

Clinical Trial Protocol LP0084-1369

Incidence of squamous cell carcinoma and other skin neoplasia in subjects with actinic keratosis treated with ingenol disoxate gel 0.018% or 0.037%, or vehicle

A phase 3 trial to compare the incidence of SCC and other skin neoplasia on skin areas treated with ingenol disoxate gel or vehicle gel for actinic keratosis on face and chest or scalp

A multi-centre, randomised, open-label, controlled, parallel group, 24-month trial

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

LEO Pharma A/S	Trial ID:	LP0084-1369
	Date:	25-Jul-2017
	EudraCT No:	2017-000228-85
	Version:	2.0

This document has been redacted using the following principles: Where necessary, information is anonymised to protect the privacy of trial participants and named personnel associated with the trial as well as to retain commercial confidential information.

Summary data are included but data on individual trial participants, including data listings, are removed. This may result in page numbers not being consecutively numbered.

Appendices to the clinical trial report are omitted.

Further details and principles for anonymisation are available in the document LEO PHARMA PRINCIPLES FOR ANONYMISATION OF CLINICAL TRIAL DATA



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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 M.Sc

Biostatistics Lead, Global Clinical Operations

PPD , MD, PhD

Medical Lead, Medical Science and Safety

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:

PPD , MD

International coordinating investigator

1.3 Acknowledgement Statement Investigators

Each participating investigator must agree to the approved clinical trial protocol and consolidated clinical trial protocol(s) comprising any subsequent amendment(s) by signing a Clinical Trial Protocol Acknowledgement Form or a similar document.



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2 Trial Identification

This clinical trial (LP0084-1369) is conducted under US IND number 118384.

EudraCT number: 2017-000228-85

Clinicaltrials.gov identifier: NCT03115476

3 Introduction and Rationale

3.1 Actinic Keratosis

Actinic keratosis (AK) is a common skin condition visible as thickened, cornified, scaly lesions and characterised histologically by atypical epithelial proliferation (1). Actinic keratoses usually develop on areas that are frequently exposed to the sun (e.g. face, ears, scalp, neck, forearms and the back of the hands).

In population studies performed in the European Union (EU) and the United States (US), reported prevalence rates for AK have been approximately 11-25% of the population, while estimates are higher in Australian studies (up to 60%) (2). Patients with AK tend to have Fitzpatrick type I or II skin that burns with sun exposure and does not tan or tans minimally (3).

There is increasing evidence that AK represents squamous cell carcinoma (SCC) *in situ* in its earliest stages (1, 4, 5). Histological evidence shows that contiguous AK is present in 97% of SCC lesions on sun-damaged skin (4). AK is linked epidemiologically to development of SCC (6), and both conditions share specific gene expression (7). If left untreated, AK may progress to SCC resulting in increased morbidity (4).

AK usually occurs on large, sun-damaged areas of the skin (field cancerisation). Field cancerisation is characterised by the epithelial surface being more susceptible to the development of AKs or malignancies than normal skin due to DNA mutations generated in epidermis as a result of excessive sun exposure. This is evidenced by the presence of multiple subclinical and clinically visible AKs as well as multifocal pre-neoplastic changes with genetic mutations (8). Once field cancerisation has developed, new AKs will continue to develop. Most treatment therapies are directed against discrete, visible AKs, and there is an unmet need for improved therapies for field treatment that will reduce the rate of recurrence of AKs.



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3.2 Experience with Investigational Medicinal Product

Ingenol disoxate gel is a novel ingenol derivative being developed for field treatment of AKs on treatment areas of up to 250 cm² (40 in²) on the face, chest and scalp.

The clinical development program for ingenol disoxate gel in AK comprises phase 1, seamless phase 1/2 and phase 2 dose (regimen) finding trials, and phase 3 trials. The phase 1 program addresses various issues potentially relevant to human safety including local tolerability, systemic safety and contact sensitization potential. One phase 1 trial investigating the biological effects by means of histopathology is ongoing. The phase 2 dose finding program is completed. The ongoing phase 3 program includes two confirmatory trials on face and chest, and two confirmatory trials on scalp investigating a 3-day treatment period with an 8-week follow up and an extended 12 month follow-up period.

The safety profile of ingenol disoxate gel is characterised by local skin responses (LSR): erythema, flaking/scaling, swelling, crusting, vesiculation/pustulation, and erosion/ulceration. In clinical trials, scores are assessed for each of these LSRs (on a scale from 0-4) and combined to a composite LSR score (on a scale from 0-24). The LSR profile observed in the ingenol disoxate development programme is consistent across anatomical locations. Typically, the LSRs peak shortly after last drug application, rapidly decline and resolve within 2 weeks. Adverse events (AEs) are predominantly application site reactions in the form of pain, pruritus and discomfort of mild or moderate intensity.

In 3 phase 1/2 dose finding trials (LP0084-1013, -1014, and -1015), ingenol disoxate gel, 0.018%, 0.037% and 0.1% were identified as effective and tolerable doses for once daily treatment for 2 consecutive days of AKs on face/chest, scalp, and trunk/extremities, respectively. With the intent of developing a dosing regimen with a better efficacy/tolerability ratio, these doses were further investigated in an open-label safety trial, Trial LP0084-1148. In this trial, dosing regimens of once daily for 3 consecutive days of ingenol disoxate gel 0.018%, 0.037%, and 0.1% for face/chest, scalp, and trunk/extremities were evaluated and were all shown to be well tolerated.

Based on the phase 2 trial results, ingenol disoxate gel, 0.018% once daily for 3 consecutive days is being investigated for treatment of the face/chest (Trials LP0084-1193 and -1194), and ingenol disoxate gel, 0.037% once daily for 3 consecutive days is being investigated for treatment of the scalp (Trials LP0084-1195 and -1196). These 4 phase 3 trials are divided into an 8-week short-term part (providing confirmatory efficacy data and short term safety data) and a 12 months extended follow up period providing data on recurrence and safety from



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Week 8 to Month 14. The present trial is an extension of the 4 ongoing phase 3 trials following the subjects for SCC and other neoplasia for additional 24 months.

The safety and preliminary efficacy of ingenol disoxate gel is presented in the Investigator's Brochure.

3.3 Trial Rationale

One of the main reasons for treating AK is the wish to abate the risk of progression of AK to SCC. This risk is in the order of 1 per 1000 AKs per year, which is in itself a small risk, but since patients can have dozens of AKs and the disease is chronic the cumulative risk for a patient can be substantial. Although it is generally assumed that removal of AKs by surgery or topical treatment will reduce the risk of progression, this has never been demonstrated in clinical trials. There may be several reasons for this lack of clinical trial evidence of a preventive effect of AK treatment on SCC risk: in general, the study of cancer development requires large cohorts and long follow-up time; even for a relatively common cancer type as SCC of the skin, this is a significant obstacle. Furthermore, the treatment whose effect on SCC risk is to be studied, can be actively allocated in the intervention period where also other treatment can be prohibited, but it is difficult to keep the exposure clean in a prolonged follow-up period. In particular, it is difficult to prohibit other treatments than the experimental treatment for AK. Finally, it is difficult to recruit patients for trials dedicated to study the risk of SCC of the skin. The latter obstacle is overcome by the design here proposed, where the population is initially followed for the treatment effect on AK whereas in the prolonged follow-up phase the emphasis shifts to long-term effects on skin neoplasia, in particular SCC.

Patients who enter trials in AK are at increased risk of developing SCC from the outset and SCCs will be observed, no matter how effective the treatment. The occurrence of even a few cases of SCC after treatment with a topical product may cast a shadow over the new product and a large, well-controlled trial would be needed to alleviate this kind of concern. This is another reason for implementing this extension protocol.

In this extension protocol, LEO will study the incidence of SCCs and other skin neoplasia in vehicle and ingenol disoxate treated patients over a period of 2 years, so that the total follow-up time for each patient will be 3 years and 2 months.

3.4 Ethical Considerations

This extension protocol does not include any experimental treatments or procedures, either active or vehicle. Patients will be seen every 6 months by a qualified dermatologist for



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assessment of the treatment area specified in the main trial LP0084-1193, -1194, -1195 or -1196.

The only restricted medication during this extension protocol is the use of ingenol mebutate and ingenol disoxate in and within 5 cm of treatment area, as field treatment or individual lesion specific treatment. If it is judged by the investigator that it is in the best interest of the patient to receive field treatment in and within 5 cm of treatment area, such a treatment is not prohibited. However, investigators will be encouraged to pursue individual lesion specific treatment options where clinically relevant and before employing field treatment. If topical treatment is indicated, ingenol mebutate and ingenol disoxate are not allowed in and within 5 cm of the treatment area. Since subjects will not be deprived of active AK treatment options, there is no ethical concern related to the treatment of subjects participating in this extension protocol.

4 Trial Objectives

4.1 Primary Objective

To compare the incidence of SCC after treatment with ingenol disoxate gel and vehicle gel.

5 Trial Endpoints

5.1 Primary Endpoint

Time to first SCC in the treatment area

5.2 Secondary Endpoints

Time to first SCC or other skin neoplasia in the treatment area

Safety Evaluations: Adverse event frequency by MedDRA Preferred Term

6 Trial Design

6.1 Overall Trial Design

This is an international, phase 3, multi-centre, randomised, open-label, parallel group, 24-month trial in subjects with AK. The subjects who qualify for this trial have previously been enrolled in LEO trials LP0084-1193, -1194, -1195, or -1196 ('main trial') in which a treatment area has been defined.



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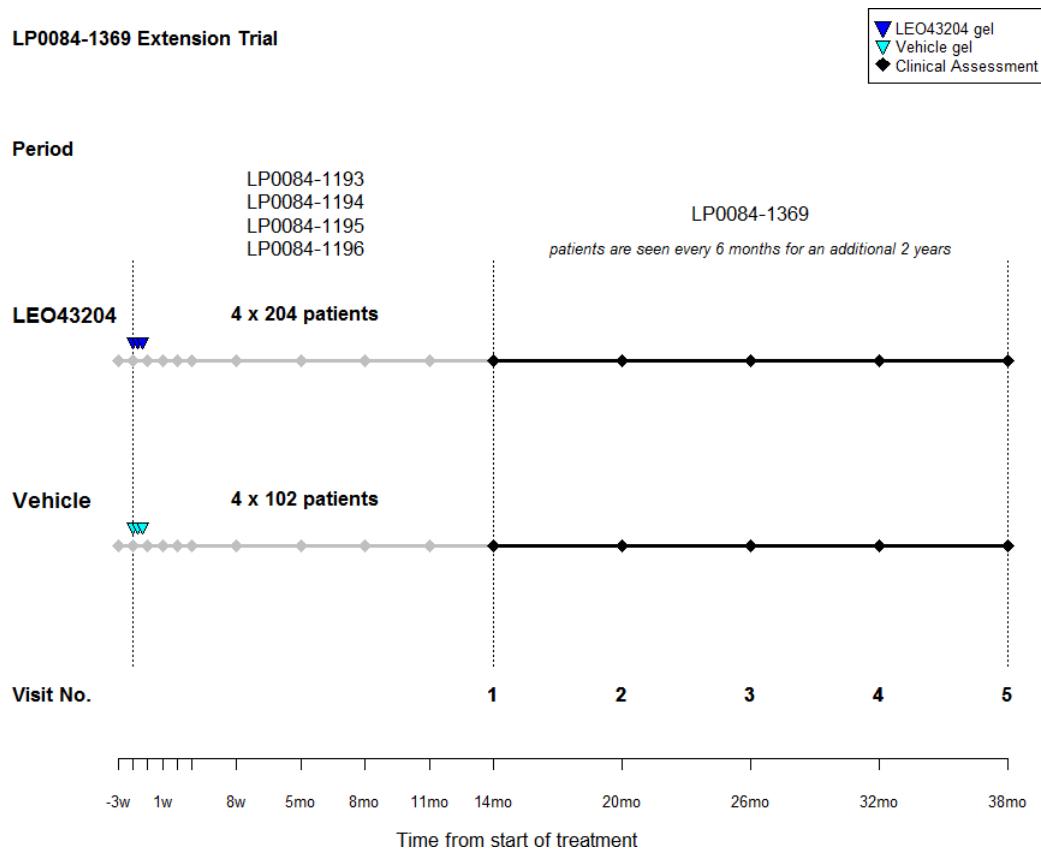
At Visit 1 (which ideally coincides with visit 11 [Month 14]) subjects will sign the trial-specific consent form in the presence of the investigator and the subject's eligibility will be checked. Additional trial visits will take place at Month 6, 12, 18, and 24.

At Visit 2-5 the treatment area will be assessed for any adverse events (AEs).

If a biopsy is taken due to suspicion of SCC or other skin neoplasia in the treatment area (see section 8.4.1), it will be sent for central review by an independent adjudication committee (IAC) with 3 expert dermatopathologists, see section 12.1.

Cryotherapy is allowed in the treatment area. Investigators are encouraged to pursue these treatment options where clinically relevant and before employing other treatments. Until end of trial, if topical treatment is indicated, ingenol mebutate and ingenol disoxate are not allowed in, and within 5 cm of the treatment area.

Figure 1 Trial Design



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6.2 Trial Schedule

Subjects are expected to participate for up to 24 months.

Planned date of first subject first visit (FSFV): Q2 2017

Planned date of last subject first visit (LSFV): Q4 2017

Planned date of last subject last visit (LSLV): Q4 2019

Estimated number of trial sites and country allocation: Approximately 80 sites in Canada, Germany, France, Italy, Spain, the United Kingdom, and USA.

6.3 Sample Size

No formal sample size calculation has been made. The sample size is determined by the number of subjects who complete Visit 11 in the confirmatory phase 3 trials (LP0084-1193, -1194, -1195, -1196) and are willing to enter the extension protocol. Two thirds would have been treated with ingenol disoxate, one third with vehicle.

6.4 Randomisation

Not applicable

6.5 Blinding

The phase 3 trials LP0084-1193, -1194, -1195, or -1196 are vehicle controlled and blinded. The blinding will, however, not be maintained during the 2 years of the extension protocol except for the blinding of the adjudication committee members, who evaluate the pathology slides from skin neoplasias in the treatment area.

7 Trial Population and Withdrawal

7.1 Subject Eligibility

The (sub)investigator should only enrol 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 Visit 1.

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.



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7.2 Inclusion Criteria

1. Signed and dated informed consent has been obtained.
2. The subject has been treated in one of the trials LP0084-1193, -1194, -1195, or -1196 and has been evaluated at Visit 11 of that trial.

7.3 Exclusion Criteria

1. The subject is in need of treatment with ingenol mebutate or ingenol disoxate in the selected treatment area*.
2. The subject is enrolled in any other interventional clinical trial.

For subjects where there is a gap between Visit 11 in one of the trials LP0084-1193, -1194, -1195, or -1196 and participation in the current trial:

1. The subject has been treated with ingenol mebutate or ingenol disoxate in the selected treatment area* after Visit 11 in one of the trials LP0084-1193, -1194, -1195, or -1196 and until participation in the current trial.
2. The subject has been enrolled in any other interventional clinical trial after Visit 11 in one of the trials LP0084-1193, -1194, -1195, or -1196 and until participation in the current trial.

7.4 Subject Screening Log

Subjects who have completed Visit 11 of the main trial and given the opportunity to enrol in this trial should be registered on the Subject Screening Log.

7.5 Subject Identification List

The (sub)investigator must maintain a list of all subjects enrolled 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 or CRO. The subject ID in the present trial and in the main trial must be the same.

* The selected treatment area that was documented in the main trial (LP0084-1193, -1194, -1195 and -1196).



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7.6 Restrictions during Trial

Concomitant treatment in the selected treatment area:

Cryotherapy and surgical procedures are allowed in the selected treatment area. Investigators will be encouraged to pursue these treatment options where clinically relevant and before employing other treatments. If topical treatment is indicated, ingenol mebutate and ingenol disoxate are not allowed in, and within 5 cm of the treatment area.

Concomitant treatment outside the selected treatment area:

No restrictions.

7.7 Discontinuation

Subject **may** be withdrawn from the trial for any of the following reasons:

<i>Adverse event (please specify)</i>	Any adverse event (AE) that the (sub)investigator considers unacceptable.
<i>Withdrawal by subject</i>	Subjects are free to withdraw from the clinical trial at any time and for any reason.
<i>Lost to follow-up</i>	
<i>Death</i>	
<i>Other (please specify)</i>	Other reasons than stated above which require the subject to (be) withdraw(n) should be specified.

If adverse event or other is selected, a specification must be supplied.

Subject **must** be withdrawn from the trial for any of the following reasons :

1. If a subject, for any reason, has used ingenol mebutate or ingenol disoxate in or within 5 cm of treatment area during this trial
2. If a subject participates in any other interventional clinical trial.

For subjects withdrawn from trial, AEs should be followed up as described in section [9.5](#).



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8 Trial Schedule and Assessments

8.1 Schedule of Trial Procedures

Table 1 Schedule of Trial Procedures

	Visit 1 ¹⁾	Visit 2	Visit 3	Visit 4	Visit 5	Unscheduled or Early Termination
Day / Month		Month 6 ²⁾	Month 12	Month 18	Month 24	N/A
Visit window	N/A	±16 days ²⁾	±16 days	±16 days	±16 days	N/A
Informed consent	X					
Inclusion/exclusion criteria	X					
Concomitant medication and procedures ³⁾		X	X	X	X	X
AE(s) ⁴⁾		X	X	X	X	X
Scarring		X	X	X	X	X
End of Trial					X	X ⁵⁾

1) Visit 1 ideally coincides with visit 11 (month 14) of the main trial and should be performed before or at Visit 2 of the present trial.
 2) Visit 2 is 6 months after visit 11 (month 14) of main trial and the visit window is relative to visit 11.
 3) Information regarding medication or treatments which may suppress the immune system in subjects or which may alter the course of AK or SCC. Also, any medications (topical or systemic) and procedures used for AEs in the treatment area.
 4) Within treatment area only (SAEs outside treatment area are only collected if deemed related to IMP in main trial or reported elsewhere in the CRF).
 5) Early termination only.

All assessments in this trial will be made in the treatment area that was documented in the main trial (LP0084-1193, -1194, -1195 and -1196). The study transparency used in the main trial should be used to reidentify the treatment area for assessment of the treated skin on the face, chest, or scalp for all visits in the present trial.



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8.2 Subject Eligibility

Refer to sections [7.2](#) and [7.3](#)

8.3 Concomitant Medication and Procedures

The following should be collected:

Information regarding medication or treatments which may suppress the immune system in subjects or which may alter the course of AK or SCC will be collected.

Information will be collected regarding concomitant medications (topical or systemic) and procedures used for AEs in the treatment area.

No other information on concomitant medications or procedures will be collected.

Use of concomitant treatment must be recorded in the subject's medical record and the CRF (e.g. treatment/drug name, route of administration, total daily dose, indication and dates of start and stop).

If Visit 1 does not coincide with Visit 11 of trial LP0084-1193, -1194, -1195 and -1196 concomitant medication and procedures for the period between the two visits must be recorded at Visit 1.



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8.4 Adverse Events

Only AEs in the treatment area (including keratoacanthoma [KA], SCC, or other skin neoplasia) will be collected. AEs must be assessed and recorded as specified in section [9](#).

If Visit 1 does not coincide with Visit 11 of the main trial (LP0084-1193, -1194, -1195 and -1196) events in the treatment area for the period between the two visits must be recorded at Visit 2.

8.4.1 Adverse EventS of Special Interest and other Skin Neoplasia

All biopsies of KA, SCC or other skin neoplasia in the treatment area should be sent for central review in the IAC, Section [12.1](#). If there are any discrepancies between the local histology report and the central pathology review, there should not be any changes in the CRF. For the central review, the local pathology laboratory will send the relevant histology slides to the investigator who will forward the slides to the CRO for distribution to the adjudication committee. Only if the original slides cannot be sent is it acceptable to use new slides made from the same tissue block.

A biopsy should be considered in the following clinical situation:

- A new lesion in the treatment area that has bled on more than 2 occasions.
- Any papular lesion that measures more than 0.5 cm in diameter (0.2 inches).
- A presumed actinic keratosis that has been treated twice with cryosurgery without resolution.

8.5 Scarring

Presence of scarring (Yes/No) in the treatment area will be recorded at visits indicated in Section [8.1](#). If scarring is present, the investigator should record in the CRF if the scarring is hypotrophic, hypertrophic or keloid. If a scarring is recorded it should also be recorded as an AE.

8.6 End of Trial

The End of Trial Form must be completed for all enrolled subjects. This includes last attended scheduled visit number and primary reason for withdrawal .



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9 Adverse Events

- AEs and serious adverse events (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

In this extension protocol, where no treatment is being administered, all AEs and SAEs occurring in the area treated in the phase 3 trials (treatment area) will be routinely collected from completion of Visit 11 in the main trial until the subject's last visit to the clinic.

SAEs occurring outside the treatment area in the main trial, and considered not related to IMP in these trials, will not be systematically collected. For an overview of which AEs should be collected, see table below.

Table 2 Overview of AEs to be Collected

AE collection		
	Inside treatment area	Outside treatment area
AEs	All	None
SAEs	All	Related to IMP in main trials Referenced elsewhere in the CRF (e.g. death on end of trial form, hospitalisation as reason for missing visit)

AEs must be assessed by medically qualified personnel. A qualified experienced dermatologist must conduct all dermatologic examinations and AE evaluation of the treatment area defined in the main trials (LP0084-1193, -1194, -1195, -1196).

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.



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9.1.1 Local Skin Responses

Local skin responses (LSR) matching the criteria in the LSR grading scale in the pivotal phase 3 trials are considered AEs in this extension protocol and should be handled and reported as such.

9.2 Reporting of Adverse Events in the CRF

AEs reported by the subject or observed by the (sub)investigator must be recorded on the AE form of the CRF 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).

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 IMP.

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 Adverse Event

Any 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

Overdose, medication error, misuse and abuse will not be reported since no IMP is given in this trial.

9.3.1 Pregnancy

Any pregnancy occurring during the main trials (LP0084-1193, -1194, -1195 and -1196) from Visit 1 until Visit 7 has been reported. This extension protocol investigates subjects following their participation in one of the four pivotal phase 3 trials without any additional treatment, hence pregnancies are not to be reported in the current trial as treatment has been finalised 14 months prior to enrollment.



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9.3.2 Aggravation of Condition

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

9.3.3 Adverse Events of Special Interest

Due to the sun-damage, the target population is prone to SCC development. Sun-damaged skin is also prone to development of keratoacanthoma (KA) as a response to local irritation and/or inflammation. To ensure that all information relevant for surveillance is collected, SCCs and KAs in the area treated in the pivotal phase 3 trials are considered adverse events of special interest (AESI).

For SCCs and KAs in the area treated in the confirmatory phase 3 trials (LP0084-1193, -1194, -1195, -1196), the relevant information will be collected in the CRF. In addition, the local 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 (defined in the main phase 3 trials) 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 the AESI will be sent for central pathology review by the procedure outlined in section [8.4](#)

9.4 Additional Reporting Requirements for Serious Adverse Events

9.4.1 Investigator Reporting Responsibilities

When reporting SAEs, the paper SAE Form – Clinical Trials, must be used, and submitted to LEO within 24 hours of first knowledge. This report should contain an assessment of available information on seriousness, severity, causal relationship to the IMP, comparator or trial procedure, the action taken, the outcome to date, and a narrative description of the course of the event.

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:



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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 anonymised 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 an SAE is expected. The relevant reference document for this clinical trial is:

For the IMP, the Investigator's Brochure, LEO 43204, Field Therapy, Edition No. 5 and subsequent updates hereof must be used (9).

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

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

For all non-US countries, all SAEs which are assessed as casually related to the IMP by either the investigator or LEO (ICH E2A Guideline), and which are unexpected (Suspected, Unexpected Serious Adverse Reactions (SUSARs)), are subject to expedited reporting to regulatory authorities and IRB(s)/IEC(s) according to the current applicable legislation in the concerned countries. Investigators will be notified of these on an ongoing basis.



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For the US, all SAEs which are assessed as casually related to the IMP 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 the current applicable legislation in the concerned countries. 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 leaves the clinical trial, the investigator should follow up on the outcome of all non-serious AEs classified as of possible/probable relationship to the investigational product for 2 months or until the 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 Trial Product

Not applicable

11 Statistical Methods

Data on skin neoplasia from the 14 months observation time in the confirmatory phase 3 trials LP0084-1193, -1194, -1195, and -1196 will be combined with the data from the present trial.

11.1 Sample Size

No formal sample size calculation has been made. The sample size is determined by the number of subjects who complete Visit 11 in the pivotal phase 3 trials (LP0084-1193, -1194, -1195, -1196) and are willing to enter the extension protocol. Two thirds have been treated with ingenol disoxate, one third with vehicle.

A total of 1200 subjects were planned be enrolled in the pivotal phase 3 trials (LP0084-1193, -1194, -1195, and -1196) and randomised 2:1 to the two treatment groups ingenol disoxate gel or vehicle gel. With 800 subjects in the ingenol disoxate treatment group and 400 subjects in the vehicle gel group, an adequate precision of the 3-year plus 2 months incidence rate can be obtained. Assuming a 3-year plus 2 months rate of 4.0%, the upper 95% confidence limit will on average be 5.36% for ingenol disoxate gel and 5.92% for vehicle gel, and assuming a 6.0% rate, the upper 95% confidence limit will on average be 7.65% for ingenol disoxate gel and 8.33% for vehicle gel.



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11.2 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 a clinical trial) will be accounted for in the clinical trial report.

All randomized subjects from the pivotal phase 3 trials (LP0084-1193, -1194, -1195, -1196) are included in the full analysis set (FAS) and will be analysed for incidence of SCC and other skin neoplasia. 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 subject from the full analysis set, a justification addressing ICH E9 will be given.

A safety analysis set will be defined by excluding subjects from the full analysis 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 .

11.3 Statistical Analysis

11.3.1 Disposition of Subjects

The reasons for leaving the trial will be presented for the FAS by last visit attended and by treatment group in the main trial. This will also be done for the enrolled and eligible subjects not included in the FAS.

11.3.2 Demographics and other Baseline Characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for all subjects, by treatment group in the main trial and by country. Presentations of age, sex, ethnicity and race and baseline AK count by treatment group will also be given by main trial.

The demographics and other baseline characteristics will be summarised for the 4 main trials combined as well as the subset of those who enter the extension trial.

Demographics include age, sex, race, ethnicity and skin type. Other baseline characteristics include anatomical location (face, chest, or scalp) of treatment area in the main trials, treatment area size, concurrent diagnoses (from medical history and indications for concomitant medication), and concomitant medication. Baseline AK characteristics will include baseline AK count for the treatment area, duration of disease, previous treatment of



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AKs (anywhere) and previous treatment of AKs in the treatment area as reported in the main trial.

11.3.3 Exposure and Treatment Compliance

11.3.4 Analysis of Primary Endpoint

The null hypothesis is that there is no difference in time to first SCC between ingenol disoxate gel and vehicle gel. The hypothesis will be tested against the two-sided alternative that there is a difference between the two treatment groups.

Primary endpoint is time to first SCC in the treatment area from Visit 2 in trials LP0084-1193, -1194, -1195 and -1196.

Only the SCC confirmed by the IAC will be used in the primary endpoint analysis.

The annual and the 3-year and 2 months cumulative incidence of first event of SCC will be calculated for each treatment group (active and vehicle) in main trial using methods of survival analysis in the presence of censoring. The cumulative incidence rates will be presented by treatment group for the event of first SCC as primary endpoint. A proportional hazards model will be fitted if the model assumptions are valid. Log-rank test comparing the two treatment groups will be performed. For descriptive purposes, as an additional analysis, the difference in cumulative incidence rates between the two arms will be estimated and presented together with its 95% confidence interval. A landmark analysis will additionally be performed in order to exclude SCC and other neoplasia reported within the first 8 weeks which are not assumed to be associated with the trial treatment. This corresponds to left-truncation of the trial period at 8 weeks, the analysis will otherwise be conducted as above. Patients who experience a SCC before the 8-week landmark time point are excluded from the landmark analysis.

11.3.5 Analysis of Secondary Endpoint

For the secondary endpoint, the null hypothesis is that there is no difference in time to first SCC or other skin neoplasia between ingenol disoxate gel and vehicle gel. The hypothesis will be tested against the two-sided alternative that there is a difference between the two treatment groups.

Secondary endpoint is time to first SCC or other skin neoplasia in the treatment area from Visit 2 in trials LP0084-1193, -1194, -1195 and -1196.



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Only the SCC or other skin neoplasia confirmed by the IAC will be used in the secondary endpoint analysis.

Analysis of the secondary endpoint will be performed as outlined above for the primary endpoint.

11.3.6 Analysis of Safety

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

11.3.6.1 Adverse Events

AEs will be coded during the course of the trial according to Medical Dictionary for Regulatory Activities (MedDRA). AEs will be presented by preferred terms and primary system organ class (SOC).

AEs from the 24-month trial period, will be summarised and included in the subject data listings by its start date. All adverse events will be considered treatment-emergent and will be included in the tabulations described in the following. In each of the tabulations, AEs are defined by MedDRA preferred terms within primary SOC.

An overall summary of the number (percentage) of subjects with any AEs, SAEs, premature discontinuations from the trial due to AEs, treatment-related AEs and severe AEs will be presented overall and by treatment group in main trial.

The number of subjects experiencing each type of AEs will be tabulated by treatment group in main trial regardless of the number of times each AE is reported by each subject. The percentage of subjects with any AEs will be compared between treatment groups by a chi-square test or Fisher's exact test (if expected cell count < 5).

Severity

The severity for each type of AE will be tabulated by treatment group in main trial. Where there are several recordings of severity for a given type of AE, severity will be taken as the most severe recording for that AE.

Causal relationship

The causal relationship to IMP for each type of AE will be tabulated by treatment group. Where there are several recordings of causal relationship to the IMP for a given type of AE, causal relationship will be taken as the most-related recording from the last report of that AE,



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since that is when the (sub)investigator will be in possession of most information and so best able to judge causal relationship.

Related AEs are defined as AEs for which the (sub)investigator has not described the causal relationship to IMP as 'not related'. The number of subjects experiencing each type of related AE will be tabulated regardless of the number of times each related AE is reported by each subject. The percentage of subjects with related AEs will be compared between treatment groups by a chi-square test or Fisher's exact test (if expected cell count < 5).

Most common adverse events

The most common AEs ($\geq 2\%$ of subjects in the active treatment group in the main trial) will be presented by treatment group.

Serious adverse events and withdrawal

SAEs will be evaluated separately and a narrative for each will be given. AEs leading to withdrawal from trial will be listed.

Adverse events of special interest

AESI will be presented by treatment group in the main trial. For the AESI the number of events with agreement and disagreement between data from the AE form in the CRF and data from the central review will be presented by treatment group. A narrative for each AESI will be given.

11.3.7 Interim Analysis

No interim analyses are planned.

11.3.8 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.



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

11.3.9 Handling of Missing Values

Missing values for time to occurrence of SCC or other neoplasia will be handled as censored observations.

12 Trial Committees

12.1 Independent Adjudication Committee

In LEO ingenol trials, squamous cell carcinoma (SCC) and keratoacanthoma (KA) inside the treatment area have been defined as an AESI. KA may be difficult for some pathologists to distinguish from SCC and may be underreported due to the fear of misdiagnosing the malignant SCC. As many AK patients are prone to SCC as well as KA due to the heavy sun damage, it is of great importance that possible tumours that occur after treatment with ingenol disoxate are diagnosed correctly. An independent adjudication committee (IAC) has therefore been assembled to provide consistent evaluation of the incidence of KA in the patient population as opposed to the incidence of SCC. The IAC comprises 3 medical doctors, who are experts in dermatopathology.

All biopsies of AESIs and other skin neoplasia in the treatment area at any time during the trial will be sent to the IAC for central review, as described in sections [8.4](#) and [9.3.3](#).

See [Appendix 4: Contact list of LEO, protocol authors, vendors, trial committees and coordinating investigators](#) for contact details on all trial committee members.

13 Case Report Forms and Data Handling

13.1 Case Report Forms (CRFs)

Data will be collected by means of Electronic Data Capture (EDC). The investigator or staff authorised by the investigator will enter subject data into electronic CRFs. Data recorded in the electronic CRFs will be accessible to the trial site and LEO personnel immediately after entry. The CRFs must be maintained in an up-to-date state by the trial site at all times.

The investigator must verify the correctness of the data entered by the site by electronically date and sign all CRFs used. This signature information will be kept in the audit trail and cannot be altered. Any correction(s) made by the (sub)investigator or authorised site staff to



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the CRF after original entry will be documented in the audit trail. Changes to data already approved will require the re-signature by the investigator. The person making the change to the data, and the date, time and reason for the change will be identified in the audit trail.

For archiving purposes, each investigator will be supplied with a copy of the CRFs for all subjects enrolled at the trial site. This is done after completion of the trial and before access to the eCRF is revoked. Audit trail information will be included. CRFs must be available for inspection by authorised representatives from LEO, from regulatory authorities and/or IEC/IRBs.

13.2 Data Handling

Subject data should be entered into the CRF as soon as possible after each visit in accordance with the requirements described in the Clinical Trial Agreement. Queries for discrepant data will be generated automatically by the system upon entry or manually by the monitor or the data manager. All queries will be raised electronically within the EDC system. This systematic validation will ensure that a clean and consistent database is provided for the statistical analysis.

13.3 Source Data

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

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.

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
- A statement from the investigator to verify that each of the eligibility criteria are met for each subject
- Subject ID
- The fact that the subject is participating in a clinical trial.



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- Other relevant medical information

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

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 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 CPM 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.



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

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

End of trial is defined as the date of the last subject's last visit in each participating country and overall (all countries).

Investigators will be informed when subject recruitment is to cease (if applicable)

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 unfavourable for the continuation of the trial.

Due to the design of this trial, there are no statistical criteria for trial termination.



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16.2 Provision for Subject Care Following Trial Completion

In order to ensure appropriate treatment of the subjects after they have completed 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 favourable 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.



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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 [(or their legally acceptable representative)] 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



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products/services, improving existing products/services, applying for marketing authorisations for products/services, marketing of products/services and other related activities.

LEO has obtained the necessary authorisations for the processing 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 IMP(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 IMP(s) and, therefore, may disclose and/or transfer information, data and/or results to other investigators, regulatory authorities and/or commercial partners.

20 Registration, reporting and publication

Basic information of this clinical trial will be registered in the global data registry, www.clinicaltrials.gov before the first subject enters into the trial. The trial may also become registered in other online data registries, according to applicable law and regulations.

Results of this trial will be posted on the corporate website of LEO in accordance with LEO's Position on Public Access to Clinical Trial Information, latest 12 months after trial completion. Results may also become reported in ClinicalTrials.gov, www.clinicaltrialsregister.eu and national data registries in accordance with applicable law and regulations after trial completion or premature termination. In the case of a multi-centre trial the first publication will be a joint multi-centre publication. Multi-centre publications will be prepared in collaboration between LEO and the members of a writing group, which shall be appointed by LEO.

Publication by an investigator of his/her trial results shall not be made public before the first multi-centre publication.



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If no multi-centre publication has been submitted for publication within eighteen months after the clinical trial has been completed or terminated at all trial sites 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 group 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 still be followed.

LEO complies with recommendations from the International Committee of Medical Journal Editors and with the positions of the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), European Federation of Pharmaceutical Industries and Associations (EFPIA), Japan Pharmaceutical Manufacturers Association (JPMA) and Pharmaceutical Research and Manufacturers of America (PhRMA) on disclosure of information about clinical trials, trial results and authorship (10).

21 Responsibilities

The international coordinating investigator (ICI) is responsible for the approval of the (Consolidated) Clinical Trial Protocol, Clinical Trial Protocol Amendment(s) and the Clinical Trial Report on behalf of all clinical trial investigators and as agreed to in an International Coordinating Investigator Agreement.

The national coordinating investigator(s) are responsible for national issues relating to the clinical trial as agreed to in a National Coordinating Investigator Agreement.

Each participating investigator is responsible for all aspects of the clinical trial conduct at his/her trial site as agreed to in a Clinical Trial Agreement.



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22 List of Abbreviations

AESI	Adverse Events of Special Interest
AE	Adverse Event
CMO	Contract Manufacturing Organisation
CPM	Clinical Project Manager
CRF	Case Report Form
CRO	Contract Research Organisation
EDC	Electronic Data Capture
FAS	Full analysis set
GCP	Good Clinical Practice
GPV	Global Pharmacovigilance
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IAC	Independent Adjudication Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
KA	Keratoacanthoma
LSR	Local Skin Response
MedDRA	Medical Dictionary for Regulatory Activities
Main trial	LEO trials LP0084-1193, -1194, -1195, or -1196
NLCRA	National Lead Clinical Research Associate
SAE	Serious Adverse Event
SOC	System Organ Class
SCC	Squamous cell carcinoma
SUSAR	Suspected Unexpected Serious Adverse Reaction
WMA	World Medical Association



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List of Appendices

[Appendix 1: Protocol Summary](#)

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Appendix 1: Protocol Summary

Name of finished/IMP	NA
Name of active substance	NA
Title of trial/trial ID/ EudraCT no.	Incidence of squamous cell carcinoma and other skin neoplasia in subjects with actinic keratosis treated with ingenol disoxate gel 0.018% or 0.037%, or vehicle / LP0084-1369 / EudraCT number: 2017-000228-85
Coordinating investigator(s)	PPD [REDACTED], MD
Sponsor's name/ address	LEO Pharma A/S Industriparken 55 DK-Ballerup
Estimated number of trial sites and distribution	Approximately 80 sites in Canada, Germany, France, Italy, Spain, the United Kingdom, and USA
Trial period	Planned First Subject First Visit (FSFV): Q2 2017 Planned Last Subject Last Visit (LSLV): Q4 2019
Main objective(s)	To compare the incidence of SCC after treatment with ingenol disoxate gel and vehicle gel
Methodology	A phase 3 trial to compare the incidence of SCC and other skin neoplasia on skin areas treated with ingenol disoxate gel or vehicle gel for multiple actinic keratosis on face and chest or scalp. The trials is a multi-centre, randomised, open-label, controlled, parallel group, 24-month trial
Number of subjects to be enrolled	No formal sample size calculation has been made. The sample size is determined by the number of subjects who complete Visit 11 in the pivotal phase 3 trials (LP0084-1193, -1194, -1195, -1196) and are willing to enter the extension protocol.
Main criteria for inclusion	<ol style="list-style-type: none"> 1. Signed and dated informed consent has been obtained. 2. The subject has been treated in one of the trials LP0084-1193, -1194, -1195, or -1196 and has been evaluated at Visit 11 of that trial.
Main criteria for exclusion	<ol style="list-style-type: none"> 1. The subject is in need of treatment with ingenol mebutate or ingenol disoxate in the selected treatment area*. 2. The subject is enrolled in any other interventional clinical trial.



	<p>For subjects where there is a gap between Visit 11 in one of the trials LP0084-1193, -1194, -1195, or -1196 and participation in the current trial:</p> <ol style="list-style-type: none"> 1. The subject has been treated with ingenol mebutate or ingenol disoxate in the selected treatment area* after Visit 11 in one of the trials LP0084-1193, -1194, -1195, or -1196 and until participation in the current trial. 2. The subject has been enrolled in any other interventional clinical trial after Visit 11 in one of the trials LP0084-1193, -1194, -1195, or -1196 and until participation in the current trial. <p>* The selected treatment area that was documented in the main trial (LP0084-1193, -1194, -1195 and -1196).</p>
IMP(s)	NA
Investigational reference product(s)	NA
Duration of treatment	NA
Main assessments	Adverse events in the treatment area that was documented in the main trials (LP0084-1193, -1194, -1195 and -1196).
Primary endpoint	Time to first squamous cell carcinoma (SCC) in the treatment area
Secondary endpoint(s)	Time to first squamous cell carcinoma (SCC) or other skin neoplasia in the treatment area
Statistical methods	<p>Data on skin neoplasia from the 14 months observation time in the main trials will be combined with the data from the present trial</p> <p>Primary endpoint: The annual and the 3-year and 2 months cumulative incidence of first event of SCC will be calculated for each treatment group (active and vehicle) using methods of survival analysis in the presence of censoring. The incidence rates will be presented for the event of first SCC as primary endpoint . A proportion hazards model will be fitted if the model assumptions are valid. Log-rank test comparing the two arms will be performed. For descriptive purposes, as an additional analysis, the difference in cumulative incidence rates between the two</p>



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arms will be estimated and presented together with its 95% confidence interval. A landmark analysis will additionally be performed in order to exclude SCC and other neoplasia reported within the first 8 weeks which are not assumed to be associated with the study treatment. This corresponds to left-truncation of the trial period at 8 weeks, which is otherwise conducted as above. Patients who experience a neoplasia before the 8-week landmark time point are excluded from the landmark analysis.



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Appendix 2: Definitions of Adverse Events and Serious Adverse Events

Adverse Event Definition

An AE 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 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 IMP. In addition, any laboratory abnormality assessed as clinically significant by the (sub)investigator must be recorded as an AE.

Serious Adverse Event Definition

An 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



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- 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.



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Appendix 3: Classification of Adverse Events

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 AE 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 AE 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 AE 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.

Causality

The *causal relation* of the AE to the use of the IMP 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 IMP.</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 IMP.</p> <p>Disappears or decreases on cessation or reduction in dose of the IMP.</p> <p>Reappears or worsens upon re-challenge.</p>
Possibly related	<p>Follows a reasonable temporal sequence from the administration of the IMP.</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 IMP.</p>
Not related	Does not follow a reasonable temporal sequence from administration of the IMP.



	<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 <u>not</u> follow a known pattern of response to the IMP.</p>
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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/re solved with sequelae	<p>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.</p> <p>The stop date of the event must be recorded. In case of a SAE, the sequelae should be specified.</p>
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.



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Appendix 4: Contact list of LEO, protocol authors, vendors, trial committees and coordinating investigators

Contact details for the clinical project manager (CPM), national lead CRA (NLCRA), medical expert and safety scientist/safety physician are provided to participating trial sites in a separate sponsor contact list.

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-2750 Ballerup

Denmark

Protocol authors

PPD [REDACTED], M.D. International Coordinating Investigator

PPD [REDACTED], Trial Statistician, LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark

PPD [REDACTED], M.D. Medical Expert, LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark

PPD [REDACTED], MSc Pharm., Safety Scientist, LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark

PPD [REDACTED], M.S., CPM, LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark

CRO(s)/vendors

PPD [REDACTED], PPD [REDACTED], PPD [REDACTED], PPD [REDACTED], USA will maintain the study portal and eLearning for study personnel

PPD [REDACTED], PPD [REDACTED], PPD [REDACTED], PPD [REDACTED], USA will manage and provide the clinical database.

PPD [REDACTED], PPD [REDACTED], PPD [REDACTED], PPD [REDACTED], PPD [REDACTED], Ireland, will provide lab kit and logistic support for AESI review.



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Independent Adjudication Committee:

Prof. PPD Department of Pathology and Laboratory Medicine, Geffen-UCLA
School of Medicine, 1250 16th Street, Santa Monica, CA 90404 USA

Prof. PPD, Department of Dermatology and Venereology, Medical University of Graz, Auenbruggerplatz, 8, A-8036 Graz, AUSTRIA

Dr. PPD Fundacion Jimenez Diaz, Avda. Reyes
Catolicos 2, 28040 Madrid, SPAIN

Coordinating investigators

International Coordinating Investigator: PPD, M.D.



Appendix 5: Protocol Amendment History

Amendment 1 (27-Jul-2017)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rationale for the amendment

The reason for the amendment is to change the definition of the FAS to include all randomised subjects from the pivotal phase 3 trials. The amendment also addresses requests for changes from the Health Authorities in Europe and US after their review of the protocol.

Note: In the table below, text added to the protocol is written in bold and deleted text has a line through it.

Section number and name	Description of change	Brief rationale
1.1.Approval Statement LEO Pharma A/S	PPD [REDACTED], PhD PPD [REDACTED] [REDACTED] M.Sc	New biostatistician
2 Trial identification	Clinicaltrials.gov identifier: NCT03115476	Include CT.gov identifier
6.1 Trial Design	(see section 8.4.1)	Clarification
6.3 Sample Size	The sample size is determined by the number of subjects who complete Visit 11 in the confirmatory phase 3 trials (LP0084-1193, -1194, -1195, -1196) and are willing to enter the extension protocol and is expected to be around 1080.	Aligned with Section 11.1
7.4 Subject Screening and Enrolment Log	Subject Screening and Enrolment Log	Correction of title of log
8.1 Schedule of Trial Procedures	4) Within treatment area only (SAEs outside treatment are only collected if deemed related to IMP in main trial or	Clarification



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Table 1	reported elsewhere in the CRF). 5) Early termination only.	
8.3 Concomitant Medication and Procedures	<p><i>The sentence: "If visit 1 (...)must be recorded at Visit 1." has been moved to the end of the section.</i></p> <p>The following should be collected:</p> <p>In addition, Information will be collected regarding concomitant medications (topical or systemic) and procedures used for AEs in the treatment area.</p>	Clarification
8.4 Adverse Events	<p>If Visit 1 does not coincide with Visit 11 of the main trial (LP0084-1193, -1194, -1195 and -1196) events in the treatment area for the period between the two visits must be recorded at Visit 28.4.1</p> <p>8.4.1 Adverse Events of Special Interest and other Skin Neoplasia</p> <ul style="list-style-type: none"> • A new lesion in the treatment area that has bled on more than 2 occasions. • Any papular lesion that measures more than 0.5 cm in diameter (0.2 inches). • A presumed actinic keratosis that has been treated twice with cryosurgery without resolution. 	Editorial change Delete repeated word and insert Heading 3 Addition of clinical guidelines for when investigators should consider biopsy of a 'suspicious' lesion
9.1 Collection of Adverse Events	SAEs occurring outside the treatment area in the main trial, and considered not related to IMP in these trials, will not be systematically collected. For an overview of which AEs should be collected, see table below.	Clarification of which AEs will be collected



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	Table 2 Overview of AEs to be Collected <i>note: the new table is not inserted here but can be found in Section 9.1</i>	
9.4.1 Investigator Reporting Responsibilities	Any SAE must be reported to LEO on When reporting SAEs, the (paper) SAE Form – Clinical Trials, must be used, and submitted to LEO within 24 hours of first knowledge	Clarification
11.1 Sample size	The total number of subjects in the trials is around 1200, and assuming 10% drop outs after 14 months, the number of subjects being offered the extension protocol will be around 1080. A total of 1200 subjects were planned be enrolled in the pivotal phase 3 trials (LP0084-1193, -1194, -1195, and - 1196) and randomised 2:1 to the two treatment groups ingenol disoxate gel or vehicle gel. With 800 subjects in the ingenol disoxate treatment group and 400 subjects in the vehicle gel group, an adequate precision of the 3-year plus 2 months incidence rate can be obtained. Assuming a 3-year plus 2 months rate of 4.0%, the upper 95% confidence limit will on average be 5.36% for ingenol disoxate gel and 5.92% for vehicle gel, and assuming a 6.0% rate, the upper 95% confidence limit will on average be 7.65% for ingenol disoxate gel and 8.33% for vehicle gel.	Rationale added



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11.2 Trial Analysis Sets	All enrolled and eligible randomized subjects from the pivotal phase 3 trials (LP0084-1193, -1194, -1195, -1196) are included in the full analysis set (FAS) and will be analysed for incidence of SCC and other skin neoplasia.	Change definition of FAS
Analysis of Primary Endpoint	<p>The null hypothesis is that there is no difference in time to first SCC between ingenol disoxate gel and vehicle gel. The hypothesis will be tested against the two-sided alternative that there is a difference between the two treatment groups.</p> <p>The annual and the 3-year and 2 months cumulative incidence of first event of SCC will be calculated for each treatment group (active and vehicle) in main trial using methods of survival analysis in the presence of censoring.</p>	Specification of the null hypothesis for the primary endpoint
Analysis of Secondary Endpoint	<p>For the secondary endpoint, the null hypothesis is that there is no difference in time to first SCC or other skin neoplasia between ingenol disoxate gel and vehicle gel. The hypothesis will be tested against the two-sided alternative that there is a difference between the two treatment groups.</p>	Specification of the null hypothesis for the secondary endpoint
14 Handling of Urgent Safety Measure	LEO must act immediately upon receipt of the urgent safety measure notification in accordance with the internal procedures and national requirements.	Request from MHRA



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23 References	<i>Reference list revised</i>	There was a disconnect between the footnotes and the references listed in section 23
List of Appendices	Appendix 5: Protocol amendment history	

