A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study to Compare Perrigo New York, Inc.'s Ingenol Mebutate Topical Gel 0.05% to Leo Pharma Inc. Picato® Topical Gel 0.05% (Ingenol Mebutate Topical Gel 0.05%), and Both Active Treatments to a Vehicle Control in the Treatment of Actinic Keratosis on the Trunk and Extremities

NCT02459795

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Protocol No.: PRG-NY-15-002

[redacted]

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PROTOCOL SIGNATURE PAGE

PROTOCOL NUMBER: PRG-NY-15-002

PROTOCOL TITLE: A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study to Compare Perrigo New York, Inc.'s Ingenol Mebutate Topical Gel 0.05% to Leo Pharma Inc. Picato® Topical Gel 0.05% (Ingenol Mebutate Topical Gel 0.05%), and Both Active Treatments to a Vehicle Control in the Treatment of Actinic Keratosis on the Trunk and Extremities

Signatures of the representatives indicate this is the agreed upon final version of the protocol:

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[redacted]

STUDY SYNOPSIS

Title:	A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study to Compare Perrigo New York, Inc.'s Ingenol Mebutate Topical Gel 0.05% to Leo Pharma Inc. Picato® Topical Gel 0.05% (Ingenol Mebutate Topical Gel 0.05%), and Both Active Treatments to a Vehicle Control in the Treatment of Actinic Keratosis on the Trunk and Extremities
Study Period:	57 Days (8 weeks)
Study Medication:	1. Ingenol Mebutate Topical Gel 0.05%, Perrigo New York, Inc. 2. Picato® Topical Gel 0.05% (Ingenol Mebutate Topical Gel 0.05%), Leo Pharma Inc. 3. Vehicle of test product, Perrigo New York, Inc.
Study Objectives:	To compare the safety and efficacy profiles of Perrigo New York, Inc.'s Ingenol Mebutate Topical Gel 0.05% to Picato® Topical Gel 0.05% (Ingenol Mebutate Topical Gel 0.05%) and to demonstrate the superior efficacy of the two active formulations over that of the vehicle in the treatment of Actinic Keratosis.
Study Design:	Subjects in this multi-center, double-blind, randomized, vehicle-controlled, parallel-group study will be enrolled into the study only after written informed consent/assent has been obtained and after all entry criteria have been met. Male and female subjects at least 18 years of age, with Actinic Keratosis will be eligible for enrollment.
Study Population:	[redacted] healthy males and females, at least 18 years of age with 4 to 8 clinically typical, visible, discrete nonhyperkeratotic, nonhypertrophic Actinic Keratosis lesions within a 25cm^2 treatment area on the trunk/extremities, who meet the inclusion/exclusion criteria, will be enrolled to obtain [redacted] modified Intent-To-Treat (mITT) and [redacted] per-protocol (PP) subjects.
Dosing:	Subjects will be randomized [redacted] to either the test product, reference product or vehicle treatment group, respectively, and will apply the topical gel [redacted] once daily for two (2) consecutive days to the selected treatment area (one contiguous skin area of approximately 25cm^2 treatment area on the trunk/extremities) avoiding contact with the eyes, mouth and other body areas during and after gel application.
Study Visits:	Clinical Evaluations will be performed at: 1. Visit 1/Day 1 (Baseline) 2. Visit 2/Day 3 (+1 day) (Post-Treatment Interim) 3. Visit 3/Day 29 (±3 days) (Interim) 4. Visit 4/Day 57 (±2 days) (End of Study) Safety will be assessed by monitoring adverse events at each visit and during a Follow-Up Phone Call/Day 15 (±3 days).
Evaluations:	At the baseline visit, the principal investigator or sub-investigator will

	examine the subject to establish the clinical diagnosis of Actinic Keratosis (defined as the presence of 4 to 8 clinically typical, visible, discrete, nonhyperkeratotic, nonhypertrophic Actinic Keratosis lesions) contained within a contiguous 25cm^2 area on the trunk or extremities ("treatment area") The number of Actinic Keratosis lesions in the selected treatment area will be counted (and a total provided) and recorded at Visit 1/ Day 1 (Baseline) and at Visit 4/Day 57 (should any exist) on source documentation and eCRFs. Additionally, new lesions not present at the baseline visit will also be counted and recorded on source documentation and eCRFs at Visit 4 or an Unscheduled Visit if applicable. At Visit 4/Day 57, the principal investigator or sub-Investigator will visually inspect the treatment area for any lesions and will confirm complete clearance of Actinic Keratosis lesion in the eCRF if lesion count is equal to zero at Visit 4/Day 57. Complete clearance is defined as the absence of clinically visible Actinic Keratosis lesions identified at Visit 1 or new lesions since Visit 1. At the baseline visit (prior to initial dosing) and each subsequent visit, application site reactions of erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration will be recorded on the source document and eCRF.
Endpoints:	The **primary efficacy endpoint** will be the proportion of subjects with clinical success defined as complete clearance (absence) of all clinically visible Actinic Keratosis lesions identified at the baseline visit and no new Actinic Keratosis lesions in the treatment area at Visit 4/Day 57.
Safety:	The incidence of all adverse events reported during the study will be summarized by treatment group. Equivalence of the test and reference with regard to safety will be evaluated by comparing the nature, severity and frequency of their adverse event profiles. In addition, the test and reference treatments' frequency and distribution of application site reactions of erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration will be summarized and compared descriptively.

ABBREVIATIONS

AE	Adverse Event
AK	Actinic Keratosis
ANOVA	Analysis of Variance
ATC	Anatomic Therapeutic Chemical (classification of drugs)
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IGA	Investigator's Global Assessment
IRB	Institutional Review Board
ITT	Intent to treat population
IUD	Intra-Uterine Device
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent To Treat population
OTC	Over the counter
PI	Principal Investigator
PP	Per protocol population
Rx	Prescription
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SPF	Sun Protection Factor
Sub-I	Sub-Investigator

1. BACKGROUND

[redacted]

[redacted]

[redacted]Perrigo New York, Inc. has developed a generic formulation of Ingenol Mebutate Topical Gel 0.05%.

2 STUDY OBJECTIVES

The objectives of this study are to compare the safety and efficacy profiles of Perrigo New York, Inc.'s Ingenol Mebutate Topical Gel 0.05% to Picato® Topical Gel 0.05% (Ingenol Mebutate Topical Gel 0.05%) and to demonstrate the superior efficacy of the two active formulations over that of the vehicle in the treatment of Actinic Keratosis.

2.1 Endpoints

The **primary efficacy endpoint** will be the proportion of subjects with clinical response of success defined as complete clearance (absence) of all clinically visible Actinic Keratosis lesions identified at the baseline visit and no new Actinic Keratosis lesions in the selected treatment area at Visit 4/Day 57.

2.2 Safety

Safety of the test and reference products will be compared by evaluating the nature, severity and frequency of their adverse event profiles. All adverse events that occur during the study (from the moment a subject signs an informed consent/assent) will be recorded. Descriptions of reactions or complaints will include the approximate date of onset, the date the adverse event ended, the severity of the adverse event, and the outcome. Comparisons between the treatment groups will be made by tabulating the frequency of subjects with one or more adverse events (classified into MedDRA terms) during the study. Pearson's Chi-Square test or Fisher's Exact test, whichever is most appropriate, will be used to compare the proportion of subjects in the two active treatment groups with any adverse event. [redacted]

[redacted]

[redacted]

3 STUDY DESIGN

3.1 Type/Design of Study

Subjects in this multi-center, double-blind, randomized, vehicle-controlled, parallel-group study will be assigned [redacted] to test product, reference product, or vehicle, respectively. The study medication will be dispensed at Visit 1/Day 1 (Baseline) to subjects meeting all entry criteria. The assigned study medication will be applied topically by spreading evenly [redacted] to the designated treatment area (one contiguous skin area of approximately 25cm^2) on the trunk or extremities once daily for two (2) consecutive days, avoiding contact with the eyes, mouth and other body areas during and after gel application.

Subjects will be healthy males and females, at least 18 years of age, with 4 to 8 clinically typical, visible and discrete, nonhyperkeratotic, nonhypertrophic Actinic Keratosis lesions within a contiguous 25cm^2 treatment area on the trunk or extremities. Visits to the study site are scheduled at Day 1, Day 3, Day 29, and Day 57. There will also be a telephone call at Day 15 to follow up on previously reported adverse events and to ask subjects about new adverse events or concomitant medications taken.

At Visit 1/Day 1 (Baseline) written informed consent/assent will be obtained. The subject's demographic profile, medical history, and prior/concomitant medication use will be recorded. A urine pregnancy test will be performed for all women of childbearing potential. A brief physical examination (including heart, lung and abdomen evaluations) including vital signs and height/weight will be recorded during baseline.

The subject's history of and current state of Actinic Keratosis will be assessed (diagnosis) and their Fitzpatrick skin type will be classified at Visit 1/Day 1 (Baseline). In addition, an application site reaction assessment and Actinic Keratosis lesion count will be performed at Visit 1/ Day 1 (Baseline), Visit 4/Day 57, and if necessary at an Unscheduled Visit. Subjects who meet all of the inclusion and none of the exclusion criteria will be enrolled in the study, dispensed [redacted] study medication, and given a daily diary to complete. Instructions on proper treatment application and completion of the diaries will be provided to subjects and their Visit 2/ Day 3 will be scheduled. During the baseline visit, the study staff will demonstrate proper medication application to the subject [redacted]. The study staff should instruct the subject to apply their second dose of study medication at approximately the same time of day on Day 2.

Subjects will return to the study site at Visit 2/Day 3 (Post-Treatment). During this visit, the completed subject diary will be collected, a new diary will be given to the subject and the Principal Investigator or designated staff will assess the subject's application site reactions provide severity scores as appropriate. Subjects will return all study medication, and study medication accountability will be done. Information on concomitant medication use and protocol compliance will be collected and reviewed. Safety will be assessed by the monitoring

of the subject's adverse events (AEs). At this visit, the Follow-Up Telephone Call/Day15, Visit 3/Day 29 and Visit 4/Day 57 will be scheduled.

A Follow-Up Telephone Call will be made by study staff to the subject at Day 15 to review and assess subject compliance (diary completion), record AEs, update concomitant medication use, and to remind the subjects of the protocol requirements and next study visit schedule.

At Visit 3/Day 29 (Interim) and Visit 4/Day 57 (End of Study), subjects will be asked if they experienced any adverse events, taken any concomitant medications and generally complied with protocol requirements. The diary dispensed at Visit 2 will be collected and reviewed with the subject, and a new diary will be dispensed at Visit 3/Day 29. The diary dispensed at Visit 3 will be collected and reviewed at Visit 4/Day 57. Safety will be assessed by the monitoring of all adverse events (AEs) and clinically significant changes from Visit 1/Day 1 (Baseline) and an application site reaction assessment will be conducted at Visit 3/Day 29 and Visit 4/Day 57.

3.2 Study Population

Healthy male and female subjects, at least 18 years of age, with 4 to 8 clinically typical, visible, discrete Actinic Keratosis lesions within a contiguous 25cm^2 treatment area on either the trunk or extremities who meet all eligibility criteria will be enrolled in this multicenter study.

4. SELECTION AND WITHDRAWAL OF STUDY SUBJECTS

4.1 Inclusion Criteria

Subjects **must** meet all of the following criteria:

1. Subject must sign an Institutional Review Board (IRB) approved written informed consent/assent for this study. Subjects under the legal age of consent for their respective state must sign an IRB approved written informed consent/assent in addition to a parent or legally authorized representative.
2. Subjects must be healthy males or females, at least 18 years of age.
3. Subjects must be in general good health and free from any clinically significant disease, other than Actinic Keratosis that might interfere with the treatment assessment of Actinic Keratosis or study evaluations.
4. Subjects must have a clinical diagnosis of Actinic Keratosis, defined as having 4 to 8 clinically typical, visible and discrete, non-hyperkeratotic, non-hypertrophic, Actinic Keratosis lesions within a contiguous 25cm^2 treatment area on either the trunk or extremities (i.e. to be designated as the treatment area).
5. [redacted]

[redacted]

6. [redacted]

7. Subjects must be willing and able to understand and comply with the requirements of the study, apply the study medication as instructed, refrain from use of all other topical Actinic Keratosis medication during the 57 day (8 week) study period, return for the required study visits, comply with therapy prohibitions, and are able to complete the study.

8. [redacted].

4.2 Exclusion Criteria

Subjects may **not** be enrolled if any of the following criteria exist:

1. Subjects who are pregnant, nursing, or planning a pregnancy within the study period.
2. Subjects who are immunocompromised or HIV positive or who have any immune-system disorders including auto-immune diseases.
3. Subjects who have or had an active herpes infection [redacted] prior to the Visit1/Day 1 (Baseline) (i.e., including presence of herpes labialis).
4. Subjects who have any evidence of systemic cancer, squamous cell carcinoma, basal cell carcinoma, or any other cancer in the treatment area.
5. [redacted].
6. Presence of any confounding skin conditions in the treatment area that may be made worse by treatment with Ingenol Mebutate gel 0.05% [redacted]
7. [redacted]
11. Subjects who have had or are scheduling elective surgery within 1 month (30 days) before or after the study period.
12. Use [redacted] prior to Visit 1/Day 1 (Baseline) or planned use during the study of:

[redacted]

13. Subjects who are undergoing treatment or received treatment with the following of Visit 1/Day 1 (Baseline) and of the selected treatment area or planned anytime during the study.
14. Use of Ingenol Mebutate gel 0.05% of Visit 1/Day 1. Previous use of Ingenol Mebutate gel 0.05% is allowed if a different treatment area was successfully treated.)
15. History of unresponsiveness, hypersensitivity or allergy to ingenol mebutate therapy and/or any ingredient in the study medication.
16. Subjects who used PUVA (psoralen plus ultraviolet A therapy), or UVB therapy in the treatment area prior to Visit 1/Day 1 (Baseline) or are planning to receive treatment with PUVA therapy, UVB therapy, nonprescription UV light sources anywhere on the body during the study.
17. Subjects who have taken systemic chemotherapy medications prior to Visit 1/Day 1 (Baseline) or planned use anytime during the study.
18.
19.
20.
21. Start of dose of hormonal treatment (oral, implanted, topical contraceptives and androgens) or planned start or change throughout the study. Use of such therapy must remain constant during the study.
22. Subject consumes excessive alcohol, abuses drugs, or has a condition that could compromise the subject's ability to comply with study requirements.
23. Participation in any clinical study involving an investigational product, agent or device (that might influence the intended effects or mask the side effects of study medication) in the 30 days prior to Visit 1/Day 1 (Baseline) or throughout the study.
24. Previous enrollment in this study or current enrollment in this study at another participating site.

25. Employee (or employee's family member) of the research center or private practice, or subjects who have a conflict of interest.
26. Subjects who in the opinion of the investigator, are unlikely to be able to follow the restrictions of the protocol and complete the study.

4.3 Medications, Supplements, Other Substances and Procedures Prohibited Before Enrollment and During the Study

The medications prohibited prior to enrollment, and required washout period, are listed in Table 4.3.1 with the subject exclusion criteria.

Table 4.3.1 Medications, Supplements, and Other Substances Prohibited for Study Entry

Prohibited Medications, Supplements, and Other Treatment	Exclusion Criteria Number	Washout Period Prior to Randomization
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]

Subjects must not take the treatments listed in TABLE 4.3.2 during study participation.

Table 4.3.2 Medications (Prescription and Over-the-Counter), Supplements, and Other Treatments Prohibited During the Study

Prohibited Medications, Over-The-counter (OTC) medications, and Treatments	Location	Exclusion Period Restrictions
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

4.4 Precautions

The following precautions are to be taken during this study:

1. Subjects should wash their hands with mild soap and water before and after applying study medication and should take care not to transfer the study medication to other body areas, including the eye. [redacted]
2. Subjects should allow the treated area to dry [redacted].
3. [redacted]
4. [redacted]
   - [redacted].
5. The study medication should not be applied to unhealed skin, open skin wounds, cuts, abrasions, infections, exfoliative dermatitis, eczematous or sunburned skin.
6. [redacted].
7. [redacted]
8. Subjects should avoid contact of the study medication with the eyes and with skin outside the selected treatment area defined by the study physician. In case of accidental exposure, the eyes should be rinsed with plenty of water and get medical care as soon as possible.
9. [redacted].
10. [redacted].
11. Subjects should limit sun exposure, including sunlamps (non-prescription UV light sources), and avoid tanning beds/booths/parlors.
12. Subjects should consult the investigator with any questions regarding concomitant medications.
13. [redacted]
14. [redacted].

5. PROCEDURES

5.1 Subject Screening and Enrollment

The study personnel will review the IRB approved informed consent form and assent form, if applicable, with each subject and give the subject an opportunity to have all questions answered before proceeding. The consent/assent form must be signed by each subject and witnessed before the subject is enrolled into the study. A copy of the signed consent/assent will be given to every subject and the original will be maintained with the subject's records. Subjects under the legal age of consent must sign an IRB approved written informed consent/assent in addition to a parent or legally authorized representative.

Subjects that require a wash-out [redacted] from their initial informed consent/assent signing must be re-consented before any further study procedures can begin.

5.2 Assignment of Subject Number

Once the subject has consented, met eligibility criteria and is considered enrolled in the study, study staff will assign a subject number to the subject. The subject number will correspond to a computer-generated randomization schedule assigning the number to one of the three study treatment groups. The subject numbers will be assigned sequentially in the order in which subjects are enrolled at each center.

5.3 Demographics/Medical History

A demographic profile and complete medical history will be recorded prior to starting study medication. The medical history will include a complete review of all current diseases and their respective treatments.

5.4 Concomitant Medications

Concurrent medications and any medications taken [redacted] prior to signing informed consent/assent will be recorded as prior/concomitant medications (using their generic name, if known) with the corresponding indication. The medications to be recorded will include prescription (Rx) and over-the-counter (OTC) medications and dietary supplements. All medications taken on either a regular or "prn" basis, including vitamins, aspirin and acetaminophen, should be recorded on this page prior to commencing the use of the study medication.

5.5 Physical Examination

The investigator, sub-investigator or appropriately delegated and qualified designee will perform a brief physical examination [redacted] prior to the subject starting study medication. [redacted]

5.6 Urine Pregnancy Test

Females of childbearing potential (excluding women who are surgically sterilized or post-menopausal for at least 2 years), in addition to having a negative urine pregnancy test, must be willing to use an acceptable form of birth control during the study. [redacted]

[redacted].

5.7 Dermatological Assessment (Diagnosis)

The investigator or sub-investigator will examine the subject to establish the clinical diagnosis of Actinic Keratosis defined as the presence of 4 to 8 clinically typical, visible, discrete, nonhyperkeratotic, nonhypertrophic Actinic Keratosis lesions, contained within a contiguous 25cm^2 area on the trunk or extremities.

5.8 Fitzpatrick Classification Scale

The Fitzpatrick skin scale classifies a person's complexion and their tolerance of sunlight. It is commonly used by many practitioners to determine how someone will respond or react to dermatological treatments, and how likely they are to get skin cancer.

At Visit/Day 1 (Baseline), the Principal Investigator (PI) or Sub-Investigator (Sub-I) will examine the subject's skin to determine the skin type by using the Fitzpatrick scale below and will indicate the skin type on the source document and eCRF.

Skin Type	Skin Color	Characteristics
I	White; [redacted]	[redacted]
II	White; [redacted]	[redacted]
III	Cream [redacted]	[redacted]
IV	Brown; [redacted]	[redacted]
V	Dark Brown; [redacted]	[redacted]
VI	Black	[redacted]

5.9 Clinical Actinic Keratosis Lesion Counting & Assessment

Each subject's initial condition and course of Actinic Keratosis will be assessed by counting the number of lesions located within the designated treatment area on the trunk or extremities. At Visit 1/Day 1 (Baseline), the PI or qualified study staff should select an area of 25cm^2 (may be of

any shape, [redacted] to be treated with the study medication gel as the designated treatment area on the trunk or extremities. This selected treatment area should have 4 to 8 visible clinically discrete Actinic Keratosis lesions. Additionally, the PI or designated staff will document the location of each lesion, the designated treatment area, and the size (in cm^2) of the treatment area at Visit 1/Day 1 (Baseline) will be marked in the subject's source documentation [redacted]

To the greatest extent possible, the same investigator who made Visit 1/Day 1 (Baseline) assessments will perform evaluations at Visit 4/Day 57. At Visit 1/Day 1 (Baseline), Visit 4/ Day 57, and Unscheduled Visit, if applicable, the number of Actinic Keratosis lesions within the treatment area will be counted and recorded in the source documentation and eCRFs. Additionally, at Visit 4/Day 57, and Unscheduled Visit, if applicable, new Actinic Keratosis lesions as compared to Visit 1/Day 1 (Baseline) will be counted and recorded in the source documentation and eCRFs. [redacted]

Complete clearance (Actinic Keratosis lesion count in the selected treatment area) at Visit 4/Day 57 will be assessed. Complete clearance is defined as absence of clinically visible Actinic Keratosis lesions (including presence of new lesions) in the selected treatment area at Visit 4/Day 57. The investigator or sub-investigator will confirm the number of lesions in the selected treatment area (including new lesions) and clinical response success if lesion count is equal to zero at Visit 4/Day 57.

[redacted].

Lesion counting must be conducted by qualified investigators or designated staff listed on the Form FDA 1572 who have been delegated these tasks by the PI. [redacted]

[redacted]

5.10 Application Site Reaction Assessment

To the greatest extent possible, the same investigator who made Visit 1/Day 1 (Baseline) assessments will assess the application site reactions, grade them according to a 5-point scale and a designated staff will record them in the source document and eCRFs at each subsequent visit. This assessment must be conducted by qualified individuals listed on the Form FDA 1572 who have been delegated this task by the PI. [redacted]

At baseline (prior to initial dosing) and each subsequent visit, application site reactions of erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration are to be recorded in the source document and eCRFs.

Application site reactions (erythema, flaking/scaling, crusting, swelling, vesiculation/ pustulation, and erosion/ulceration) are not to be recorded as adverse events unless they result in either:

- The temporary discontinuation of the study medication.
- The discontinuation of the subject from the study.
- The use of a new concomitant medication in order to treat this event.

Any other application site reaction not listed above (such as pain, pruritus and infection) should be recorded as adverse events in the source document and eCRFs.

The following scale will be used for the Application Site Reaction Assessment:

Site Reaction	Description
Erythema	[redacted]
Flaking/scaling	[redacted]
Crusting	[redacted]
Swelling	[redacted]
Erosion/ulceration	[redacted]
Vesiculation/Pustulation	[redacted]

Site Reaction	Grading Criteria				
	0				

5.11 Study Medication Use, Patient Instructions and Diary

Each subject's drug kit box contains [redacted] 0.47 gram tubes. At the baseline visit, the subject will apply the contents of one of the tubes at the site under study staff supervision and that tube will be placed back in the drug kit box. The second tube will be given to the subject to take home with them for their second application along with a diary. Their Day 2 application should be applied at approximately the same time as the Day 1 application. Additionally, the study staff must ensure subjects understand the instructions for applying the study medication and refrigerate the study medication at home all times.

Subjects must not use the study medication for more than 2 consecutive days.

At Visit 2/Day 3 the study medication will be collected to visually assess compliance. Compliance will also be determined from the diary, in which the subject will be instructed to record if they applied their second dose of medication or not. After the compliance evaluation, empty, filled and partially used tubes will be collected and kept by the site.

Subjects will wash the designated treatment area with a mild soap by using only the hands and pat dry with a soft towel [redacted] before applying the study medication. The study medication from one tube will be applied to the selected treatment area, one contiguous skin area of 25 cm^2 area. After spreading the study medication [redacted] over the treatment area, [redacted]. Subjects should wash their

[redacted]

hands with mild soap and water immediately after applying the study medication gel and take care not to transfer the applied study medication gel during and after application to other areas, including the eyes. If the treatment area is on the back of the hands (not palm), the subject should wash only the fingertip which was used for applying the gel. [redacted]

Subjects will be instructed to not use any other topical treatments or products other than the study medication gel or approved moisturizer in the selected treatment area during the two-day treatment period.

Diaries will be dispensed for each enrolled subject. The subjects will be instructed to complete their diary after applying the subsequent dose of study medication. At Visit 2/Day 3, the study personnel will review the diary to determine subject dosing compliance, confirm use of any prohibited medications, assess AEs and a new diary will be dispensed to all subjects. At each subsequent visit, study personnel will review the diary card to determine if the subject used any prohibited medications, assess AEs and dispense a new diary (a diary will not be dispensed at Visit 4/ Day 57). In addition, each study subject will be reminded to return the previously dispensed tube (regardless of content) at Visit 2/Day 3 and the completed diary at the next visit. Study personnel will schedule the subject's next visit prior to the subject's departure.

5.12 Visit Specific Procedures

The following sections outline the procedures required at each visit.

5.12.1 Visit 1/Day 1 (Baseline)

Prospective subjects will visit the study center and will be examined by the principal investigator or delegated staff. The following procedures will be performed at the baseline visit:

- [redacted]

[redacted]

- [redacted]
- [redacted]

5.12.2 Visit 2/Day 3 (±1 day)

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

5.12.3 Follow-up Phone Call /Day 15 (± 3 days)

- [redacted]
- [redacted]
- [redacted]
- [redacted]

5.12.4 Visit 3/Day 29 (± 3 days)

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

5.12.5 Visit 4/Day 57 (± 2days) End of Study /Early Termination Visit

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

5.12.6 Unscheduled

An unscheduled visit is allowed at any time if in the investigator's opinion it is warranted. If the investigator assesses the subject's condition and determines that the subject's condition has worsened to the degree that it is unsafe for the subject to continue in the study, the subject may be discontinued from the study as a treatment failure, and a standard of care treatment

may be advised at the investigator's discretion. The following procedures may be performed at the Unscheduled/Early Termination Visit.

5.13 Summary of Assessments

The schedule of visits and procedures to be conducted at each visit are summarized in the Schedule of Study Procedures.

[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						

[redacted]

5.14 Screen Failures

A screen failure is a subject who received information about the study, including signing an informed consent/assent, and possibly performing some study related procedures but was not enrolled, dispensed and applied study medication. Screen failures information will not be entered in the database and will not be included in any data analyses.

5.15 Protocol Deviations/Violations

This study will be conducted as described in this protocol except for an emergency situation in which the protection, safety, and well-being of the subject requires immediate intervention, based on the judgment of the investigator or a responsible, appropriately trained and credentialed professional(s) designated by the investigator. In the event of a significant deviation from the protocol due to an emergency, accident or mistake, the investigator or designee must contact Perrigo/[redacted] contacts in Section 14 (Appendix A) at the earliest possible time.

[redacted]

[redacted]

Subjects with any variation from the protocol that would not interfere with the effect of or the accurate assessment of the assigned study treatment, may be included in both PP and mITT analyses.

5.16 Subject/Treatment Compliance

Subjects will apply the medication to the designated treatment area at approximately the same time once daily for 2 consecutive days. [redacted]. Compliance will be determined from the diary card, in which the subject will be instructed to record all applications made or missed. The first and last dates of treatment should be recorded in the source document and eCRFs. The total number of applied and missed applications should also be recorded. Applications will be considered missed if the study medication was not applied on Day 1 or Day 2 of the treatment period. Subjects will be considered compliant if they apply both daily doses on study Days 1-2. Subjects will be considered non-compliant if one (1) or more doses are missed. The study medication tube will be collected by the study site at appropriate visits or early termination.

5.17 Discontinuation/Withdrawal of Study Subjects

Subjects will be removed from the study for any of the following reasons:

- The subject withdraws his or her consent/assent for any reason.
- The subject's condition has worsened to the degree that the investigator feels it is unsafe for the subject to continue in the study.
- Subject did not meet entry criteria.
- The subject's medication code is unblinded.
- An adverse event (AE) including inter-current illness, occurs for which the subject desires to discontinue treatment or the investigator determines that it is in the subject's best interest to be discontinued.
- The subject is lost to follow-up. The investigator will document efforts to attempt to reach the subject twice by telephone and will send a certified follow-up letter before considering that subject lost to follow-up. All attempts must be thoroughly recorded.
- The subject becomes pregnant during the course of the trial.
- Lack of efficacy (treatment failure) (subject's own withdrawal or investigator removal from study)
- Investigator Discretion

- Significant protocol violation or non-compliance with the study protocol that could interfere with the effect or accurate assessment of the assigned study treatment.

A subject will not be allowed to re-enroll in the study after they have been discontinued.

The reasons for a subject being discontinued will be documented in the source document, eCRFs and the enrollment log.

If a subject is discontinued from the study for any reason, the Visit 4/ Day 57 End of Study Visit/Early Termination Visit procedures should be completed and any outstanding data and study medication should be collected. Data, in addition to the primary reason for discontinuation and the date of removal, will be recorded in the source document and the End of Study eCRF.

[redacted]

[redacted]

6. MATERIALS AND SUPPLIES

6.1 Study Medication

The study medication supplied by Perrigo Israel Pharmaceuticals, Ltd. will consist of:

Test Product: Ingenol Mebutate Topical Gel 0.05%,
Perrigo New York, Inc. [redacted]

Reference Product: Picato® Topical Gel 0.05% (Ingenol Mebutate Topical Gel 0.05%), manufactured by Leo Pharma Inc.

Vehicle: Vehicle of test product
Perrigo New York, Inc [redacted]

6.2 Medication Management

6.2.1 Labeling, Packaging and Distribution

The study medication assigned to each subject number will be determined by a computer-generated randomization schedule. Study medication is labeled and packaged, according to the random code, so that neither the subject nor the investigator can identify the treatment.

All study medications will be supplied to the subjects in 0.47 gram tubes. Each subject's treatment unit will consist of one kit box containing [redacted] tubes of study medication. The outer label of the box will not contain any information that could identify the treatment group to which the subject was assigned. The kit box labels will include the name of Perrigo Israel Pharmaceuticals, Ltd., study protocol number, subject number and initials, directions for use and storage, and warnings: "For Topical Use Only." "Not for Ophthalmic, Oral, or Intravaginal Use" and "Caution: New Drug - Limited by Federal (or United States) law to investigational use."

The tear-off portion of each label contains the identity of the medication in the tube. The investigator will not remove the occluding layer of the label unless absolutely necessary to provide medical treatment to a subject in an emergency and preferably with prior authorization from Perrigo or designee whenever possible. If the occluded portion of the label is removed, each involved subject(s) will be discontinued from the study and the reason will be noted on the source document and eCRFs.

The tear-off portion has an adhesive backing to affix to the study medication dispensing log that will be maintained at the investigator site. The individual boxes are numbered sequentially and should be dispensed in order.

6.2.2 Retention Samples

Each investigational site where study medication is dispensed to at least one subject will be required to randomly select [redacted] retain samples. The retention samples must be stored under labeled conditions [in a refrigerator at 36°-46°F (2-8°C); excursions permitted to 32°-59°F (0°-15°C)] even after the study has concluded. The investigator will maintain one randomly selected block of study medication for each shipment of study medication received. As per the Code of Federal Regulations Part 21, Section 320.38(e), "Each reserve sample shall be stored under conditions consistent with product labeling and in an area segregated from the area where testing is conducted and with access limited to authorized personnel. Each reserve sample shall be retained for a period of at least 5 years following the date on which the application or supplemental application is approved, or, if such application or supplemental application is not approved, at least 5 years following the date of completion of the bioavailability study in which the sample from which the reserve sample was obtained was used." The investigator will store the retain sample study medication until such time as notification is received from Perrigo that the samples are no longer required.

6.2.3 Storage and Test Article Accountability

Study articles used to conduct this study will be maintained under adequate security by the investigator or designee. Study test articles will be stored in a refrigerator at a temperature of 36°- 46°F (2-8°C); excursions permitted between 32°- 59°F (0°-15°C) in a secured area. Subjects must be instructed to keep the study medication refrigerated at home. Each investigator site will ensure that the temperature of study drug is monitored and recorded throughout the study. The medication should not be frozen, kept away from heat and kept tightly closed. The

investigator will not supply study test articles to any person not enrolled in this study, or to any physician or scientist except those named as sub-investigators.

The clinic personnel at each investigator site will keep a running inventory of study test articles dispensed that will include subject numbers assigned and the date each is dispensed and used. A study medication accountability form will be provided to the investigator to document all medications received, dispensed by and used by each subject. At the conclusion of the study all unused, partially used, and empty containers must be inventoried by the monitor and returned to Perrigo or designee, for destruction, except for the retention samples that must remain at the Investigator site.

6.2.4 Randomization

Randomization will be performed according to a computer generated randomization scheme where the treatment group designation has been assigned to the subject number. The treatment designation will remain blinded until the final database is closed. An independent third party will hold the randomization code throughout the study. The randomization scheme will be a block randomization, with each [redacted] subjects assigned to Test: Reference: Placebo [redacted].

6.2.5 Procedure for Breaking the Blind

The investigator, staff at the study site, study monitors, and data analysis/management personnel are blinded to the subject assignment. In the event of an emergency, the specific subject treatment may be identified by removing the overlay of the blinded label for each subject at each investigator site, which is attached to the study medication log. However, every effort should be made to maintain the blind. **The investigator must not scratch off the occluding layer of the label unless absolutely necessary to provide medical treatment to a subject in an emergency situation. When possible, the investigator site should inform Perrigo or designee**. The reason for breaking the blind must be clearly documented in the source documentation and eCRFs and the subject discontinued from the study.

7. ADVERSE REACTIONS

The potential adverse reactions of generic Ingenol Mebubate Topical Gel 0.05% are anticipated to be similar to those observed in Picato® Topical Gel (Ingenol Mebutate Topical Gel 0.05%). The most common adverse reactions related to treatment with Picato® Topical Gel include local skin reactions, application site pain, application site pruritus, application site irritation, and nasopharyngitis . Eye disorders, including severe eye pain, eyelid edema, eyelid ptosis, and periorbital edema can occur after exposure. Severe local skin reactions such as vesiculation/pustulation, erosion/ulceration can occur.

7.1 Departure from the Protocol for Individual Subjects

When an emergency occurs requiring a departure from the protocol for a subject, departure will be only for that subject. In such circumstances, the investigator or other physician in attendance will contact the Medical Monitor or Perrigo by telephone and follow up with a written description within one day. The overseeing IRB should also be notified.

7.2 Definitions

An adverse event (AE) is defined as any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

A serious adverse event (SAE) is an adverse event that results in any of the following outcomes:

- death
- life-threatening event (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death)
- requires in-subject hospitalization or prolongs hospitalization
- a persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- congenital anomaly/birth defect
- Other adverse events that may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject or may require medical or surgical intervention to prevent one of the previously listed outcomes.

Immediately Reportable Adverse Events (IRAE): Any serious AE or any AE that necessitates discontinuation of study medication, including pregnancy.

Unexpected Adverse Event: An unexpected event is any adverse drug experience, the specificity or severity of which is not consistent with the current approved product labeling (package insert, Appendix D) for the study medication, the Investigator's Brochure, or as described in the clinical protocol and consent materials.

Intensity of Adverse Events: The maximum intensity of an AE during a day should be recorded on the eCRF. If the intensity of an AE changes over a number of days, then separate entries should be made having distinct onset dates for the changes in severity.

Mild - AEs are usually transient, requiring no special treatment, and do not interfere with subject's daily activities.

Moderate - AEs typically introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.

Severe - AEs interrupt a subject's usual daily activity and traditionally require systemic drug therapy or other treatment.

Causal Relationship to Study Medication: The following criteria should be used in assessing the apparent causal relationship of an AE to study medication.

Definitely - The AE:
- follows a reasonable temporal sequence from study medication administration
- abates upon discontinuation of the study medication (dechallenge)
- is confirmed by reappearance of the reaction on repeat exposure

Probably - The AE:
- follows a reasonable temporal sequence from study medication administration
- abates upon discontinuation of the study medication (dechallenge)
- cannot be reasonably explained by the known characteristics of the subject's state

Possible - The AE:
- follows a reasonable temporal sequence from study medication administration
- but that could readily be produced by a number of other factors

Unlikely - The AE:
- follows a reasonable temporal sequence from study medication administration
- could have been produced by either the subject's clinical state or by study medication administration

Not related - The AE:
- does not have a reasonable temporal association with the administration of study medication
- has some other obvious explanation for the event

7.3 Eliciting and Reporting of Adverse Events

The investigator will periodically assess subjects for the occurrence of adverse events. In order to avoid bias in eliciting adverse events, the subject or parent/legally authorized representative should be asked a non-specific question (e.g., "How have you been feeling since your last visit?") to assess whether any AE has been experienced since the last visit. All adverse events (as defined in Section 7.2), either observed by the Investigator or one of his/her medical collaborators, or reported by the participant spontaneously, or in response to direct questioning, will be reported and documented in the source and the study reporting forms. When reporting an adverse event, the Investigator must assign a severity grade to each event and declare an opinion on the relatedness of the event to the study medication or procedure. Serious or unexpected adverse events must be reported to Perrigo and [redacted] ***within 24 hours*** of when the Investigator first learns of the occurrence of the event.

Adverse events will be documented in source and recorded in a timely manner on eCRFs. Adverse events (i.e., worsening of Actinic Keratosis*) that are identified at the last assessment visit (or the early termination visit), must be recorded on the AE eCRF with the status of the AE noted.

** Worsening of the subject's Actinic Keratosis may be expected from application of the study medication. Therefore, this will not be considered an AE unless one or more of the following occurs: 1) alternative treatment required; 2) subject is discontinued by the Principal Investigator for worsening of AK.*

Adverse event reporting begins from the signing of informed consent/assent. Adverse events should be followed until resolved or 30 days after the final study treatment. In any case, serious adverse events that are not resolved or considered to be chronic within 30 days of the final study treatment must be followed by the investigator until they become resolved or are considered to be chronic (stabilized for at least 30 days). All events that are ongoing at this time will be recorded as ongoing on the eCRF.

7.3.1 Expedited Reporting Responsibilities of the Study Center

For any serious or unexpected adverse event, Perrigo must be notified ***within 24 hours*** of when the Investigator first learns of the occurrence of the event. Expedited reporting requirements for serious adverse events are described below. Adequate information must be collected with supporting documentation to complete a standard report for submission to Perrigo. The adverse event term on the AE eCRF and the SAE report should agree exactly. Special attention should be given to recording hospitalizations and concomitant medications.

Subjects with unresolved adverse event(s) or serious adverse event(s) should be followed by the investigator until the events are resolved, events determined to be chronic or the subject is lost to follow-up. Resolution means the subject has returned to the baseline state of health, or the investigator does not expect any further improvement or worsening of the adverse event. The investigator should continue to report any significant follow-up information to Perrigo up to the point that the event has resolved. Any serious adverse event reported by the subject to the investigator that occurs within 30 days after the last assessment, and are determined by the investigator to be reasonably associated with the use of the study medication, should be reported to Perrigo within 24 hours of when the Investigator first learns of the occurrence of the event.

When reporting a serious adverse event (SAE) the Investigator (or the designated staff) will promptly report any serious adverse event or pregnancy by telephone to [redacted] immediately after the investigator becomes aware of the event. An SAE form should be completed and sent by fax, email, or overnight courier to [redacted] within 24 hours of knowledge of the event by the site. In many cases, only preliminary information will be available. Appropriate follow up information should be sought (hospital discharge summaries, operative reports etc.) and a follow up SAE report form submitted. A designation of causality from the study medication should always be included with a follow up report. Assess and report the causality of the event.

7.3.2 Submitting an Expedited Safety Report to the IRB

Once [redacted] receives all supporting documentation for the reported event, the Medical Monitor, in conjunction with Perrigo, will determine if the safety report is eligible for expedited review. [redacted] will log the initial event and will notify Perrigo that an event has been reported within 1 business day after initial receipt. [redacted] will complete the review of the event, enter information into their safety database and generate the report. This form, as well as other supporting documentation, will be forwarded to [redacted] Medical Monitor for review. [redacted] will finalize the report and distribute it to Perrigo within 2 days after initial receipt. When expedited safety reporting to regulatory authorities is indeed required, the Investigator should review and update any newly available materials at once. Follow-up queries may be issued to the study center to further clarify the event.

Each expedited safety report will routinely include a brief cover memorandum, the completed report, and any additional pertinent information recommended by [redacted], Perrigo, or study Medical Monitor. Once the report is assembled, the Principal Investigator must submit the expedited safety report to the IRB within the required reporting timeframe. Follow-up reports should be submitted when requested or when pertinent information becomes available.

When a Principal Investigator receives an expedited safety report from [redacted] or Perrigo detailing adverse events occurring at other study centers under this protocol, it must be promptly submitted to the study center's IRB. The Principal Investigator must retain a copy of such reports as submitted to their IRB in the site's study Regulatory Binder.

7.4 SAE & AEs Requiring Discontinuation of Study Drug, including Pregnancies

ANY SAE, WHICH OCCURS AFTER A SUBJECT HAS ENTERED THE STUDY, WHETHER OR NOT RELATED TO STUDY MEDICATION, MUST BE REPORTED TO [redacted] AND PERRIGO IMMEDIATELY (WITHIN 24 HOURS) VIA TELEPHONE OR FACSIMILE. IF INITIALLY REPORTED VIA TELEPHONE, THIS MUST BE FOLLOWED-UP BY A FACSIMILE OF THE WRITTEN SAE REPORT WITHIN 24 HOURS OF THE CALL TO [redacted].

Non-serious events that require discontinuation of study medication (including laboratory abnormalities) should be reported to Perrigo immediately and within 1 working day.
Subjects who discontinue due to experiencing adverse events should be followed clinically until their health has returned to baseline status, or until all parameters have returned to normal. It is expected that the investigator will provide or arrange appropriate supportive care for the subject.

A subject who experiences a severe adverse event related to study drug will be discontinued from the study.

The notification about any serious adverse event should be directed to:

[redacted]

[redacted]

[redacted]

7.4.1 Pregnancy

At the time a Principal Investigator or delegated staff becomes aware that a study participant became pregnant following study participation, the Principal Investigator or Study Coordinator will report the pregnancy immediately by phone and/or by faxing a completed Pregnancy Report to [redacted] within one working day of being notified of the pregnancy report.

The report will include the following elements:

- Participant (mother's) coded study identifier;
- Date of participant's last menstrual period;
- Total accumulated dose of study treatment administered to date;
- Date of study medication administration

The investigator will follow the subject until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days within completion of the pregnancy.

Upon delivery, miscarriage or abortion, the Principal Investigator or Study Coordinator must forward a follow-up Pregnancy Report with any relevant information on the present condition of the fetus to [redacted] , including:

- Mother's coded study identifier(s);
- Gestational age at delivery, miscarriage or abortion;
- Birth weight, gender, length and head circumference, if available;
- Apgar scores recorded after birth, if available;
- Any abnormalities.

If the outcome of the pregnancy **meets the criteria for immediate classification of an SAE** (e.g., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the investigator will report the event by phone and by faxing a completed SAE report form to [redacted] within one working day of being notified of the pregnancy report.

If the trial is completed before the outcome of the pregnancy is known, [redacted] will assume the responsibility for following up on the pregnancy. [redacted] will contact the Investigator or Study coordinator on or around the potential expected date of delivery to follow-up on the outcome of pregnancy and will also check on the status of the infant 8 weeks post-delivery. Upon awareness of the pregnancy outcome and known status of the infant following 8 weeks of delivery, the investigator will complete the applicable pregnancy report forms and fax to [redacted] within 1 day of being notified.

7.5 Post Study Adverse Events

7.5.1 Non-serious Adverse Events

Adverse events that are identified at the last assessment visit (or the early termination visit) must be recorded on the AE eCRF with the status of the AE noted.

7.5.2 Serious Adverse Events

Serious adverse events that are identified on the last assessment visit (or the early termination visit) must be recorded on the AE eCRF page and reported to Perrigo according to the procedures outlined above. Subjects with unresolved previously reported serious adverse events, or any new serious adverse events identified on the last assessment visit, should be followed by the investigator until the events are resolved, or the subject is lost to follow-up. Resolution means the subject has returned to the baseline state of health, or the investigator does not expect any further improvement or worsening of the adverse event. The investigator should continue to report any significant follow-up information to Perrigo up to the point that the event has resolved. Any serious adverse event reported by the subject to the investigator that occurs after the last assessment, and are determined by the investigator to be reasonably associated with the use of the study drug, should be reported to Perrigo.

8. STATISTICAL ANALYSIS

The sections that follow highlight sample size determination and the planned analyses for this study. A statistical analysis plan (SAP) will be prepared separately from this protocol which gives descriptions of the statistical methods, models, hypotheses and subject populations to be analyzed. The SAP will be completed and approved before locking the database and unblinding the study and will serve as a companion to the protocol and the *de facto* documentation of the proposed statistical evaluation. The SAP will be completed and finalized prior to breaking the blind.

8.1 Statistical Analysis Plan

8.1.1 Analysis Populations

The following populations are defined for the purpose of analyses:

- Intent-to-Treat (ITT) (safety population): Any subject that was randomized and received and used study medication.

- Modified Intent-to-Treat (mITT): Any subject that was randomized, met eligibility criteria, received and used study medication, and that has at least one post-baseline efficacy assessment.

- Per Protocol (PP): Any subject:
  - Who met eligibility criteria
  - Who was randomized and received and used study medication
  - Who applied the study medication on Days 1-2 [redacted]
  - Who completed Visit 4/Day 57 (End of Study/Early Termination Visit) within window OR was discontinued from the study [redacted].
  - Without significant protocol violations that could have interfered with the administration of the treatment or the precise evaluation of treatment efficacy

[redacted]

[redacted]

8.1.2 Planned Analysis

All subjects who received study medication will be evaluated for safety. The efficacy analysis will be conducted on both the PP and the mITT subject populations. Two-sided hypothesis testing will be conducted for tests. Resulting p-values less than 0.05 will be considered statistically significant. No adjustments of p-values for multiple comparisons will be made. No interim analyses are planned. SAS software will be used for all data analyses and tabulations.

The treatment response will be summarized by treatment group for the end-of-study evaluation. The primary efficacy endpoints will be the proportion of subjects with clinical response of success defined as complete clearance (absence) of all clinically visible Actinic Keratosis lesions identified at the Baseline visit and no new Actinic Keratosis lesions in the treatment area at Visit 4/Day 57.

[redacted].

8.1.3 Sample Size Considerations

[redacted]

[redacted]

[redacted]

8.1.4 Efficacy Measures and Analysis

Clinical endpoints

The primary efficacy measure will be the proportion of subjects with clinical response of success defined as complete clearance (absence) of all clinically visible Actinic Keratosis lesions identified at the baseline visit and no new Actinic Keratosis lesions in the treatment area at Visit 4/Day 57.

Equivalent efficacy

For the proportion of subjects with clinical success, the Test treatment will be considered to be therapeutically equivalent to the Reference treatment if the 90% confidence interval on the difference between Test and the Reference proportions is contained within the interval –20% to +20%. The confidence interval will be constructed using Wald's method with Yates' continuity correction.

[redacted]

Superiority

Superiority will be demonstrated if both the active treatments (Test and Reference) are shown to be superior to the vehicle.

The proportion of subjects with clinical success for each active treatment will be compared to that of the Vehicle using a Z-test with Yates' continuity correction.

All hypothesis tests will be two-sided at a significance level of $\alpha = 0.05$, except confidence intervals which will be based on $\alpha = 0.10$ (i.e. 90% coverage). [redacted].

[redacted]

8.1.5 Safety and Adverse Events Analysis

The frequency and percent of subjects with adverse events will be summarized by MedDRA (Version 15.1) system organ class and preferred term and by severity and relationship to study drug for all three treatment groups. The adverse events reported by at least five percent of the subjects in any treatment group will also be tabulated. The comparable safety of the Test and Reference treatments will be evaluated by statistical comparison of the proportion of subjects who reported any adverse events. The test and reference treatments' frequency and distribution of application site reactions of erythema, flaking/scaling, crusting, swelling, vesiculation/postulation, and erosion/ulceration will be summarized and compared descriptively. Safety comparisons will be performed only for the safety intent-to-treat population.

8.2 Comparability of Subjects at Baseline

The statistical significance of any treatment group difference in the distribution of categorical variables such as gender will be tested using Cochran–Mantel–Haenszel (CMH) test for general association adjusted for site. Continuous variables, such as age, will be analyzed using a two-way analysis of variance (ANOVA) model with site and treatment as a fixed effect.

9. CONSENT/ASSENT CONSIDERATIONS AND PROCEDURES

It will be made clear to the subject that, for the purposes of the study, they are consenting only for topical application of medication or vehicle. Investigators may discuss the availability of the study and the possibility for entry with a potential subject without first obtaining consent/assent. However, informed consent/assent must be obtained and documented prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from current medication(s). When this is done in anticipation of, or in preparation for, the research, it is considered to be part of the research.

The study must be approved in writing by an appropriate IRB as defined by FDA regulations. A copy of the Letter of Approval from the IRB, which also contains specific identification of the documents approved, must be received by Perrigo prior to study commencement.

Periodic status reports must be submitted to the IRB at least annually as required by the site's IRB, as well as notification of completion of the study and a final report within three months of study completion or termination. A copy of all reports submitted to the IRB must be sent to Perrigo.

The investigator(s) has both ethical and legal responsibility to ensure that each subject being considered for inclusion in this study is given a full explanation of the protocol. This shall be documented on a written informed consent/assent form, which shall be approved by the same Institutional Review Board (IRB) responsible for approval of this protocol. Each informed consent/assent form shall include the elements required by FDA regulations in 21 CFR Part 50. The investigator agrees to obtain approval from Perrigo of any written informed consent/assent form used in the study, preferably prior to submission to the IRB.

Once the appropriate essential information has been provided to the subject and fully explained by the investigators (or a qualified designee) and it is felt that the subject understands the implications of participating, the IRB-approved written informed consent/assent form shall be signed by the subject (or their parent/legally authorized representative) and the person obtaining consent/assent (investigator or designee). The subject shall be given a copy of the signed informed consent/assent form and the investigator shall keep the original on file.

If the subject fails to meet the inclusion/exclusion criteria at the conclusion of the screening phase, the subject will be withdrawn from screening. In the event that the subject is re-screened for study participation, a new informed consent/assent form must be signed.

9.1 Subject Confidentiality

All participants are concerned for the individual subject's privacy and, therefore, all subject data will be identified only by a subject identification number and subject initials. However, in compliance with federal guidelines regarding the monitoring of clinical studies and in fulfillment of his/her obligations to Perrigo, it is required that the investigator permit the study monitor, a Perrigo authorized representative, and/or FDA representative to review that portion of the subject's medical record that is directly related to the study. This shall include all study relevant documentation including subject medical histories to verify eligibility, laboratory test result reports to verify transcription accuracy, admission/discharge summaries for hospital stays occurring while the subject is enrolled in the study and autopsy reports for deaths occurring during the study.

As part of the required content of informed consent/assent, the subject must be informed that his/her medical chart may be reviewed by Perrigo, Perrigo authorized representative, or a representative of the FDA. Should access to the medical record require a separate waiver or authorization, it is the investigator's responsibility to obtain such permission from the subject in writing before the subject is entered into the study.

To preserve the subject's confidentiality, the data collected will be available only to the investigators of the study, their support staff, Perrigo, and possibly the FDA.

All reports and communications relating to the subject in the study will identify each subject only by the subject's initials and by the subject number. The investigator agrees to furnish Perrigo with complete subject identification, if necessary on a confidential follow-up form, which will be used for the purpose of a long-term follow-up, if needed. This will be treated with strict adherence to professional standards of confidentiality and will be filed at Perrigo under adequate security and restricted accessibility.

10. RECORDS MANAGEMENT

10.1 Data Collection

Database set-up will be performed by [redacted] in collaboration with the Electronic Data Capture (EDC) vendor, using an appropriate fully validated, 21 CFR Part 11 compliant Electronic Data Capture (EDC) system. eCRFs will be provided to each site via a secured web link. All applicable study data collected on each subject will be recorded by approved site personnel into the eCRF. Only authorized site personnel will be able to enter/modify/correct data to the eCRF.

Approved staff at [redacted] will verify all data entered into eCRFs for completeness and accuracy with reference to the source documents and records and will issue manual data queries to correct missing data or discrepancies found against the source within the EDC system.

Data validation will consist of automated and manual edit checks that are created directly into EDC. Automated edit checks will be executed on all data points defined and documented by the study team and data management. Study metrics will be reported from the EDC system.

After all data have been verified by approved staff at [redacted], an Investigator or Sub-Investigator (listed on Form FDA 1572) is required to review and approve all eCRFs prior to database lock and breaking of the blind.

After database lock, each site will be provided with a CD that will include the eCRF data from their site for local archival purposes.

Quality assurance verification via a 10% database audit of eCRF data will be conducted before the treatment assignment code is broken.

10.2 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include, but are not limited to, progress notes and screening logs. All source documents pertaining to this study will be maintained by the investigators and made available for inspection by authorized persons. The original signed informed consent form for each participating subject shall be filed with records kept by the investigators and a copy given to the subject.

10.3 File Management at the Study Site

It is the responsibility of the investigator to ensure that the study center file is maintained in accordance with Section 8 of the International Conference on Harmonization (ICH) Guideline for Good Clinical Practices (GCP).

10.4 Records Retention at the Study Site

FDA regulations require all investigators participating in clinical drug studies to maintain detailed clinical data for one of the following periods:

a) A period of at least two years following the date on which a New Drug Application is approved by the FDA;
b) A period of two years after Perrigo New York notifies the investigator that no further application is to be filed with the FDA.

The investigator must not dispose of any records relevant to this study without either (1) written permission from Perrigo New York or (2) providing an opportunity for Perrigo to collect such records. The investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this study, including any data clarification forms (DCFs) received from Perrigo. Such documentation is subject to inspection by Perrigo and the FDA.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Monitoring

Perrigo has ethical, legal and scientific obligations to carefully follow this study in a detailed and orderly manner in accordance with established research principles and FDA regulations. All medical records (source documents) of the subjects participating in this study must be presented for review and verification of eCRFs.

11.2 Auditing

Perrigo (or representative) may conduct audits at the study center(s). Audits will include, but are not be limited to, drug supply, presence of required documents, the informed consent process, and comparison of case report forms with source documents. The investigator agrees to participate with audits conducted at a reasonable time in a reasonable manner.

Regulatory authorities worldwide may also audit the investigator during or after the study. The investigator should contact Perrigo New York immediately if notified of such an audit, and must fully cooperate with the audits conducted at a reasonable time in a reasonable manner.

12. ETHICS AND RESPONSIBILITY

This study must be conducted in compliance with the protocol, the United States Food and Drug Administration (FDA) regulations, any other countries regulations, and ICH GCP Guidelines.

13. USE OF INFORMATION AND PUBLICATION

All information supplied by Perrigo in connection with this study and not previously published, is considered confidential information. This information includes, but is not limited to, data, materials (i.e. the clinical protocol, eCRFs), equipment, experience (whether of a scientific, technical, engineering, operational, or commercial nature), designs, specifications, know-how, product uses, processes, formulae, costs, financial data, marketing plans and direct selling systems, customer lists and technical and commercial information relating to customers or business projections used by Perrigo in its business. Any data, inventions, or discoveries collected or developed, as a result of this study is considered confidential. This confidential information shall remain the sole property of Perrigo shall not be disclosed to any unauthorized person or used in any unauthorized manner without written consent of Perrigo and shall not be used except in the performance of the study. As such, confidential study-related information should not be included on the curriculum vitae of any participating investigator or study staff.

The information developed during the course of this clinical study is also considered confidential, and will be used by Perrigo in connection with the development of the drug. The

information may be disclosed as deemed necessary by Perrigo. To allow the use of the information derived from this clinical study, the investigator is obliged to provide Perrigo with complete test results and all data developed in the study. The information obtained during this study may be made available to other investigators who are conducting similar studies.

The investigator shall not make any publication related to this study without the express written permission of Perrigo. [redacted]

[redacted]

INVESTIGATOR AGREEMENT

PROTOCOL NUMBER: PRG-NY-15-002

PROTOCOL TITLE: A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study to Compare Perrigo New York, Inc.'s Ingenol Mebutate Topical Gel 0.05% to Leo Pharma Inc. Picato® Topical Gel 0.05% (Ingenol Mebutate Topical Gel 0.05%), and Both Active Treatments to a Vehicle Control in the Treatment of Actinic Keratosis on The Trunk and Extremities

I have carefully read the foregoing protocol and agree that it contains all the necessary information for conducting this study safely. I will conduct this study in strict accordance with this protocol, ICH Guidelines for Good Clinical Practices, the Code of Federal Regulations, the Health Insurance Portability and Accountability Act (HIPAA) and any local regulatory requirements and will attempt to complete the study within the time designated. I will provide access to copies of the protocol and all other information relating to pre-clinical and prior clinical experience submitted by Perrigo to all personnel responsible to me who participate in the study. I discuss this information with them to assure that they are adequately informed regarding the drug and conduct of the study. I agree to keep records on all subject information in accordance with FDA regulations.

_____

Principal Investigator's Printed Name

_____

Principal Investigator's Signature

_____

Date

APPENDICES

Appendix A: Study Personnel Contacts

[redacted]

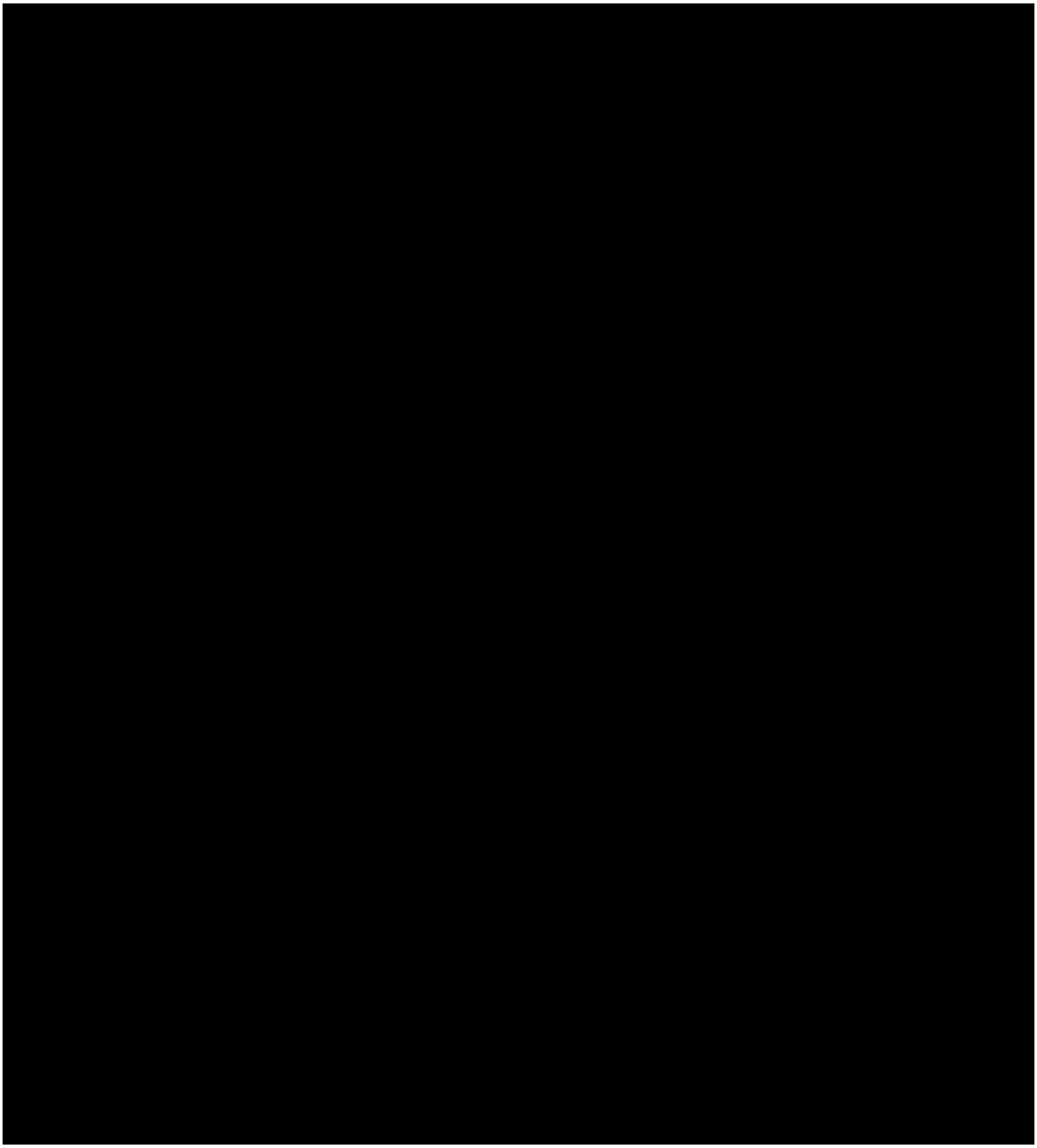
Appendix B: Instructions for the patient

[redacted]

[redacted]

[redacted]

Appendix C: Trunk and Extremities



REFERENCES

1. Summary Basis of Approval Picato® Topical Gel (Ingenol Mebutate Gel).
2. Package insert Picato® Topical Gel (Ingenol Mebutate Gel) dated Jan 2011, revised 01/2012.
3. www.picato.com
4. Salassche SJ. Epidemiology of Actinic Keratosis and Squamous Cell Carcinoma. J Am Acam Dermatol. 2000, 42 (1Pt 2): 4
5. Epidemiology, Natural History, and Diagnosis of Actinic Keratosis http://www. uptodate.com/Contents/epidemiology-natural-history-and-diagnostic-of-actinic-keratosis
6. Actinic Keratosis- Topic Overview http://www.webmd.com/skin-problems-and-to-treatments/tc/actinic-keratosis-topic-overview.
7. Berman B, Bienstock L, Kuritsky L, Mayeaux E.J, Tyring S. Actinic Keratosis: Sequela and Treatments. J Family Practice. May 2006: 1-8
8. McIntyre W, Downs R. M, Bedwell S. Treatment Options for Actinic Keratosis. American Family Physician Web Site at www.aafp.org/afp. 2007
9. http://aik-friendsnfamily.blogspot.com/2014/12/human-body-diagram-kids.html