Clinical Research Protocol

Safety and efficacy of ingenol mebutate gel 0.015% for treatment of actinic keratosis on the face in solid organ transplant recipients.

Protocol Number:	Version 1.0
Version Date:	December 21, 2015
Investigational Product:	Ingenol Mebutate gel 0.015%
IND Number:	
Development Phase:	Not applicable.
Sponsor:	Investigator Initiated Protocol
Funding Organization:	Leo Pharma 1 Sylvan Way Parsippany, NJ 07054 USA
Principal Investigator:	Name: Sarah Arron, MD, PhD Telephone: 415-353-9684 Fax: 415-353-7838 E-mail: Sarah.Arron@ucsf.edu

Approval:

_____ _____

PI or Sponsor Signature (Name and Title) *Date*

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PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing Leo Pharma with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: Version 1.0

Protocol Title: Safety and efficacy of ingenol mebutate gel 0.015% for treatment of actinic keratosis on the face in solid organ transplant recipients.

Protocol Date: December 21, 2015

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Investigator Signature *Date*

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Print Name and Title

Site # _____

Site Name _____

Address _____

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Phone Number _____

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LIST OF ABBREVIATIONS

AE	adverse event
AK	Actinic keratosis
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CRF	case report form
CRP	C-reactive protein
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
LOCF	last observation carried forward
LSR	Local skin response
NSAID	nonsteroidal anti-inflammatory drug
OTR	organ transplant recipients
PI	Principal Investigator
PK	pharmacokinetic
SAE	serious adverse experience
SAP	Statistical Analysis Plan
SCC	squamous cell carcinoma
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamate pyruvate transaminase

PROTOCOL SYNOPSIS

TITLE	Safety and efficacy of ingenol mebutate gel 0.015% for treatment of actinic keratosis on the face in solid organ transplant recipients
SPONSOR	Investigator Initiated Protocol
FUNDING ORGANIZATION	Leo Pharma
NUMBER OF SITES	1
RATIONALE	Actinic keratoses (AK) are patches of dysplastic keratinocytes arising in sun-damaged skin. These lesions are precursors to cutaneous squamous cell carcinoma (SCC), and are treated to prevent progression to SCC. First-line therapy for AK include cryotherapy and curettage, which target clinically visible lesions but do not address the subclinical lesions in the field of ultraviolet radiation damage. Field therapy includes topical chemotherapy, immunotherapy, and photodynamic therapy. Ingenol mebutate is the active compound found in Euphorbia peplus sap, and has been approved for treatment of actinic keratoses in immunocompetent patients. Ingenol mebutate 0.015% is favored over other topical treatments for treatment of actinic keratoses on the face due to the brief treatment course, high clearance rate, and resolution without sequelae. There are no data on safety of this medication in immunosuppressed solid organ transplant recipients (OTR). OTR have a high incidence of AK and high risk of developing SCC, and require frequent field therapy. In addition, OTR generally have a higher burden of AK and require treatment of a larger surface area than the 25 cm^2 area labeled for ingenol mebutate 0.015%. We plan to investigate the safety and efficacy of ingenol mebutate 0.015% in OTR, with a treatment area up to 100cm^2. The rationale for an increased dose and surface area for treatment in this study is that OTR typically have an extensive burden of AK, requiring treatment of larger areas such as those described here. The proposed treatment regimen better reflects the 'real world' need for treatment of a larger surface area while evaluating the safety and local site reactions associated with this treatment regimen.
STUDY DESIGN	This is a single arm, open-label safety study.
PRIMARY OBJECTIVE	To assess the safety of topical ingenol mebutate for treatment of the face in solid organ transplant recipients.

SECONDARY OBJECTIVES	To evaluate the efficacy of ingenol mebutate for reduction of actinic keratoses on the face in organ transplant recipients. To investigate the local skin response to ingenol mebutate in organ transplant recipients. To investigate the effect of topical treatment with ingenol mebutate on patient reported outcomes of pain and quality of life in organ transplant recipients.
NUMBER OF SUBJECTS	20
SUBJECT SELECTION CRITERIA	Inclusion Criteria: • Adults at least 18 years old. • Subject must be a solid organ transplant recipient at least one year from the date of transplantation. • Subjects must be in stable health as confirmed by medical history, per investigator judgement. • Subjects must be able to read, sign, and understand the informed consent. • Subjects have at least 4 and no more than 20 clinically typical, visible actinic keratoses in a treatment area of approximately 100cm^2 on the face. Treatment areas will include a single cheek (nasofacial sulcus to tragus, malar cheekbone to jawline and avoiding the lower eyelid and mouth); the forehead (hairline to eyebrows, extending laterally to the root of the helix). • Subject must be willing to forego any other treatments on the face, including cryotherapy, tanning bed use and excessive sun exposure while in the study. • Subject is willing and able to participate in the study and to comply with all study requirements including concomitant medication and other treatment restrictions. • If subject is a female of childbearing potential she must have a negative urine pregnancy test result prior to study treatment initiation and must agree to use an approved method of birth control while enrolled in the study. Exclusion Criteria: • Subjects with an unstable medical condition as deemed by the clinical investigator. • Subjects with a history of bone marrow or stem cell transplantation. • Subjects with non-melanoma skin cancer in the treatment area.

	• Subjects with any dermatologic disease in the treatment area that may be exacerbated by the treatment proposed or that might impair the evaluation of AKs. • Women who are pregnant, lactating, or planning to become pregnant during the study period. • Subjects who have previously been treated with ingenol mebutate in study area within the past 8 weeks. • Subjects who have used any topical prescription medications for actinic keratosis on the study area within 8 weeks prior to study treatment initiation. • Subjects who have used any topical prescription medications for other reason on the study area within 4 weeks prior to study treatment initiation. • Subjects who are currently participating in another clinical study or have completed another clinical study with an investigational drug or device on the study area within 30 days prior to study treatment initiation. • Subjects with known hypersensitivity to Picato gel or any of the inactive ingredients: isopropyl alcohol, hydroxyethyl cellulose, citric acid monohydrate, sodium citrate, or benzyl alcohol.
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Ingenol Mebutate, 0.015% topical gel Subjects will treat a 100 cm^2 area of the skin daily for 3 days based on the per label dosing for the 0.015% concentration, and assuming a deliverable dose weight of 0.25g. Therefore, 4 tubes of the 0.15% concentration will be used in the treatment area per day, for 3 consecutive treatment days, for a total of 12 tubes of the 0.015% concentration per patient. This will deliver a dose of 1.5 mcg per cm^2 of treated area each day. Subjects will be instructed to open one tube at a time and apply contents to one 25 cm2 skin quadrant, and then repeat for each of the remaining three quadrants. The first application will be performed in clinic under the guidance of the study coordinator.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be on study for up to 57 days **Screening:** up to 14 days **Treatment:** 3 days **Follow-up:** 54 days The total duration of the study is expected to be 8 months. 6 months for subject recruitment and 2 months for final subject follow-up.

CONCOMMITANT MEDICATIONS	Allowed: Bland topical emollients such as Eucerin, Cetaphil. 1% topical hydrocortisone cream or ointment allowed after D4 at the discretion of the investigator. Prohibited: Any topical prescription medication on the treatment area during the study.
EVALUATIONS	
PRIMARY ENDPOINT	The primary outcome will be the safety endpoint of the incidence rate of patients who experience: 1) Any adverse event (AE) ascertained by patient report, physician evaluation, or laboratory value. 2) One or more serious adverse events (SAE) as defined by CTCAEv4 3) Adverse events leading to study drug discontinuation.
SECONDARY ENDPOINTS	Efficacy: • Reduction in number of actinic keratoses: defined as the percent change in actinic keratosis count in the target treatment area on Day 57, as compared to the baseline lesion count. • Partial clearance of lesions: defined as the proportion of patients with a reduction of 75% of more in the number of clinically visible AKs in the target treatment area at Day 57, compared to baseline. • Complete clearance of lesions: defined as the proportion of patients with complete clearance of actinic keratoses in the target treatment area. Local skin response: • Local skin response (LSR) as measured by visual assessment by the investigator using a 4 point scale on six responses for a maximum total of 24, according to the LSR scoring scale. Patient Reported Outcomes: • Pain as measured by the 0-10 VAS Numeric Pain Distress Scale (0 = no pain, 5 = moderate pain, 10 = unbearable pain). • Patient quality of life as measured by Skindex-16 survey
STATISTICS **Primary Analysis Plan**	This is a small descriptive study, with the primary safety endpoint of the incidence rate of patients who experience: 1) Any adverse event (AE) ascertained by patient report, physician evaluation, or laboratory value, 2) One or more serious adverse events (SAE) as defined by CTCAEv4, and 3) Adverse events leading to study drug discontinuation. The safety analysis will be based on the safety population, which is defined as all randomized patients who have received at least one dose of study medication and who have had at least one post-baseline

	safety evaluation. Adverse events will be explored for trends or heterogeneity between the two transplant subgroups; lung and kidney. If there is evidence for a difference between groups, the subgroups will be reported separately. The mean maximum LSR composite score, the VAS score, and the Skindex-16 scores and trend in scores over the study visits will be reported as descriptive data. The composite LSR score will be compared to historical controls (Lebwohl et al, NEJM 2012). The efficacy analysis will be based on the intent-to-treat (ITT) population. In the ITT population, patients will be counted in the treatment group upon informed consent, regardless of receiving any dose of study medication. For efficacy analysis, all missing values due to patient early termination from the study will be imputed using last observation carried forward (LOCF) method, as appropriate. For each patient, the Baseline values will be defined as those values recorded at Day 1 prior to dosing or Screening as appropriate. Patients who are lost-to-follow-up after Baseline will be included to the ITT population carrying forward their Baseline values, i.e., these patients will be considered as treatment failures. Percent reduction in number of actinic keratoses and proportions of patients with partial and complete clearance of actinic keratoses will be presented descriptively and visualized as histograms. These scores will be compared to historical controls (Lebwohl et al, NEJM 2012).
Rationale for Number of Subjects	This is a pilot descriptive sample, not powered for analysis. The sample size of 20 patients is selected to achieve a reportable sample size in two subgroups of organ transplant recipients.

1 BACKGROUND

Ingenol mebutate is the active compound found in Euphorbia peplus sap, and has been approved for treatment of actinic keratoses in immunocompetent patients. Ingenol mebutate 0.015% is favored over other topical treatments for treatment of actinic keratoses on the face due to the brief treatment course, high clearance rate, and resolution without sequelae. There are no data on safety of this medication in immunosuppressed solid organ transplant recipients (OTR). OTR have a high incidence of AK and high risk of developing SCC, and require frequent field therapy.

2 STUDY RATIONALE

Actinic keratoses (AK) are precursors to cutaneous squamous cell carcinoma (SCC), and are treated to prevent progression to SCC. First-line therapy for AK include cryotherapy and curettage, which target clinically visible lesions but do not address the subclinical lesions in the field of ultraviolet radiation damage. Field therapy includes topical chemotherapy, immunotherapy, and photodynamic therapy. Ingenol mebutate is the active compound found in Euphorbia peplus sap, and has been approved for treatment of actinic keratoses in immunocompetent patients. Ingenol mebutate 0.015% is favored over other topical treatments for treatment of actinic keratoses on the face due to the brief treatment course, high clearance rate, and resolution without sequelae.

There are no data on safety of this medication in immunosuppressed solid organ transplant recipients (OTR). OTR have a high incidence of AK and high risk of developing SCC, and require frequent field therapy. In addition, OTR generally have a higher burden of AK and require treatment of a larger surface area than the 25 cm^2 area labeled for ingenol mebutate 0.015%. We plan to investigate the safety and efficacy of ingenol mebutate 0.015% in OTR, with a treatment area up to 100 cm^2.

The rationale for an increased dose and surface area for treatment in this study is that OTR typically have an extensive burden of AK, requiring treatment of larger areas such as those described here. The proposed treatment regimen better reflects the 'real world' need for treatment of a larger surface area while evaluating the safety and local site reactions associated with this treatment regimen.

2.1 Risk / Benefit Assessment

The risks of ingenol mebutate are primarily local site reactions of redness, flaking, crusting, swelling, blisters, or erosions. These typically begin at day 1 of treatment. The adverse reactions reported in >=2% of patients treated with ingenol mebutate were application site pain, pruritus, and infection; periorbital edema, and headache. We will monitor the patients at day 4 and counsel them on mitigating site reactions with gentle skin care, cold packs, pain control if needed. Patients will also be counseled to carefully avoid the eye and lip area. We expect the infection rate in OTR to be less than the reported

rate of 3% as the majority of OTR are on routine antibiotic prophylaxis; any infections will be recorded as adverse events and treated according to standard of care.

If a patient has a (1) local skin response score of 3 or greater in any individual category, and (2) associated symptoms unrelieved by supportive care such as ice packs and nonsteroidal anti-inflammatory drug (NSAID), then 1% topical hydrocortisone cream or ointment is allowed after Day 4 at the discretion of the investigator.

Ingenol mebutate has accepted benefits for AK which outweigh the risks. OTR have a high burden of AK and frequently require multiple rounds of field treatment to reduce this sign of ultraviolet radiation induced skin damage. Other treatments require long-term applications or in-office light; ingenol has the benefit of being a short course. Ingenol mebutate is approved for immunocompetent patients, but there is no safety data in OTR. Despite this, the medication has been frequently used off-label in OTR and is generally believed to be safe due to the absence of systemic absorption. One recent case reported brisk local site reaction without systemic adverse events.

It is difficult to obtain insurance coverage for ingenol mebutate in OTR without demonstrating failure of multiple other treatments for AK. Participants in this study will also benefit from access to ingenol mebutate.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective is to assess the safety of topical ingenol mebutate 0.015 % for treatment of the face in solid organ transplant recipients.

3.2 Secondary Objectives

The secondary objectives are (1) to evaluate the efficacy of ingenol mebutate for reduction of actinic keratoses on the face in organ transplant recipients; (2) to investigate the local skin response to ingenol mebutate in organ transplant recipients; (3) to investigate the effect of topical treatment with ingenol mebutate on patient reported outcomes of pain and quality of life in organ transplant recipients.

4 STUDY DESIGN

4.1 Study Overview

This is a single arm, open-label interventional study of ingenol mebutate 0.015% in solid organ transplant recipients. Twenty subjects are planned; 10 kidney transplant recipients and 10 lung transplant recipients. These populations have been selected as they represent the spectrum of solid organ transplantation: kidney transplant recipients are the largest transplant population, but have lower levels of immunosuppression and skin cancer risk. Lung transplant recipients have the highest burden of skin cancer and actinic keratoses.

Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be enrolled into the study.

The following treatment regimens will be used:

- Experimental treatment: Ingenol mebutate 0.015%, topical gel
- Placebo or Comparator: None

Total duration of subject participation will be 57 days. Total duration of the study is expected to be 8 months.

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be the safety endpoint of the incidence rate of patients who experience (1) any adverse event ascertained by patient report, physician evaluation, or laboratory value; (2) one or more serious adverse events as defined by CTCAEv4; (3) adverse events leading to study drug discontinuation.

The primary efficacy endpoint will be assessed from screening to Day 57 or study completion.

5.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are efficacy, local skin response, and patient reported outcomes. These endpoints will be assessed from screening to Day 57 or study completion.

Efficacy:

- Reduction in number of actinic keratoses: defined as the percent change in actinic keratosis count in the target treatment area on Day 57, as compared to the baseline lesion count.
- Partial clearance of lesions: defined as the proportion of patients with a reduction of 75% of more in the number of clinically visible AKs in the target treatment area at Day 57, compared to baseline.
- Complete clearance of lesions: defined as the proportion of patients with complete clearance of actinic keratoses in the target treatment area.

Local skin response:

Local skin response (LSR) as measured by visual assessment by the investigator using a 4 point scale on six responses for a maximum total of 24, according to the LSR scoring scale.

Patient Reported Outcomes:

- Pain as measured by the 0-10 VAS Numeric Pain Distress Scale (0 = no pain, 5 = moderate pain, 10 = unbearable pain).
- Patient quality of life as measured by Skindex-16 survey

5.3 Safety Evaluations

Evaluations include: adverse event reporting, clinical laboratory sampling, and physician evaluation. Adverse event reporting and physician evaluation will occur at every visit, if applicable. Clinical laboratory sampling will occur at Screening, Day 4, Day 29, Day 57, and early termination (if applicable). Physical Examination will occur at Screening, Day 1, Day 29, and early termination (if applicable).

6 SUBJECT SELECTION

6.1 Study Population

Subjects with a solid organ transplant at least one year from the date of transplantation, with a diagnosis of AK, who meet the inclusion and exclusion criteria, will be eligible for participation in this study.

6.2 Inclusion Criteria

1. Adults at least 18 years old.
2. Subject must be a solid organ transplant recipient at least one year from the date of transplantation.
3. Subjects must be in stable health as confirmed by medical history, per investigator judgement.
4. Subjects must be able to read, sign, and understand the informed consent.
5. Subjects have at least 4 and no more than 20 clinically typical (non-hyperkeratotic/hypertrophic), visible actinic keratoses in a treatment area of approximately 100cm^2 on the face. Treatment areas will include a single cheek (nasofacial sulcus to tragus, malar cheekbone to jawline and avoiding the lower eyelid and mouth); the forehead (hairline to eyebrows, extending laterally to the root of the helix).
6. Subject must be willing to forego any other treatments on the face, including cryotherapy, tanning bed use and excessive sun exposure while in the study.
7. Subject is willing and able to participate in the study and to comply with all study requirements including concomitant medication and other treatment restrictions.
8. If subject is a female of childbearing potential she must have a negative urine pregnancy test result prior to study treatment initiation and must agree to use an approved method of birth control while enrolled in the study.

6.3 Exclusion Criteria

1. Subjects with an unstable medical condition as deemed by the clinical investigator.

2. Subjects with a history of bone marrow or stem cell transplantation.
3. Subjects with non-melanoma skin cancer in the treatment area.
4. Subjects with hyperkeratotic or hypertrophic AKs.
5. Subjects with any dermatologic disease in the treatment area that may be exacerbated by the treatment proposed or that might impair the evaluation of AKs.
6. Women who are pregnant, lactating, or planning to become pregnant during the study period.
7. Subjects who have previously been treated with ingenol mebutate in study area within the past 8 weeks.
8. Subjects who have used any topical prescription medications for actinic keratosis on the study area within 8 weeks prior to study treatment initiation.
9. Subjects who have used any topical prescription medications for other reason on the study area within 4 weeks prior to study treatment initiation.
10. Subjects who are currently participating in another clinical study or have completed another clinical study with an investigational drug or device on the study area within 30 days prior to study treatment initiation.
11. Subjects with known hypersensitivity to Picato gel or any of the inactive ingredients: isopropyl alcohol, hydroxyethyl cellulose, citric acid monohydrate, sodium citrate, or benzyl alcohol.

7 CONCURRENT MEDICATIONS

All subjects should be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies.

7.1 Allowed Medications and Treatments

Standard therapy for OTR is allowed except for treatments noted in the exclusion criteria described above and as noted in the prohibited medications section below.

If a patient has a (1) local skin response score of 3 or greater in any individual category, and (2) associated symptoms unrelieved by supportive care such as ice packs and nonsteroidal anti-inflammatory drug (NSAID), then 1% topical hydrocortisone cream or ointment is allowed after Day 4 at the discretion of the investigator.

7.2 Prohibited Medications and Treatments

The following medications are prohibited during the study and administration will be considered a protocol violation: any topical prescription medication on the treatment area during the study.

8 STUDY TREATMENTS

8.1 Method of Assigning Subjects to Treatment Groups

All eligible subjects that have enrolled in the study will be supplied with open-label ingenol mebutate 0.015% gel. The investigator or study staff will record the kit number dispensed to each subject.

8.2 Blinding

Not applicable. This is an open-label study.

8.2.1 Formulation of Test Product

Not applicable.

8.2.2 Formulation of Control Product

Not applicable.

8.2.3 Packaging and Labeling

Ingenol mebutate 0.015% gel is supplied in cartons containing 4 single use tubes.

Each carton (kit) of ingenol mebutate 0.015% will be labeled with the required FDA warning statement, the protocol number, the name of the investigator, patient number, and directions for patient use and storage. Each tube will be labeled with the expiration date.

8.3 Supply of Study Drug at the Site

Leo Pharma will ship ingenol mebutate 0.015% gel to the investigational site. The initial ingenol mebutate 0.015% shipment will be shipped after site activation (i.e., all required regulatory documentation has been received by Leo Pharma and a contract has been executed). Subsequent ingenol mebutate 0.015% gel shipments will be made after site request for resupply.

8.3.1 Dosage/Dosage Regimen

Ingenol mebutate 0.015% gel will be applied topically once a day, for three continuous days. Ingenol mebutate 0.015% gel will be applied to the subject's forehead, left cheek, OR right cheek. Each kit contains 4 tubes of ingenol mebutate 0.015% gel, and subjects will apply 1 kit per day to the investigator-determined site.

Subjects should not apply ingenol mebutate 0.015% gel immediately after taking a shower, or less than 2 hours before bedtime. Subjects MUST AVOID eyes, lips, and mouth while applying ingenol mebutate 0.015% gel.

8.3.2 Dispensing

The investigator or other training study staff will dispense ingenol mebutate 0.015% gel to subjects. Subjects will also be given application instructions (Appendix III).

8.3.3 Administration Instructions

Ingenol mebutate 0.015% gel will be applied topically once a day, for three continuous days. Each kit contains 4 tubes of ingenol mebutate 0.015% gel, and subjects will apply 1 kit per day. Subjects should not apply ingenol mebutate 0.015% gel immediately after taking a shower, or less than 2 hours before bedtime. Subjects should use a new tube for each application.

Ingenol mebutate 0.015% gel will be applied to the subject's forehead, left cheek, OR right cheek. Subjects should visualize each application site (forehead, left cheek, or right cheek) as divided into 4 quadrants. Each kit contains 4 tubes; 1 tube is to be applied to each quadrant. The investigator will specify the application site and instructions during Screening.

A detailed subject hand-out containing the following application instructions will also be provided at Baseline:

1. Open a new tube of ingenol mebutate 0.015% gel.
2. Squeeze gel from the tube onto a fingertip.
3. Apply gel onto the center of Quadrant 1, spreading the gel evenly over the entire skin quadrant.
4. Check off Quadrant 1 on instruction sheet after gel is applied.
5. Open a 2nd tube of ingenol mebutate 0.015% gel.
6. Squeeze gel from the tube onto a fingertip.
7. Apply gel onto the center of Quadrant 2, spreading the gel evenly over the entire skin quadrant.
8. Check off Quadrant 2 on instruction sheet after gel is applied.
9. Open a 3rd tube of ingenol mebutate 0.015% gel.
10. Squeeze gel from the tube onto a fingertip.
11. Apply gel onto the center of Quadrant 3, spreading the gel evenly over the entire skin quadrant.
12. Check off Quadrant 3 on instruction sheet after gel is applied.
13. Open a 4th tube of ingenol mebutate 0.015% gel.
14. Squeeze gel from the tube onto a fingertip.
15. Apply gel onto the center of Quadrant 4, spreading the gel evenly over the entire skin quadrant.
16. Check off Quadrant 4 on instruction sheet after gel is applied.
17. Allow the treated area to dry for 15 minutes.
18. Wash hands right away after applying ingenol mebutate 0.015% gel.
19. After use, place tubes into the bag provided, and return to study site at the next visit.

Subjects are not responsible for medication re-supply, as they will be provided with enough tubes at Baseline. Subjects MUST AVOID eyes, lips, and mouth while applying ingenol mebutate 0.015% gel.

8.4 Supply of Study Drug at the Site

Kits of ingenol mebutate 0.015% gel will be supplied to each subject at Baseline/Day 1. All subjects will be receiving the ingenol mebutate 0.015% gel, as there is no placebo control in this protocol.

8.4.1 Storage

Ingenol mebutate 0.015% gel should be stored by the study site in a refrigerator, 2 to 8ºC (36 to 46ºF). If the temperature of ingenol mebutate 0.015% gel storage in the clinic exceeds or falls below this range, this should be reported to Leo Pharma and captured as a deviation. Subjects will be instructed to store ingenol mebutate 0.015% gel in original packaging, in a refrigerator according to the instructions outlined on the Drug Administration Instructions.

Ingenol mebutate 0.015% gel tubes must be kept away from children at all times.

8.5 Study Drug Accountability

An accurate and current accounting of the dispensing and return of ingenol mebutate 0.015% gel tubes for each subject will be maintained on an ongoing basis by a member of the study site staff. The number of ingenol mebutate 0.015% gel tubes dispensed and returned by the subject will be recorded on the Investigational Drug Accountability Record.

8.6 Measures of Treatment Compliance

Subjects will be asked to keep a patient diary (on the Subject Instructions for Use sheet) noting their application of ingenol mebutate 0.015% gel. Subjects will be asked to bring their patient diary to Visit 4, to assess compliance.

9 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject or subject's legal representative. If appropriate, assent must also be obtained prior to conducting any study-related activities.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at Screening and at Study Day 1, 4, 15, 29, 57, and at early termination (if applicable). Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded at Screening.

9.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded at Screening.

9.1.4 Physical Examination

A complete physical examination will be performed by either the investigator or a subinvestigator who is a physician at Screening and at Day 1, 29, and early termination (if applicable). New abnormal physical exam findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

9.1.5 Actinic Keratoses (AK) count

An AK count will be performed to count the lesions in the treatment area. AK count will be performed at Screening, Day 1, Day 29, Day 57, and early termination (if applicable).

9.1.6 Local Skin Response (LSR)

LSR is measured by visual assessment by the investigator using a 4 point scale on 6 responses for a maximum total of 24. The points are assessed using the LSR scale (Appendix III) : The 6 responses are: Erythema, Flaking/Scaling, Pustulation/Vesiculation, Crusting, Swelling, and Erosion/Ulceration. The mean maximum LSR composite score and trend in score over the study visits will be reported as descriptive data and compared to historical controls. LSR assessment will performed at every visit.

9.1.7 Visual Analog Scale (VAS) Pain Assessment

Patients will be asked to rate their pain on a VAS numeric pain distress scale where 0 = no pain, 5 = moderate pain, 10 = unbearable pain. The (VAS) Numeric Pain Distress scale will be administered on Day 1, Day 4, Day 15, Day 29, Day 57, and early termination (if applicable).

9.1.8 Skindex-16

Skindex-16 is used to measure quality of life in patients with skin diseases. The Skindex-16 will be administered on Day 1, Day 4, Day 15, Day 29, Day 57, and early termination (if applicable).

9.1.9 Photography

The investigator or trained study stuff will photograph the subject's treatment area on Day 1, Day 4, Day 15, Day 29, Day 57, and early termination (if applicable). Prior to photographing the treatment area, study staff will (1) photograph a subject identification card including: subject's initials, subject number, visit day and date; and (2) place a light-balanced sticker in the treatment area.

9.1.10 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study drug will be recorded on the case report form (CRF).

9.2 Clinical Laboratory Measurements

Clinical laboratory measurements will be performed at Screening, Day 4, Day 29, and early termination (if applicable). If a subject's medical record contains hematology and blood chemistry profile results within 14 days of Screening, the existing values may be used and Screening laboratory measurements are not required. If a subject's medical record contains hematology and blood chemistry profile results within 5 days of Day 29, the existing values may be used and additional laboratory measurements are not required.

9.2.1 Hematology

Blood will be obtained and sent to each site's clinical hematology lab for a complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, white blood cell differential, and platelet count).

9.2.2 Blood Chemistry Profile

Blood will be obtained and sent to the site's clinical chemistry lab for determination of serum sodium, potassium, chloride, bicarbonate, random glucose, BUN, creatinine, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT).

9.2.3 Pregnancy Test

A urine pregnancy test will be obtained from female subjects who are of childbearing age prior to their participation in the study, and at Day 1.

9.2.4 Urinalysis

Not applicable.

10 EVALUATIONS BY VISIT

The following is a list of evaluations scheduled to occur at each visit. Screening and Visit 2 visits can occur on the same day.

10.1 Visit 1 (Screening, Day -14 to 1)

1. Review the study with the subject and obtain written informed consent and HIPAA authorization.
2. Assign the subject a unique screening number.
3. Record demographics data.
4. Record medical history, including a history of actinic keratosis, diagnosis date, and prior actinic keratosis treatments.
5. Record concomitant medications.
6. Perform a complete physical examination.

7. Perform an actinic keratosis count.
8. Collect blood for clinical laboratory tests (chemistry and hematology).
9. Collect urine sample and perform urine pregnancy test (if applicable).
10. Continue to Visit 2 procedures (can occur on the same day), or schedule subject for Visit 2/ Day 1.

10.2 Visit 2 (Day 1)

1. Record any Adverse Events.
2. Concomitant medications review.
3. Perform a complete physical examination.
4. Perform an actinic keratosis count.
5. Perform a local skin response assessment.
6. Subject to perform a VAS pain assessment.
7. Subject to complete the Skindex-16.
8. Perform photography in treatment area.
9. Collect urine sample and perform urine pregnancy test (if applicable).
10. Dispense a kit of ingenol mebutate 0.015% gel; subject will complete the first application under the investigator's supervision in the clinic.
11. Dispense subject 2 additional kits for use on Day 2 and Day 3. Subject will also be provided with a detailed application instructions hand-out.
12. Schedule subject for Visit 3/ Day 4.

10.3 Visit 3 (Day 4)

1. Record any Adverse Events.
2. Record changes to concomitant medications.
3. Review subject diary for compliance.
4. Perform a local skin response assessment.
5. Subject to perform a VAS pain assessment.
6. Subject to complete the Skindex-16.
7. Perform photography in treatment area.
8. Collect blood for clinical laboratory tests (chemistry and hematology).
9. Schedule subject for Visit 4/ Day 15.

10.4 Visit 4 (Day 15)

1. Record any Adverse Events.
2. Record changes to concomitant medications.

3. Perform a local skin response assessment.
4. Subject to perform a VAS pain assessment.
5. Subject to complete the Skindex-16.
6. Perform photography in treatment area.
7. Schedule subject for Visit 5/ Day 29.

10.5 Visit 5 (Day 29)

1. Record any Adverse Events.
2. Record changes to concomitant medications.
3. Perform complete physical examination.
4. Perform an actinic keratosis count.
5. Perform a local skin response assessment.
6. Subject to perform a VAS pain assessment.
7. Subject to complete the Skindex-16.
8. Perform photography in treatment area.
9. Collect blood for clinical laboratory tests (chemistry and hematology).
10. Schedule subject for Visit 6/ Day 57.

10.6 Visit 6 (Day 57)

1. Record any Adverse Events.
2. Record changes to concomitant medications.
3. Perform an actinic keratosis count.
4. Perform a local skin response assessment.
5. Subject to perform a VAS pain assessment.
6. Subject to complete the Skindex-16.
7. Perform photography in treatment area.

10.7 Early Termination Visit (if required)

1. Record any Adverse Events.
2. Record changes to concomitant medications.
3. Perform complete physical examination.
4. Perform an actinic keratosis count.
5. Perform a local skin response assessment.
6. Subject to perform a VAS pain assessment.

7. Subject to complete the Skindex-16.
8. Perform photography in treatment area.
9. Collect blood for clinical laboratory tests (chemistry and hematology).
10. Collect urine sample and perform urine pregnancy test (if applicable).

11 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current U.S. package insert or of greater severity or frequency than expected based on the information in the U.S. package insert.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it

	occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

11.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

11.2.1 Serious Adverse Experience Reporting

The study site will document all SAEs that occur (whether or not related to study drug) per UCSF CHR Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

12 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 Early Discontinuation of Study Drug

A subject may be discontinued from study treatment at any time if the subject, or the investigator feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

Subject withdrawal of consent

Subject is not compliant with study procedures

Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment

Protocol violation requiring discontinuation of study treatment

Lost to follow-up

Positive pregnancy test (females)

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents Refer to Section 10 for early termination procedures.

12.3 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject or the investigator feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. As noted above, subjects who discontinue study treatment early (i.e., they withdraw prior to Visit 6) should have an early discontinuation visit. Refer to Section 10 for early termination procedures. Subjects who withdraw after

Visit 2 but prior to Visit 6 should be encouraged to come in for a final visit (and the procedures to be followed would include those for their next scheduled visit).

12.4 Replacement of Subjects

Subjects who withdraw from the study treatment will not be replaced.

Subjects who withdraw from the study will not be replaced.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject or investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

Failure to meet inclusion/exclusion criteria

Failure to apply ingenol mebutate 0.015% gel per protocol.

Use of a prohibited concomitant medication

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by the Investigator. A copy of the form will be filed in the site's regulatory binder.

14 DATA SAFETY MONITORING

Due to the scope of this study, there will be no formal Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC). This is an open-label, single-center study for an FDA-approved medication, and the investigator will have access to all study data.

15 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

15.1 Data Sets Analyzed

All eligible patients who are enrolled in the study and receive at least one dose of the study drug (the Safety Population) and who have had at least one post-baseline safety evaluation will be included in the safety analysis.

15.2 Demographic and Baseline Characteristics

The following demographic variables at screening will be summarized: race, gender, age, height and weight.

15.3 Analysis of Primary Endpoint

This is a small descriptive study, with the primary safety endpoint of the incidence rate of patients who experience:

1) Any adverse event (AE) ascertained by patient report, physician evaluation, or laboratory value, 2) One or more serious adverse events (SAE) as defined by CTCAEv4, and 3) Adverse events leading to study drug discontinuation.

Adverse events will be explored for trends or heterogeneity between the two transplant subgroups; thoracic and abdominal. If there is evidence for a difference between groups, the subgroups will be reported separately.

15.4 Analysis of Secondary Endpoints

Safety and tolerability data will be summarized by each secondary endpoint.

The mean maximum LSR composite score, the VAS score, and the Skindex-16 scores and trend in scores over the study visits will be reported as descriptive data. The composite LSR score will be compared to historical controls (Lebwohl et al, NEJM 2012).

The efficacy analysis will be based on the intent-to-treat (ITT) population. In the ITT population, patients will be counted in the treatment group upon informed consent, and receipt of at least one dose of study medication.

For efficacy analysis, all missing values due to patient early termination from the study will be imputed using last observation carried forward (LOCF) method, as appropriate. For each patient, the Baseline values will be defined as those values recorded at Day 1 prior to dosing or Screening as appropriate. Patients who are lost-to-follow-up after Baseline will be included to the ITT population carrying forward their Baseline values, i.e., these patients will be considered as treatment failures.

Percent reduction in number of actinic keratoses and proportions of patients with partial and complete clearance of actinic keratoses will be presented descriptively and visualized as histograms. These scores will be compared to historical controls (Lebwohl et al, NEJM 2012).

15.5 Interim Analysis

Not applicable.

15.6 Sample Size and Randomization

This is a pilot descriptive sample, not powered for analysis. The sample size of 20 patients is selected to achieve a reportable sample size in two subgroups of organ transplant recipients.

16 DATA COLLECTION, RETENTION AND MONITORING

16.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific paper Case Report Form (CRF) when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected, but will be identified by a site number, subject number and initials.

If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

16.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

16.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Query reports (Data Clarification Requests) pertaining to data omissions and discrepancies will be forwarded to the Investigators and study monitors for resolution. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

16.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

16.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to authorized representatives of Leo Pharma , IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which Leo Pharma is required to maintain study records and, therefore, should be contacted prior to removing study records for any reason.

16.6 Subject Confidentiality

In order to maintain subject confidentiality, only a site number, subject number and subject initials will identify all study subjects on CRFs and other documentation. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

17 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

17.1 Protocol Amendments

Any amendment to the protocol will be written by the investigator.. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

17.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating

procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, U.S. package insert, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigator to Leo Pharma prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

17.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to Leo Pharma for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to Leo Pharma and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to Leo Pharma for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

17.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the investigator, Leo Pharma, and participating institution. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

17.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol, except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
5. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with Leo Pharma.
6. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
7. Promptly report to the IRB and Leo Pharma all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
8. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
9. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

APPENDIX 1. SCHEDULE OF STUDY VISITS

Study Visit Activities	Screening (-14 to 1)	Day 1	Day 4	Day 15	Day 29	Day 57	Early Termination
Assess study eligibility	X						
Informed Consent/ HIPAA	X						
Medical History/ Demographics/ Previous therapies and Procedures	X						
Physical exam	X	X			X		X
CBC Auto Differential	X		X		X		X
CMP (Chem20)	X		X		X		X
AK Count	X	X			X	X	X
Local skin response Assessment		X	X	X	X	X	X
VAS Pain Assessment		X	X	X	X	X	X
Skindex-16		X	X	X	X	X	X
Photography		X	X	X	X	X	X
Con meds/procedures	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Ingenol mebutate dispensing		X					
Ingenol mebutate accountability			X				X
Urine pregnancy	X	X					X

APPENDIX II. SUBJECT INSTRUCTIONS FOR USE

Instructions for Use
Ingenol Mebutate gel, 0.015%

Be sure that you read, understand, and follow these Instructions for Use before you use ingenol mebutate gel, 0.015% for the first time.

Treatment Diary

Day 1: Did you apply all 4 tubes to the treatment area?

☐ Quadrant 1 ☐ Quadrant 2 ☐ Quadrant 3 ☐ Quadrant 4

☐ No, please specify reason: _____

Day 2: Did you apply all 4 tubes to the treatment area?

☐ Quadrant 1 ☐ Quadrant 2 ☐ Quadrant 3 ☐ Quadrant 4

☐ No, please specify reason: _____

Day 3: Did you apply all 4 tubes to the treatment area?

☐ Quadrant 1 ☐ Quadrant 2 ☐ Quadrant 3 ☐ Quadrant 4

☐ No, please specify reason: _____

IMPORTANT:

- **Always use ingenol mebutate gel exactly as your study doctor tells you**. Check with your study doctor if you are not sure.
- Only use ingenol mebutate gel to treat actinic keratosis on your assigned study treatment area.

- **Assigned study treatment area:** _____
- Apply ingenol mebutate gel to the skin area to be treated 1 time each day for 3 days in a row. Day 1 will be applied at your study visit, days 2 and 3 will be applied at home.
- Wash your hands well with soap and water after applying it. After applying ingenol mebutate gel, be careful to keep ingenol mebutate gel on treated area from coming into

contact with your eyes. Irritation may happen if you get ingenol mebutate gel in your eyes.

- Use a new kit (4 tubes) for each day of treatment. Avoid touching the treatment area or doing activities that cause a lot of sweating for 6 hours after applying ingenol mebutate gel. After 6 hours you may wash the treatment area with a mild soap and water.

DO NOT:

- apply right after taking a shower or less than 2 hours before bedtime.
- **get ingenol mebutate gel in, around, or near your eyes. Do not touch your eyes while you are applying ingenol mebutate gel (if you accidentally get ingenol mebutate gel in your eyes**, flush them with large amounts of water and get medical care as soon as possible).
- **get ingenol mebutate gel in, around, or near your lips and mouth.**

Applying Ingenol Mebutate gel

Step 1. Open a new kit (containing 4 tubes) each time you use ingenol mebutate gel.

Step 2. Select the first tube. Remove cap from tube just before use. (See Figure A).

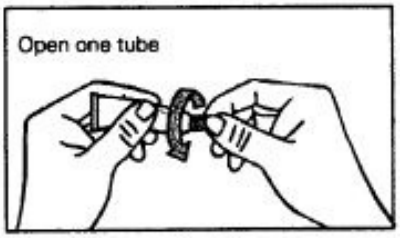


Figure A

Step 3. Squeeze the gel from the tube onto a fingertip. (See Figure B).

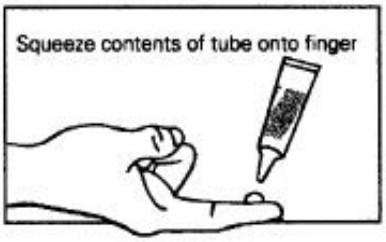


Figure B

Step 4. Visually divide your (treatment area – cheek or forehead) into 4 quadrants. (See Figure C).

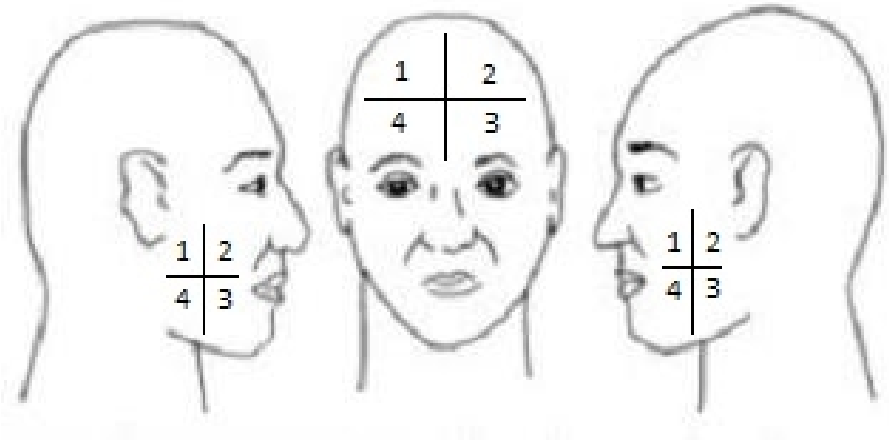


Figure C

Step 5. Apply gel onto the center of Quadrant 1, spreading the gel evenly over the entire skin quadrant.

Step 6: Select the second tube.

Step 7: Remove cap from the tube, and squeeze the gel from the tube onto a fingertip.

Step 8: Apply gel onto the center of Quadrant 2, spreading the gel evenly over the entire skin quadrant.

Step 9: Select the third tube.

Step 10: Remove cap from the tube, and squeeze the gel from the tube onto a fingertip.

Step 11: Apply gel onto the center of Quadrant 3, spreading the gel evenly over the entire skin quadrant.

Step 12: Select the fourth tube.

Step 13: Remove cap from the tube, and squeeze the gel from the tube onto a fingertip.

Step 14: Apply gel onto the center of Quadrant 4, spreading the gel evenly over the entire skin quadrant.

Step 15: DO NOT get in, around or near your eyes, lips, and mouth. Allow the gel to dry for 15 minutes.

Step 16: Wash your hands right away after applying the gel. (See Figure D).

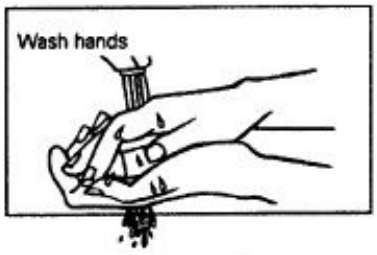


Figure D

Step 17: After use, place tubes into the bag provided, and return to study site at your next visit.

Repeat the above steps for each day of treatment.

How should I store the Ingenol Mebutate gel?

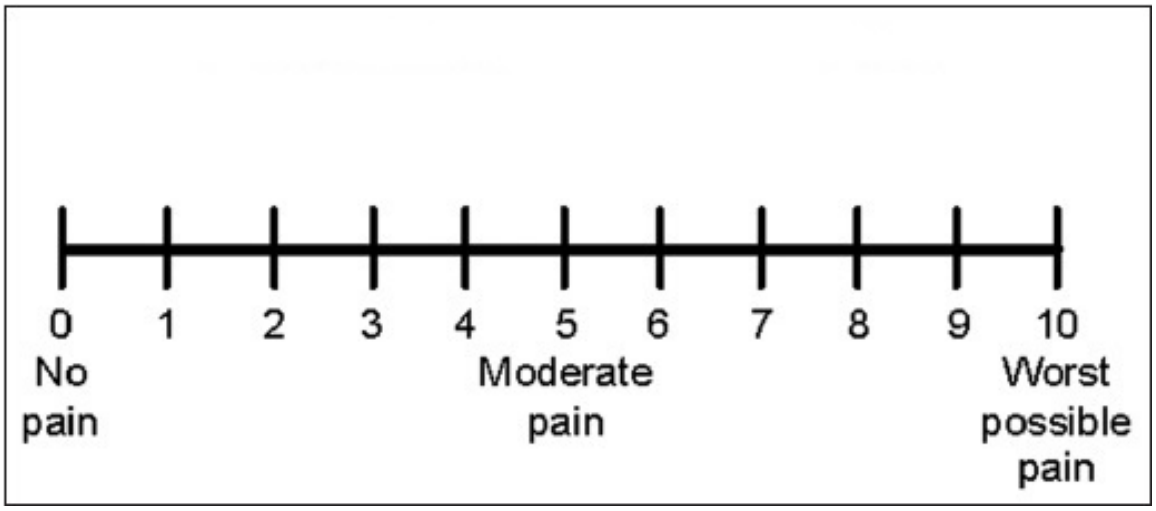
- Store the gel in a refrigerator at 36°F to 46°F (2°C to 8°C). Do not freeze.
- The gel has an expiration date (exp) marked on the end of the tube. Do not use the gel after this date.
- After use, place tubes into the bag provided, and return to study site at your next visit.

APPENDIX III. LOCAL SKIN RESPONSE ASSESSMENT

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, specific to lesions	Crusting <50%	Crusting >50%	Crusting extending outside treatment area
Swelling	Not present	Slight, lesion specific edema	Palpable edema extending beyond individual lesions	Confluent and/or visible edema	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

APPENDIX IV. VAS PAIN ASSESSMENT

How would you rate your pain over the last 24 HOURS?



APPENDIX V. SKINDEX-16

During the past week, how often have you been bothered by:		Never Bothered ↓			●			Always Bothered ↓
1.	Your skin condition **itching**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
2.	Your skin condition **burning** or **stinging**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
3.	Your skin condition **hurting**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
4.	Your skin condition **being irritated**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
5.	The **persistence / reoccurrence** of your skin condition .	☐0	☐1	☐2	☐3	☐4	☐5	☐6
6.	**Worry** about your skin condition (For example: that it will spread, get worse, scar, be unpredictable, etc)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
7.	The **appearance** of your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
8.	**Frustration** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
9.	**Embarrassment** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
10.	**Being annoyed** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
11.	**Feeling depressed** about your skin condition	☐0	☐1	☐2	☐3	☐4	☐5	☐6
12.	The effects of your skin condition on your **interactions with others** (For example: interactions with family, friends, close relationships, etc)	☐0	☐1	☐2	☐3	☐4	☐5	☐6
13.	The effects of your skin condition on your **desire to be with people**	☐0	☐1	☐2	☐3	☐4	☐5	☐6
14.	Your skin condition making it hard to **show affection** . .	☐0	☐1	☐2	☐3	☐4	☐5	☐6
15.	The effects of your skin condition on your **daily activities**.	☐0	☐1	☐2	☐3	☐4	☐5	☐6
16.	Your skin condition making it hard to **work or do what you enjoy**	☐0	☐1	☐2	☐3	☐4	☐5	☐6

Have you answered every item? Yes ☐ No ☐