjects should avoid occluding the treatment area with tightly fitting clothing, hairpiece or jewelry.
- Subjects should be advised not to allow other persons (including children) and pets to come into contact with the treatment area 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) and should wear protective clothing over the treatment area when exposed to sunlight.

### **10.3 Precaution/Over Dosage**

#### **10.3.1 Skin Exposure**

The most common LSRs reported in previous clinical studies using Picato are erythema, flaking/scaling, and crusting. Less common LSRs include swelling/edema, vesiculation/pustulation, and erosion/ulceration. Completed clinical trials have shown LSRs to be transient and resolved within a couple of weeks.

In a low percentage of patients treated on face or scalp, swelling around the eyes or on the eyelids may develop to a point where it may be considered clinically significant. In such cases these AEs should be recorded as periorbital edema 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.

#### **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 patient 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 LEO.

### **10.3.3 Other Exposure**

Picato 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 delivered as commercial packages/bulk/filled containers needing filling and/or final labeling for clinical study use.

## **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.

At the site, the IP must be stored in a refrigerator at between 2°C and 8°C (36°F to 46°F). The refrigerator temperature must be monitored continuously and recorded. Do not freeze.

IP will be dispensed to the subjects at the site and will be applied at home. Subjects will be instructed to place the tubes in the home refrigerator as soon as possible. The tubes should be:

- stored sufficiently segregated from foodstuffs.
- stored safely to ensure against inadvertent exposure to non-participants (including children and pets).

## **10.6 Drug Accountability and Compliance Checks**

### **10.6.1 Drug Accountability**

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

The subject should return all dispensed IP, whether used or unused, at Visit 2, 6 and /or 10 (Week 1, 5 and/or 9). An inventory must be kept of the IP given to and returned by each subject treated in the trial. This inventory must be available for inspection by LEO, when necessary.

### **10.6.2 Trial Product Destruction or Return**

Any unused LEO supplied drugs must be destroyed or return as instructed by LEO Entity upon finalization of the study. If destroyed, documentation of such destruction must be provided to LEO Entity, at the latest together with the Final Report.

### **10.6.3 Treatment Compliance**

At Visit 2, 6 and/or 10, the subject should be asked how many tubes of IP were used and if she/he has used the IP as prescribed. Compliance/non-compliance and the reason for non-compliance must be recorded in the subject's trial records.

## **11. Ethics and Regulatory Authorities**

### **11.1 Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and Regulatory Authorities**

Written approval or favorable opinion must be obtained from relevant IRB/IECs prior to the enrollment 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.

### **11.2 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.

### **11.3 Subject Information and Informed Consent**

All subjects shall receive written and verbal information concerning the clinical trial. This information will emphasize 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.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the trial.

A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

## **12 Progress and Final Reports**

The investigator is responsible for compiling and submitting progress reports to LEO at the end of each reporting period. Progress reports should describe the progress that has been made towards completion of the study, all relevant findings, any developments and the spend of the funding received from LEO. The progress reports should be submitted on a quarterly basis, calculated from the Effective Date.

The investigator is also responsible for compiling and submitting a final report to relevant authorities and LEO to provide an overview of the study in its entirety, including the findings. The final report should be submitted no later than six (6) months after the completion of the study or, in case of premature termination, thirty (30) days after the date of termination of the Agreement between LEO and the Sponsor.

Reports must be delivered by courier, certified mail, registered mail in writing, to the parties as follows:

LEO Pharma Inc.  
Attn.: Xochitl Jimenez, Medical Science Liaison  
7 Giralda Farms, 2<sup>nd</sup> Floor, Madison, NJ 07940

With a copy to LEO Pharma A/S at:

LEO Pharma A/S  
Attn.: Henny Bang Jakobsen  
Industriparken 55, 2750 Ballerup, Denmark

### 13 References

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## **14 List of Appendices**

Appendix 1: Identifying and Documenting the Treatment Area

Appendix 2: Local Skin Reaction Grading Scale

Appendix 3: Definitions of Adverse Events and Serious Adverse Events

Appendix 4: Classification of Adverse Events

## 15 Appendix 1: Identifying and Documenting the Treatment Area

All subjects qualifying for this trial must have at least 10 clinically typical, visible and discrete MCs in the treatment area. This area of skin will be referred to as the treatment area and will be documented using a '3-point landmark technique' on the study transparencies.

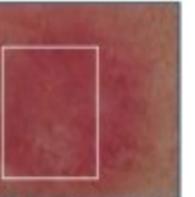
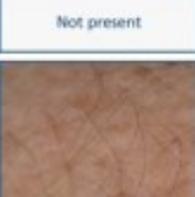
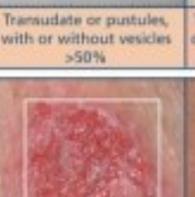
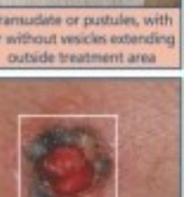
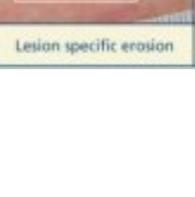
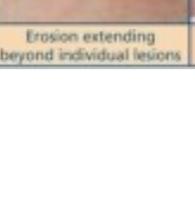
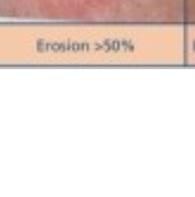
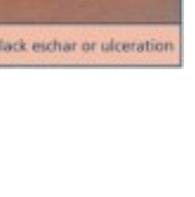
Instructions are provided below.

### *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.
3. When the treatment area is on the face, cut a hole for the nose.
4. 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.)
5. Mark the outline of the treatment area on the provided transparency.
6. Use the transparency to locate the treatment area for subsequent trial visits. When realigning the transparency, use the documented anatomical landmarks to accurately duplicate transparency placement.
7. Retain the transparency as part of the subject's source documents.

Ensure that the treatment area has been sufficiently marked on the skin to assist the subject to identify where the trial medication is to be applied.

**16 Appendix 2: Local Skin Reaction Grading Scale**

Grade	0	1	2	3	4
<b>Erythema</b>					
	Not present	Slightly pink <50%	Pink or light red >50%	Red, restricted to treatment area	Red extending outside treatment area
<b>Flaking/Scaling</b>					
	Not present	Isolated scale, specific to lesions	Scale <50%	Scale >50%	Scaling extending outside treatment area
<b>Crusting</b>					
	Not present	Isolated crusting	Crusting <50%	Crusting >50%	Crusting extending outside treatment area
<b>Swelling</b>					
	Not present	Slight, lesion specific oedema	Palpable oedema extending beyond individual lesions	Confluent and/or visible oedema	Marked swelling extending outside treatment area
<b>Vesiculation/ Pustulation</b>					
	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
<b>Erosion/ Ulceration</b>					
	Not present	Lesion specific erosion	Erosion extending beyond individual lesions	Erosion >50%	Black eschar or ulceration

## 17 Appendix 3: Definitions of Adverse Events and Serious Adverse Events

### 17.1 Adverse Event Definition

*An adverse event is defined as any untoward medical occurrence in a patient 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 unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (ICH Harmonized Tripartite Guideline for Good Clinical Practice, E6 (R1)).*

This definition includes:

- accidental injuries, events related to trial procedures, reasons for any unfavorable 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.

### 17.2 Serious Adverse Event Definition

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

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization. Planned hospitalization or planned prolonged hospitalization 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
- is a medically important condition. Events that may not be immediately life threatening or result in death or hospitalization but may jeopardize 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 bronchospasm, blood dyscrasias and convulsions that do not result in hospitalization, development of drug dependency or drug abuse

## 18 Appendix 4: Classification of Adverse Events

### 18.1 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.

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

### 18.3 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.