Dermatology beyond the skin

Cover Page

Official title: Risk of Squamous Cell Carcinoma on Skin Areas Treated With Ingenol Mebutate Gel, 0.015% and Imiquimod Cream, 5%
LEO Pharma number: LP0041-63
NCT number: NCT01926496
Date: 13-MAR-2013

Consolidated Clinical Study Protocol

Risk of Squamous Cell Carcinoma on Skin Areas Treated with Ingenol Mebutate Gel, 0.015% and Imiquimod Cream, 5%

A phase 4 trial comparing the cumulative incidence of SCC after treatment with ingenol mebutate and imiquimod for multiple actinic keratoses on face and scalp

A multi-centre, randomised, two-arm, open label, active-controlled, parallel group, 36-month trial

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

LEO Pharma A/S
Global Clinical Operations

Protocol Code Number: **LP0041-63**
Date: **13-MAR-2013**

Version: **FINAL**
EudraCT Number: **2012-003112-31**

1 CLINICAL STUDY PROTOCOL APPROVAL/ACKNOWLEDGE

1.1 APPROVAL STATEMENT LEO PHARMA A/S

On behalf of LEO Pharma A/S, only the head of Medical Department and the head of Biostatistics and Data Management are authorised to approve the Clinical Study Protocol and Consolidated Clinical Study Protocol(s) comprising any subsequent amendment(s).

The following persons have approved this Clinical Study Protocol using electronic signatures as presented on the last page of this document:

PPD

Head of Biostatistics and Data Management

PPD

Head of Medical Department

1.2 APPROVAL STATEMENT INTERNATIONAL CO-ORDINATING INVESTIGATOR

It is the responsibility of the international co-ordinating investigator to approve the Clinical Study Protocol and Consolidated Clinical Study Protocol(s) comprising any subsequent amendment(s).

The following person has approved this Clinical Study Protocol by manually signing the International Co-ordinating Investigator Clinical Study Protocol Approval Form adjoined as a separate page to this document:

Prof Rolf Markus Szeimies

International co-ordinating investigator

1.3 ACKNOWLEDGE STATEMENT INVESTIGATOR(S)

Each participating investigator must agree to the approved Clinical Study Protocol and Consolidated Clinical Study Protocol(s) comprising any subsequent amendment(s) by signing the Investigator (Consolidated) Clinical Study Protocol Agreement Form.

2 PROTOCOL STATEMENT

2.1 COMPLIANCE WITH GOOD CLINICAL PRACTICE

This Clinical Study Protocol is designed to comply with the guideline produced by the International Conference on Harmonisation (ICH) on the topic Good Clinical Practice (GCP) as well as other relevant guidelines issued by ICH, primarily the efficacy guidelines.

3 PROTOCOL SYNOPSIS

Name of finished/ investigational product:	Ingenol mebutate gel, 0.015%
Name of active substance:	Ingenol mebutate
Title of trial/ protocol code number:	Risk of Squamous Cell Carcinoma on skin areas treated with Ingenol Mebutate Gel, 0.015% and Imiquimod Cream 5% LP0041-63
Co-ordinating investigator(s):	International-co-ordinating investigator: Prof Rolf Markus Szeimies, Germany National co-ordinating investigators will be appointed in each participating country.
Estimated number of trial sites and distribution:	Approximately 17 sites in France, 15 sites in Germany and 16 sites in the United Kingdom
Trial period:	First subject first visit planned Q2 2013 Last subject last visit planned Q2 2018
Main objective(s):	**Primary Objective:** To compare the cumulative incidence of squamous cell carcinoma (SCC) after treatment with ingenol mebutate gel and imiquimod cream. **Secondary Objectives** To compare the cumulative incidence of neoplasia and the short-term and 12-month efficacy of ingenol mebutate gel with imiquimod cream.

Methodology:

This is a phase 4, multi-centre, randomised, two-arm, open label, active-controlled, parallel group, 36-month trial.

All subjects who qualify for inclusion in this trial are to have 5 to 9 clinically typical, visible and discrete actinic keratosis (AK) lesions (confirmed by histopathology of one of the AKs prior to randomisation) within a contiguous 25 cm^2 treatment area on the face or scalp. This area of skin will be referred to as the 'selected treatment area'. Subjects will be randomised in a 1:1 ratio to the following treatment arms:

- Arm A: Ingenol mebutate gel 0.015% applied daily for 3 consecutive days to the selected treatment area followed by 8 weeks' rest. Retreatment for another 3 consecutive days if the treatment field is not completely cleared of AKs at Week 8

- Arm B: Imiquimod 5% cream applied 3 days per week for 4 weeks to the selected treatment area followed by 4 weeks' rest. Retreatment for 4 weeks if the treatment field is not completely cleared of AKs at Week 8.

Study visits will take place at Screening (Visit 1), during the treatment period on Days 1 and 4, Weeks 2, 4 and 8 (Visits 2 to 6) for initial treatment and, if retreatment is required, on Week 8+3 days and Weeks 10, 12, and 16 (Visits 7 to 10). During the Follow-up period visits will take place at Week 20 and Months 12, 18, 24, 30 and 36 (Visits 11 to 16).

At the Screening (Visit 1) subjects will sign the study-specific consent form in the presence of the (Sub)investigator and subject's eligibility will be checked and the selected treatment area will be identified. A 3-4 mm punch biopsy will be taken of one AK lesion in the

selected treatment area for histological confirmation of AK.

Treatment Period (Day 1 to Week 16)
At Day 1 (Visit 2), the subject eligibility will be confirmed and subjects will be randomised to treatment with either ingenol mebutate gel or imiquimod cream. The selected treatment area will be marked on the skin and the first dose will be applied under the supervision and management of the trial personnel. Subsequent doses will be applied at home. At the next visits (Day 4 and Weeks 2 and 4; Visits 3 to 5) a clinical assessment of neoplasia in the selected treatment area will be performed. If there is suspicion of SCC, basal cell carcinoma (BCC), or other neoplasia when clinical assessment is performed, a 3-4mm punch biopsy will be taken and trial treatment will be stopped but the subject will remain in the trial. The selected treatment area will be assessed for local skin responses (LSRs) and any adverse events (AEs). At Week 8 (Visit 6), a clinical assessment of the selected treatment area will be performed as for previous visits. An AK count in the selected treatment area will also be conducted.

At Week 8, subjects who are completely cleared in the selected treatment area will continue into the Follow-up Period. Subjects, who are not completely cleared in the selected treatment area will have a second treatment cycle and will attend visits at Week 8+3 days and Weeks 10, 12, and 16 (Visits 7 to 10). The assessments will be the same as during the first treatment cycle. After the second treatment cycle (Week 16) subjects will enter the Follow-up Period.

Until the first visit of the follow-up period (Week 20), no

other treatments and procedures are allowed in, and within 5 cm of the selected treatment area. Outside the selected treatment area (up to within 5 cm), procedures such as cryotherapy will be allowed; field therapy (e.g. imiquimod) will not be allowed.

Follow-up Period (Visits from Week 20 to Month 36).
Visits will be performed at Week 20 and Months 12, 18, 24, 30 and 36 (Visits 11 to16), at which a clinical assessment of neoplasia in the selected treatment area will be performed. If there is suspicion of SCC, BCC, or other neoplasia when clinical assessment is performed, a 3-4mm punch biopsy will be taken. An AK count in the selected treatment area will be conducted.

From Week 20 until Month 36 procedures such as cryotherapy will be allowed in, and within 5 cm of the selected treatment area. Further, at the discretion of the Investigator and according to nationally available product and treatment guidelines, the same treatment as originally administered is allowed (imiquimod or ingenol mebutate). Cross-over between imiquimod and ingenol mebutate is not allowed. Investigators will be encouraged to pursue these treatment options where clinically relevant before employing other treatments.

Outside the selected treatment area (up to within 5 cm) all treatments will be allowed, although investigators will be encouraged to avoid cross-over between imiquimod and ingenol mebutate.

Unscheduled/Early Termination
Upon completion of the last visit or during the study, an unscheduled visit may be required for any subject with a severe reaction, suspected pregnancy or an unresolved

	treatment-related AE or LSR (Local Skin Responses), if deemed clinically significant by the investigator. Only assessments that require follow-up will be conducted if the subject is continuing in the trial. For early termination all trial assessments scheduled should be performed.
Number of subjects entered:	A total of 480 subjects will be enrolled in the trial and randomised in a 1:1 ratio to the two treatment groups. With 240 patients in each treatment group an adequate precision of the 3-year incidence rate can be obtained. Assuming a 3-year rate of 1.0%, the upper 95% confidence limit will on average be 2.26%, and assuming a 2.5% rate, the upper 95% confidence limit will on average be 4.48%,
Main criteria for inclusion:	1. Following verbal and written information about the trial, subject must provide informed consent documented by signing the Informed Consent Form (ICF) prior to any trial-related procedures 2. Subjects with 5 to 9 clinically typical, visible and discrete AKs within a contiguous 25 cm^2 treatment area on the face or scalp. Actinic keratosis should be confirmed by histopathology of one of the AKs prior to randomisation 3. Subject at least 18 years of age.
Main criteria for exclusion:	1. Location of the selected treatment area: • on the periorbital skin • on the perioral skin/around the nostrils • within 5 cm of an incompletely healed wound • within 10 cm of a suspected BCC or SCC or other neoplasia 2. Selected treatment area lesions that have atypical clinical appearance (e.g., hypertrophic, hyperkeratotic or cutaneous horn) 3. History of SCC, BCC, malignant melanoma or other neoplasia in the selected treatment area

4. History or evidence of skin conditions other than the trial indication that would interfere with evaluation of the trial medication in the selected treatment area (e.g., eczema, unstable psoriasis, xeroderma pigmentosum)
5. Use of ingenol mebutate and/or imiquimod in and within 5 cm of the selected treatment area within 2 years prior to Screening (Visit 1).

Investigational product: Ingenol mebutate gel, 0.015%, supplied in a kit of 3 single use, unit dose tubes for topical application.

Reference product: Imiquimod 5% cream supplied in a kit of 12 single use, unit dose sachets for topical application

Duration of treatment: Each subject will receive a maximum of 2 treatment cycles during the treatment period (Day 1 to Week 16). The Follow-up period will start at Week 16 and continue until Month 36. Each subject will attend a minimum of 12 visits (16 visits if a second treatment cycle is required).

Planned duration:

- Treatment period: 16 weeks including an Initial Treatment Cycle of 8 weeks and a Second Treatment Cycle of 8 weeks (only given when AKs are observed after completion of the First Treatment Cycle).
- Follow-up Period: up to 32 months (from Week 16 to Month 36)

Assessments: Identification of the selected treatment area and dermatologic assessments of the selected treatment area must be performed by a dermatologist (board-certified or equivalent). The same dermatologist should attempt to perform all dermatologic examinations of each individual subject.

Investigator assessment

Identification of the selected treatment area

Identification of the selected treatment area and documen-

	tation on a study transparency using a three-point landmark technique (See Appendix IV). Biopsy and histological confirmation of one AK lesion prior to randomisation. Clinical assessment of the selected treatment area Clinical assessment of the selected treatment area. Biopsy if there is suspicion of SCC or other neoplasia. All visits. Local skin responses At all visits from baseline up to Week 20, assessments of LSRs in the selected treatment area using the LSR Grading Scale (See Appendix III). AK lesion count Recording of the number of clinically visible AK lesions identified in the selected treatment area on Day 1, Weeks 8, 16 (if retreated), and 20, and Months 12, 18, 24, 30 and 36. Adverse events Recording of the adverse events at all visits. Adverse events to be reported during the different phases of the trial are detailed in section 10.7.5.1. **Laboratory assessment:** - Biopsy and histological confirmation of one AK lesion prior to randomisation. - Biopsy if there is suspicion of SCC or other neoplasia. All visits.
Primary end point/ response criterion:	Diagnosis of SCC (defined as invasive SCC i.e. excludes SCC in situ) in treatment field across the 3-year trial period.

Secondary end point/ response criterion:	1. Diagnosis of SCC and other neoplasia in the treatment field over a 3-year period. 2. Complete clearance after the last treatment cycle (at Week 8 or 16) 3. Partial (at least 75%) clearance after the last treatment cycle (at Week 8 or 16) 4. Complete clearance at 12 months, defined as no AKs at any time in the selected treatment area at any time from the last treatment cycle at Week 8 or 16 through to Month 12.
Safety evaluation:	Incidence of Local Skin Responses (LSRs) Incidence of adverse events (AEs) Incidence of serious adverse events (SAEs)
Statistical methods:	**Analysis of Primary Endpoint** The 3-year cumulative incidence will be calculated for each treatment group using methods of survival analysis for estimation of cumulative incidence in the presence of censored time-to-event data. Annual incidence rates will also be presented for each group. The cumulative incidence rates will be presented for the event of SCC as primary endpoint and for SCC and other neoplasia as secondary. No formal test comparing the two arms 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 confidence interval. **Analysis of Secondary Endpoints** Complete clearance and partial clearance will be estimated and compared between treatment groups using the Cochran–Mantel–Haenszel test. **Adverse Events** The primary analysis will be performed on adverse events

occurring within initial treatment cycle, i.e. within 8 weeks of the start of treatment.

Local Skin Responses
The incidence and grade of LSRs will be summarised by treatment arm overall at each visit and by anatomical location (face/scalp). Local skin response grades will be summarised by frequency counts and descriptive statistics by treatment arm for each of the six individual LSRs: erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration.

An interim analysis of trial data, obtained when approximately half of the trial period has elapsed, will be conducted (approximately 3 years after study start). The interim analysis will not impact the conduct of this trial.

3.1 SCHEDULE/CHART OF TRIAL PROCEDURES

3.1.1 Screening and Treatment Period

	Screening	**Treatment Period**								
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7[1]**	**8[1]**	**9[1]**	**10[1]**
Day/Week (window)	(-42 to -14 days)	**Day 1**	**Day 4** (+2 days)	**Week 2** Day 15 (±2 days)	**Week 4** Day 29 (± 3 days)	**Week 8** Day 57 (±3 days)	3 days after Visit 6 (+2 days)	**Week 10** 14 days after Visit 6 (±2 days)	**Week 12** 28 days after Visit 6 (± 3 days)	**Week 16** 56 days after Visit 6 (± 3 days)
Informed consent	X[2]									
In-/exclusion criteria	X	X[3]								
Medical/surgical History	X									
Concurrent diagnosis	X	X[3]								
AK and SCC treatment history	X									
Concomitant medications, treatments, procedures	X	X	X	X	X	X	X	X	X	X
Brief physical exam[4]	X	X				X				X
Vital signs	X									
Demographics	X									
Height and weight	X									
Fitzpatrick skin type	X									
Urine pregnancy test[5]	X					X				X
Identify selected treatment area	X									
Mark selected treatment area on skin		X				X[1]				
Biopsy of one AK lesion	X									
Biopsy if suspicion of SCC etc.			X	X	X	X	X	X	X	X
Randomisation		X								
AK count	X	X				X				X

	Screening	Treatment Period								
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7[1]**	**8[1]**	**9[1]**	**10[1]**
Day/Week (window)	(-42 to -14 days)	**Day 1**	**Day 4** (+2 days)	**Week 2** Day 15 (±2 days)	**Week 4** Day 29 (± 3 days)	**Week 8** Day 57 (±3 days)	3 days after Visit 6 (+2 days)	**Week 10** 14 days after Visit 6 (±2 days)	**Week 12** 28 days after Visit 6 (± 3 days)	**Week 16** 56 days after Visit 6 (± 3 days)
Dispense medication		X				X[1]				
Return medication			X[7]		X[6]		X[7]		X[6]	
Compliance			X	X[6]	X[6]		X	X[6]	X[6]	
Field assess-ment for SCC, BCC or neoplasia			X	X	X	X	X	X	X	X
Local skin response (LSR)		X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X

1. Only for subjects who are not completely cleared in the selected treatment area at Week 8. Subjects who have cleared should proceed to the Follow –up period at Visit 11
2. Can be performed prior to Visit 1
3. To be checked at Visit 2
4. Including general appearance, regional lymph nodes and dermatologic examination of the skin in general
5. Females of childbearing potential only
6. Imiquimod only
7. Ingenol mebutate only

3.1.2 Follow-up Period

Visit Number	**11**	**12**	**13**	**14**	**15**	**16**
Week/Month (window)	**Week 20** (±14 days)	**Month 12** (±14 days)	**Month 18** (±28 days)	**Month 24** (±28 days)	**Month 30** (±28 days)	**Month 36** (± 28 days)
Concomitant medications, treatments, procedures	X	X	X	X	X	X
Field assessment for SCC, BCC or neoplasia	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X
AK count	X	X	X	X	X	X
Brief physical exam[4]		X	X	X	X	X

Note: Unscheduled/Early Termination

Upon completion of the last visit or during the study, an unscheduled visit may be required for any subject with a severe reaction, suspected pregnancy or an unresolved treatment-related AE or LSR, if deemed clinically significant by the investigator. Only assessments that require follow-up will be conducted if the subject is continuing in the trial. For early termination all trial assessments scheduled should be performed if possible.

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

4.1 LIST OF ABBREVIATIONS

5-FU	5-fluorouracil
ADR	Adverse Drug Reaction
AE	Adverse Event
AK	Actinic Keratosis
BCC	Basal Cell Carcinoma
CRF	Case Report Form
CRO	Contract Research Organisation
CMO	Contract Manufacturing Organisation
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPV	Global Pharmacovigilance
ICH	International Conference on Harmonisation
ICTM	International Clinical Trial Manager
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IWR	Interactive Web Response System
LSR	Local Skin Response
NLCRA	National Lead Clinical Research Associate
NMSC	Non-Melanoma Skin Cancer
RDC	Remote Data Capture
SAE	Serious Adverse Event
SCC	Squamous Cell Carcinoma
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure

SUSAR	Suspected Unexpected Serious Adverse Reaction
UVA	Ultraviolet light A
UVB	Ultraviolet light B
WMA	World Medical Association

4.2 DEFINITION OF TERMS

Assessment
A (cluster of) characteristic(s) measured and/or recorded for a subject.

Certified Copy
A certified copy is a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original (FDA Guidance for Industry, Computerized Systems Used in Clinical Investigations, May 2007).

Concomitant Medication
Any medication taken by a subject during the clinical trial apart from the investigational product.

Enrolled Subject
A subject for whom informed consent has been obtained and a CRF number assigned.

Fraud
Fabrication of data, selective and undisclosed rejection of undesired results, substitution with fictitious data, deliberately incorrect use of statistical methods for the purposes of reaching other conclusions than those warranted by the data, misinterpretation of results and conclusions, plagiarism of results or entire articles from other researchers, misrepresentation of other researchers' results, unwarranted authorship, and misleading application for positions or funds.

International Clinical Trial Manager (ICTM)
The person appointed by LEO Pharma A/S to be the main international representative responsible for all aspects of a clinical trial as outlined in Global Clinical Operations SOPs.

Clinical trial agreement
A contract between on the one hand LEO Pharma A/S and/or a Contract Research Organisation (CRO) and on the other hand an investigator and/or the institution specifying the conditions for the co-operation in the clinical trial and the investigator's and/or the institution's responsibilities.

Investigator Staff Signature Form
A form used:
1. for the investigator to delegate trial related tasks/duties
2. for trial site staff to sign and date to accept delegation
3. for trial site staff to document signature and initials
4. for the investigator to authorise tasks/duties delegated

Investigator Trial File
The collection of trial documents required by Global Clinical Operations SOPs LEO Pharma A/S, ICH Guidelines and/or regulatory requirements to be on file at the trial site.

LEO Pharma A/S
LEO Pharma A/S refers to the sponsor of the clinical trial.

LEO Pharma A/S affiliate
An affiliated company of LEO Pharma A/S authorised to manage certain clinical trial related activities for LEO Pharma A/S.

Monitor
A person appointed by LEO Pharma A/S to carry out monitoring of a clinical trial.

National Lead CRA (NLCRA)
The person appointed by LEO Pharma A/S to be the national representative responsible for all aspects of a clinical trial within a country as outlined in Global Clinical Operations SOPs.

Randomisation Code List
A list of (sequential) numbers to each of which a treatment is allocated (assigned). Treatment may be revealed as a code letter (e.g. A, B, …) or by directly revealing the specific treatment (investigational product).

Response Criterion
An assessment or a transformation of the assessment(s) described on a subject level for which a statistical analysis is performed, i.e. a p-value or a confidence interval is stated, or for which tabulation serves as important supportive evidence of efficacy/safety.

Subject Identification List
A summary list kept by the investigator in the Investigator Trial File which records the names of all subjects enrolled and the date of enrolment in the trial at that trial site. The list includes each subject's corresponding CRF number to allow the investigator/institution to reveal the identity of any subject if required.

Subject Screening Log
A document kept by the investigator which identifies patients/subjects who have signed the informed consent.

Subject Screening Log is synonymous with Patient Screening Log.

Subject Study Card
A card given to a subject by the trial site at the time trial medication is first dispensed to a subject to identify that the subject is having treatment with an investigational product.

Writing committee
An appointed committee participating in the writing of a multi-centre publication.

5 ETHICS

5.1 INDEPENDENT ETHICS COMMITTEES (IECs) OR INSTITUTIONAL REVIEW BOARDS (IRBs)

The clinical trial must be approved by/receive favourable opinion from relevant Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) prior to the enrolment of subjects.

Any amendments to the approved clinical trial must likewise, as required, be approved by/receive favourable opinion from relevant IRBs/IECs prior to implementation.

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

5.2 ETHICAL CONDUCT OF THE TRIAL

This clinical trial will be conducted to conform to the principles of the World Medical Association (WMA), Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and last revised in Seoul in October 2008 by the WMA General Assembly (see Appendix II).

5.3 ETHICAL CONSIDERATION STATEMENT

Actinic keratosis (AK) is a common skin condition which is linked to the development of squamous cell carcinoma (SCC) (1), and both conditions share specific gene expression (2).

Current treatment options for AK lesions consist of cryotherapy, photodynamic therapy, and topical products. Cryotherapy and photodynamic therapy can be painful and cryotherapy often leaves areas of hyper- or hypopigmentation (3, 4). Curettage (with or without electro-surgery) and excisional surgery are alternatives to cryotherapy (5). Topical products include 5-fluorouracil (5-FU), diclofenac, and imiquimod, and are commonly used as field treatment for multiple lesions over larger skin areas (6, 7, 8, 9, 10, 11, 12, 13, 14). The duration of treatment required for these topical products ranges from 2 to 16 weeks. It has been previously documented that longer treatment durations reduce patient compliance (15).

A new topical product, ingenol mebutate gel, has been developed for the treatment of actinic keratosis on both head (face and scalp) and non-head locations (trunk and extremities). The duration of treatment with ingenol mebutate gel is once daily for either 2 or 3 consecutive days (for non-head and head locations respectively) which provides an advantage for treatment compliance and patient convenience in those subjects treated with ingenol mebutate gel. Ingenol mebutate gel has been approved in the US in January 2012, in Brazil in July 2012 and in the European Union (EU) and Australia in November 2012 under the trade name Picato®.

Imiquimod cream is a topical immune response modifier and a 5% formulation has been approved for the treatment of AKs in the US and Europe (Aldara®) with different dosage regimens. The safety and efficacy of imiquimod has been demonstrated in controlled clinical trials for both dose regimens (16, 17, 19, 18, 20). In this study, subjects in the imiquimod group will be treated according to the EU dosage regimen corresponding to one application on 3 days per week for 4 weeks, with a 4-week treatment pause followed, if necessary, by another 4-week treatment period.

The clinical programme for the development of ingenol mebutate gel for the face and scalp has initially focused on one treatment cycle of 3 days. Since the label for imiquimod already includes an option to repeat treatment after the first treatment cycle (12, 14), the present trial will extend the treatment regimen of ingenol mebutate gel to two cycles for patients who have recalcitrant disease. Whereas the clinical development program used only one cycle comprising 2 or 3 days of treatment, the present trial will allow retreatment with at least one extra cycle of treatment if clinically indicated. In an ongoing trial of repeat use of ingenol mebutate 140 subjects have been randomized 2:1 to either a repeat cycle of ingenol mebutate or vehicle, i.e. approximately 95 subjects have been subjected to repeat cycles of ingenol mebutate (study code LP0041-22). The trial is ongoing with no safety concerns raised.

Since AK is a chronic disease and neither imiquimod nor ingenol mebutate are universally effective, need will arise in many subjects after the randomised treatment period for other treatment(s) than the intervention stipulated by the protocol. In such cases the choice should be to repeat the initial treatment (imiquimod or ingenol mebutate) as previously given to the subject (cross-over between imiquimod and ingenol mebutate is not allowed) or apply lesion-based cryotherapy. In order to avoid confounding of the results, other treatments should be avoided for as long as medically permissible.

The safety of ingenol mebutate gel has been established in an extensive clinical programme (21). Localised application site disorders (e.g., pruritus, pain, irritation) and LSRs, particularly erythema and flaking/scaling are the main characteristics of the safety profile of ingenol mebutate gel. The application site disorders were generally mild or moderate in intensity. Subjects enrolled in this trial will be limited as to what concomitant medications/procedures they may receive, depending on the trial period and whether they require treatment inside or outside the selected treatment area. In particular, cross-over for any one subject between ingenol mebutate gel and imiquimod is not allowed. Every effort has been made to ensure that subjects may at all times receive relevant treatment for their condition, alternative options for concomitant treatment have been provided. These restrictions are therefore not considered to be a risk to subject safety since treatment options are still available.

Actinic Keratosis lesions are usually diagnosed clinically rather than histologically. But when there is doubt as to the clinical differentiation between AKs and SCCs, histological confirmation may be necessary (23). In this trial, biopsies will be performed in order to confirm the clinical assessment of AK at screening and also if there is suspicion of SCC/BCC or other neoplasia.

In order for the necessary biopsies to be associated with as little discomfort as possible, the area will be anaesthetised. All the test procedures will be performed at the study centre. The biopsies taken if SCC/BCC or other neoplasia is suspected will be sent to a central laboratory for assessment. The results will be emailed to the investigator as soon as possible so that they can be discussed with the subject. In case of a local skin response, the affected skin areas will be closely monitored and appropriate medical care administered if required to minimise the discomfort, if any, for the subject.

In order to ensure safety, particularly in order to capture development of SCC in any subject in due time for the subject to receive further treatment, all subjects participating in the trial will be under careful supervision of an experienced investigator during the entire course of the trial.

5.4 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 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.

A Study Subject Card will be given to a subject by the site personnel at the time investigational product is first dispensed, to identify that the subject is having treatment with an investigational product.

5.5 HANDLING OF PERSONAL DATA

Subjects shall be asked to consent that their personal data are recorded, collected, processed and may be transferred to EU and non-EU countries in accordance with any national legislation regulating privacy and data protection.

Personal data shall be handled and processed by all relevant parties involved in the clinical trial in accordance with any national legislation regulating privacy and data protection as well as in accordance with the general terms and conditions of the authorisation granted by the Danish Data Protection Agency to LEO Pharma A/S as set forth in the attached Appendix I. LEO Pharma A/S is considered data controller for this clinical trial.

6 TRIAL ADMINISTRATIVE STRUCTURE

6.1 SPONSOR

LEO Pharma A/S is the sponsor of the clinical trial.

6.2 LEO PHARMA A/S AFFILIATES AND CRO(S)

LEO Pharma A/S has transferred certain clinical trial related activities to the LEO Pharma A/S affiliate(s) and/or to the CRO(s) relevant for the conduct of the clinical trial.

LEO Pharma, France
LEO Pharma GmbH, Germany
LEO Laboratories, UK

The manufacture of investigational product ingenol mebutate is performed at either of the two manufacturing sites:
LEO Laboratories Ltd., 285 Cashel Road, Crumlin, Dublin 12, Ireland
or
DPT Laboratories Ltd., 307 E. Josephine Street, San Antonio, Texas 78215, United States

Dispensing of components for the manufacture of ingenol mebutate gel at DPT Laboratories Ltd. is performed at:
DPT Laboratories Ltd., 3300 Research Plaza, San Antonio, Texas 78235, United States

The manufacture of investigational product imiquimod is performed at:
MEDA AB, Pipers väg 2A, 170 73 Solna, Sweden.

Almac Clinical Services, 9 Charlestown Road, Seagoe Industrial Estate, Craigavon BT63 5PW, United Kingdom will be responsible for drug storage, packaging, labelling, distribution and destruction of investigational product as agreed to in a Service Agreement/Contract.

Almac Clinical Technologies, Seagoe Industrial Estate, Craigavon BT63 5UA, United Kingdom, will be responsible for the Interactive Web Response (IWR) System for allocation of trial medication kit numbers and randomisation, as agreed to in a Service Agreement/Contract.

ACM Global Central Laboratory, 23 Hospital Fields Road, York, YO10 4ZD, UK will be responsible for provision of kits and shipment of the skin punch biopsies as agreed to in a Service Agreement/Contract.

PPD , MD, Department of Dermatology, Medical University of Graz, Auenbruggerplatz 8, A-8036 Graz, Austria will be responsible for histological assessment of the skin punch biopsies as agreed to in a Service Agreement/Contract.

6.3 LEO PHARMA A/S PERSONNEL

6.3.1 International Clinical Trial Manager (ICTM)

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6.3.2 National Lead CRAs (NLCRAs)

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PPD , Senior Clinical Research Associate, LEO Laboratories Limited, Longwick Road, Princes Risborough, Buckinghamshire HP27 9RR, United Kingdom, Tel. PPD , Fax: PPD , e-mail: PPD

6.3.3 Sponsor's Medical Expert

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6.3.4 Safety Scientist/Safety Physician, Global Pharmacovigilance

PPD , MSc PhD, Principal PV Scientist, LEO Pharma A/S, Industriparken 55, 2750 Ballerup, Denmark, Tel.: PPD , Fax: PPD , e-mail: PPD

6.3.5 Study Statistician

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6.3.6 Study Data Manager

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6.4 PROTOCOL AUTHOR(S)

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PPD MD, Klinik für Dermatologie und Allergologie, Klinikum Vest GmbH, Behandlungszentrum, Knappschaftskrankenhaus Recklinghausen, Dorstener Str. 151 45657 Recklinghausen, Germany, Tel.: PPD
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PPD , BSc (Hons) FICR, Medical Writer, Diamond Clinical Ltd, 3 Manor Courtyard, Hughenden Avenue, High Wycombe, HP13 5RE, United Kingdom, Tel.: PPD , e-mail: PPD

6.5 INVESTIGATORS AND TRIAL COMMITTEES

6.5.1 International Co-ordinating Investigator

The international co-ordinating investigator is responsible for approval of the (Consolidated) Clinical Study Protocol, Clinical Study Protocol Addendum(s), (Consolidated) CRF and the Clinical Study Report on behalf of all trial investigators and as agreed to in an International Co-ordinating Investigator Agreement.

Prof Rolf Markus Szeimies MD, Klinik für Dermatologie und Allergologie, Klinikum Vest GmbH, Behandlungszentrum, Knappschaftskrankenhaus Recklinghausen, Dorstener Str. 151

45657 Recklinghausen, Germany, Tel.: PPD ,
e-mail: PPD

6.5.2 National Co-ordinating Investigator(s)

The national co-ordinating investigator(s) are responsible for national issues relating to the clinical trial as agreed to in a National Co-ordinating Investigator Agreement.

The contact details of participating national co-ordinating investigator(s) are provided outside the protocol.

6.5.3 Investigators

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.

The contact details of each participating investigator are provided outside the protocol in the 'National Clinical Trial Applications'.

6.5.4 Trial Committees

Not applicable

6.6 AGREEMENTS

Before the initiation of any clinical trial related activities by the investigators/clinical trial committee(s)/LEO Pharma A/S affiliate(s)/CRO(s) listed above, the relevant parties must have entered into a written agreement regulating those activities.

7 INSURANCE

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

8 INTRODUCTION AND RATIONALE

This is a phase 4 trial comparing the cumulative incidence of SCC over a period of up to 3 years after treatment with ingenol mebutate or imiquimod for multiple AKs on face and scalp. The trial will be conducted in approximately 48 centres in France, Germany and the United Kingdom in accordance with applicable national regulatory requirements.

8.1 ACTINIC KERATOSIS

Actinic keratosis is a common skin condition visible as thickened, cornified, scaly lesions and characterised histologically by atypical epithelial proliferation (24). Actinic keratoses usually develop on areas that are frequently exposed to the sun (e.g., face, ears, scalp, neck, forearms, and back of the hands). Patients with AK often express embarrassment, worry, and irritation related to the change in appearance of their skin and unsightly nature of the lesions (25, 26). In addition to the emotional strain, AK lesions can be painful and easily traumatised causing bleeding (26, 27, 28, 29).

In population studies performed in the EU and US, reported prevalence rates for AK have been approximately 11-25% of the population, while estimates are higher in Australian studies (up to 60%) (24). Patients with AK tend to have Fitzpatrick type I or II skin (fair skin) which burns with sun exposure and does not tan (28).

In the context of AK, the skin of patients with AKs shows field cancerisation, characterised by the epithelial surface of the photodamaged area being susceptible to the development of additional AKs or a malignancy. This is evidenced by the presence of multiple subclinical and clinically visible AK lesions as well as multifocal preneoplastic changes with genetic mutations (30). There is also increasing evidence that AK represents SCC in situ in its earliest stages (15, 24, 31). Histological evidence shows that contiguous AK is present in 97% of SCC lesions on sun-damaged skin (15). Actinic keratosis is linked epidemiologically to development of SCC (1), and both conditions share specific gene expression (2). If left untreated, AK may regress, or alternatively, may progress to SCC, with significant morbidity and possible lethal outcome (15).

Predicting which AKs may progress to SCC is not possible, nor is the conversion rate for an AK to SCC clear: the transformation rate from an AK lesion to SCC within one year has been reported to be <1:1000 (32). Further mathematical modelling of these data has predicted that for an individual with an average of 7.7 AKs, the probability of at least one transforming within a 10-year period is approximately 10% (33).

Diagnosis of AKs is based upon the clinical presentation (23). When there is doubt as to the clinical differentiation between AKs and SCCs, histological confirmation may be necessary (23).

8.2 INVESTIGATIONAL PRODUCT DESCRIPTION

8.2.1 Ingenol Mebutate

The formulation of ingenol mebutate gel contains ingenol mebutate as the active ingredient and benzyl alcohol, hydroxyethyl cellulose, isopropyl alcohol, citric acid, sodium citrate, and purified water as inactive ingredients.

Ingenol mebutate is an ingenol derivative extracted from *Euphorbia peplus* (*E. peplus*), a member of the Spurge family. The sap of *E. peplus* has been used to treat a number of skin conditions including warts, corns, waxy growths, and skin cancer since the 1800s (34, 35, 36). Results from an early proof of concept study using the crude sap of *E. peplus* (known as study PEP001) confirmed anecdotal community-based evidence of activity against AK and non-melanoma skin cancer (NMSC) when used topically. Ingenol mebutate was identified as the principal active component responsible for the selective cytotoxic effects of *E. peplus* sap, based on its antitumour effects both in vitro and in vivo (37). The mechanism of action in AK is not fully understood. In vivo and in vitro models have shown a dual mechanism of action for the effects of ingenol mebutate: 1) induction of local lesion cell death, and 2) promoting an inflammatory response characterised as infiltration of neutrophils and other immunocompetent cells (38, 39, 40, 41, 42, 43, 44). This mechanism of action distinguishes ingenol mebutate from current therapeutic options and provides a rationale for substantially shorter durations of treatment (2 to 3 days) compared to approved topical AK products.

The clinical development programme for ingenol mebutate gel has investigated the efficacy and safety for the treatment of AKs in either a 3-day regimen on the face and/or scalp or 2-day regimen on the trunk and/or extremities. Ingenol mebutate gel applied topically for 2 or 3 days has been shown effective for field treatment of actinic keratoses (21, 22). Localised application site disorders (e.g., pruritus, pain, irritation) and LSRs (particularly erythema and flaking/scaling) are the main characteristics of the safety profile of ingenol mebutate gel. The application site disorders are generally mild or moderate in intensity. Local skin response data captured via specific LSR grading have shown that the LSRs are transient, peaking around Day 4 when applied on the face/scalp and between Days 3-8 when applied to trunk/extremities and typically resolve without sequelae within 2 or 4 weeks (on the face/scalp or trunk/extremities, respectively) of application (22). Furthermore, application of ingenol mebutate gel does not produce scarring (22).

Ingenol mebutate gel was first approved in the US in January 2012, in Brazil in July 2012 and in the EU and Australia in November 2012 under the trade name Picato®.

With regard to the risk of development of SCC in trial subjects, it should be noted that there is an inherent background risk of conversion of AKs to SCC (see above, section 8.1). The trial objective is to further explore the incidence of SCC to examine whether there is an additional comparative risk following AK treatment with one or other field treatment. Data from the clinical development programme hitherto have not indicated such a risk for ingenol mebutate (the Combined Trials for Field Treatment of AK Lesions, $N^{ingenol\ mebutate}$ =1165, $N^{vehicle}$ =632):

- SCC with any location on the body occurred with similar frequency between groups (11 (0.9%) vs. 5 (0.8%) for ingenol mebutate gel vs. vehicle)
- SCC inside the selected treatment area occurred with similar frequency between groups (3 (0.3%) vs. 2 (0.3%) for ingenol mebutate gel vs. vehicle).

Further, in the long-term follow up programme, a total of 198 patients who had demonstrated complete clearance of AK lesions (following treatment with ingenol mebutate gel (184 patients) or vehicle (14 patients)) at Day 57 were followed for possible lesion recurrence and also for safety within the selected treatment area: no SCCs were reported for any of the patients in the 12-month period.This trial seeks to further examine the incidence of SCC for up to 3 years after treatment, within a controlled trial environment rather than as a post-marketing surveillance exercise relying on capture of spontaneous reports.
The trial is a phase 4 post-approval commitment to the European Medicines Agency (EMA).

Please see the Summary of Product Characteristics (SmPC) for ingenol mebutate for further non-clinical and clinical information (21).

8.2.2 Imiquimod

Imiquimod is a topical immune response modifier and a 5% formulation has been approved for the treatment of AKs in the US and Europe (Aldara® cream) with a different dosage regimen. The dose regimen in Europe is one application 3 days per week for 4 weeks, with a 4-week treatment pause followed, if necessary, by another 4-week treatment period. The dose regimen in the US is two applications per week for 16 weeks. In this trial, subjects in the imiquimod group will be treated according to the EU dosage regimen.

Imiquimod is an immune response modifier. In animal models imiquimod has been shown to stimulate the immune system by activating antigen-presenting cells such as monocytes⁄

macrophages and dendritic cells to produce interferon and other cytokines and chemokines, which leads to the stimulation of the adaptive immune response.

The safety and efficacy of imiquimod applied 3 times per week for one or two courses of 4 weeks, separated by a 4-week treatment-free period has been demonstrated in two double-blind vehicle controlled clinical trials , (see more information in the SmPC of Aldara®, Appendix V).

The rate of progression to SCC was reported to be 1.6% (2/128 patients) within one year. There are no data on recurrence and progression rates beyond 1 year (Appendix V).

8.3 TRIAL RATIONALE

The purpose of this trial is to evaluate the risk of SCC after the treatment with ingenol mebutate gel. Imiquimod has been chosen for comparison as the treatment that is most comparable marketed field treatment with regard to efficacy. The cumulative incidence of SCC in a cohort of subjects with multiple AKs on the face or scalp who have been treated with ingenol mebutate gel or imiquimod cream will be evaluated.

To ensure accurate diagnosis a biopsy of a representative lesion will be taken to confirm AK prior to randomisation. Further, the biopsy is expected to identify a number of subjects who have SCC at screening and are therefore not eligible for the trial. In order to increase the likelihood of detecting an increased risk, if any, the subjects in both groups will be treated for 2 cycles if complete clearance is not obtained at Week 8. To obtain a reasonable number of SCC cases, subjects will be followed for 3 years and will be assessed for SCC (and other neoplasias) in the treatment area at regular intervals.

The overall design will be a two-arm trial where patients are initially all treated with one cycle of either ingenol mebutate gel or imiquimod cream according to the normal treatment schedule for face and scalp. Subjects in the imiquimod group will be treated according to the approved EU dosage regimen. After 8 weeks, patients who are completely cleared of all AKs in the selected treatment area will continue further observation in the Follow-up period, whereas those who are not cleared will be retreated with a second treatment cycle. For the purpose of this trial the minimum period between the two treatment cycles, i.e. the period between the initial treatment cycle and possible retreatment, will be 8 weeks which is the time

when the treatment response would be evaluated in clinical practice for both products. Adverse events, LSRs and efficacy will also be compared between the two treatments.

Since AK is a chronic disease and neither imiquimod nor ingenol mebutate are universally effective, need may arise in some subjects after the randomised treatment period for other treatment(s) in the selected treatment area than the intervention stipulated by the protocol. In such cases the choice should be to repeat the initial treatment (imiquimod or ingenol mebutate) as previously given to the subject (cross-over between imiquimod and ingenol mebutate is not allowed) or apply lesion-based cryotherapy. In order to avoid confounding of the results, other treatments will be avoided for as long as medically permissible.

9 TRIAL OBJECTIVES

9.1 PRIMARY OBJECTIVE

To compare the cumulative incidence of SCC after treatment with ingenol mebutate gel and imiquimod cream.

The primary response criterion is diagnosis of SCC (defined as invasive SCC i.e. excludes SCC in situ) in the treatment field across the 3-year trial period.

9.2 SECONDARY OBJECTIVES

To compare the cumulative incidence of neoplasia and the short-term and 12-month efficacy of ingenol mebutate gel with imiquimod cream.

The secondary response criteria are:

1. Diagnosis of SCC and other neoplasia in the treatment field over a 3-year period.
2. Complete clearance after the last treatment cycle (at Week 8 or 16)
3. Partial (at least 75%) clearance after the last treatment cycle (at Week 8 or 16)
4. Complete clearance at 12 months, defined as no AKs in the selected treatment area at any time from the last treatment cycle at Week 8 or 16 through to Month 12.

10 INVESTIGATIONAL PLAN

10.1 TRIAL DESIGN

10.1.1 Overall Design

This is a phase 4, multi-centre, randomised, two-arm, open label, active-controlled, parallel group, 36-month trial.

All subjects who qualify for this trial are to have 5 to 9 clinically typical, visible and discrete AK lesions (confirmed by histopathology of one of the AKs prior to randomisation) within a contiguous 25 cm^2 treatment area on the face or scalp. This area of skin will be referred to as the selected treatment area.

In case of baldness or partial baldness, the forehead should be defined by the previous hairline.

Subjects will be randomised in a 1:1 ratio to the following treatment arms:

- Arm A: Ingenol mebutate gel 0.015% applied daily for 3 consecutive days to the selected treatment area followed by 8 weeks' rest. Retreatment for another 3 consecutive days if the treatment field is not completely cleared of AKs at Week 8
- Arm B: Imiquimod 5% cream applied 3 days per week for 4 weeks to the selected treatment area followed by 4 weeks' rest. Retreatment for 4 weeks if the treatment field is not completely cleared of AKs at Week 8.

Study visits will take place at Screening (Visit 1), during the treatment period on Days 1 and 4, Weeks 2, 4 and 8 (Visits 2 to 6) for initial treatment and, if retreatment is required, on Week 8+3 days and Weeks 10, 12, and 16 (Visits 7 to 10). During the Follow-up period visits will take place at Week 20 and Months 12, 18, 24, 30 and 36 (Visits 11 to 16).

10.1.2 Individual Phases

At the Screening (Visit 1) subjects will sign the study-specific consent form in the presence of the investigator and subject's eligibility will be checked and the selected treatment area will be identified. A biopsy will be taken of one AK lesion in the selected treatment area for histological confirmation of AK.

Treatment Period (Day 1 to Week 16)
At Day 1 (Visit 2), the subject eligibility will be confirmed and subjects will be randomised to treatment with either ingenol mebutate gel or imiquimod cream. The selected treatment area will be marked on the skin and the first dose will be applied under the supervision and management of the trial personnel. Subsequent doses will be applied at home.

At the next visits (Day 4 and Weeks 2 and 4; Visits 3 to 5) a clinical assessment of the selected treatment area will be performed. The selected treatment area will be assessed for local skin responses (LSRs) and any adverse events (AEs). If there is suspicion of SCC, BCC, or other neoplasia when clinical assessment is performed, a biopsy will be taken and trial treatment will be stopped but the subject will remain in the trial. At Week 8 (Visit 6), a clinical assessment of the selected treatment area will be performed as for previous visits. An AK count in the selected treatment area will also be conducted.

At Week 8, subjects who are completely cleared in the selected treatment area will continue into the Follow-up Period. Subjects, who are not completely cleared in the selected treatment area will have a second treatment cycle and will attend visits at Week 8+3 days and Weeks 10, 12, and 16 (Visits 7 to 10). The assessments will be the same as during the first treatment cycle. After the second treatment cycle subjects will enter the Follow-up Period.

Until the Follow-up period (Week 20), no other treatments and procedures are allowed in, and within 5 cm of the selected treatment area. Outside the selected treatment area (up to within 5 cm), procedures such as cryotherapy will be allowed; field therapy will not be allowed.

Follow-up Period (Week 16 to Month 36).
Visits will be performed at Week 20 and Months 12, 18, 24, 30 and 36 (Visits 11 to16), at which a clinical assessment of neoplasia in the selected treatment area will be performed. If there is suspicion of SCC, BCC, or other neoplasia when clinical assessment is performed, a biopsy will be taken. An AK count in the selected treatment area will be conducted.

From Week 20 until Month 36 procedures such as cryotherapy will be allowed in, and within 5 cm of the selected treatment area. Further, at the discretion of the Investigator and according to nationally available product and treatment guidelines, the same treatment as originally administered is allowed (imiquimod or ingenol mebutate). Cross-over between imiquimod

and ingenol mebutate is not allowed. Investigators will be encouraged to pursue these treatment options where clinically relevant before employing other treatments.

Outside the selected treatment area (up to within 5 cm) all treatments will be allowed, although investigators will be encouraged to avoid cross-over between imiquimod and ingenol mebutate.

10.1.3 Individual Visits

Screening (Visit 1, -42 to -14 days)

Eligibility will be checked according to the inclusion and exclusion criteria and the subject will sign the study-specific consent form in the presence of the investigator or his/her designee prior to any screening procedures taking place.

The following information will be recorded:

- Date of birth, sex, race, ethnic origin (self-report), height, weight, Fitzpatrick skin type, relevant medical/surgical history, concurrent diagnoses, concomitant medication, AK and SCC treatment history.
- Abbreviated physical examination including general appearance, regional lymph nodes and dermatologic examination of the skin in general.
- Vital signs (resting blood pressure and heart rate) and oral or ear temperature.

The selected treatment area will be identified by the dermatologist and documented on the study transparency using a three-point landmark technique. Detailed instructions for the three-point landmark technique are given in Appendix IV.

A biopsy will be taken of one AK lesion in the selected treatment area (see 10.7.4) for histological confirmation of AK.

Female subjects of childbearing potential will have a urine pregnancy test.

Visit 2 (Day 1)

Subject eligibility will be checked according to the inclusion and exclusion criteria. Once eligibility is confirmed, assessment of the selected treatment area, including LSRs and AK lesion count will be performed.

The subjects will be randomised to treatment with either ingenol mebutate gel or imiquimod cream. A trial medication kit will be assigned through an Interactive Web Response (IWR) System. The selected treatment area will be marked on the skin and the first dose of study medication will be applied under the supervision and management of the trial personnel (the subsequent doses will be applied at home).

Visit 3 (Preferred on Day 4, with a visit window of +2 days)

Visit 3 will include:

- Clinical assessment of neoplasia in the selected treatment area (biopsy if there is suspicion of SCC, BCC or other neoplasia)
- Dermatologic examination of the selected treatment area(s) including LSRs
- Reporting of (S)AEs (see Table 2)
- Reporting of concomitant medication, treatments and procedures
- Return of trial medication (only for subjects treated with ingenol mebutate)
- Trial medication compliance

Visit 4 (Week 2, Day 15 ± 2 days)

Visit 4 will include:

- Clinical assessment of neoplasia in the selected treatment area (biopsy if there is suspicion of SCC, BCC or other neoplasia)
- Dermatologic examination of treated selected treatment area(s) including LSRs
- Reporting of (S)AEs (see Table 2)
- Reporting of concomitant medication, treatments and procedures
- Trial medication compliance (for subjects treated with imiquimod)

Visit 5 (Week 4, Day 29 ± 3 days)

Visit 5 will include:

- Clinical assessment of neoplasia in the selected treatment area (biopsy if there is suspicion of SCC, BCC or other neoplasia)
- Dermatologic examination of the selected treatment area(s) including LSRs
- Reporting of (S)AEs (see Table 2)
- Reporting of concomitant medication, treatments and procedures
- Return of trial medication and trial medication compliance (for subjects treated with imiquimod)

Visit 6 (Week 8, Day 57 ± 3 days)

Visit 6 will include:

- Clinical assessment of neoplasia in the selected treatment area (biopsy if there is suspicion of SCC, BCC or other neoplasia)
- Dermatologic examination of the selected treatment area including LSRs and AK count.
- Reporting of (S)AEs (see Table 2)
- Reporting of concomitant medication, treatments and procedures
- Urine pregnancy test for female subjects of childbearing potential
- An abbreviated physical examination

Subjects who are not completely cleared in the selected treatment area will be retreated with a Second Treatment Cycle (Visits 7 to 16). At this visit the first dose of study medication will be applied under the supervision and management of the trial personnel (the subsequent doses will be applied at home).

Subjects, who are completely cleared in the selected treatment area (an AK count of zero), will continue in the Follow-up Period until trial completion at Month 36 (Visits 11 to 14).

Visit 7 – Only if Retreatment is required (3 days after Visit 6 with a visit window of +2 days)

Visit 7 will include:

- Clinical assessment of neoplasia in the selected treatment area (biopsy if there is suspicion of SCC, BCC or other neoplasia)
- Dermatologic examination of the selected treatment area(s) including LSRs
- Reporting of (S)AEs (see Table 2)
- Reporting of concomitant medication, treatments and procedures
- Return of trial medication (for subjects treated with ingenol mebutate)
- Trial medication compliance

Visit 8 – Only if Retreatment is required (Week 10, 14 days ± 2 days after Visit 6)

Visit will include:

- Clinical assessment of neoplasia in the selected treatment area (biopsy if there is suspicion of SCC, BCC or other neoplasia)
- Dermatologic examination of the selected treatment area(s) including LSRs

- Reporting of (S)AEs (see Table 2)
- Reporting of concomitant medication, treatments and procedures
- Trial medication compliance (for subjects treated with imiquimod)

Visit 9 – Only if Retreatment is required (Week 12, 28 days ± 3 days after Visit 6)

Visit 9 will include:

- Clinical assessment of neoplasia in the selected treatment area (biopsy if there is suspicion of SCC, BCC or other neoplasia)
- Dermatologic examination of the selected treatment area(s) including LSRs
- Reporting of (S)AEs (see Table 2)
- Reporting of concomitant medication, treatments and procedures
- Return of trial medication and trial medication compliance (for subjects treated with imiquimod)

Visit 10 – Only if Retreatment is required (Week 16, 56 days ± 3 days after Visit 6)

Visit 10 will include:

- Clinical assessment of neoplasia in the selected treatment area (biopsy if there is suspicion of SCC, BCC or other neoplasia)
- Dermatologic examination of selected treatment area including LSRs and AK count
- Reporting of (S)AEs (see Table 2)
- Reporting of concomitant medication, treatments and procedures
- Urine pregnancy test for female subjects of childbearing potential
- Abbreviated physical examination

Visit 11 (Week 20 ± 14 days)

Visit 11 will include:

- Clinical assessment of neoplasia in the selected treatment area (biopsy if there is suspicion of SCC, BCC or other neoplasia)
- Dermatologic examination of selected treatment area including AK count
- Reporting of (S)AEs (see Table 3)
- Reporting of concomitant medication, treatments and procedures

Visit 12 (Month 12 ± 14 days)

Visit 12 will include:

- Clinical assessment of neoplasia in the selected treatment area (biopsy if there is suspicion of SCC, BCC or other neoplasia)
- Dermatologic examination of selected treatment area including AK count
- Reporting of (S)AEs (see Table 3)
- Reporting of concomitant medication, treatments and procedures
- Abbreviated physical examination

Visit 13 (Month 18 ± 28 days)

Visit 13 will include:

- Clinical assessment of neoplasia in the selected treatment area (biopsy if there is suspicion of SCC, BCC or other neoplasia)
- Dermatologic examination of selected treatment area including AK count
- Reporting of (S)AEs (see Table 3)
- Reporting of concomitant medication, treatments and procedures
- Abbreviated physical examination

Visit 14 (Month 24 ± 28 days)

Visit 14 will include:

- Clinical assessment of neoplasia in the selected treatment area (biopsy if there is suspicion of SCC, BCC or other neoplasia)
- Dermatologic examination of selected treatment area including AK count
- Reporting of (S)AEs (see Table 3)
- Reporting of concomitant medication, treatments and procedures
- Abbreviated physical examination

Visit 15 (Month 30 ± 28 days)

Visit 15 will include:

- Clinical assessment of neoplasia in the selected treatment area (biopsy if there is suspicion of SCC, BCC or other neoplasia)
- Dermatologic examination of selected treatment area including AK count
- Reporting of (S)AEs (see Table 3)
- Reporting of concomitant medication, treatments and procedures

- Abbreviated physical examination

Visit 16 (Month 36 ± 28 days)

Visit 16 will include:

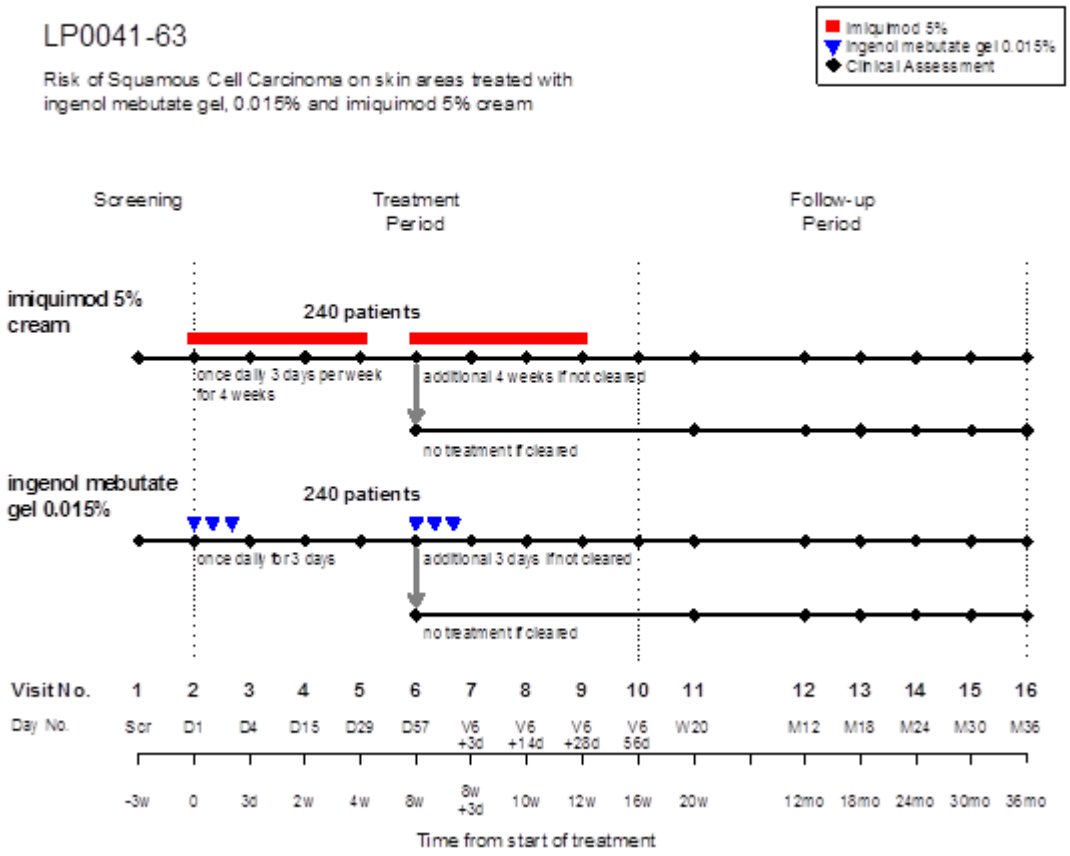
- Clinical assessment of neoplasia in the selected treatment area (biopsy if there is suspicion of SCC, BCC or other neoplasia)
- Dermatologic examination of selected treatment area including AK count
- Reporting of (S)AEs (see Table 3)
- Reporting of concomitant medication, treatments and procedures
- Abbreviated physical examination

Unscheduled/Early Termination

Upon completion of the last visit or during the study, an unscheduled visit may be required for any subject with a severe reaction, suspected pregnancy or an unresolved treatment-related AE or LSR, if deemed clinically significant by the investigator. Only assessments that require follow-up will be conducted if the subject is continuing in the trial. For early termination, all trial assessments scheduled should be performed if possible.

10.1.4 Study Design Diagram

Figure 1 Study Design



10.2 TIME SCHEDULE

Planned date of first subject first visit: Q2 2013
Planned date of last subject first visit: Q2 2015
Planned date of completion of last subject: Q2 2018

10.3 NUMBER OF SUBJECTS/SAMPLE SIZE

A total of 480 subjects will be enrolled in the trial and randomised 1:1 to the two treatment groups. With 240 patients in each treatment group an adequate precision of the 3-year incidence rate can be obtained. Assuming a 3-year rate of 1.0%, the upper 95% confidence limit

will on average be 2.26%, and assuming a 2.5% rate, the upper 95% confidence limit will on average be 4.48%.

10.4 CRITERIA FOR SUBJECT SELECTION (IN- AND EXCLUSION)

Following receipt of verbal and written information about the clinical trial, the subject must provide **signed and dated informed consent** before any trial related activity is carried out.

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

10.4.1 Inclusion Criteria

1. Following verbal and written information about the trial, subject must provide informed consent documented by signing the Informed Consent Form (ICF) prior to any trial-related procedures
2. Subjects with 5 to 9 clinically typical, visible and discrete AKs within a contiguous 25 cm² treatment area on the face or scalp. Actinic keratosis should be confirmed by histopathology of one of the AKs prior to randomisation.
3. Subject at least 18 years of age
4. Female subjects must be of either:
   a. Non-childbearing potential, i.e. post-menopausal or have a confirmed clinical history of sterility (e.g. the subject is without a uterus) or,
   b. Childbearing potential, provided there is a confirmed negative urine pregnancy test prior to trial treatment, to rule out pregnancy.
5. Female subjects of childbearing potential [1] must be willing to use highly effective methods of contraception (Pearl index < 1%) at study entry until Week 20. These methods of contraception are defined as:
   - abstinence (when this is in line with the preferred and usual lifestyle of the subject)
   - vasectomised partner (partner should be the sole partner for the subject)
   - an intrauterine device
   - double barrier method defined as two distinct methods (either two actual barrier methods or one actual barrier method and one hormonal method)

[1] Female subjects are considered of childbearing potential unless they have been hysterectomised or have undergone tubal ligation or have been post-menopausal for at least one year prior to first visit..

- hormonal contraceptive (oral hormonal birth control, oestrogenic vaginal ring, percutaneous contraceptive patches, implants and injectables) for at least one menstrual cycle prior to enrolment.

10.4.2 Exclusion Criteria

1. Location of the selected treatment area:
   - on the periorbital skin
   - on the perioral skin/around the nostrils
   - within 5 cm of an incompletely healed wound
   - within 10 cm of a suspected BCC or SCC or other neoplasia
2. Selected treatment area lesions that have atypical clinical appearance (e.g., hypertrophic, hyperkeratotic or cutaneous horn).
3. History of SCC, BCC, malignant melanoma or other neoplasia in the selected treatment area.
4. History or evidence of skin conditions other than the trial indication that would interfere with evaluation of the trial medication in the selected treatment area (e.g., eczema, unstable psoriasis, xeroderma pigmentosum).
5. Use of ingenol mebutate and/or imiquimod in and within 5 cm of the selected treatment area within 2 years prior to Screening (Visit 1).
6. Use of cosmetic or therapeutic products and procedures which could interfere with the assessments of the treatment area.
7. Anticipated need for hospitalisation or out-patient surgery prior to Day 15 in the initial treatment cycle. Note that cosmetic/therapeutic procedures are not excluded if they fall outside of the criteria detailed in Prohibited Therapies or Medications (see Exclusion Criteria Nos. 18- 19).
8. Known sensitivity or allergy to any of the ingredients in ingenol mebutate gel or imiquimod cream.
9. Organ transplant recipients
10. Immunosuppressed subjects (for example HIV patients)
11. Clinical diagnosis/history or evidence of any medical condition that would expose a subject to an undue risk of a significant AE or interfere with assessments of safety and efficacy during the course of the trial, as determined by the investigator's clinical judgment
12. Presence of acute sunburn within the selected treatment area
13. Current enrolment or participation in a clinical trial within 30 days of entry into this trial.

14. Subjects previously randomised in the trial.
15. Female subjects who are breastfeeding.
16. Subjects who are institutionalised by court order or by the local authority
17. In the opinion of the investigator, the subject is unlikely to comply with the Clinical Study Protocol (e.g. alcoholism, drug dependency or psychotic state)

Prohibited Therapies and/or Medications: within 4 weeks prior to Screening (Visit 1):

18. Treatment with immunomodulators (e.g., azathioprine), cytotoxic drugs (e.g., cyclophosphamide, vinblastine, chlorambucil, methotrexate, podophyllin, camptothecin) or interferon /interferon inducers.
19. Treatment with systemic medications that suppress the immune system (e.g., cyclosporine, prednisone, methotrexate).

10.4.3 Subject Screening Log

A subject screening (enrolment) log will be maintained by the site during the trial. All subjects who sign the informed consent will be included on the screening log and in the CRF.

10.4.4 Subject Registration

At Visit 1, each subject will be assigned the next (ascending) CRF book number available at the trial site. The CRF book number is a unique subject identifier used throughout the trial, in lieu of the subject's name.

It is completely distinct from the trial medication kit number(s) assigned to the subject.

10.5 WITHDRAWAL CRITERIA

The investigator is free to withdraw the subject at any time for medical reasons.
Subjects **may** withdraw for any of the following reasons:

1. *Unacceptable adverse events or LSRs*: any adverse event or LSR that the investigator or the subject considers unacceptable.
2. *Exclusion criteria*: any exclusion criteria which emerge/become apparent during the subject's participation in the clinical trial.
3. *Voluntary withdrawal*: subjects will be free to withdraw from the clinical trial at any time and for any reason.
4. *Other reasons*: other reasons than stated above which requires the subject to (be) withdraw(n) should be specified.

Subjects, who are discovered, after randomisation, not to have fulfilled all in-/exclusion criteria at time of enrolment, should be withdrawn from treatment unless the investigator, based on clinical and ethical evaluation, finds withdrawal from treatment inappropriate. If a biopsy is taken for suspicion of neoplasia in the treatment area, the subject should likewise be withdrawn from treatment.

Such deviation(s) from the (Consolidated) Clinical Study Protocol must be reported to LEO Pharma A/S (and the IEC/IRB, as appropriate) and recorded in the Clinical Study Report.

Subjects who withdraw from the trial should be asked to complete the early termination visit.

Reason(s) for withdrawal will be recorded in the CRF.

Subjects withdrawn after randomisation will not be substituted.

10.6 INVESTIGATIONAL PRODUCTS

10.6.1 Ingenol Mebutate

Finished product (brand) name (if available)/name investigational product	Ingenol mebutate gel, 0.015% / Picato®
Formulation	Gel
Active ingredient name/concentration	Ingenol mebutate 0.015% w/w
Excipients	Isopropyl alcohol Ph. Eur. Hydroxyethyl cellulose Ph. Eur. Benzyl alcohol Ph. Eur. Citric acid monohydrate Ph. Eur. Sodium citrate dihydrate Ph. Eur. Purified water Ph. Eur.
Pack size(s)	0.47 g
Manufacturer's name of bulk medication (IP)	LEO Laboratories Ltd, Ireland or DPT Laboratories Ltd., US
Certifier's name of bulk medication (IP)	LEO Pharma A/S
Supplier's name	Almac Clinical Services

Manufacturer's name of subject treatment packages	Almac Clinical Services
Certifier's name of subject treatment packages	LEO Pharma A/S

10.6.2 Imiquimod

Finished product (brand) name (if available)/name investigational product	Imiquimod Cream, 5% / Aldara®
Formulation	Cream
Active ingredient name/concentration	Imiquimod 5% w/w
Excipients	Isostearic alcohol Benzyl alcohol Cetyl alcohol Stearyl alcohol White soft paraffin Polysorbate 60 Sorbitan stearate Glycerol Methyl hydroxybenzoate (E218) Propyl hydroxybenzoate (E216) Xanthan gum Purified water
Pack size(s)	250 mg
Manufacturer's name of bulk medication (IP)	Meda AB, Sweden
Certifier's name of bulk medication (IP)	Meda AB
Supplier's name	Almac Clinical Services
Manufacturer's name of subject treatment packages	Almac Clinical Services
Certifier's name of subject treatment packages	LEO Pharma A/S

10.6.3 Packaging of Investigational Products

The trial medication will be packaged individually for each subject in two separate trial medication kits each containing either 3 single use unit-dose tubes of Ingenol mebutate gel 0.015% or 12 single use, unit-dose sachets of Imiquimod cream 5%. The trial medication kit and the unit dose tubes/sachets are intended to remain together throughout the trial.

The trial medication kit and unit dose tubes/sachets will be identified by a label in compliance with national laws and regulations.

10.6.4 Storage of Investigational Products

10.6.4.1 Ingenol mebutate gel

At the site, the kits will be stored in a refrigerator (2ºC – 8ºC) in a secure and restricted access area. Refrigerator temperature at the investigational site must be monitored continuously and recorded.

Following dispensing, subjects should place the trial medication kit in the home refrigerator as soon as possible after returning from the Day 1 visit. The trial medication kit should be refrigerated and stored in a place segregated from foodstuffs to avoid exposure to the trial medication. The investigational products should also be refrigerated in a safe and secure manner inaccessible to children and pets.

10.6.4.2 Imiquimod cream

At the site, the kits will be stored in a cool place (below 25ºC) in a secure and restricted access area.

Following dispensing, subjects should store the sachets in a cool place (below 25ºC) in a safe and secure manner inaccessible to children and pets.

10.6.5 Administration of Investigational Products

10.6.5.1 Ingenol Mebutate

Route of administration	Topical on selected treatment area on face or scalp
Dosing range	One unit-dose tube
Dosing frequency	Once daily application for 3 consecutive days
Daily maximum	One unit-dose tube
Time of day for dosing	No specific requirements
Relation of time of dosing to dietary intake	No specific requirements

Trial medication (ingenol mebutate gel, 0.015% gel) will be applied followed immediately by hand washing.

The first unit dose will be applied during the Day 1 visit(s) (Visit 2 and Visit 6 in case of retreatment) under the supervision of trial site personnel and the second and third doses will be applied at home.

At Day 1 (Visit2), the subjects will be instructed by the site personnel on how to handle and apply the trial medication and a Patient Safety and Study Medication Instruction Sheet will be provided to the subjects.

If retreatment is required the same procedure should be followed as for the first treatment cycle and the site personnel should confirm that the subject has a Patient Safety and Study Medication Instruction Sheet and knows how to apply the trial medication.

10.6.5.2 Imiquimod

Route of administration	Topical on selected treatment area on face or scalp
Dosing range	One unit-dose sachet
Dosing frequency	Once daily application for 3 days/week (e.g. Monday, Wednesday and Friday) for 4 weeks
Daily maximum	One unit-dose sachet
Time of day for dosing	Prior to normal sleeping hours
Relation of time of dosing to dietary intake	No specific requirements

Trial medication (imiquimod cream, 5%) will be applied followed immediately by hand washing.

At Day 1 (Visit 2), the subjects will be instructed by the site personnel on how to handle and apply the trial medication and a Patient Safety and Study Medication Instruction Sheet will be provided to the subjects.

The first unit dose will be applied during the Day 1 visit(s) (Visit 2 and Visit 6 in case of retreatment) under the supervision of trial site personnel and subsequent doses will be applied at home.

If retreatment is required the same procedure should be followed as for the first treatment cycle and the site personnel should confirm that the subject has a Patient Safety and Study Medication Instruction Sheet and knows how to apply the trial medication.

10.6.5.3 Instructions to be followed by Site Personnel

The following guidelines should be followed by the site personnel when instructing the subject on how to apply trial medication prior to the application on Day 1 in each treatment cycle:

1. Ensure that all evaluations have been completed prior to the dispensing of the trial medication and that the kit number stated on the trial medication label matches the kit number assigned by the IWR System.
2. Ensure the selected treatment area has been marked on the study transparency with a permanent ink marker using the three-point landmark technique (see Appendix IV).

3. Ensure the corners of the selected treatment area have been marked on the skin using the study transparency to assist with identification of the selected treatment area, before the first unit dose of trial medication is applied.
4. Ensure the subject understands that trial medication should be applied using a fingertip and hands should be washed immediately after application. Contact with skin other than the selected treatment area and application finger or inhalation of the trial medication must be avoided.
5. Ensure the subject understands how to store the trial medication at home.
6. Ensure the subject is instructed to return the trial medication kit with all dispensed tubes/sachets to the site at Visit 3 (for ingenol mebutate treated subjects) or Visit 5 (for imiquimod treated subjects). In the case of retreatment, kits should be returned at Visits 7 and 9 for ingenol mebutate or imiquimod treated subjects, respectively.
7. Ensure that the subject is instructed with post-treatment guidelines and provided with a Patient Safety and Study Medication Instruction Sheet for the relevant treatment.
8. Ensure that if the subject needs assistance with application of treatment that the subject assisting is also instructed and that they must follow the Patient Safety and Study Medication Instructions.

10.6.5.4 Trial Medication Application

Ingenol Mebutate

Study medication should be applied once daily for three days in a row onto the selected treatment area:

- Open a new tube each time you use this medication. Remove the cap just before use.
- Squeeze the entire contents of the tube onto a fingertip.
- Gently rub the gel onto the treatment area.
- Recap the tube and return the tube to the study medication kit.
- Wash your hands with soap and water immediately after applying the gel.
- Allow the treated skin area to dry for at least 15 minutes.
- Do not apply medication immediately after taking a shower or less than 2 hours before bedtime.
- Do not wash the areas where you applied the gel for at least 6 hours after you apply it. After this period, the treatment area may be washed using mild soap and water.
- Do not touch the treatment area yourself or allow anyone or any pets to touch the treatment area for a period of 6 hours after applying the gel.
- Do not cover the treated area with air- or water-tight bandages after application.

- Avoid excessive sun exposure (e.g., sunbathing, tanning booths) and wear protective clothing over the treated area when exposed to sunlight.

Imiquimod
Study medication should be applied 3 times per week (eg. Monday, Wednesday and Friday) for 4 weeks onto the selected treatment area:

- Before application wash your hands and the treatment area with mild soap and water and dry thoroughly.
- Cream should be applied prior to normal sleeping hours.
- Open a new sachet each time you use this medication.
- Gently rub the cream onto the treatment area until the cream vanishes.
- Return the used sachet to the study medication kit.
- Wash your hands carefully after applying the cream.
- Do not wash the area where you applied the gel for approximately 8 hours after you apply it. After this time the treatment area should be washed with mild soap and water.
- Do not cover the skin with air- or water-tight bandages after application.
- Avoid excessive sun exposure (e.g., sunbathing, tanning booths) and wear protective clothing over the treated area when exposed to sunlight.

10.6.6 Precautions/Overdosage

A summary of the most relevant information is presented here. Further details are available in the SmPC for ingenol mebutate and for imiquimod (Appendix V).

10.6.6.1 Ingenol Mebutate

Skin Exposure
The most common LSRs reported in the AK studies were erythema, flaking/scaling, and crusting. Less common LSRs included swelling/edema, vesiculation/pustulation, and erosion/ ulceration. The mean maximum composite LSR score for patients treated with ingenol mebutate gel, 0.015% was 9.1 (SD, 4.1) compared with 1.8 (SD, 1.6) for patients treated with vehicle, with the majority of patients having a maximum score on Day 4 and return to baseline by Day 29.

Studies in healthy volunteers showed no evidence of skin sensitisation, phototoxicity, or photosensitisation following the application of ingenol mebutate gel.

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

Ocular Exposure

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

Any suspected exposure should be documented and brought to the attention of the monitor. If ocular exposure does occur, the strategies discussed above for management of treatment of exposure are recommended.

Other Exposure

If ingenol mebutate is inhaled, assist the exposed person to breathe fresh air. If breathing is difficult, provide supplemental oxygen, if possible, and seek medical assistance. If ingenol mebutate is swallowed, and if the person is conscious, assist the exposed person to irrigate the mouth with copious amounts of water and seek immediate medical assistance. Do not induce vomiting.

10.6.6.2 Imiquimod

Rarely, intense local inflammatory reactions including skin weeping or erosion can occur after only a few applications of imiquimod cream. Local inflammatory reactions may be accompanied, or even preceded by, flu-like systemic signs and symptoms including malaise, pyrexia, nausea, myalgias and rigors. An interruption of dosing should be considered.

Contact with eyes, lips and nostrils should be avoided. Use of an occlusive dressing is not recommended. Imiquimod should be used with caution in subjects with reduced haematologic reserve.

Following accidental ingestion, nausea, emesis, headache, myalgia and fever could occur after a single dose of 200 mg imiquimod which corresponds to the content of approximately 16 sachets. The most clinically serious adverse event reported following multiple oral doses of 200 mg was hypotension which resolved following oral or intravenous fluid administration.

10.6.6.3 Reproductive Precautions

Women of child-bearing potential may be considered for enrolment if they: 1) have a negative urine pregnancy test before study treatment to rule out pregnancy per the protocol; and 2) are willing to consent to use effective (i.e., as detailed in the protocol) contraception until Week 20. All such women will be tested for pregnancy. Any woman who becomes pregnant, before completion of the Treatment Period, will be monitored, up to and following, the birth of the child.

10.6.6.4 Hypersensitivity

Use of ingenol mebutate gel and imiquimod cream is contraindicated in subjects with a known hypersensitivity to any ingredient in the formulation.

10.6.7 Treatment Assignment

At Day 1 (Visit 2) subjects will be randomised centrally to treatment with ingenol mebutate gel or imiquimod cream in a 1:1 ratio stratified by country, anatomical location (face or scalp) and history of SCC (none or previous SCC) through the IWR system. The system will assign a unique trial medication kit number to each subject. The unique kit number assigned to each subject has to be recorded in the CRF.

10.6.7.1 Randomisation Code List

During the clinical trial, the randomisation files will be kept in a secure area at Almac Clinical Technologies inaccessible to staff involved with the conduct and administration of the clinical trial until the trial database is locked.

10.6.7.2 Subject Identification List

The investigator will maintain a list of all subjects included in the trial at the trial site including each subject's identity, date of enrolment and corresponding CRF book number so

that any subject may be identified if required for any reason. The list is kept by the investigator and will not be copied to LEO Pharma A/S.

10.6.8 Blinding of the Trial

Not applicable as this is an open-label trial.

10.6.9 Breaking the Randomisation Code

10.6.9.1 Un-blinding of Individual Subject Treatment

Not applicable as this is an open-label trial.

10.6.9.2 Un-blinding of the Clinical Trial

Not applicable.

10.6.10 Drug Accountability and Compliance Checks

The investigator is fully responsible for the investigational products at the trial site. Dispensing of investigational products may be delegated to, e.g. a hospital pharmacy as locally applicable.

The person responsible for dispensing the investigational products will be responsible for maintaining adequate control of the investigational products and for documenting all transactions with them. Investigational products must be stored in a safe and secure place, and proper dispensing arrangements must be made.

10.6.10.1 Sponsor-Investigator Drug Accountability

All trial medication kits supplied by Almac Clinical Services on behalf of LEO Pharma A/S will be returned to Almac Clinical Services and be fully accounted for by the monitor with the help of the person responsible for dispensing trial medication. Accountability will be documented by use of drug accountability forms, including information of number of used/unused tubes/sachets per kit.

10.6.10.2 Investigator-Subject Drug Accountability

Subjects will be instructed to return the trial medication kit (containing all dispensed tubes/sachets) to the site for assessment of trial medication compliance as follows:

- At the Day 4 visit(s) after the first application for subjects treated with ingenol mebutate
- At the Week 4 visit(s) after the first application for subjects treated with imiquimod

An inventory (Individual Drug Accountability Form) will be kept of the trial medication given to and returned by each subject enrolled in the trial. This inventory must be available for inspection during monitoring visits and will be checked by the monitor to ensure correct dispensing of trial medication.

10.6.10.3 End of Trial Drug Accountability

Almac Clinical Services will be responsible for overall trial medication reconciliation with trial medication kits and destruction when the trial is completed.

10.6.10.4 Treatment Compliance

The subject will be asked if she/he has used the trial medication as prescribed to assess treatment compliance as follows:

- At the Day 4 visit(s) after the first application for subjects treated with ingenol mebutate
- At the Day 4, Week 2 and Week 4 visit(s) after the first application for subjects treated with imiquimod

If this is not the case, the degree and nature of non-compliance has to be specified and recorded in the CRF.

10.6.11 Prior and Concomitant Treatment

Prior to the trial

Prohibited treatments and procedures prior to trial entry are detailed in the Exclusion Criteria; see Section 10.4.2 for full details.

During the trial

Use of non-marketed/other investigational products are not permitted during the entire trial period.

Concomitant Medications, Treatments and Procedures from start of treatment until Week 20

All concomitant medication currently being taken at time of Day 1 (Visit 2) must be recorded in the CRF, along with the reasons for administration of the medication or treatment as well as location, described as the selected treatment area, outside the selected treatment area or not applicable.

No other treatments and procedures are allowed in, and within 5 cm of the selected treatment area. Treatment for SCC or any other malignancy is allowed.
Outside the selected treatment area (up to within 5 cm), procedures such as cryotherapy will be allowed; field therapy will not be allowed.

Any new medication started from Day 1 (Visit 2) until Week 20 must be recorded in the CRF, along with the reason for administration of the medication or treatment.

Prohibited treatments and procedures for the selected treatment area during the treatment period are detailed in Table 1.

Table 1: Prohibited concomitant treatments from the start of treatment until Week 20

Prohibited Treatment	Location
Cosmetic or therapeutic procedures (e.g., use of liquid nitrogen, surgical excision, curettage, dermabrasion, medium or greater depth chemical peel, laser resurfacing)	within 5 cm of the selected treatment area
Use of keratolytic topical therapeutic products (e.g., alpha- and beta- hydroxy acids, including glycolic acid, lactic acid and other fruit acids, salicylic acid, topical retinoids, urea or light chemical peels):	within 5 cm of the selected treatment area
Topical medicated creams, ointments, lotions, gels, foams or spray, including topical steroids.	within 5 cm of the selected treatment area *Note, may be used 12 days after last treatment with investigational product*
Topical non-medicated/non-irritant lotions/creams/gels/sunscreens	within 5 cm of the selected treatment area. Prohibited on treatment days. Subject should wash the treatment area with mild soap and water prior to use.
Any topical medications or treatments that might influence the intended effects or mask the side effects of treatment, such as topical corticosteroids	within 5 cm of the selected treatment area. *Note, may be used 12 days after last treatment with investigational product*
Artificial tanners	within 5 cm of the selected treatment area
Treatment/therapy with UVA or UVB	Anywhere
Excessive or prolonged exposure to ultraviolet light (e.g., sunlight, tanning beds)	Anywhere

5-FU, imiquimod, diclofenac sodium, ingenol mebutate or photodynamic therapy	Anywhere (other than as study medication)
Immunomodulators (e.g., azathioprine), cytotoxic drugs (e.g., cyclophosphamide, vinblastine, chlorambucil, podophyllin, camptothecin) or interferon/ interferon inducers	Not applicable (excluded)
Medications that suppress the immune system (e.g., cyclosporine, prednisone, methotrexate)	Not applicable (excluded)
Systemic retinoids (e.g., isotretinoin, acitretin, bexarotene) or biologic/monoclonal antibody therapies (e.g, alefacept, infliximab rituximab).	Anywhere during the study
Other investigational drugs, agents or devices or any chemotherapy for cancer treatment or any medications or treatments that might influence the intended effects or mask the side effects of trial medication	Not applicable (excluded)

Concomitant Medication, Treatments and Procedures from Week 20 in the Follow-up Period:

In the Follow-up Period information will be collected regarding:

- concomitant medications, treatments and procedures used in the selected treatment area
- all use of ingenol mebutate or imiquimod whether inside or outside the selected treatment area
- medication or treatments which may suppress the immune system in the subjects

Procedures such as cryotherapy will be allowed in, and within 5 cm of the selected treatment area. Further, at the discretion of the Investigator and as according to nationally available product and treatment guidelines, the same treatment as originally administered is allowed (imiquimod or ingenol mebutate). Cross-over between imiquimod and ingenol mebutate is **not** allowed. Investigators will be encouraged to pursue these treatment options where clinically relevant and before employing other treatments.

Outside the selected treatment area (up to within 5 cm) all treatments will be allowed, although investigators will be encouraged to avoid cross-over between imiquimod and ingenol mebutate.

No other information on concomitant medications, treatments or procedures will be collected for subjects.

10.7 TRIAL PROCEDURES

10.7.1 Schedule of Trial Procedures

Screening and Treatment Period

	Screening	**Treatment Period**								
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7[1]**	**8[1]**	**9[1]**	**10[1]**
Day/Week (window)	(-42 to -14 days)	**Day 1**	**Day 4** (+2 days)	**Week 2** Day 15 (±2 days)	**Week 4** Day 29 (± 3 days)	**Week 8** Day 57 (±3 days)	3 days after Visit 6 (+2 days)	**Week 10** 14 days after Visit 6 (±2 days)	**Week 12** 28 days after Visit 6 (± 3 days)	**Week 16** 56 days after Visit 6 (± 3 days)
Informed consent	X[2]									
In-/exclusion criteria	X	X[3]								
Medical/surgical History	X									
Concurrent diagnosis	X	X[3]								
AK and SCC treatment history	X									
Concomitant medications, treatments, procedures	X	X	X	X	X	X	X	X	X	X
Brief physical exam[4]	X	X				X				X
Vital signs	X									
Demographics	X									
Height and weight	X									
Fitzpatrick skin type	X									
Urine pregnancy test[5]	X					X				X
Identify selected treatment area	X									
Mark selected treatment area on skin		X				X[1]				
Biopsy of one AK lesion	X									
Biopsy if suspicion of SCC etc.			X	X	X	X	X	X	X	X
Randomisation		X								
AK count	X	X				X				X

	Screening	Treatment Period								
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7[1]**	**8[1]**	**9[1]**	**10[1]**
Day/Week (window)	(-42 to -14 days)	**Day 1**	**Day 4** (+2 days)	**Week 2** Day 15 (±2 days)	**Week 4** Day 29 (± 3 days)	**Week 8** Day 57 (±3 days)	3 days after Visit 6 (+2 days)	**Week 10** 14 days after Visit 6 (±2 days)	**Week 12** 28 days after Visit 6 (± 3 days)	**Week 16** 56 days after Visit 6 (± 3 days)
Dispense medication		X				X[1]				
Return medication			X[7]		X[6]		X[7]		X[6]	
Compliance			X	X[6]	X[6]		X	X[6]	X[6]	
Field assess-ment for SCC, BCC or neoplasia			X	X	X	X	X	X	X	X
Local skin response (LSR)		X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X

1. Only for subjects who are not completely cleared in the selected treatment area at Week 8. Subjects who have cleared should proceed to the Follow –up period at Visit 11
2. Can be performed prior to Visit 1
3. To be checked at Visit 2
4. Including general appearance, regional lymph nodes and dermatologic examination of the skin in general
5. Females of childbearing potential only
6. Imiquimod only
7. Ingenol mebutate only

Follow-up Period

Visit Number	**11**	**12**	**13**	**14**	**15**	**16**
Week/Month (window)	**Week 20** (±14 days)	**Month 12** (±14 days)	**Month 18** (±28 days)	**Month 24** (±28 days)	**Month 30** (±28 days)	**Month 36** (± 28 days)
Concomitant medications, treatments, procedures	X	X	X	X	X	X
Field assessment for SCC, BCC or neoplasia	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X
AK count	X	X	X	X	X	X
Brief physical exam[4]		X	X	X	X	X

Note: Unscheduled/Early Termination
Upon completion of the last visit or during the study, an unscheduled visit may be required for any subject with a severe reaction, suspected pregnancy or an unresolved treatment-related AE or LSR, if deemed clinically significant by the investigator. Only assessments that require follow-up will be conducted if the subject is continuing in the trial. For early termination all trial assessments scheduled should be performed if possible.

10.7.2 Subject Eligibility

Subject eligibility for the clinical trial will be checked according to the inclusion and exclusion criteria as specified in 10.4.1 and 10.4.2 at screening (Visit 1) and confirmed at Day 1 (Visit 2).

At Screening (Visit 1) subjects' demographic details (date of birth, sex, race, ethnic origin, height, weight, Fitzpatrick skin type) will be recorded. The subject will self-report their ethnicity (Hispanic or Latino, not Hispanic or Latino), and race (American Indian or Alaska Native; Asian, Black or African American; Native Hawaiian or Other Pacific Islander; White, Other). Relevant medical/surgical history, concurrent diagnosis, skin diseases and AK and SCC treatment history will also be recorded.

The subject's height will be measured without shoes and weight will be determined with indoor clothing and without shoes.

The abbreviated physical examination will include general appearance, regional lymph nodes and dermatologic examination of the skin in general.

Vital signs (resting blood pressure and heart rate) and oral or ear temperature will be recorded.

For female subjects of childbearing potential a urine pregnancy test will be performed at visits specified in 10.7.1.

Concomitant medication, treatments and procedures will be recorded at visits specified in 10.7.1.

Skin type of the subjects will be assessed by the investigator and recorded according to the following classification:

Fitzpatrick Skin Types

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

Relevant medical history (including first date of AK diagnosis) and concomitant diagnoses will be recorded at the screening visit (Visit 1) and will be confirmed at Visit 2.

The selected treatment area will be identified by the dermatologist and documented on the study transparency using a three-point landmark technique. Detailed instructions for the three-point landmark technique are given in Appendix IV. A biopsy will be taken of one AK lesion in the selected treatment area (see 10.7.4) for histological confirmation of AK prior to randomisation at Day 1 (Visit 2).

10.7.3 Clinical Assessment

10.7.3.1 Investigator Assessments

Identification of the selected treatment area and dermatologic assessments of the selected treatment area must be performed by a dermatologist (board-certified or equivalent). The same dermatologist should attempt to perform all dermatologic examinations of each individual subject.

The (sub)investigator will make the following clinical assessments:

Identification of the selected treatment area

At Visit 1 identification of the selected treatment area should be documented on a study transparency using a three-point landmark technique (See Appendix IV). At all subsequent

visits, the transparency should be used to re-locate the selected treatment area for assessment of the treated skin on the face or scalp.

Clinical Assessment of Neoplasia in the selected treatment area

At all visits clinical assessment of the selected treatment area for neoplasia will be performed. If there is suspicion of SCC, BCC, or other neoplasia, a biopsy will be taken (see 10.7.4).

Local Skin Responses

Assessment of local skin responses in the selected treatment area using the LSR Grading Scale should be performed at visit days as specified in the schedule of trial procedures (10.7.1).

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

AK lesion count

The number of clinically, visible AK lesions identified in the selected treatment area should be recorded at the visit days specified in the schedule of trial procedures (Section 10.7.1). At Visit 1, the subject should have 5-9 clinically typical, visible and discrete AK lesions.

10.7.3.2 Subject assessments

Not Applicable

10.7.4 Laboratory Assessments

10.7.4.1 Central Analysis

Histological Assessments:

At Screening (Visit 1) a 3-4 mm punch biopsy will be taken from an AK in the selected area to confirm the diagnosis of AK as follows:

The biopsy area will be cleaned with an appropriate disinfectant. The skin will be numbed using an anaesthetic injection with a vasoconstrictor, e.g. adrenaline. Biopsies will be taken using a 3-4-mm disposable punch. If possible, the punch should contain tissue from the subcutis. The biopsy specimen will be removed from the punch very gently using forceps. Care should be taken not to squeeze the biopsy. The biopsy is transferred immediately into a plastic tube of approximately 10 mL containing 8 mL 10% neutral buffered formalin (formalin [40% formaldehyde] diluted 10 times in phosphate buffered saline, pH 7.4). It should be assured that the biopsy is submerged completely in the fixative. Specimens will be labelled with the study number (LP0041-63), subject (CRF) number and Visit. Haemostasis will be secured by pressure with gauze and stitching, if considered necessary. The (stitched) biopsy site will be left uncovered or sealed with Steristrip® as required.

The formalin fixed tissue will be shipped to the central pathology laboratory. The central laboratory's assessment determines whether the inclusion criterion of presence of AK in the biopsy is fulfilled.

Biopsies taken because of suspicion of SCC/BCC or other neoplasia will be processed as described above. The formalin fixed tissue will be shipped to a central pathology laboratory. The central laboratory will have a maximal turn-around time of 2 weeks to e-mail the evaluation back to the investigator for appropriate clinical action. Further details will be agreed with the central laboratory as to the number of pathologists to be involved in the final diagnosis of an SCC and the procedures to be employed to obtain agreement.

10.7.4.2 Local Analysis

A urine pregnancy test will be performed at the trial site at the visits specified in 10.7.1. in female subjects of child-bearing potential.

10.7.5 Adverse Events

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 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)).

A Serious Adverse Event (SAE) is any untoward medical occurrence that

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

or

- other medically important conditions*), including SCC and BCC within the selected treatment area

*) 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 of such events are allergic broncospasm, blood dyscrasias and convulsions.

Global Pharmacovigilance, LEO Pharma A/S is responsible for the assessment of headquarter expectedness according to LEO Pharma A/S procedures. The relevant reference document for this clinical trial is current version of the SmPC for ingenol mebutate gel (21) and subsequent updates as agreed between the head of Medical Department, and the medical director, Global Pharmacovigilance, LEO Pharma A/S. The current version of the SmPC for imiquimod (Aldara®) (appendix V) will be used for the assessment of expectedness for imiquimod.

At all visits, after Visit 1, the subject will be asked a non-leading question by the (sub)investigator: “How have you felt since I saw you last?” No specific symptoms will be asked for.

If there are no AEs to record (see Table 2 and Table 3 for reportable AEs), no further questions will be asked and “NO” should be stated. In case there are one or more AEs to record, “YES” should be stated and the investigator will record the event term, intensity, duration, suspected causal relationship to the investigational product and outcome.

It is important that the investigator also observes the subject for any changes not reported by the subject and records these changes where reportable (see Table 2 and Table 3).

Only medically qualified personnel must assess AEs. A dermatologist (board-certified or equivalent) must do all dermatologic examinations, LSRs and AE evaluation in the selected treatment area.

If the informed consent is obtained before Visit 1, any medical changes until Visit 1 should be included in the medical history and not reported as an AE.

10.7.5.1 Reporting of Adverse Events

Events reported by the subject or observed by the (sub)investigator and that fall into any of the categories below must be recorded on the adverse event page of the CRF:

Table 2: Adverse Event Reporting for Visits until Week 20

Adverse Event	Inside treatment area	Outside treatment area *including non-cutaneous events*
BCC/SCC	All BCC/SCCs should be recorded in the CRF and reported to LEO as SAEs.	All serious and non-serious BCC/SCCs should be recorded in the CRF. Serious BCC/SCCs should be reported to LEO as SAEs.
Other AEs	All AEs and SAEs should be recorded in the CRF. Serious AEs should be reported to LEO as SAEs.	All AEs and SAEs should be recorded in the CRF. Serious AEs should be reported to LEO as SAEs.

Table 3: Adverse Event Reporting for Visits after Week 20

Adverse Event	Inside treatment area	Outside treatment area *including non-cutaneous events*
BCC/SCC	All BCC/SCCs should be recorded in the CRF and reported to LEO as SAEs.	All serious and non-serious BCC/SCCs should be recorded in the CRF. Only serious BCC/SCCs related to the treatment should be reported to LEO as SAEs.
Other AEs	All AEs and SAEs should be recorded in the CRF. Serious AEs should be reported to LEO as SAEs.	Only SAEs related to the treatment should be recorded in the CRF. These should be reported to LEO as SAEs.

Please note: Local Skin Responses which match the criteria in the LSR Grading Scale are to be reported as LSRs in the CRF and not as AEs even if they require treatment. Any treatment should be recorded on the Concomitant medication page of the CRF together with the most important LSR (e.g. swelling should be reported as swelling-LSR).

Adverse events should be described in the following manner:

The **nature** of the event will be described 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 adverse events the anatomical **location** of the adverse event must be part of the adverse event description and may be described as the 'in the selected treatment area', 'within 5 cm of the selected treatment area', 'more than 5 cm from the selected treatment area' (with further specification for BCC/SCCs) or 'not applicable'.

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

- **Mild**: The adverse event does not interfere in a significant manner with the subject's normal functioning level and requires no medical intervention.
- **Moderate:** The adverse event interferes with the subject's normal functioning level and may or may not require medical intervention.
- **Severe:** The adverse event produces significant impairment of the subject's functioning or requires medical intervention.

The **duration** of the event will be reported as the start date and stop date of the event.

For AEs recorded on Day(s) of starting treatment, it should be specified whether the AE started prior to or after first application of trial medication.

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

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

Possibly related
- Follows a reasonable temporal sequence from administration of the investigational product
- Could also be reasonably explained by the subject's clinical state, environmental or toxic factors or other therapies administered to the subject
- Follows a known pattern of response to the investigational product

Not related
- Does not follow a reasonable temporal sequence from administration of the investigational product

- Is better explained by other factors like the subject's clinical state, environmental or toxic factors or other therapies administered to the subject
- Does not follow a known pattern of response to the investigational product

Not assessable

- The adverse event cannot yet be judged otherwise because present information is insufficient or contradictory. A final assessment (i.e. probably, possibly or not related) shall be made as more information becomes available, at the latest when the subject has completed the trial.

The **outcome** of the event will 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, however, not yet completely resolved. Follow-up on the event is required until final outcome is established.
• Not recovered/not resolved	Event is still ongoing. Follow-up on the event is required until final outcome is established.
• 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.
• Fatal	The subject has died as a consequence of the event. Date of death is recorded as stop date for the adverse event.
• Unknown	Unknown to investigator, e.g. subject lost to follow-up.

Upon completion of the last visit, an unscheduled visit may be required for any subject with an unresolved, treatment-related AE or LSR, if deemed clinically significant by the investigator.

Once a subject has completed the clinical trial, the investigator should follow up for outcome on all non-serious adverse events classified as possibly/probably related to the investigational product for 6 months or until final outcome is determined, whichever comes first.

10.7.5.2 Other events to be reported

Pregnancy

Pregnancy which occurs during a clinical trial must be reported to LEO Pharma A/S within one calendar day of first knowledge using the Pregnancy Follow-up Form supplied by LEO Pharma A/S. All pregnancies must be followed up until delivery or termination.

Overdose

Any overdose defined as any higher dose than prescribed for the individual subject must be reported on the adverse event form of the CRF book. AEs originating due to the overdose must be documented on a separate line.

Aggravation of condition

Any clinically significant aggravation/exacerbation/worsening of the initially treated condition compared to baseline, judged by an overall medical assessment, must be reported as an AE.

10.7.6 Serious adverse events

10.7.6.1 Reporting of Serious Adverse Events

Any Serious Adverse Event (SAE), related or unrelated to the investigational product or any trial procedure after signature of the Informed Consent Form must be reported to LEO Pharma A/S on the (paper) **Serious Adverse Event Form – Clinical Trial** within **one calendar day, with the exception that:**

- After Week 20, non-related serious adverse events outside the treatment area should *not* be reported to LEO Pharma A/S (see Table 2 and Table 3)

An LSR classified as a SAE must be reported on the adverse event form in the CRF and reported to LEO Pharma A/S on the paper *Serious Adverse Event Form (SAE) – Clinical Trial*.

Note: Planned hospitalisation or planned prolonged hospitalisation do not fulfil the criteria for being an SAE. The elective nature of the event must be clearly documented in the subject's medical record.

SAEs must be reported on the adverse event form of the CRF book. Additionally reports must be made using the paper *Serious Adverse Event (SAE) Form – Clinical Trial***,** supplied by LEO Pharma A/S. Apart from the assessment of the intensity, causal relationship to the investigational product(s) and/or trial procedures, the action taken and the outcome to date, this report must contain a comprehensive narrative description of the course of the event.

The completed LEO *Serious Adverse Event (SAE) Form – Clinical Trial* must be faxed or scanned and e-mailed Global Pharmacovigilance at LEO Pharma A/S:

LEO Pharma A/S Head Quarter
Denmark, Global Pharmacovigilance
Industriparken 55, DK-2750 Ballerup, Denmark
Global Pharmacovigilance Fax: +45 72 26 32 87
E-mail: drug.safety@leo-pharma.com

All other relevant reports of diagnostic procedures, hospital records, autopsy reports etc. must be included, as applicable or upon request from Global Pharmacovigilance.

The IRB(s)/IEC(s), regulatory authorities and concerned investigators will be notified of SAEs according to current regulation and local requirements.

All Suspected, Unexpected Serious Adverse Reactions (SUSARs) are subject to expedited reporting to regulatory authorities.

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

10.7.7 Source Data

Source data*: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)*. (ICH E6, 1.51).

Source documents*: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).* (ICH E6, 1.52).

Source Data Verification (SDV) is a key function in assuring the sponsor that clinical trial information is recorded and handled in a way that allows its accurate reporting, interpretation and verification. Monitors will, during the conduct of the clinical trial, perform SDV to confirm the accuracy and completeness of CRFs by verifying selected (as specified below) data recorded in the CRF against data recorded in source documents to ensure such records are consistent.

To enable SDV, it is essential that what constitutes source data/documents (see definition above) for the clinical trial data to be collected in the CRF as well as where such data can be found at the trial site is established and agreed with the investigator at each trial site and documented prior to initiation of the clinical trial.

Source data cannot be entered directly into the CRF. 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 may be entered on a worksheet only if the clinical trial requires capture of data, which are normally not part of the subject's medical record.

For this clinical trial, the following parameters collected in the CRF should be verifiable from source documents available at the trial site:

- Date of trial visits and date leaving the clinical trial
- Relevant medical history and diagnosis, including AK and other skin diseases
- Nature of contraception used by the subject and result of pregnancy test(s), when applicable
- Data for evaluation of eligibility criteria
- Abbreviated physical examination
- Dispensation/administration of trial medication and compliance
- Concomitant medication (including changes) and diagnoses
- Subject demographics (e.g. sex, date of birth)
- Adverse events, (nature, dates)
- LSRs and AK lesion count
- Dates and reason for any biopsy
- Biopsy results

In addition to the above, the following should be added to the subject's medical record in chronological order, i.e. when these are allocated to the subject:

- Date(s) of conducting the informed consent process including date of provision of subject information
- Date of enrolment
- CRF book number
- Study medication kit number(s)
- The fact that the subject is participating in a clinical trial in AK including treatment with ingenol mebutate gel, 0.015% or imiquimod cream, 5% for 36 months

10.8 EFFICACY EVALUATION

Evaluation of efficacy is a secondary objective.

10.8.1 Secondary Efficacy Response Criteria

The secondary response criteria are:

- Complete clearance after the last treatment cycle (at Week 8 or 16)
- Partial (at least 75%) clearance after the last treatment cycle (at Week 8 or 16)
- Complete clearance at 12 months, defined as no AKs at any time in the selected treatment area at any time from the last treatment cycle at Week 8 or 16 through to Month 12.

10.9 SAFETY EVALUATION

The evaluation of the risk of SCC is the primary objective of this trial.

10.9.1 Primary Response Criterion

Diagnosis of SCC (defined as invasive SCC i.e. excludes SCC in situ) in the treatment field across the 3-year trial period

10.9.2 Secondary Safety Response Criterion

Diagnosis of SCC and other neoplasia in the treatment field over a 3-year period.

10.9.3 Safety Evaluation

- Incidence and severity of LSRs
- Incidence of AEs
- Incidence of SAEs

10.9.4 Evaluation of (Serious) Adverse Events

Any (serious) adverse events reported.

10.9.5 Evaluation of Laboratory Data

Not applicable

10.10 STATISTICAL ANALYSIS

All hypotheses will be tested using two-sided tests with a significance level of 0.05. The null hypothesis for all treatment arm comparisons is that there is no difference between the arms versus the two-sided alternative that there is a difference between the treatment arms.

Study results will be summarised into tabulations, listings and figures where appropriate.

10.10.1 Subject Qualification for Analysis

All subjects for whom a signed informed consent is obtained and a CRF is started will be accounted for in the study report.
Efficacy analyses will be based on the Full Analysis Set (FAS), which is defined as all randomized subjects. Safety analyses will be based on the Safety Analysis Set, which is defined as all subjects who receive an initial study treatment and have safety data available.

A per protocol (PP) analysis set will be used as safety and efficacy subsets and will be defined as subjects in the FAS who complete the trial without major protocol deviations. The composition of the PP analysis set will be determined and documented in reviews of the study database. The safety and efficacy analyses based on the PP analysis set will be performed to support the results obtained for the primary and secondary safety and efficacy endpoints.

10.10.2 Subjects Disposition

Frequencies of the analysis sets, in total and by treatment arm, will be tabulated. Also reasons for premature discontinuations from treatment and from the trial will be presented for the FAS.

10.10.3 Baseline Characteristics

Descriptive statistics of demographic and other baseline characteristics will be presented for the FAS. Demographics will include age, sex, race, ethnic origin and skin types. Other baseline characteristics will include height, weight, vital signs, body temperature, other diagnoses and concomitant medication. Baseline AK characteristics will include treatment location (face or scalp) and baseline lesion count.

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

10.10.4 Analysis of Efficacy

Analysis of Secondary Efficacy Endpoints

The secondary efficacy endpoints are listed in section 10.8.1.

The complete and partial clearance rates after the last treatment cycle as well as the complete clearance rates at 12 months will be compared between the two treatment arms using a Cochran–Mantel-Haenszel stratified by country, anatomical location and history of SCC. The ratio of rates will be estimated together with its 95% confidence interval.

10.10.5 Stratification

Randomisation will be stratified by country, anatomical location (face or scalp) and history of SCC (none or previous SCC). Three countries are identified with a total of 48 investigational sites. Roughly 10 subjects will be enrolled at each site.

10.10.6 Safety Analysis

10.10.6.1 Analysis of Primary and Secondary Safety Endpoints

The primary endpoint and secondary safety endpoint are listed in sections 10.9.1 and 10.9.2 respectively. Both endpoints will follow the same method of analysis.

The 3-year cumulative incidence will be calculated for each treatment group using methods of survival analysis for estimation of cumulative incidence in the presence of censored time-to-event data. Annual incidence rates will also be presented for each group. The cumulative incidence rates will be presented for the event of SCC as primary endpoint and for SCC and other neoplasia as secondary. No formal statistical test comparing the two arms 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, conditional on patients' responses at Week 20, will additionally be performed in order to exclude SCC and other neoplasia reported within the first 20 weeks which are not assumed to be associated with the study treatment. Patients who experience a neoplasia before the 20-week landmark time point are excluded from the time-to-event analysis, which is otherwise conducted as above.

10.10.6.2 Adverse Events

Reporting of adverse events will be based on the Safety Analysis Set.

All adverse events recorded will be reported in listings. The investigator's verbatim term of each adverse event will be mapped to SOC and preferred terms using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus.

An overall summary of the number (percentage) of subjects with any treatment emergent adverse events (TEAEs), SAEs, premature discontinuations from treatment or from the trial due to adverse events, treatment related AEs, LSRs, severe AEs (maximum intensity indicated as severe in the CRF) will be presented. The overall and treatment related AE summary will also be presented by trial period of the start date of AEs: until Week 20, from Week 20 until Month 12, Month 12 to 24, Month 24 to 36).

The number and percent of subjects with AEs will be tabulated by body system and preferred term for the above summaries. Within a specific body system or preferred term, the subject will be counted only once if more than one event is reported. Summaries will be presented by decreasing frequency.

Listings will be provided for all subjects with SAEs and study discontinuations due to adverse events.

10.10.6.3 Local Skin Responses

The incidence and grade of LSRs will be summarised by treatment arm at each assessement visit by anatomical location based on the Safety Analysis Set. Local skin response grades will be summarised by frequency counts and descriptive statistics by treatment arm and visit for each of the six individual LSRs: erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration.

A composite (sum) score will be obtained by summing the six individual LSR scores at each visit. The composite score and change from baseline will be summarized by treatment arm at each visit using descriptive statistics. The visit of occurrence of maximal intensity will be tabulated.

Local skin responses will be converted into MedDRA preferred terms applying the following conversions seen in Table 4. These adverse events will be reported separately from adverse events recorded on the adverse event form in the CRF.

Table 4: Conversion of LSRs to MedDRA Preferred Terms

LSR Term	**LSR Grade**	**MedDRA Preferred Term**
Erythema	1-4	Application site erythema
Flaking/Scaling	1-4	Application site exfoliation.
Crusting	1-4	Application site scab
Swelling	1-4	Application site swelling
Vesiculation/Pustulation	1	Application site vesicles
	2-4	Application site pustules
Erosion/Ulceration	1-3	Application site erosion
	4	Application site ulcer

10.10.6.4 Laboratory Safety Examinations

Not applicable.

10.10.7 Interim Analysis

An interim analysis of trial data, obtained when approximately half of the trial period has elapsed, will be conducted. Assuming the time schedule shown in section 10.2, this will be prepared 3 years after study start. The interim analysis will not impact the conduct of this trial.

10.11 TRIAL COMMITTEES

A trial committee is not regarded applicable, as all safety issues will be handled by experienced investigators at the sites.

10.12 QUALITY ASSURANCE/AUDIT

LEO Pharma A/S has implemented a system of quality assurance, including all elements described in this protocol. Within this system company Standard Operating Procedures (SOPs) are implemented to ensure that clinical trials are conducted in compliance with regulatory requirements and Good Clinical Practice (GCP). Quality control is applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

Trial sites, facilities, laboratories and all data (including sources) and documentation must be available for GCP audit by LEO Pharma A/S or inspection by competent authorities.

Any aspect of the clinical trial may be subject to audit by LEO Pharma A/S and/or inspection by regulatory authorities (national or foreign) or IEC/IRB. Such audits/inspections may take place at the sponsor's site(s) or at any trial site including, pharmacies etc.

The monitor will, in case of audit, announce this in advance to the (sub)investigator and, if possible, be present at the particular trial site during the audit.

The site staff should assist in all aspects of audit/inspection.

10.12.1 Trial Monitoring

LEO Pharma A/S, as sponsor of this clinical trial, is responsible to the regulatory authorities for assuring the proper conduct of the clinical trial with regard to protocol adherence and

validity of the data recorded in the CRFs. The company has therefore assigned persons to monitor this trial. Their duties are to serve as the principal link between (sub)investigators and LEO Pharma A/S and advise the investigator on the collection and maintenance of accurate, complete, legible, well organised and easily retrievable data for the clinical trial. In addition, they will explain to the investigators any aspect of the (conduct of the) clinical trial, including interpretation of the protocol, the purpose of collecting the specified data and reporting responsibilities.

In order to perform their role effectively, monitors and persons involved in quality assurance and inspections (see above) will need direct access to primary subject data, e.g. medical records, laboratory reports, appointment books etc. Because this affects the subject's confidentiality, this fact is included on the Subject Information Sheet and Informed Consent Form.

This clinical trial is organised by LEO Pharma A/S and all enquiries should be made to a member of LEO Pharma A/S staff (see section 6.3, LEO Pharma A/S Personnel).

10.13 CASE REPORT FORM BOOKS AND DATA HANDLING

10.13.1 Case Report Forms (CRFs)

In this clinical trial data will be collected by means of Remote Data Capture (RDC). The investigator or staff authorised by the investigator will enter subject data into electronic CRFs designed by LEO Pharma A/S. A uniquely numbered CRF book will be used for each subject enrolled. Data recorded in the electronic CRFs will be accessible to site staff through a secure internet connection immediately after entry. The CRFs must be maintained in an up-to-date condition at all times by the investigator.

The investigator, or sub-investigator(s) authorised by the investigator, will electronically sign all sections of CRFs used. This signature information (incl. date of signature) will be kept in the audit trail and cannot be altered. Only medically qualified (sub)investigators can sign data on clinical assessments/safety. Any correction(s) made by the investigator or authorised site staff to the CRF after original entry will be documented in the audit trail. Changes to data already approved, requires the re-signature of the investigator or authorised staff. The person making the change and the date, time and reason for the change will be identified in the audit trail.

The trial monitor will check the CRFs for accuracy and completeness and perform source data verification preferably no later than 12 weeks after each subject visit. For archiving purposes each investigator will be supplied with a copy of the CRFs, for all subjects enrolled at the trial site, via an electronic medium at completion of the trial. Audit trail information will be included. CRFs will be available for inspection by authorised representatives from LEO Pharma A/S (e.g. audit by the quality assurance department), from regulatory authorities and/or IEC/IRBs.

10.13.2 Data Handling

Subject data should be entered into the electronic CRF in a timely manner by authorised site staff. Data will be entered by site staff and systematic data validation will be performed through the discrepancy management system within the data collection software. Queries for discrepant data may be generated automatically by the system upon entry or generated manually by the monitor or the study data manager. All queries, whether generated by the system or by a user, will be in an electronic format. This systematic validation will ensure that a clean and consistent database is provided prior to the statistical analysis being performed.

10.14 PROTOCOL AMENDMENTS

Neither the investigator(s) nor LEO Pharma A/S will change the Clinical Study Protocol without written agreement between LEO Pharma A/S and the international co-ordinating investigator. Any modification considered substantial requires approval/favourable opinion by the appropriate regulatory authority and IEC/IRB.

Protocol amendments are issued as Consolidated Clinical Study Protocols comprising all current amendments. Consolidated Clinical Study Protocols become effective when written approval has been provided by the international co-ordinating investigator, the head of Medical Department and the head of Biostatistics and Data Management, LEO Pharma A/S, and approval/favourable opinion from regulatory authorities and/or IEC/IRB has been obtained, as required.

Alternatively, a protocol addendum may be issued to comply with national/regional specific requirements. A protocol addendum becomes effective when written approval has been provided by the international co-ordinating investigator, the head of Medical Department and the head of Biostatistics and Data Management, LEO Pharma A/S, and the and ap-

proval/favourable opinion from the relevant regulatory authorities and/or IEC/IRB has been obtained, as required.

10.15 COMPLETION OF TRIAL

10.15.1 Trial Completion Procedures

The end of trial is the date of the last subject's last visit.

Investigators will be informed when subject recruitment is to cease.

Trial enrolment will be stopped at a trial site when the total requested number of subjects for the clinical trial has been obtained, irrespective of the specific site's planned inclusion number.

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

LEO Pharma A/S may stop the clinical trial prematurely after consultation with the international co-ordinating investigator, e.g. if the subject recruitment is so slow that the clinical trial cannot be completed within a reasonable time frame. Notification of such premature termination/suspension of the trial will be given to regulatory authorities and IECs/IRBs, as required.

10.15.2 Provision for Subject Care Following Trial Completion

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

10.15.3 Archiving of Trial Documents

The investigator at each trial site must make arrangements to store the essential trial documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) including the Investigator Trial File, until LEO Pharma A/S informs the investigator that the documents are no longer to be retained.

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 completion of the trial (e.g. in case of inspection from regulatory authorities).

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

At present according to ICH Guideline:

Essential documents should be retained until at least 2 years after last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor. ***It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.*** (ICH E6, 4.9.5)

11 USE OF INFORMATION

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

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

12 PUBLICATION

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

This clinical trial is a multi-centre clinical trial, and publication by an investigator of his/her trial results shall not be made before the first multi-centre publication is made public. Such multi-centre publication will be prepared in collaboration between LEO Pharma A/S and the members of a writing committee, which shall be appointed by LEO Pharma A/S.

If there is no multi-centre publication within eighteen (18) months after the clinical trial has been completed or terminated at all trial sites and all data has been received, defined as data base 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 Pharma A/S a copy of all such manuscripts, and LEO Pharma A/S shall have rights to review and comment. Upon the request of LEO Pharma A/S 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 Pharma A/S, delay the publication or presentation to allow LEO Pharma A/S to protect its inventions and other intellectual property rights described in any such manuscripts. In case the first multi-centre publication is still on-going and has not been made public at the time of notification, LEO Pharma A/S and the Writing Committee may also delay the publication or presentation if the manuscript is deemed to harm the ongoing multi-centre publication.

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

LEO Pharma A/S also subscribes to the joint position of the innovative pharmaceutical industry (45) for public disclosure of clinical trial results in a free, publicly accessible database, irregardless of outcome.

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Appendix I

English translation of the Danish Data Protection Agency's terms and conditions for the processing of clinical trial data by medical companies

English translation of the Danish Data Protection Agency's terms and conditions for the processing of clinical trial data by medical companies[*)]

Listed below please find an English version of the general terms and conditions, set by the Danish Data Protection Agency, in cases involving authorisation for the processing of sensitive data by medical companies conducting continuous clinical trials of medical products. Circumstances may warrant some variation in the terms and conditions in concrete cases.

AUTHORISATION to process personal data

The Data Protection Agency hereby grants authorisation for processing of personal data for the purpose of the Company's continuous clinical trials, cf. section 50(1)(i) of the Danish Act on Processing of Personal Data. In this connection, the Data Protection Agency lays down the following terms:

General terms

Period of validity: The authorisation is valid until further notice.

1. LEO Pharma A/S - hereinafter called the "Company" is responsible for compliance with these present terms.

2. The data may be used for the sole purpose of performing clinical trials.

3. The Company shall once a year to the Data Protection Agency submit an overview of new, commenced trials as well as a corresponding overview of which trials have been completed in the past year. The overview shall contain as a minimum a title of the trial and name and address of the clinically responsible investigator.

*) Source: Letter dated 07-Mar-2003 from the Danish Data Protection Agency (Datatilsynet) to the Danish Association of Pharmaceutical Industries (LIF)

4. Processing of personal data must be performed only by the controller or at the instance of the controller and at his responsibility. It is the responsibility of the controller that compliance of the terms is always observed when data are processed.

5. Any person processing personal data must be cognizant of these present terms.

6. The terms must be complied with also where processing is made by a data processor.

7. Facilities used for storage and processing of the data must be organized and fitted up in order to prevent unauthorized access.

8. Data processing must be organized in such a manner that data are protected against accidental or unlawful destruction, loss or impairment. Furthermore, the necessary control should be exercised to ensure that no inaccurate or misleading data are processed. Inaccurate or misleading data or data processed in contravention of the above Act or of these terms shall be rectified or erased.

9. Data must not be kept in a form that makes it possible to identify the data subject for a longer period than is necessary for the implementation of the project.

10. If results from the clinical trial are published this must be done so that it is impossible to identify individual persons.

11. It is a condition that compliance is made with related terms, if any, laid down in accordance with other legislation.

Electronic data

12. Identification data must be encrypted or replaced by a code number or the like. Alternatively, all data can be stored encrypted. Encryption keys, code keys etc. must be stored securely and separate from the personal data.

13. Access to project data can be obtained only through the use of a confidential password. A password must be replaced at least once a year and when conditions dictate it.

14. If personal data are transferred over the Internet or other external network, the necessary security measures must be taken to ensure that the data do not come to the knowledge of any unauthorized third parties. As a minimum, the data must be encrypted during transmission. Transmission of sensitive personal data requires strong encryption. When using internal networks, it must be ensured that unauthorized persons are unable to obtain access to the data.

15. Removable storage media, safety copies of data etc. must be stored securely and under lock and so that unauthorized access is prevented.

Manual data

16. Manual clinical trial materials, including print-outs, failure lists and control lists etc., as well as other material which may directly or indirectly be linked with specific persons, must be stored securely under lock and so that unauthorized access is prevented.

Bio-bank and biological material

17. Samples with biological material and biological material in bio-banks must be stored securely under lock so that unauthorized access is prevented and in such a manner that it is ensured that the material is not lost, impaired or accidentally or illegally destroyed.

18. Biological material marked with civil registration number or name must be stored subject to special safety requirements.

19. The Company shall lay down internal guidelines for storage of biological material relative to the individual trials, and guidelines for storage of biological material in bio-banks. The guidelines shall be updated at least once a year.

Information to be provided to the data subject (trial subject)

20. Where the personal data are to be obtained from the trial subject (through interviews, questionnaires, clinical or para-clinical examination, treatment, observation etc.), detailed

data about the project shall be distributed/forwarded to the trial subject. The trial subject must be informed of the name of the controller, the purpose of the project and of the fact that it is voluntary to participate and that consent may be withdrawn at any time. Where the data are to be disclosed to be used for other scientific or statistical purposes, the trial subject shall be advised also of the purpose of the disclosure and identity of recipients, if applicable.

The data subject should furthermore be advised that the project is notified to the Data Protection Agency in accordance with Act on Processing of Personal Data, and that the Agency has laid down specific terms to be complied with for the project for the purpose of protecting the data subject's privacy.

Disclosure of data

21. Disclosure of data identifying individuals to a third party may take place for other statistical or scientific purposes only.

22. Disclosure may be made only subject to prior approval of the Data Protection Agency. The Data Protection Agency may lay down new terms for the disclosure as well as the recipient's data processing.

    Disclosure of data may, however, take place in accordance with the below-mentioned authorisation to disclose data.

Right of access to personal data

23. The subject of the trial i.e. the data subject has no right of access to the data being processed concerning himself, cf. Section 32(4) of the Act on Processing of Personal Data. This Act does not prevent the grant of access.

Processing by a data processor

24. The Data Protection Agency's conditions shall apply also to processing by a data processor.

25. When data are processed by a data processor, a written agreement shall be made between the controller and the data processor. The agreement shall stipulate that the data processor acts on behalf of the controller only and that the data must not be used for the data processor's own purposes. The controller shall furthermore request sufficient data from the data processor to ensure that the Data Protection Agency's terms can and will be complied with.

26. Where the data processor is established in another Member State it shall, furthermore, appear from the agreement that such other regulations on safety measures with regard to data processors that may be in force in the Member State in question, shall apply also to the data processor in question.

Erasure of data

27. Data in the individual trials shall be erased, made anonymous or destroyed no later than at the expiry of the storage period stipulated by the GCP-rules. It must not subsequently be possible to identify individuals participating in the trial.

28. Alternatively, the data may be transferred for further storage in archive in accordance with the rules of the archive legislation

29. Erasure of data from electronic media shall take place in such a manner that it is impossible to recover the data.

Transfer of data to third countries

30. Transfer of data to third countries, including for the purpose of processing by a data processor, requires the Data Protection Agency's prior approval.

    Transfer may take place in accordance with the below-mentioned transfer authorisation.

31. Transfer may, however, take place without approval of the Data Protection Agency if the data subject has given his explicit consent. The data subject can withdraw his consent.

32. Transfer of data shall take place by courier or registered mail. In case of electronic transmission the necessary security measures shall be taken to prevent unauthorized access. As a minimum, the data must be safely encrypted during the entire transmission. Transfer of sensitive personal data requires strong encryption.

Changes of the notified data processing

33. The Data Protection Agency shall prior to implementation be notified of significant changes to the data processing (in the form of a change to an existing notification). Less significant changes may be notified to the Data Protection Agency subsequently, however not later than four (4) weeks after the implementation.

Discontinuance of notified data processing

34. The Company shall notify the Data Protection Agency immediately if the company discontinues carrying out the notified data processing.

AUTHORISATION to disclose data

In connection with its notification the Company has applied for authorisation to disclose data.

The Company has applied for authorisation to disclose data to relevant national and international health and medicines authorities in connection with an application for marketing authorization.

Furthermore, the Company has applied for authorisation to disclose data concerning adverse events to national and international health and medicines authorities according to national and international law on reporting of adverse events in clinical trials.

The Data Protection Agency hereby grants authorisation to the disclosure, cf. Section 10(3) of Act on Processing of Personal Data.

The authorisation in granted on the following terms:

Period of validity: The authorisation is valid until further notice.

1. The relevant data may be disclosed to national and international health and medicines authorities in connection with an application for marketing authorization; to national and international health and medicines authorities according to national and international law on reporting of adverse events in clinical trials.

2. Only data required in the specific situation concerned may be disclosed.

3. The data may be disclosed to the recipient only in a form that does not identify individual persons. It must thus not be possible for the recipient on the basis of the received data alone to identify the persons related to the data.

4. The Company shall at any time be able to verify to the Data Protection Agency which transfers of data have been made.

AUTHORISATION to transfer personal data to third countries

In connection with its notification the Company has applied for authorisation to transfer personal data to third countries. The company wishes to transfer data for the purpose of data processing to be carried out by named data processors in third countries.

Furthermore, the Company wishes to transfer data to health and medicines authorities in third countries to comply with these countries' law on reporting of adverse events in clinical trials and in connection with applications for a marketing authorization.

According to Section 50(2) of Act on Processing of Personal Data, transfer of sensitive data to third countries can take place with the authorisation of the Data Protection Agency. According to section 50 (5), the Data Protection Agency may lay down more detailed conditions for the carrying out of the processing operations for reasons of protection of the privacy of the data subject in question.

The Data Protection Agency hereby grants authorisation to transfer data to third countries, cf. Section 50(2) of Act on Processing of Personal Data.

The authorisation is granted on the following terms:

Period of validity: The grant is valid until further notice.

1. Data may be transferred for processing by data processors with whom the Company has an agreement on data processing, and to health and medicines authorities in third countries in order to comply with the law of these countries on reporting of adverse events in clinical trials and in connection with an application for marketing authorization.

2. When data are transferred to and from third countries the necessary safety measurements must be taken to ensure that the data are not abused and to prevent unauthorized access. The data shall be delivered personally or sent by courier or registered post. Electronic transmission of data may take place only if the data are securely encrypted during the entire transmission. Transfer of sensitive personal data requires strong encryption.

3. Transfer of data to third countries takes place at the responsibility of the Company. The Company must therefore in each individual case assess whether the relevant transfer can take place, especially in consideration of the recipient's data safety. If it is assessed that the level of protection at the recipient's place is not adequate, transfer is not allowed.

4. The Company shall be able at any time to verify to the Data Protection Agency to which third countries data have been transferred and the purpose of this.

The following terms furthermore apply to transfer to data processors in third countries.

5. Processing of the data must take place only at the instance of the Company and at the Company's responsibility.

6. The Company shall always be in a position to notify the Data Protection Agency of the data processor's name and address.

7. Prior to any transfer of data a written agreement shall be made with the recipient to the effect that the Data Protection Agency's conditions for processing of the data in Denmark shall be complied with when the data processor processes the data.

8. As responsible for the processing, the Company shall obtain information sufficient to ensure that the terms of the Data Protection Agency are complied with.

9. When the data are no longer to be processed by the data processor they must be erased or returned to the Company.

The terms of the Data Protection Agency are valid until further notice. The Data Protection Agency reserves the right to take up the terms for revisions at a later date, if required.

Appendix II

Declaration of Helsinki [last amended Seoul 2008]

Policy

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimenta-

tion. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or commu-

nity stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individ-

ual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a

research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

33. The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or

34. Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

35. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

36. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

37. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

22.10.2008

Appendix III

Local Skin Response Grading Scale

Local Skin Response Grading Scale

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

Grade	0	1	2	3	4
Erythema	Not present	Slightly pink <50%	Pink or light red >50%	Red, restricted to treatment area	Red extending outside treatment area
Flaking/Scaling	Not present	Isolated scale, specific to lesions	Scale <50%	Scale >50%	Scaling extending outside treatment area
Crusting	Not present	Isolated crusting	Crusting <50%	Crusting >50%	Crusting extending outside treatment area

Local Skin Response Grading Scale

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

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

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Appendix IV

Documentation of the Selected Treatment Area on the Study Transparency

Identifying and Documenting the Selected Treatment Area

All subjects qualifying for this trial are to have 5 to 9 clinically typical, visible and discrete AK lesions within a contiguous 25 cm^2 treatment area on the face or scalp.

This area of skin will be referred to as the "selected treatment area" and will be documented using a "3-point landmark technique" on the study transparency.

Instructions for the 3-point landmark technique study transparency are described below. Transparencies (pre-marked 1 cm^2 grid) and markers will be provided to the study sites.

Three point landmark technique for the study transparency

1. Complete information (e.g. CRF number) on the transparency using a fine-tipped indelible marker.
2. Place the transparency over the selected treatment area.
3. Map and label at least 3 anatomical landmarks on the transparency which are in the vicinity of the selected treatment area. These landmarks should not change during the study (e.g. ear, eyebrow, scars, moles, birthmarks, bony landmarks, etc.)
4. Mark the outline of the selected treatment area (contiguous 25 cm^2), containing the lesions on the provided 1 cm^2 grid transparency. Ensure that the selected treatment area contains 25 unit areas, each unit area being 1 cm^2 in size.
5. Use the transparency to locate the selected treatment area for subsequent study visits. When re-aligning the transparency, use the documented anatomical landmarks to duplicate transparency placement.
6. At the start of treatment visit in a treatment cycle (Day 1 or Week 8 if retreatment is required), mark the location/corners of the selected treatment area on the skin using the fine-tipped indelible marker so that the subject can identify where the trial medication is to be applied for the second and third applications.

Appendix V

Imiquimod Summary of Product Characteristics

Summary of Product Characteristics last updated on the eMC: 24/06/2010

Aldara 5% Cream

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1. NAME OF THE MEDICINAL PRODUCT

ALDARA 5% cream

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2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 12.5 mg of imiquimod in 250 mg cream (5 %).

100 mg of cream contains 5 mg of imiquimod.

Excipients:
Methyl hydroxybenzoate (E218)
Propyl hydroxybenzoate (E216)
Cetyl alcohol
Stearyl alcohol

For a full list of excipients, see section 6.1.

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3. PHARMACEUTICAL FORM

Cream.
White to slightly yellow cream.

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4. CLINICAL PARTICULARS

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4.1 Therapeutic indications

Imiquimod cream is indicated for the topical treatment of :

• External genital and perianal warts (condylomata acuminata) in adults.

• Small superficial basal cell carcinomas (sBCCs) in adults.

• Clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses (AKs) on the face or scalp in immunocompetent adult patients when size or number of lesions limit the efficacy and/or acceptability of cryotherapy and other topical treatment options are contraindicated or less appropriate.

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4.2 Posology and method of administration

Posology

The application frequency and duration of treatment with imiquimod cream is different for each indication.

External genital warts in adults:
Imiquimod cream should be applied 3 times per week (example: Monday, Wednesday, and Friday; or Tuesday, Thursday, and Saturday) prior to normal sleeping hours, and should remain on the skin for 6 to 10 hours. Imiquimod cream treatment should continue until the clearance of visible genital orperianal warts or for a maximum of 16 weeks per episode of warts.
For quantity to be applied see 4.2 Method of administration.

Superficial basal cell carcinoma in adults:
Apply imiquimod cream for 6 weeks, 5 times per week (example: Monday to Friday) prior to normal sleeping hours, and leave on the skin for approximately 8 hours.
For quantity to be applied see 4.2 Method of administration.

Actinic keratosis in adults
Treatment should be initiated and monitored by a physician. Imiquimod cream should be applied 3 times per week (example: Monday, Wednesday and Friday) for four weeks prior to normal sleeping hours, and left on the skin for approximately 8 hours. Sufficient cream should be applied to cover the treatment area. After a 4-week treatment-free period, clearance of AKs should be assessed. If any lesions persist, treatment should be repeated for another four weeks.
The maximum recommended dose is one sachet. The maximum recommended treatment duration is 8 weeks.
An interruption of dosing should be considered if intense local inflammatory reactions occur (see section 4.4) or if infection is observed at the treatment site. In this latter case, appropriate other measures should be taken. Each treatment period should not be extended beyond 4 weeks due to missed doses or rest periods.
If the treated lesion(s) show an incomplete response at the follow-up examination at 4-8 weeks after the second treatment period, a different therapy should be used (see section 4.4)

Information applicable to all indications:
If a dose is missed, the patient should apply the cream as soon as he/she remember and then he/she should continue with the regular schedule. However the cream should not be applied more than once a day.

Paediatric patients

Use in the paediatric patient population is not recommended. There are no data available on the use of imiquimod in children and adolescents in the approved indications.

Aldara should not be used in children with molluscum contagiosum due to lack of efficacy in this indication (see section 5.1).

Method of administration

External genital warts:

Imiquimod cream should be applied in a thin layer and rubbed on the clean wart area until the cream vanishes. Only apply to affected areas and avoid any application on internal surfaces. Imiquimod cream should be applied prior to normal sleeping hours. During the 6 to 10 hour treatment period, showering or bathing should be avoided. After this period it is essential that imiquimod cream is removed with mild soap and water. Application of an excess of cream or prolonged contact with the skin may result in a severe application site reaction (see sections 4.4, 4.8 and 4.9). A single-use sachet is sufficient to cover a wart area of 20 cm^2 (approx. 3 $inches^2$). Sachets should not be re-used once opened. Hands should be washed carefully before and after application of cream. Uncircumcised males treating warts under the foreskin should retract the foreskin and wash the area daily (see section 4.4).

Superficial basal cell carcinoma:

Before applying imiquimod cream, patients should wash the treatment area with mild soap and water and dry thoroughly. Sufficient cream should be applied to cover the treatment area, including one centimetre of skin surrounding the tumour. The cream should be rubbed into the treatment area until the cream vanishes. The cream should be applied prior to normal sleeping hours and remain on the skin for approximately 8 hours. During this period, showering and bathing should be avoided. After this period it is essential that imiquimod cream is removed with mild soap and water.

Sachets should not be re-used once opened. Hands should be washed carefully before and after application of cream.

Response of the treated tumour to imiquimod cream should be assessed 12 weeks after the end of treatment. If the treated tumour shows an incomplete response, a different therapy should be used (see section 4.4).

A rest period of several days may be taken (see section 4.4) if the local skin reaction to imiquimod cream causes excessive discomfort to the patient, or if infection is observed at the treatment site. In this latter case, appropriate other measures should be taken.

Actinic keratosis:

Before applying imiquimod cream, patients should wash the treatment area with mild soap and water and dry thoroughly. Sufficient cream should be applied to cover the treatment area. The cream should be rubbed into the treatment area until the cream vanishes. The cream should be applied prior to normal sleeping hours and remain on the skin for approximately 8 hours. During this period, showering and bathing should be avoided. After this period it is essential that imiquimod cream is removed with mild soap and water. Sachets should not be re-used once opened. Hands should be washed carefully before and after application of cream.

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4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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4.4 Special warnings and precautions for use

External genital warts, superficial basal cell carcinoma and actinic keratosis:

Avoid contact with the eyes, lips and nostrils.

Imiquimod has the potential to exacerbate inflammatory conditions of the skin.

Imiquimod cream should be used with caution in patients with autoimmune conditions (refer to section 4.5). Consideration should be given to balancing the benefit of imiquimod treatment for these patients with the risk associated with a possible worsening of their autoimmune condition.

Imiquimod cream should be used with caution in organ transplant patients (refer to section 4.5). Consideration should be given to balancing the benefit of imiquimod treatment for these patients with the risk associated with the possibility of organ rejection or graft-versus-host disease.

Imiquimod cream therapy is not recommended until the skin has healed after any previous drug or surgical treatment. Application to broken skin could result in increased systemic absorption of imiquimod leadling to a greater risk of adverse

events (refer to section 4.8 and 4.9)

The use of an occlusive dressing is not recommended with imiquimod cream therapy.

The excipients methylhydroxybenzoate (E218), propylhydroxybenzoate (E216), cetyl alcohol and stearyl alcohol may cause allergic reactions.

Rarely, intense local inflammatory reactions including skin weeping or erosion can occur after only a few applications of imiquimod cream. Local inflammatory reactions may be accompanied, or even preceded, by flu-like systemic signs and symptoms including malaise, pyrexia, nausea, myalgias and rigors. An interruption of dosing should be considered.

Imiquimod should be used with caution in patients with reduced haematologic reserve (refer to section 4.8d).

External genital warts:

There is limited experience in the use of imiquimod cream in the treatment of men with foreskin-associated warts. The safety database in uncircumcised men treated with imiquimod cream three times weekly and carrying out a daily foreskin hygiene routine is less than 100 patients. In other studies, in which a daily foreskin hygiene routine was not followed, there were two cases of severe phimosis and one case of stricture leading to circumcision. Treatment in this patient population is therefore recommended only in men who are able or willing to follow the daily foreskin hygiene routine. Early signs of stricture may include local skin reactions (e.g. erosion, ulceration, oedema, induration), or increasing difficulty in retracting the foreskin. If these symptoms occur, the treatment should be stopped immediately. Based on current knowledge, treating urethral, intravaginal, cervical, rectal or intra-anal warts is not recommended. Imiquimod cream therapy should not be initiated in tissues where open sores or wounds exist until after the area has healed.

Local skin reactions such as erythema, erosion, excoriation, flaking and oedema are common. Other local reactions such as induration, ulceration, scabbing, and vesicles have also been reported. Should an intolerable skin reaction occur, the cream should be removed by washing the area with mild soap and water. Treatment with imiquimod cream can be resumed after the skin reaction has

moderated.

The risk of severe local skin reactions may be increased when imiquimod is used at higher than recommended doses (see section 4.2). However, in rare cases severe local reactions that have required treatment and/or caused temporary incapacitation have been observed in patients who have used imiquimod according to the instructions. Where such reactions have occurred at the urethral meatus, some women have experienced difficulty in urinating, sometimes requiring emergency catheterisation and treatment of the affected area.

No clinical experience exists with imiquimod cream immediately following treatment with other cutaneously applied drugs for treatment of external genital or perianal warts. Imiquimod cream should be washed from the skin before sexual activity. Imiquimod cream may weaken condoms and diaphragms, therefore concurrent use with imiquimod cream is not recommended. Alternative forms of contraception should be considered.

In immunocompromised patients, repeat treatment with imiquimod cream is not recommended.

While limited data have shown an increased rate of wart reduction in HIV positive patients, imiquimod cream has not been shown to be as effective in terms of wart clearance in this patient group.

Superficial basal cell carcinoma:

Imiquimod has not been evaluated for the treatment of basal cell carcinoma within 1 cm of the eyelids, nose, lips or hairline.

During therapy and until healed, affected skin is likely to appear noticeably different from normal skin. Local skin reactions are common but these reactions generally decrease in intensity during therapy or resolve after cessation of imiquimod cream therapy. There is an association between the complete clearance rate and the intensity of local skin reactions (e.g. erythema). These local skin reactions may be related to the stimulation of local immune response. If required by the patient's discomfort or the severity of the local skin reaction, a rest period of several days may be taken. Treatment with imiquimod cream can be resumed after the skin reaction has moderated.

The clinical outcome of therapy can be determined after regeneration of the

treated skin, approximately 12 weeks after the end of treatment.

No clinical experience exists with the use of imiquimod cream in immunocompromised patients.

No clinical experience exists in patients with recurrent and previously treated BCCs, therefore use for previously treated tumours is not recommended.

Data from an open label clinical trial suggest that large tumours (>7.25 cm^2) are less likely to respond to imiquimod therapy.

The skin surface area treated should be protected from solar exposure.

Actinic keratosis

Lesions clinically atypical for AK or suspicious for malignancy should be biopsied to determine appropriate treatment.

Imiquimod has not been evaluated for the treatment of actinic keratoses on the eyelids, the inside of the nostrils or ears, or the lip area inside the vermilion border.

There are very limited data available on the use of imiquimod for the treatment of actinic keratoses in anatomical locations other than the face and scalp. The available data on actinic keratosis on the forearms and hands do not support efficacy in this indication and therefore such use is not recommended.

Imiquimod is not recommended for the treatment of AK lesions with marked hyperkeratosis or hypertrophy as seen in cutaneous horns.

During therapy and until healed, affected skin is likely to appear noticeably different from normal skin. Local skin reactions are common but these reactions generally decrease in intensity during therapy or resolve after cessation of imiquimod cream therapy. There is an association between the complete clearance rate and the intensity of local skin reactions (e.g. erythema). These local skin reactions may be related to the stimulation of local immune response. If required by the patient's discomfort or the intensity of the local skin reaction, a rest period of several days may be taken. Treatment with imiquimod cream can be resumed after the skin reaction has moderated.

Each treatment period should not be extended beyond 4 weeks due to missed doses or rest periods.

The clinical outcome of therapy can be determined after regeneration of the treated skin, approximately 4-8 weeks after the end of treatment.

No clinical experience exists with the use of imiquimod cream in immunocompromised patients.

No data are available on re-treating actinic keratoses that have cleared after one or two courses of treatment and subsequently recur, and any such use is therefore not recommended.

Data from an open-label clinical trial suggest that subjects with more than 8 AK lesions showed a decreased rate of complete clearance compared to patients with less than 8 lesions.

The skin surface area treated should be protected from solar exposure.

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4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. This includes studies with immunosuppressive drugs. Interactions with systemic drugs would be limited by the minimal percutaneous absorption of imiquimod cream.

Due to its immunostimulating properties, imiquimod cream should be used with caution in patients who are receiving immunosuppressive medication (see Section 4.4).

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4.6 Pregnancy and lactation

For imiquimod no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see 5.3). Caution should be exercised when prescribing to pregnant women.

As no quantifiable levels (>5 ng/ml) of imiquimod are detected in the serum after single and multiple topical doses, no specific advice can be given on whether to use or not in lactating mothers.

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4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. From the undesirable effects noted in section 4.8, it is unlikely that treatment will have any effect on the ability to drive and use machines.

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4.8 Undesirable effects

a) General Description:

External genital warts:

In the pivotal trials with 3 times a week dosing, the most frequently reported adverse drug reactions judged to be probably or possibly related to imiquimod cream treatment were application site reactions at the wart treatment site (33.7% of imiquimod treated patients). Some systemic adverse reactions, including headache (3.7%), influenza-like symptoms (1.1%), and myalgia (1.5%) were also reported.

Patient reported adverse reactions from 2292 patients treated with imiquimod cream in placebo controlled and open clinical studies are presented below. These adverse events are considered at least possibly causally related to treatment with imiquimod.

Superficial basal cell carcinoma:

In trials with 5 times per week dosing 58% of patients experienced at least one adverse event. The most frequently reported adverse events from the trials judged probably or possibly related to imiquimod cream are application site disorders, with a frequency of 28.1%. Some systemic adverse reactions, including back pain (1.1%) and influenza-like symptoms (0.5%) were reported by imiquimod cream patients.

Patient reported adverse reactions from 185 patients treated with imiquimod cream in placebo controlled phase III clinical studies for superficial basal cell carcinoma are presented below. These adverse events are considered at least possibly causally related to treatment with imiquimod.

Actinic keratosis

In the pivotal trials with 3 times per week dosing for up to 2 courses each of 4 weeks, 56% of imiquimod patients reported at least one adverse event. The most frequently reported adverse event from these trials judged probably or possibly related to imiquimod cream was application site reactions (22% of imiquimod treated patients). Some systemic adverse reactions, including myalgia (2%) were reported by imiquimod treated patients.

Patient reported adverse reactions from 252 patients treated with imiquimod cream in vehicle controlled phase III clinical studies for actinic keratosis are

presented below. These adverse events are considered at least possibly causally related to treatment with imiquimod.

b) Tabular Listing of adverse events:

Frequencies are defined as Very common (≥1/10), Common (≥1/100 to <1/10) and Uncommon (≥1/1,000 to <1/100). Lower frequencies from clinical trials are not reported here.

	External genital warts (3x/ wk,16wks) N = 2292	**Superficial basal cell carcinoma (5x/wk, 6 wks) N = 185**	**Actinic keratosis (3x/wk, 4 or 8 wks) N = 252**
Infections and infestations:			
Infection	Common	Common	Uncommon
Pustules		Common	Uncommon
Herpes simplex	Uncommon		
Genital candidiasis	Uncommon		
Vaginitis	Uncommon		
Bacterial infection	Uncommon		
Fungal infection	Uncommon		
Upper respiratory tract infection	Uncommon		
Vulvitis	Uncommon		
Rhinitis			Uncommon
Influenza			Uncommon
Blood and lymphatic system disorders:			
Lymphadenopathy	Uncommon	Common	Uncommon
Metabolism and			

nutrition disorders:			
Anorexia	Uncommon		Common
Psychiatric disorders:			
Insomnia	Uncommon		
Depression	Uncommon		Uncommon
Irritability		Uncommon	
Nervous system disorders:			
Headache	Common		Common
Paraesthesia	Uncommon		
Dizziness	Uncommon		
Migraine	Uncommon		
Somnolence	Uncommon		
Eye disorders			
Conjunctival irritation			Uncommon
Eyelid oedema			Uncommon
Ear and labyrinth disorders:			
Tinnitus	Uncommon		
Vascular disorders:			
Flushing	Uncommon		
Respiratory, thoracic and mediastinal disorders:			
Pharyngitis	Uncommon		
Rhinitis	Uncommon		

Nasal congestion			Uncommon
Pharyngo laryngeal pain			Uncommon
Gastrointestinal disorders:			
Nausea	Common	Uncommon	Common
Abdominal pain	Uncommon		
Diarrhoea	Uncommon		Uncommon
Vomiting	Uncommon		
Rectal disorder	Uncommon		
Rectal tenesmus	Uncommon		
Dry mouth		Uncommon	
Skin and subcutane-ous tissue disorders:			
Pruritus	Uncommon		
Dermatitis	Uncommon	Uncommon	
Folliculitis	Uncommon		
Rash erythematous	Uncommon		
Eczema	Uncommon		
Rash	Uncommon		
Sweating increased	Uncommon		
Urticaria	Uncommon		
Actinic keratosis			Uncommon
Erythema			Uncommon
Face oedema			Uncommon
Skin ulcer			Uncommon

Musculoskeletal and connective tissue disorders:			
Myalgia	Common		Common
Arthralgia	Uncommon		Common
Back pain	Uncommon	Common	
Pain in extremity			Uncommon
Renal and urinary disorders:			
Dysuria	Uncommon		
Reproductive system and breast disorders:			
Genital pain male	Uncommon		
Penile disorder	Uncommon		
Dyspareunia	Uncommon		
Erectile dysfunction	Uncommon		
Uterovaginal prolapse	Uncommon		
Vaginal pain	Uncommon		
Vaginitis atrophic	Uncommon		
Vulval disorder	Uncommon		
General disorders and administration site conditions:			
Application site pruritus	Very common	Very common	Very common
Application site pain	Very common	Common	Common
Application site burning	Common	Common	Common

Application site irritation	Common	Common	Common
Application site erythema		Common	Common
Application site reaction			Common
Application site bleeding		Common	Uncommon
Application site papules		Common	Uncommon
Application site paraesthesia		Common	Uncommon
Application site rash		Common	
Fatigue	Common		Common
Pyrexia	Uncommon		Uncommon
Influenza-like illness	Uncommon	Uncommon	
Pain	Uncommon		
Asthenia	Uncommon		Uncommon
Malaise	Uncommon		
Rigors	Uncommon		Uncommon
Application site dermatitis			Uncommon
Application site discharge		Uncommon	Uncommon
Application site hyperaesthesia			Uncommon
Application site inflammation		Uncommon	

Application site oedema		Uncommon	Uncommon
Application site scabbing		Uncommon	Uncommon
Application site scar			Uncommon
Application site skin breakdown		Uncommon	
Application site swelling		Uncommon	Uncommon
Application site ulcer			Uncommon
Application site vesicles		Uncommon	Uncommon
Application site warmth			Uncommon
Lethargy		Uncommon	
Discomfort			Uncommon
Inflammation			Uncommon

c) Frequently occurring adverse events:

External genital warts:

Investigators of placebo controlled trials were required to evaluate protocol mandated clinical signs (skin reactions). These protocol mandated clinical sign assessments indicate that local skin reactions including erythema (61%), erosion (30%), excoriation/flaking/scaling (23%) and oedema (14%) were common in these placebo controlled clinical trials with imiquimod cream applied three times weekly (see section 4.4). Local skin reactions, such as erythema, are probably an extension of the pharmacologic effects of imiquimod cream.
Remote site skin reactions, mainly erythema (44%), were also reported in the placebo controlled trials. These reactions were at non-wart sites which may have been in contact with imiquimod cream. Most skin reactions were mild to moderate in severity and resolved within 2 weeks of treatment discontinuation. However, in

some cases these reactions have been severe, requiring treatment and/or causing incapacitation. In very rare cases, severe reactions at the urethral meatus have resulted in dysuria in women (see section 4.4).

Superficial basal cell carcinoma:

Investigators of the placebo controlled clinical trials were required to evaluate protocol mandated clinical signs (skin reactions). These protocol mandated clinical sign assessments indicate that severe erythema (31%) severe erosions (13%) and severe scabbing and crusting (19%) were very common in these trials with imiquimod cream applied 5 times weekly. Local skin reactions, such as erythema, are probably an extension of the pharmacologic effect of imiquimod cream.
Skin infections during treatment with imiquimod have been observed. While serious sequelae have not resulted, the possibility of infection in broken skin should always be considered.

Actinic keratosis

In clinical trials of imiquimod cream 3 times weekly for 4 or 8 weeks the most frequently occurring application site reactions were itching at the target site (14%) and burning at the target site (5%). Severe erythema (24%) and severe scabbing and crusting (20%) were very common. Local skin reactions, such as erythema, are probably an extension of the pharmacologic effect of imiquimod cream. See 4.2 and 4.4 for information on rest periods.
Skin infections during treatment with imiquimod have been observed. While serious sequelae have not resulted, the possibility of infection in broken skin should always be considered.

d) Adverse events applicable to all indications:

Reports have been received of localised hypopigmentation and hyperpigmentation following imiquimod cream use. Follow-up information suggests that these skin colour changes may be permanent in some patients. In a follow-up of 162 patients five years after treatment for sBCC a mild hypopigmentation was observed in 37% of the patients and a moderate hypopigmentation was observed in 6% of the patients. 56% of the patients have been free of hypopigmentation; hyperpigmentation has not been reported.
Clinical studies investigating the use of imiquimod for the treatment of actinic

keratosis have detected a 0.4% (5/1214) frequency of alopecia at the treatment site or surrounding area. Postmarketing reports of suspected alopecia occurring during the treatment of sBCC and EGW have been received.
Reductions in haemoglobin, white blood cell count, absolute neutrophils and platelets have been observed in clinical trials. These reductions are not considered to be clinically significant in patients with normal haematologic reserve. Patients with reduced haematologic reserve have not been studied in clinical trials. Reductions in haematological parameters requiring clinical intervention have been reported from postmarketing experience. There have been postmarketing reports of elevated liver enzymes.
Rare reports have been received of exacerbation of autoimmune conditions.
Rare cases of remote site dermatologic drug reactions, including erythema multiforme, have been reported from clinical trials. Serious skin reactions reported from postmarketing experience include erythema multiforme, Stevens Johnson syndrome and cutaneous lupus erythematosus.

e) Paediatric patients:

Imiquimod was investigated in controlled clinical studies with paediatric patients (see sections 4.2 and 5.1). There was no evidence for systemic reactions. Application site reactions occurred more frequently after imiquimod than after vehicle, however, incidence and intensity of these reactions were not different from that seen in the licensed indications in adults. There was no evidence for serious adverse reaction caused by imiquimod in paediatric patients.

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4.9 Overdose

When applied topically, systemic overdosage with imiquimod cream is unlikely due to minimal percutaneous absorption. Studies in rabbits reveal a dermal lethal dose of greater than 5 g/kg. Persistent dermal overdosing of imiquimod cream could result in severe local skin reactions.

Following accidental ingestion, nausea, emesis, headache, myalgia and fever could occur after a single dose of 200 mg imiquimod which corresponds to the content of approximately 16 sachets. The most clinically serious adverse event reported following multiple oral doses of ≥200 mg was hypotension which resolved following oral or intravenous fluid administration.

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5. PHARMACOLOGICAL PROPERTIES

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5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Chemotherapeutics for topical use, antivirals : ATC Code : D06BB10.

Imiquimod is an immune response modifier. Saturable binding studies suggest a membrane receptor for imiquimod exists on responding immune cells. Imiquimod has no direct antiviral activity. In animal models imiquimod is effective against viral infections and acts as an antitumour agent principally by induction of alpha interferon and other cytokines. The induction of alpha interferon and other cytokines following imiquimod cream application to genital wart tissue has also been demonstrated in clinical studies.

Increases in systemic levels of alpha interferon and other cytokines following topical application of imiquimod were demonstrated in a pharmacokinetic study.

External genital warts:

Clinical Efficacy

The results of 3 phase III pivotal efficacy studies showed that treatment with imiquimod for sixteen weeks was significantly more effective than treatment with vehicle as measured by total clearance of treated warts.

In 119 imiquimod-treated female patients, the combined total clearance rate was 60% as compared to 20% in 105 vehicle-treated patients (95% CI for rate difference: 20% to 61% , $p<0.001$). In those imiquimod patients who achieved total clearance of their warts, the median time to clearance was 8 weeks.

In 157 imiquimod-treated male patients, the combined total clearance rate was 23% as compared to 5% in 161 vehicle-treated patients (95%CI for rate difference: 3% to 36% , $p<0.001$). In those imiquimod patients who achieved total clearance of their warts, the median time to clearance was 12 weeks.

Superficial basal cell carcinoma:

Clinical efficacy:

The efficacy of imiquimod 5 times per week for 6 weeks was studied in two double-blind vehicle controlled clinical trials. Target tumours were histologically confirmed single primary superficial basal cell carcinomas with a minimum size of 0.5 cm^2 and a maximum diameter of 2 cm. Tumours located within 1 cm of the

eyes, nose, mouth, ears or hairline were excluded. In a pooled analysis of these two studies, histological clearance was noted in 82% (152/185) of patients. When clinical assessment was also included, clearance judged by this composite endpoint was noted in 75% (139/185) of patients. These results were statistically significant ($p<0.001$) by comparison with the vehicle group, 3% (6/179) and 2% (3/179) respectively. There was a significant association between the intensity of local skin reactions (e.g. erythema) seen during the treatment period and complete clearance of the basal cell carcinoma.
Five -year data from a long-term open-label uncontrolled study indicate that an estimated 77.9% [95% CI (71.9%, 83.8%)] of all the subjects who initially received treatment became clinically clear and remained clear at 60 months.

Actinic keratosis:

Clinical efficacy:
The efficacy of imiquimod applied 3 times per week for one or two courses of 4 weeks, separated by a 4 week treatment-free period, was studied in two double-blind vehicle controlled clinical trials. Patients had clinically typical, visible, discrete, nonhyperkeratotic, nonhypertrophic AK lesions on the balding scalp or face within a contiguous 25 cm^2 treatment area. 4-8 AK lesions were treated. The complete clearance rate (imiquimod minus placebo) for the combined trials was 46.1% (CI 39.0%, 53.1%).
One-year data from two combined observational studies indicate a recurrence rate of 27% (35/128 patients) in those patients who became clinically clear after one or two courses of treatment. The recurrence rate for individual lesions was 5.6% (41/737). Corresponding recurrence rates for vehicle were 47% (8/17 patients) and 7.5% (6/80 lesions). The rate of progression to squamous cell carcinoma (SCC) was reported in 1.6% (2/128 patients).
There are no data on recurrence and progression rates beyond 1 year.

Paediatric patients:
The approved indications genital warts, actinic keratosis and superficial basal cell carcinoma are conditions not generally seen within the paediatric population and were not studied.
Aldara Cream has been evaluated in four randomised, vehicle controlled, double-blind trials in children aged 2 to 15 years with molluscum contagiosum (imiquimod n = 576, vehicle n = 313) . These trials failed to demonstrate efficacy of

imiquimod at any of the tested dosage regimens (3x/week for ≤ 16 weeks and 7x/week for ≤ 8 weeks).

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5.2 Pharmacokinetic properties

External genital warts, superficial basal cell carcinoma and actinic keratosis:

Less than 0.9% of a topically applied single dose of radiolabelled imiquimod was absorbed through the skin of human subjects. The small amount of drug which was absorbed into the systemic circulation was promptly excreted by both urinary and faecal routes at a mean ratio of approximately 3 to 1. No quantifiable levels (>5 ng/ml) of drug were detected in serum after single or multiple topical doses.

Systemic exposure (percutaneous penetration) was calculated from recovery of carbon-14 from [14C] imiquimod in urine and faeces.

Minimal systemic absorption of imiquimod 5% cream across the skin of 58 patients with actinic keratosis was observed with 3 times per week dosing for 16 weeks. The extent of percutaneous absorption did not change significantly between the first and last doses of this study. Peak serum drug concentrations at the end of week 16 were observed between 9 and 12 hours and were 0.1, 0.2, and 1.6 ng/mL for the applications to face (12.5 mg, 1 single-use sachet), scalp (25 mg, 2 sachets) and hands/arms (75 mg, 6 sachets), respectively. The application surface area was not controlled in the scalp and hands/ arms groups. Dose proportionality was not observed. An apparent half-life was calculated that was approximately 10 times greater than the 2 hour half-life seen following subcutaneous dosing in a previous study, suggesting prolonged retention of drug in the skin. Urinary recovery was less than 0.6% of the applied dose at week 16 in these patients.

Paediatric patients:
The pharmacokinetic properties of imiquimod following single and multiple topical application in paediatric patients with molluscum contagiosum (MC) have been investigated. The systemic exposure data demonstrated that the extent of absorption of imiquimod following topical application to the MC lesional skin of the paediatric patients aged 6-12 years was low and comparable to that observed in healthy adults and adults with actinic keratosis or superficial basal cell carcinoma. In younger patients aged 2-5 years absorption, based on C_{max} values, was higher compared to adults.

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5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, mutagenicity and teratogenicity.

In a four-month rat dermal toxicity study, significantly decreased body weight and increased spleen weight were observed at 0.5 and 2.5 mg/kg; similar effects were not seen in a four month mouse dermal study. Local dermal irritation, especially at higher doses, was observed in both species.

A two-year mouse carcinogenicity study by dermal administration on three days a week did not induce tumours at the application site. However, the incidences of hepatocellular tumours among treated animals were greater than those for controls. The mechanism for this is not known, but as imiquimod has low systemic absorption from human skin, and is not mutagenic, any risk to humans from systemic exposure is likely to be low. Furthermore, tumours were not seen at any site in a 2-year oral carcinogenicity study in rats.

Imiquimod cream was evaluated in a photocarcinogenicity bioassay in albino hairless mice exposed to simulated solar ultraviolet radiation (UVR). Animals were administered imiquimod cream three times per week and were irradiated 5 days per week for 40 weeks. Mice were maintained for an additional 12 weeks for a total of 52 weeks. Tumours occurred earlier and in greater number in the group of mice administered the vehicle cream in comparison with the low UVR control group. The significance for man is unknown. Topical administration of imiquimod cream resulted in no tumour enhancement at any dose, in comparison with the vehicle cream group.

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6. PHARMACEUTICAL PARTICULARS

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6.1 List of excipients

isostearic acid
benzyl alcohol
cetyl alcohol
stearyl alcohol
white soft paraffin
polysorbate 60

sorbitan stearate
glycerol
methyl hydroxybenzoate (E218)
propyl hydroxybenzoate (E216)
xanthan gum
purified water.

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6.2 Incompatibilities

Not applicable.

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6.3 Shelf life

2 years.

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6.4 Special precautions for storage

Do not store above 25°C.

Sachets should not be re-used once opened.

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6.5 Nature and contents of container

Boxes of 12 or 24 single-use polyester/aluminium foil sachets, containing 250 mg of cream.

Not all pack sizes may be marketed.

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6.6 Special precautions for disposal and other handling

No special requirements.

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7. MARKETING AUTHORISATION HOLDER

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Sweden

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8. MARKETING AUTHORISATION NUMBER(S)

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