CLINICAL STUDY PROTOCOL

1. COVER AND SIGNATURE PAGES

1.1 Title Page

Clinical Study Number:	VDA-CP-03
Original Clinical Protocol Date:	09 June 2016
Clinical Protocol Amendment	2
Clinical Protocol Amendment 2 Date	31 October 2016
Study Drug Identification:	VDA-1102
Clinical Protocol Version	1.0
Clinical Protocol Title:	A Phase 2 Randomized, Double-Blind, Placebo-Controlled, Parallel-Cohort Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of Once-Daily Application of Topical VDA-1102 Ointment for 28 Days in Subjects with Actinic Keratosis
Study Phase:	Phase 2
U.S. IND Number	125468
Sponsor:	Vidac Pharma Ltd. 10 Hartom Street, 2nd floor Har Hotzvim, Jerusalem, Israel 9777510
Sponsor Signatory:	Oren M. Becker, Ph.D. Vidac Pharma Ltd. Chief Executive Officer
Sponsor Medical Monitor:	Chaim M. Brickman, M.D. Vidac Pharma Ltd. Vice-President for Clinical Affairs
Study Principal Investigator:	Mark Lebwohl, M.D. Mount Sinai Medical Center New York, NY

1.2 Signature Pages

1.2.1 Clinical Signature Page

Title: A Phase 2 Randomized, Double-Blind, Placebo-Controlled, Parallel-Cohort Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of Once-Daily Application of Topical VDA-1102 Ointment for 28 Days in Subjects with Actinic Keratosis

Oren M. Becker, Ph.D.
Chief Executive Officer or designee

Signature: _____

Date: 05 Nov 2016

Chaim M. Brickman, M.D.
VP for Clinical Affairs or designee
Sponsor Medical Monitor

Signature: _____

Date: 05 Nov 2016

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1.2.2 Investigator Signature Page

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I have read and understand this protocol and concur with the study design. I agree to participate as an Investigator and to conduct the study in accordance with the protocol, the Food and Drug Administration (FDA) Code of Federal Regulations (CFR) for Good Clinical Practice (GCP), the International Conference on Harmonization (ICH) Guidelines and local regulations. I will make a reasonable effort to complete the study in the time noted. I will provide the contents of this protocol to study staff under my direct supervision that need to know the contents to conduct the study. I will discuss this information with the study staff to ensure they are fully informed about the study and the test articles. I will provide the contents of the protocol to the responsible Institutional Review Board(s). These disclosures may be made, providing the contents are not used in any other clinical study and they are not disclosed to any other person or entity without prior written consent from the Sponsor or designee. This condition does not apply to disclosure required by government regulations or laws; however, I agree to give prompt notice to the Sponsor or designee of any such disclosure.

I understand the study may be terminated or enrollment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the interests of the study subjects. I understand that any changes to the protocol must be approved in writing by Vidac Pharma and the relevant Institutional Review Board before implementation, except where necessary to eliminate apparent immediate hazards to the subjects.

Investigator's Name: _____

Investigator's Signature: _____

Date: __ __ / __ __ __ / __ __ __ __ Site Number: _____

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2. PROTOCOL SYNOPSIS

Title of Study: A Phase 2 Randomized, Double-Blind, Placebo-Controlled, Parallel-Cohort Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of Once-Daily Application of Topical VDA-1102 Ointment for 28 Days in Subjects with Actinic Keratosis

Study Center(s): Approximately 6 sites in the US and 3 in Israel

Study Duration: 11 months	**Phases of Development:** Phase 2

Study Objectives:

Primary Objective: To compare the reduction on Day 56 in the number of the actinic keratosis (AK) lesions in the Treatment Field of subjects receiving once-daily topical 5% or 10% VDA-1102 ointment for 28 days to the reduction in the number of AK lesions in subjects receiving placebo.

Secondary Objectives:

- To evaluate the systemic and local (skin) safety and tolerability of once-daily topical application of 5% or 10% VDA-1102 ointment or placebo for 28 days in adult subjects with AK.
- To assess the systemic exposure of VDA-1102 and jasmonic acid, its primary metabolite, at selected time points during topical application of 5% or 10% VDA-1102 ointment or placebo for 28 days in adult subjects with AK.

Exploratory Objectives:

- To compare the proportion of subjects receiving 28 days of 5% or 10% VDA-1102 who on Day 56 had complete clearance of AK lesions to subjects receiving placebo.
- To compare the reduction on Day 84 in the number of the actinic keratosis (AK) lesions in the Treatment Field of subjects receiving once-daily topical 5% or 10% VDA-1102 ointment for 28 days to the reduction in the number of AK lesions in subjects receiving placebo.

Study Design:

This Phase 2 clinical trial is a multi-center, randomized, double-blind, placebo-controlled, multiple-dose, parallel-cohort study involving the once-daily non-occluded, topical dermal application of the study drug (5% or 10% VDA-1102 ointment, or placebo) for 28 days.

Approximately 84 subjects will be enrolled in this study in order to obtain at least 75 evaluable subjects by the end of the trial. Fifteen (15) of these subjects will constitute a Nested Phase 1b Safety Study Sub-Cohort, and a maximum of 18 of the 84 subjects will be included in a PK Study Sub-Cohort. These 2 sub-cohorts may overlap and are described below.

To qualify for the study, subjects aged 18 (inclusive) or older must have signed informed consent and met the study enrollment criteria that include having 4-8 discrete Grade 1 or 2 AK

lesions within a 25 cm^2 area on the scalp or face ("the Treatment Field"). Subjects will be randomly assigned in a double-blind fashion to 1 of 3 parallel treatment cohorts (5%, or 10% VDA-1102, or placebo, respectively) in a ratio of 1:1:1. Randomized subjects will apply a single thin application of the study drug to their Treatment Field for 28 days.

This clinical trial will include 3 study periods.

Screening Period (Day -21 through Day 1 Pre-Dose):

During the **Screening Visit** (up to 21 days pre-dose) subjects who have given written informed consent will undergo safety assessments including medical and medication histories, adverse event (AE) documentation, vital signs, limited physical examination, clinical laboratory testing, 12-lead electrocardiograms (ECGs), dermatologic examination, and Treatment Field identification, as well as other qualifying procedures.

At the **Day 1 Pre-Dose Visit**, eligible subjects will return to the investigative site for baseline assessments as well as final eligibility screening. The 18 subjects enrolled in the PK Study Sub-Cohort (described below) will have a baseline blood sampling for PK analysis. Subjects who continue to meet the enrollment criteria will undergo randomization to 1 of 3 treatment groups: 5% VDA-1102, 10% VDA-1102, or placebo.

Three times during the Screening and Day 1 Pre-Dose Visits, subjects will be trained and tested in proper application of the study drug to the Treatment Field with the help of a flexible plastic stencil ("Treatment Field Template"). Subjects unable to apply the study drug properly will be excluded, unless they are accompanied by a dosing partner willing and able to properly dose the subject each evening.

Treatment Period (Day 1 Dosing through Day 28):

During the **Day 1 Dosing Visit**, randomized subjects (or their dosing partner) will apply the first dose of the study drug under the supervision of the site personnel in order to further assure proper application.

From Day 1 through Day 27, subjects will continue dosing the study drug to their respective Treatment Fields each evening while at home. Subjects will visit their respective investigative sites on **Day 7 and Day 14** for safety and efficacy assessments, drug accountability, and re-training in proper application of the study drug. In addition, subjects in the PK Study Sub-Cohort will undergo a single blood sampling at approximately 12 h after the prior evening's dose. On the **Day 28 Visit**, subjects will return to the clinic for safety and efficacy assessments. Subjects in the PK Study Sub-Cohort will have timed blood samples taken at approximately 12, 15, 18 and 21 hours after their Day 27 evening dose and a 24-hour Holter monitor will be attached.

During the Treatment Period, site personnel will communicate once-weekly with each subject in order to assure study drug compliance, review dosing instructions, and remind subjects of their next study visit.

Observation Period (Day 29 through 84):

Subjects will visit their respective investigative site on **Days 35** and **56** for efficacy and safety assessments. On **Day 84** subjects will return to the sites for their final efficacy and safety assessments. Subjects with continuing AEs will be scheduled for follow-up evaluation, as appropriate.

Nested Phase 1b Safety Sub-Cohort: The first 15 (PK and non-PK) subjects enrolled in the trial will undergo on Day 7 the safety examinations planned for all other subjects plus physical examination, clinical laboratory and ECG assessments. Once all 15 subjects in this Nested Phase 1b Safety Sub-Cohort have completed their Day 7 Visit, safety data (including AEs, LSR scores, clinical laboratory results, and ECG data) from Day 1 through Day 7 will be reviewed in a blinded fashion by a safety committee. During this blinded interim safety review, enrolled subjects will continue dosing the study drug and study enrollment will remain open.

PK Study Sub-Cohort: Of the approximate 84 subjects to be enrolled in this trial, a maximum of 18 subjects at select sites will undergo blood sampling for PK analysis on Day 1 Pre-Dose as well as on Days 7, 14, 28, and 35. In addition, the PK Study Sub-Cohort will undergo 24-hour cardiac Holter monitoring on Day 28. Subjects included in this Sub-Cohort may also be included in the Nested Phase 1b Safety Sub-Cohort if they are in one of the first 15 subjects to be enrolled into the study.

Number of Randomized Subjects (planned): Approximately 84 (3x28) subjects will be randomized in order to complete the study with at least 75 (3x25) subjects anticipated to be available for efficacy analysis.

Maximum Time Subjects May Remain in the Study: Subjects may participate in this study for a maximum of approximately 117 days (21 Screening Period + 32 Treatment Period + 64 Observation Period)

Study Endpoints:

Primary Efficacy Endpoint: Change from baseline in the number of AK lesions in the Treatment Field of each subject on Day 56.

Safety Endpoints: Assessment of AEs, vital signs, physical examinations, clinical laboratory parameters, Local Skin Reaction (LSR) Scores, and electrocardiograms.

Pharmacokinetic Endpoints: Assessment of the systemic exposure of VDA-1102 and its primary metabolite jasmonic acid at selected time points during topical application of 5% or 10% VDA-1102 ointment for 28 days in adult subjects with AK.

Exploratory Endpoints: The percentage of subjects achieving complete clearance of AK lesions within the Treatment Field on Day 56.

Change from baseline in the number of AK lesions in the Treatment Field of each subject on

Day 84.

Statistical Analyses:

Efficacy Analysis

Efficacy analysis will be based on changes from baseline to Day 56 in AK lesions. Comparative analysis of the changes will be applied between each of the active groups versus the placebo group using the two-sample t-test or non-parametric Wilcoxon-Mann-Whitney rank sum test for independent samples or Median test (as is appropriate). In the event that the number of baseline lesions is different between the treatment groups, then relative changes (%) will be analyzed as well.

The overall change and the trend of differences in the changes over time between the groups will be analyzed using mixed-effect model for repeated measures. The model will include changes at any time, the fixed effect time and the interaction of treatment and time. The model will be adjusted for baseline measures and for other relevant covariates.

Interim Efficacy Analysis (IEA)

A single interim efficacy analysis will be conducted as soon as 50% of the subjects have completed their Day 56 Visit. The objective of the IEA is to evaluate the probability of achieving the primary efficacy endpoint at the conclusion of the study. The unblinded data for the interim analysis sub-set will be analyzed by an independent statistician.

The result of the IEA will be a calculated effect size and t-value, which will be based on the difference in the change from baseline in the number of AK lesions for each of the active groups as compared to the placebo group. If baseline measure differs between the groups, then relative change (%) will be tested. The total significance level of 5% was divided between the interim efficacy analysis (0.005) and the final analysis (0.045). The spending function calculation for alpha will be performed using the O'Brien-Fleming methods. In case the distribution of the outcome variable does not approximate normality, the appropriate non-parametric methods will be considered for the interim analysis.

Safety Analysis

The safety end point data will be summarized for the ITT population. AEs will be categorized by System Organ Class (SOC) and Preferred Terms (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 or higher. The incidence of AEs, as well as the intensity and relationship to study drug, will be summarized by treatment group. Safety will also be assessed by evaluating findings of physical examinations, vital signs, Local Skin Reaction Scores, clinical laboratory test results, 12-lead ECG tracings, drug exposure, concomitant medications, and withdrawals/terminations. Clinical and laboratory data will be presented by dose group. Continuous variables will be described as the mean, median, standard deviation, and minimum and maximum values of n observations. Categorical data will be described with contingency tables including frequency and percent. These findings will be

summarized and compared between treatments and within treatment groups compared to findings from baseline evaluations.

3. TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS

Abbreviation	Definition
ß	Beta
°C	Degrees Celsius
µg	Microgram
µL	Microliter
µm	Micron
AE	Adverse event
AIDS	Acquired Immunodeficiency Syndrome
AK	Actinic keratosis
ALT	Alanine aminotransferase
AM	Morning
API	Active Pharmaceutical Ingredient
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve from time zero (t_0) to the time of the last measured sample (t_{last})
$AUC_{0-\tau}$	Area under the plasma concentration-time curve from time zero to the last measurable concentration
BID	Twice daily
BL	Baseline
BMI	Body Mass Index
CFR	Code of Federal Regulations
cm	Centimeter
C_{max}	Peak plasma concentration
COA	Certified Ophthalmic Assistant
COT	Certified Ophthalmic Technician
CPK	Creatinine phosphokinase
CRF	Case Report Form
CRO	Contract Research Organization
D5W	5% Dextrose
dL	Deciliter
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDTA	Ethylenediamine tetraacetic acid
eg	Exempli gratia, for example
EP	Electrophysiology
eRT	eResearch Technology, Inc.
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	estimated glomerular filtration rate
Hr(s)	Hour(s)
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form

Abbreviation	Definition
ICH	International Conference on Harmonisation
IEA	Interim Efficacy Analysis
I.e.	Id est, in other words
IID	FDA's database on Inactive Ingredients
IND	Investigational New Drug
IOP	Intraocular pressure
IRB	Institutional Review Board
IRT	Interactive Responsive Technology
ITT	Intent-to-Treat
IU	International Units
IV	Intravenous
IWRS	Interactive Web Randomization System
Kg	Kilogram
K_i	Inhibition constant
L	Liter
LLOQ	Lower Level of Quantification
LSR	Local skin reaction
mcg	Microgram(s)
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
Min	Minutes
mL	Milliliter
mmHg	Millimeters of mercury
Ms	Milliseconds
MTD	Maximally Tolerated Dose
NA	Not applicable
NCE	New chemical entity
NEI	National Eye Institute
Ng	Nanogram
nM	Nanomoles
NSAID	Non-steroidal anti-inflammatory drugs
OD	Right eye
Oz / ozs	Ounce / ounces
PBS	Phosphate buffered saline
pg	Picogram
PI	Primary Investigator
pH	hydrogen ion concentration
PK	Pharmacokinetic
PM	Evening
prn	Pro re nata (as needed)
PSA	Prostate-Specific Antigen
PT	Preferred Term
QAM	Each morning

Abbreviation	Definition
QD	Once daily
QOL	Quality of Life
QPM	Each evening
QS	Quantum statis, the amount which is needed.
QTcB	QTc interval corrected using Bazett's formula
QTcF	QTc interval corrected using Fridericia's formula
SD	Standard Deviation
SAE	Serious adverse even
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-emergent adverse event
$t_{½}$	Terminal plasma half-life
T_{max}	Time of the peak plasma concentration
ULN	Upper limit of normal
US	United States
UVB	Ultraviolet B light
V_{ss}	Volume of distribution at steady state

5. BACKGROUND AND RATIONALE

5.1 Indication

VDA-1102 is a small molecule new chemical entity (NCE) under development for the treatment of patients with actinic keratosis (AK).

5.2 Actinic Keratosis and Current Approaches to Treatment

Actinic keratosis (AK) is one of the most common dermatologic diagnoses and affects an estimated 58 million people in the United States. Estimated treatment costs in 2004 were $1.2 billion (Warino 2006). AK is generally present as rough patches or papules with erythema and scaling on sun-exposed skin, predominantly in older individuals with fair skin (Fitzpatrick skin types I-III). The lesions are often asymptomatic, but they may itch or be tender to the touch. Histologically, AK is characterized by keratinocyte atypia in the deeper epidermis, with defective maturation of the superficial epidermis (Cohen, 2010). The most common reason for treatment is to prevent cutaneous squamous cell carcinoma (cSCC). Although the risk of progression to invasive SCC for a specific lesion may be low, it is widely regarded that 60% to 97% of SCCs originate from AKs (Hurwitz 1995, Mittelbronn, 1998). This estimate is supported by considerable genetic analysis that demonstrates shared chromosomal abnormalities and progressive changes in gene expression between AK and SCC (Kanjilal, 1995, Ortonne, 2002, Kanellou, 2008, Padilla, 2010). Consequently, AK is often referred to as cSCC *in situ* (Heaphy, 2000, Oppel, 2004, Röwert-Huber, 2007) and is part of the continuum of transformation from normal skin to AK and cSCC (Ziegler, 1994, Stockfleth, 2013).

Since AK results from malignant processes in sun-exposed skin (mainly face, scalp, and extremities), it is often necessary to treat entire fields and not only the individual lesions. Cryosurgery and laser-based therapies are less effective for this indication. Currently the most common topical drugs and treatments for field-treatments of AK are 5-fluorouracil (5FU), imiquimod cream, ingenol mebutate gel, photodynamic therapy (PDT), and diclofenac sodium in hyaluronic acid (Chetty, 2015).

5.3 Unmet Medical Need

Current AK therapies are inadequate and pose significant challenges to public health. Nearly all field treatments are associated with painful severe local skin reactions ranging from necrosis to inflammation which reduce treatment compliance (Shergill 2014). Cryotherapy and surgery are used to treat a limited number of lesions. However, these may leave unsightly scars or hypopigmentation and patients often require repeat treatments.

The limited tolerability of most current treatments greatly decreases the willingness of patients to be retreated. Diclofenac sodium is the only drug available that is well tolerated.

However, it requires daily application for prolonged periods, shares the contraindications and potential side effects of the non-steroidal anti-inflammatory drug, and its long-term efficacy is still unknown. Consequently, AK patients often elect to avoid treatment and seek medical help only after their lesions have become esthetically intolerable or have advanced to invasive cSCC tumors. .

In contrast, VDA-1102 has the potential for a significantly more desirable benefit-risk ratio. The drug induces neither necrosis nor an inflammatory reaction. VDA-1102 would mitigate people's avoidance of treatment and the often required re-treatment of their chronic, recurrent skin disease.

5.4 Nonclinical Summary

The two GLP toxicology studies were: 1) a 28-day repeated dose oral toxicity study in rats with a recovery phase and toxico-kinetics, and 2) a 28-day topical dermal toxicity study in male and female minipigs with a recovery phase and toxico-kinetics.

An MTD for the local application of VDA-1102 was not reached at the highest feasible concentration tested (20%). As discussed below in Section 5.6.2, the relative doses of VDA-1102 fed to rats and applied to the skin of minipigs were much higher than the exposures in the proposed clinical study.

Full details of the non-clinical studies performed to date are found in the accompanying Investigator's Brochure.

5.5 VDA-1102 Clinical Summary

Study VDA-CP-01 (titled, "A Phase 1 Randomized, Double-Blinded, Placebo-Controlled, Dose-Escalation Study in Healthy Older-Adult Volunteers to Evaluate the Safety, Tolerability, and Pharmacokinetics of a Single Topical Dermal Application of VDA-1102 Ointment") was recently completed and preliminary blinded data are available. Healthy female volunteers without reproductive potential and male volunteers, aged 35-70, were sequentially assigned to 1 of 3 consecutive treatment cohorts (5%, 10% or 20% VDA-1102 ointment, respectively). Five subjects were randomized in a double-blind fashion in each dose cohort with 4 subjects to receive active VDA-1102 ointment and 1 subject to receive matched placebo (0% VDA-1102; vehicle control). A total of 15 subjects were randomized: 12 subjects received active VDA-1102 and 3 received placebo.

There were no deaths, serious adverse events, or early study discontinuations in this study. There were a total of 11 adverse events reported (whose treatment assignment is still unknown). All the AEs were mild, short-lived, and reversible. There were no clinically significant changes in study drug application sites, vital signs, physical examinations, clinical

laboratory results, ECGs, or Holter monitors for any individual subject at any time point regardless of treatment.

Plasma concentrations of VDA-1102 and its main metabolite, jasmonic acid were below the level of quantification of the LC/MS/MS bioanalytical assay (1 ng/mL and 50 ng/mL, respectively).

Further details of the results of this trial are provided in the VDA-1102 Investigator's brochure.

There are currently no ongoing clinical trials in which VDA-1102 is being administered.

5.6 Study Rationale

5.6.1 Rationale for Study Design and Subject Population

(i) Efficacy

VDA-1102 has shown relevant pharmacological effects *in vivo* in the UVB-induced SKH-1 hairless mice model of actinic keratosis and skin cancer. In this pre-clinical study, dermal application of VDA-1102 led to a significant ($p < 0.0001$) reduction in the number of lesions relative to vehicle, that was comparable to the reduction noted with the comparative control compound ingenol mebutate (Picato®) 0.05%. Clinical effects were observed within a week or two of treatment initiation, although full clinical benefit was observed after 3-4 weeks.

In this clinical protocol, study drug will be applied once-daily for 28 days to the Treatment Field on the scalp or face subjects with AK. Approximately 84 male and female subjects aged 18 or older with 4-8 discrete Grade 1 and/or 2 AK lesions who sign informed consent and meet the study enrollment criteria will be randomly assigned in a double-blinded fashion to 1 of 3 parallel treatment cohorts (5% or 10% VDA-1102 ointment, or placebo) at a ratio of 1:1:1. The primary endpoint of this study is reduction in the number of AK lesions in the Treatment Field on Day 56.

(ii) Safety

The results from the toxicology studies and the estimated safety margins indicate that daily dermal application of 250 mg of VDA-1102 ointment for 28 days at doses as high as 20% to an area of 25 cm^2 do not pose an untoward risk for evaluation in the target patient population. Specifically, topical application once-daily for 28 days of 5% or 10% VDA-1102 ointment to 10% of the minipigs body surface area in the nonclinical toxicology program resulted in no significant systemic safety findings and only mild, reversible skin findings.

In the completed Phase 1a clinical trial (Section 5.5 above), no safety concerns were identified following a single-dose of approximately 250 mg of 5%, 10%, or 20% VDA-1102 applied once to a 25 cm^2 area on the forehead of healthy older-adult volunteers. PK analysis

demonstrated that there were no detectable concentrations of VDA-1102 or its primary metabolite, jasmonic acid.

In this study a lower dose of 200 mg of 5% or 10% VDA-1102 ointment will be applied for 28 days to an area of 25 cm^2. Safety assessments will be performed throughout the Phase 2a study. In addition, the first 15 subjects enrolled in the trial will be defined as a Nested Phase 1b Safety Sub-Cohort. Available safety data (including AEs, LSR scores, clinical laboratory results, and ECG data) from Day 1 through Day 7 from these 15 subjects will be reviewed in a blinded fashion by a safety committee consisting of 2 independent investigators (not involved in the evaluation of subjects in the study) and the Study Safety Monitor.

(iii) Pharmacokinetics

In preclinical PK studies, VDA-1102 was rapidly metabolized, forming jasmonic acid as its inactive primary metabolite, regardless of the animal species or the route of administration. In all cases, the amount of JA in the blood equaled or exceeded the concentrations of VDA-1102 in the blood. In a 28-day dermal toxicity study in male and female minipigs, 5%, 10% or 20% of VDA-1102 ointment was applied once daily to 10% of the body surface area. Blood levels of VDA-1102 were essentially below the LLOQ on Day 1 and very low and highly variable on Day 28. Blood concentrations of the primary metabolite jasmonic acid on Day 1 were detected only in the 20% VDA-1102 ointment group On Day 28, blood levels of jasmonic acid were detected at all dose levels and were higher than that on Day 1, likely related to slow transdermal absorption as it appeared that steady state levels were present on Day 28.

In the completed Phase 1a clinical trial (Section 5.5 above), there were no detectable concentrations of VDA-1102 or its primary metabolite, jasmonic acid following a single-dose of approximately 250 mg of 5%, 10%, or 20% VDA-1102 that was applied once to a 25 cm^2 area on the forehead of healthy older-adult volunteers.

In the current study, approximately 84 subjects will be dosed once each evening for 28 days with approximately 200 mg of study drug. Eighteen subjects will be enrolled into a PK Study Sub-Cohort and will undergo plasma sampling on Days 7, 14, 28, and 35 for PK assessment. Holter monitoring will be performed for 24 hours on Day 28 in all subjects enrolled in the PK Study Sub-Cohort so that relevant ECGs tracings corresponding to peak levels (if detected) of VDA-1102 and/or jasmonic acid may be extracted once the PK/exposure data are available.

5.6.2 Dose and Posology Justification

The doses to be evaluated in this clinical trial are approximately 200 mg of 0%, 5%, and 10% VDA-1102 topical ointment, spread evenly (unoccluded) over a 25 cm^2 area of skin on the face or scalp of subjects with actinic keratosis.

Table 1 lists the mg/kg/day exposures in non-clinical toxicology studies as compared to the exposure planned in the proposed human trial. Data is presented as dose ratios rather than exposure ratios, because *in vivo*, trans-dermal absorption of VDA-1102 and its primary metabolite, jasmonic acid, appears to be minimal (minipig and human single doses) as determined with a sensitive bioanalytical assay.

The relative doses of VDA-1102 fed to rats and applied to the skin of minipigs were much higher than the highest dose (10% VDA-1102) to be applied in this study (Table 1).

Table 1: VDA-1102 doses tested in the pivotal 28-day non-clinical studies compared to the proposed clinical doses

Dose Group	Exposure VDA-1102 (mg/kg/day)	Exposure HED (mg/kg/day)	Exposure (mg/m^2/day)	Remarks
Proposed Phase 2a Clinical Study				
Ointment 5%	0.166		6.2	Assuming body weight of 60 kg
Ointment 10%	0.333		12.3	
Exposure Levels in Completed Non-Clinical Studies:				
28-Day Oral Toxicity Study in Rats				
Low dose	100	17		
Intermediate dose	300	48		**NOAEL**
High dose	800	129		Mild and at least partially reversible adverse effects
28-Day Dermal Toxicity Study in Minipigs				
Ointment 5%	15	10.7	405 [1]	**NOAEL** for local toxicity
Ointment 10%	30	21.4	810	Minimal local effects
Ointment 20%	60	42.9	1620	**NOAEL** for systemic toxicity

[1] Minipigs weighed <25 kg, therefore a converting factor of 27 was used.

Tables 2 and **Table 3** compare the proposed clinical doses to the systemic HED NOEALs in mg/kg/day, and to the systemic NOAEL in mg/m^2/day, respectively, determined in the two toxicology studies performed in minipig and rat. As can be seen from these tables, the highest planned dose in early clinical studies, 200 mg of 10% VDA-1102 ointment, is approximately 135-fold below the non-clinical systemic HED NOEAL levels determined in both species, rat and minipig.

Table 2: Comparison of the proposed clinical doses to the non-clinical HED NOAELs in mg/kg/day

Dose Group	Exposure VDA-1102 (mg/kg/day)		
	Early Clinical Studies	NOAEL 28-Day Oral Rat (HED)	NOAEL 28-Day Dermal Minipig (HED)
Ointment 5%	0.166	48	42.9
Ointment 10%	0.333		
Ointment 20%	0.666		

Table 3: Comparison of the proposed clinical doses to the non-clinical NOAELs in mg/m^2/day

Dose Group	Exposure VDA-1102 (mg/m^2/day)	
	Early Clinical Studies	NOAEL 28-Day Dermal Minipig
Ointment 5%	6.2	1620
Ointment 10%	12.3	

Based upon the non-clinical toxicology data and the safety findings from the Phase 1 clinical trial, VDA-1102 will be advanced to Phase 2 development. The doses in this clinical trial (200 mg of 5% or 10% VDA-1102 once daily for 28 days) are well below the nonclinical systemic HED NOEAL levels determined in both rats and minipigs. Furthermore, the daily dose proposed (~200 mg) is below the ~250 mg single dose administered in the Phase 1 clinical trial in healthy older-adult volunteers in order to more closely approximate the 200 mg dose administered in the non-clinical toxicology studies and to reduce the local and systemic exposures in humans.

6. STUDY OBJECTIVES

Study Objectives:

Primary Objective: To compare the reduction on Day 56 in the number of the actinic keratosis (AK) lesions in the Treatment Field of subjects receiving once-daily topical 5% or 10% VDA-1102 ointment for 28 days to the reduction in the number of AK lesions in subjects receiving placebo.

Secondary Objectives:

- To evaluate the systemic and local (skin) safety and tolerability of once-daily topical application of 5% or 10% VDA-1102 ointment or placebo for 28 days in adult subjects with AK.
- To assess the systemic exposure of VDA-1102 and jasmonic acid, its primary metabolite, at selected time points during topical application of 5% or 10% VDA-1102 ointment or placebo for 28 days in adult subjects with AK.

Exploratory Objectives:

- To compare the proportion of subjects receiving 28 days of 5% or 10% VDA-1102 who on Day 56 had complete clearance of AK lesions to subjects receiving placebo.
- To compare the reduction on Day 84 in the number of the actinic keratosis (AK) lesions in the Treatment Field of subjects receiving once-daily topical 5% or 10% VDA-1102 ointment for 28 days to the reduction in the number of AK lesions in subjects receiving placebo.

7. STUDY DESCRIPTION

7.1 Study Design – Study Periods, Days, and Visits

Approximately 84 subjects, aged 18 or older, who sign informed consent and meet the study enrollment criteria, will be randomized to 1 of 3 parallel treatment cohorts (5% or 10% VDA-1102 ointment, or placebo) in a 1:1:1 ratio. The clinical trial will include 3 study periods (Figure 1 and Table 4).

Screening Period – Subjects who have given written consent to participate in the trial will undergo safety and qualifying procedures between Day -21 and Day -1 (**Screening Visit**). At this visit, the subject's Treatment Field will be identified and the subject will be trained to precisely measure and apply the study drug without actually applying ointment to their Treatment Field. Subjects unable to express the proper dose from the study drug tube and/or unable to identify their Treatment Field will be required to bring a dosing partner to the next study visit in order to proceed in the study.

Subjects who meet all the study's inclusion criteria and none of the exclusion criteria will return on Day 1 for baseline assessments to ensure they still meet the study enrollment criteria (**Day 1 Pre-Dose Visit)**. During this visit, the Treatment Field selected at the Screening Visit will be requalified. If the field previously chosen fails to requalify, a new Treatment Field must be found or the subject must be excluded for failure to meet Inclusion Criterion #3 (Section 8.1). Subjects will be trained and tested twice during this visit for proper dose measurement (using the Dosing Cards 13.6.2), proper identification of the Treatment Field (using the Treatment Field Template 22.4), and precise dosing of that field using the template (stencil). Subjects (or their dosing partner) who are unable to express the proper dose from the study drug tube and/or are unable to precisely identify their Treatment Field will also be considered ineligible for the study (Inclusion Criterion #4, Section 8.1).

Subjects who continue to meet all the study enrollment criteria following the Day 1 Pre-Dose Visit will be randomized in a double-blinded fashion and proceed to the Day 1 Dosing Visit. Subjects enrolled in the PK Study Sub-Cohort will have a pre-dose blood sample drawn.

Treatment Period – At the **Day 1 Dosing Visit**, subjects will apply the assigned study drug (i.e., active VDA-1102 or placebo) under the supervision of site personnel. Details of the study drug application are found in Section 13.6.

From Day 1 through Day 27 subjects will apply the study each evening approximately 2 hours before bedtime. Site personnel will communicate with the subject once-weekly.

On **Day 7** and **Day 14** all subjects will return to the investigative site for safety and efficacy assessments. At each site visit, the subject's study drug will be weighed and the result will be recorded. At each visit, the subject will be re-trained in proper dose application to their Treatment Field. Subjects in the PK Study Sub-Cohort will have a blood sample taken

approximately 12 hours after their evening respective Day 6 and Day 13 evening doses. Subjects in the Nested Phase 1b Safety Sub-Cohort will undergo an additional physical examination, 12-lead ECG, and clinical laboratory assessment on Day 7.

Subjects will return to the site on **Day 28** for safety and efficacy assessments. Subjects in the PK Study Sub-Cohort will undergo blood sampling for analysis at approximately 12, 15, 18, and 21 hours after their Day 27 study drug application. Remaining study drug will be collected from all subjects at this visit.

Observation Period – On **Day 35** subjects will return to the site for efficacy and safety assessments. Subjects in the PK Study Sub-Cohort will undergo a single untimed blood sampling. Subjects in the PK Study Sub-Cohort will have a PK sample drawn at the time of their visit. Subjects will return to the sites on Day 56 for efficacy and safety assessments. At the End-of-Study visit on **Day 84**, final efficacy and safety assessments will be performed followed by discharge from the study. Any subject with active TEAE(s) will be followed beyond this scheduled visit until resolution.

Figure 1. Study Design Schematic

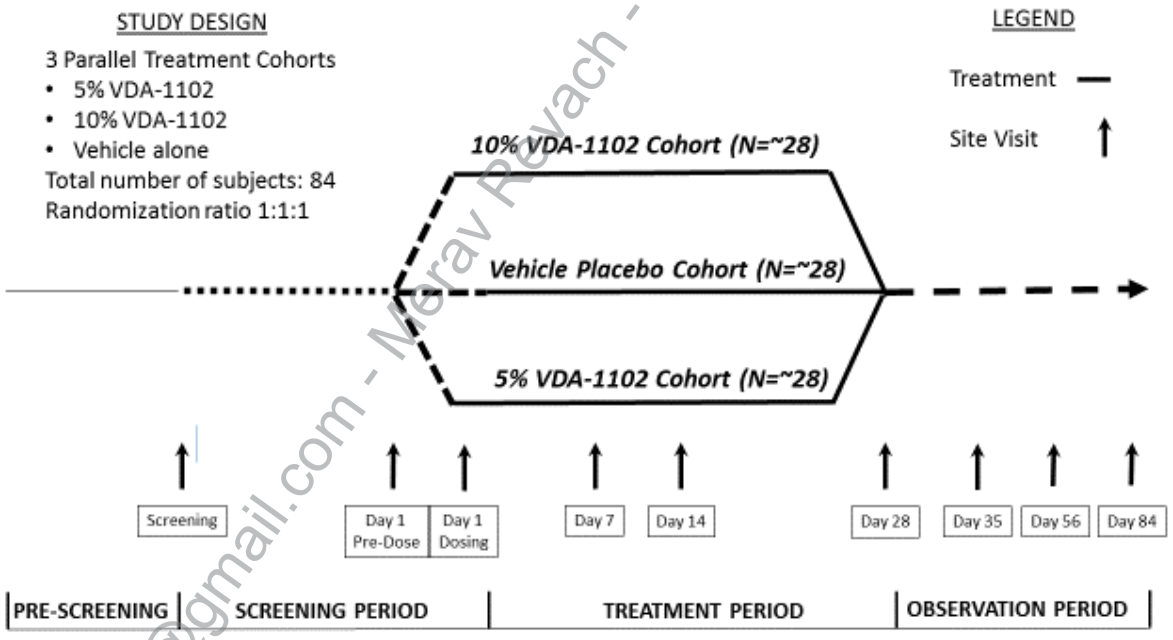

Table 4: Periods, Study Day, and Visits

PERIODS	SCREENING	TREATMENT				OBSERVATION		
STUDY DAYS	Day -21 to Day -1	Day 1		Day 7±2	Day 14±2	Day 28±4	Day 35 ±2	Day 56 ±4	Day 84 ±4
VISITS	Screening Visit(s)	Day 1 Pre-Dose Visit	Day 1 Dosing Visit	Day 7 Visit	Day 14 Visit	Day 28 Visit	Day 35 Visit	Day 56 Visit	Day 84 Visit
PURPOSE	• Screening Procedures • Baseline Assessments • Study drug application testing/ training • Randomization • PK sampling (PK Study Sub-Cohort)	• Dosing Study Drug • Safety & Efficacy Assessments • PK sampling (PK Study Sub-Cohort) • Drug accountability					• Safety & Efficacy Assessments • Day 35 PK sampling (PK Study Sub-Cohort)		

7.2 Table of Study Assessments

Tables 5 and 6 are the Schedule of Assessments for all subjects enrolled in the trial. Table 6 is the Schedule of Assessments for subjects enrolled in the PK Study Sub-Cohort.

Table 5: Schedule of Assessments for all Subjects

Table 6, below, indicates the additional assessments to be performed on subjects enrolled in the PK sub-cohort.

Period	**SCREENING PERIOD**		**TREATMENT PERIOD**				**OBSERVATION PERIOD**		
Study Day	**Day -21 to Day -1**	**Day 1**		**Day 7±2**	**Day 14±2**	**Day 28±4**	**Day 35±2**	**Day 56±4**	**Day 84±4**
Procedure\Visit	**Screening**	**Day 1 Pre-Dose**	**Day 1 Dosing**	**Day 7**	**Day 14**	**Day 28**	**Day 35**	**Day 56**	**Day 84**
ICF procedures, signature, dating confirmed	√								
Enrollment criteria and/or safety data review	√	√							
Demographics and Medical History	√								
Adverse events reporting	√	√		√	√	√	√	√	√
Concomitant medications recorded	√	√		√	√	√	√	√	√
Vital signs	√	√		√	√	√	√		
Physical examination	√	√		√ [1]	√	√	√		
Height / Weight / BMI calculated	√								
12-Lead ECG	√	√		√ [1]	√	√			
Clinical laboratory testing	√	√		√ [1]	√	√			
Fitzpatrick skin type		√							
Treatment Field Selection	√	√							
AK lesions in the Treatment Field count and grade	√	√		√	√	√	√	√	√
Local Skin Reaction Score		√		√	√	√	√	√	√
Study drug measurement & application review	√	√ twice		√	√				
Pregnancy test (urine) at the site	√	√				√		√	
Subject randomization		√							
Application of the study drug each evening			√ Day 1 through Day 27						
Supervised study drug application at the site			√						
Trial instruction review / Closure procedure	√		√	√	√	√	√	√	√
Telephone contact by study staff		Once-weekly communication between site visits							
Photographs of Treatment Field (at selected sites only)		√						√	√
Study drug & tools given subject, as needed			√	√	√				
Study drug accountability/dosing compliance [2]		√		√	√	√			

[1] Only subjects enrolled in the Phase 1b Safety Cohort will undergo these assessments.

[2] Weigh study tube / record dates of any doses missed between Days 1 and 28

Table 6: Table of Assessments for PK Study Sub-Cohort

The following table indicates additional evaluations to those listed in Table 6 to be performed only in subjects enrolled in the PK Study Sub-Cohort.

Period	**SCREENING PERIOD**		**TREATMENT PERIOD**			**OBSERVATION PERIOD**		
Study Day	**Day -21 to Day -1**	**Day 1**		**Day 7±2**	**Day 14±2**	**Day 28±4**	**Day 35±2**	**Day 56±4**	**Day 84±4**
Procedure\Visit	**Screening**	**Day 1 Pre-Dose**	**Day 1 Dosing**	**Day 7**	**Day 14**	**Day 28**	**Day 35**	**Day 56**	**Day 84**
Additional Exclusion Criteria	√								
24-hour Holter monitor attached						√			
Toxicology screen	√								
Blood sampling for PK[1]		√		√	√	4 √	√		

[1] One pre dose PK sample will be collected at the Day 1 pre-dose Visit, At the Day 7, Day 14 and Day 28 Visits, a sample will be collected when the subject arrives at the site (or approximately 12 hours after the last study drug application the previous evening). At the Day 28 Visit, three additional PK samples will be collected at 15, 18 and 21 hours (±30 mins) after the Day 27 evening dose. A final sample will be collected at the Day 35 Visit, at any time during that visit with the time noted.

7.3 Nested Phase 1b Safety Sub-Cohort

The first 15 (PK and non-PK) subjects enrolled in the trial will undergo on Day 7 the safety examinations planned for all other subjects plus a physical examination, clinical laboratory tests, and an ECG assessment. Once all 15 subjects in this Nested Phase 1b Safety Sub-Cohort have completed their Day 7 Visit, available blinded safety data (including AEs, LSR scores, clinical laboratory results, and ECG data) from Day 1 through Day 7 will be reviewed within 10 business days by a safety committee consisting of 2 Board-certified physicians not involved in the trial and the Study Medical Monitor (a Board-certified Allergist and Internist). During this blinded interim safety review, enrolled subjects will continue dosing the study drug and study enrollment will remain open.

7.4 PK Study Sub-Cohort

Of the approximate 84 subjects to be enrolled in this trial, a maximum of 18 subjects (who meet more stringent enrollment criteria than the other subjects enrolled) at select sites, will undergo blood sampling for PK analysis on Day 1 Pre-Dose as well as on Days 7, 14, 28, and 35 (Table 6). In addition, these subjects will undergo 24-hour cardiac Holter monitoring on Day 28 so that ECGs may be extracted based upon the other safety findings and the plasma PK data.

Subjects included in this sub-cohort may also be included in the Nested Phase 1b Safety Sub-Cohort if they are one of the first 15 subjects to be enrolled into the study.

7.5 Safety Reporting

7.5.1 Expedited Reporting to Sponsor and CRO

In addition to the reporting requirements for serious adverse events (SAEs) described in Section 16, all severe AEs must be reported to the Study Medical Monitor and the site's CRO contact within 24 hours.

All dose holidays and adjustments (described in Section 7.6 below) must be reported to the Study Safety Monitor (Sponsor) and the site's CRO contact within 24 hours. Such occurrences must be documented in the eCRF along with the reason for their occurrence.

In addition, if at any time during the course of the trial a potentially serious safety finding is noted by an Investigator, the Sponsor's Study Medical Monitor and the site's CRO contact must be notified within 24 hours.

7.6 Dose Holidays and Adjustments

Subject may be offered the following options at the Investigator's discretion:

a) To temporarily stop the study drug for up to 7 days and to re-assess within that period;

b) To temporarily stop the study drug for up to 7 days and instruct the subject to re-start the study drug application every other evening. The study drug may even be advanced to once-daily application as tolerated; or

c) To stop the study drug for the duration of the trial but follow the subject otherwise as planned.

Bland moisturizers may be recommended at any time to any subject to manage LSRs. However, the moisturizer should be applied no sooner than 6 hours after dosing and the Treatment Field should be washed with mild soap before the next study drug application.

7.7 Study Endpoints

Primary Efficacy Endpoint: Change from baseline in the number of AK lesions within the Treatment Field of each subject on Day 56.

Safety Endpoints: Assessment of AEs, vital signs, physical examinations, clinical laboratory parameters, Local Skin Reaction (LSR) Scores, and electrocardiograms.

Pharmacokinetic Endpoint: Assessment of the systemic exposure of VDA-1102 and its primary metabolite jasmonic acid at selected time points during topical application of 5% or 10% VDA-1102 ointment for 28 days in adult subjects with AK.

Exploratory Endpoints: The percentage of subjects achieving complete clearance of AK lesions within the Treatment Field on Day 56.

Change from baseline in the number of AK lesions within the Treatment Field of each subject on Day 84.

8. SUBJECT ELIGIBILITY AND WITHDRAWAL CRITERIA

8.1 Inclusion Criteria

Subjects fulfilling all of following criteria may be eligible for study participation.

1. Subject has signed and dated the ICF prior to any study-related procedure not part of normal medical care;
2. Subject is aged 18 years or older and is able and willing to comply with the contraception requirements described in Section 12.7.2;
3. Subject at the Screening and Day 1 Pre-Dose Visits has a minimum of 4 and a maximum of 8 discrete Grade 1-2 AK (see AK Grades, Section 11.1.1) lesions within a single 25 cm^2 area of skin on their scalp or face that meet the criteria for the AK Lesions and Treatment Field listed in Sections 11.1.2 and 11.1.3, respectively.
4. Subject (or their dosing partner) has demonstrated adequate precision applying the study drug to the Treatment Field during the Screening and Day 1 Pre-Dose Visits.

8.2 Exclusion Criteria

Subjects fulfilling any of the following criteria will be excluded from study participation:

1. Subject is the PI or any Sub-Investigator, research assistant, pharmacist, Study Coordinator, staff directly involved in the trial, and/or any immediate family member (first degree relative, spouse, adoptees, legal dependents) of any staff directly involved in the trial;
2. Subject has screening results that (a) are clinically significant and have not been approved in writing by the Safety Monitor; (b) suggest an unstable medical condition; (c) preclude the subject's participation out of concern for the subject's safety; or (d) suggest a condition that might confound the subject's data.
3. Subject is: (a) pregnant; (b) lactating; (c) planning to become pregnant during the study, or (d) fertile (as defined in Section 12.7.1) and they or their fertile partner is unable or unwilling to use the contraceptive methods discussed in Section 12.7.2;
4. Subject has any skin pathology, known dermatologic disease, or medical condition that could interfere with the evaluation of the test product or requires the use of an interfering topical or systemic therapy;
5. Subject is immunosuppressed (e.g., organ transplant recipients, HIV, systemic chemotherapy, graft vs. host disease, receiving dialysis, etc.);
6. Subject is currently enrolled in a clinical trial or has received an investigational drug or been treated with an investigational device within 21 days prior to Screening.

7. Subject is unable to comply with the sun protection techniques or the limitations placed on tanning, medicinal products, activities, or foods listed in Section 12.6;
8. Subject has (a) an unstable medical, psychiatric, or social problem; (b) self-reported alcohol or illicit drug dependency; (c) communication or motor deficit; or (d) any similar condition that could place the subject at a safety risk or might interfere with the performance of the trial activities, completion of the trial, and/or interpretation of the subject's data or risk the safety of the subject.
9. Subject may be unreliable for the study including subjects who engage in excessive alcohol intake or drug abuse, or subjects who are unable to return for scheduled follow-up visits.
10. Subject has a known sensitivity to propylene glycol, caprylic acid, dimethyl sulfoxide (DMSO), petrolatum, or paraffin wax.
11. Subject is unwilling to avoid any form of therapy, emollients, moisturizers, makeup, sunscreens, etc. to the Treatment Field from Screening through Day 84 except for bland emollients prescribed by the site Investigator.
12. Subject has used any of the following topical treatments in the Treatment Field:
    - Topical retinoids (e.g. tazarotene, adapalene, tretinoin) within 8 weeks of Screening, or
    - Microdermabrasion, laser ablative treatments, ALA-PDT, chemical peels, 5-FU, diclofenac, imiquimod, ingenol, or other topical treatments for AK or that might impact AK within 12 weeks of Screening.
13. Subject has used systemic retinoid therapy within 6 months of Screening Visit.
14. Subject has a history of malignancy within 5 years of Screening other than adequately-treated carcinoma in-situ of the cervix and non-metastatic basal cell or squamous cell carcinoma of the skin.
15. Subject had major surgery within 60 days of Day 1 or plans to have major surgery during the study; or
16. Subject has any reason that will preclude repeated venipuncture.

Additional Exclusion Criteria for Subjects in the PK Study Sub-Cohort:

17. Subject has a Body Mass Index (BMI) of ≤18 and ≥35;
18. Subject within 4 weeks of Screening had major blood loss or donated blood or a blood component;

19. Subject has any clinically significant medical abnormality or chronic disease that may interfere with the absorption, metabolism, or excretion of the investigational product. This includes such conditions as hepatic, renal, cardiac, or pulmonary disease or an estimated glomerular filtration rate <60 milliliters per minute;
20. Subject (self-reported) abused drugs or alcohol within 3 years of screening or used tobacco, smoking cessation products, or products containing nicotine within three months of Screening;
21. Subject has positive toxicology or drug, at Screening other than a benzodiazepine for sleep that the subject is willing to avoid during the trial and is negative upon re-test during Screening;
22. Subject is unable or unwilling avoid alcoholic beverages, smoking, nicotine products, and any medications unapproved by the Investigator from Screening through Day 35; or
23. Subject was exposed to any paint solvents or pesticides within 4 weeks of Screening.

8.3 Subjects Withdrawn, Terminated, or Lost to Follow-Up

Subjects who are terminated by the PI, who withdraw from the study, or who are lost to follow-up and who received at least one dose of the study drug will not be replaced.

8.4 Subject Withdrawal

Subjects may withdraw their consent at any time and for any reason.

Subjects who have applied at least 1 study drug dose and would like to withdraw from the study will be offered to attend all of the scheduled study visits and to undergo the planned safety and efficacy assessments.

8.5 Subjects Leaving the Trial

8.5.1 Termination by the Investigator

The Investigator may terminate a subject from the study at any time, due to: (a) trial misconduct, (b) violation of the rules of the site, (c) protocol violation; (d) pregnancy, or (e) unexpected personal issues that arose during the trial.

Subjects who have applied at least 1 dose of the study drug and are terminated from the study will be asked to attend all of the scheduled study visits through Day 84, as appropriate.

If an Investigator (or designee) is of the opinion that continued daily dosing may be detrimental to a subject's well-being, that subject may be offered the options discussed in Section 7.6 (Dose Holidays and Adjustments) following consultation with the Safety Medical Monitor.

8.5.2 Subjects Who Wish to Withdraw

If a subject who received at least 1 dose of the study drug wishes to withdraw from the trial, study staff should ask the subject to complete as many as possible of the planned evaluations scheduled through Day 84, as appropriate. If the subject declines, the subject should be asked to undergo the Day 28 safety and efficacy procedures.

Subjects may also be offered the options listed in Section 7.6.

8.5.3 Subjects Lost to Follow-Up

In the case of a subject lost to follow-up, attempts to contact the subject must be made and documented in the subject's files.

Subjects who received at least 1 dose of the study drug, were lost to follow-up, and re-contacted, will be encouraged to rejoin the trial.

- If the subject missed ≤ 7 consecutive days of study drug, the subject will be encouraged to continue in the trial as usual.
- If the subject missed >7 consecutive days of treatment, the subject will be considered a major deviator.

9. PROCEDURES FOR SAFETY AND PHARMACOKINETIC EVALUATIONS

9.1 General Considerations

No procedures (including Screening activities) may be performed before informed consent has been obtained, with a copy of the ICF given to the subject and another copy placed in the subject's medical records.

The Investigator will use their judgment when determining the clinical significance of any findings.

9.2 Pre-Screening

Sites are encouraged to pre-screen subjects prior to consenting. The FDA guidance regarding which pre-screening procedures may be performed may be found on the FDA web site at: http://www.fda.gov/RegulatoryInformation/Guidances/ucm126430.htm.

9.3 Screening Period Evaluations

9.3.1 Demographics

The birth date, gender, race, and ethnicity of each subject will be documented in the eCRF.

9.3.2 Fitzpatrick Skin Types

Fitzpatrick skin types will be classified as follows:

Type I: Pale white skin, always burns, and never tans.
Type II: White skin, usually burns easily, tans minimally.
Type III: Light brown skin, burns moderately, tans uniformly.
Type IV: Moderate brown skin, burns minimally, always tans well.
Type V: Dark brown, rarely burns, tans very easily.
Type VI: Deeply pigmented dark brown to black skin, never burns deeply.

9.3.3 Medical History

Medical history, including any diseases, all past surgeries including skin procedures, and psychiatric illnesses will be documented in the CRF of enrolled subjects.

Each subject will be questioned regarding any planned elective procedures that may occur during or following completion of the study, and these must be documented in the subject's medical record and the medical history section of the CRF.

9.4 Safety Measures

9.4.1 Adverse Events

The investigator will determine during the course of all study periods whether any AEs have occurred. Sections 15 and 16 , respectively, contain additional information with regard to AEs and SAEs.

9.4.2 Vital Signs, Weight, Height, and BMI

Throughout the study, vital signs (resting blood pressure, heart rate, temperature, and respiratory rate) will be obtained with the subject sitting or lying, after the subject has rested for at least 2 minutes.

Heart rates are best obtained electronically, if available. If heart rate data are obtained electronically, the results may not be obtained from an ECG scheduled at the same time. If these data are obtained manually, a minimum observation period of 30 sec is required.

Respiratory rate will be determined following a minimum observation of 30 sec.

The subject's height and weight will be documented in the CRF during the Screening visit.

BMI calculations will be performed as per the BMI calculator on the National Heart, Lung, and Blood Institute web site: http://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm. This site offers the option to enter either standard or metric data.

9.4.3 Physical Examination

The physical examinations performed during the trial will include skin, external eyes, oral cavity, nodes, lungs, heart, abdomen, extremities, and gross motor neurologic examination.

All abnormal acute and chronic findings must be recorded whether they are new or were recorded previously in the CRF. For example, a surgical scar should be recorded on every scheduled physical examination.

10. CLINICAL LABORATORY TESTS

Blood and urine sampling will occur as listed in Section 12.4 and the Table of Study Assessments (Section 7.2). All blood samples will be drawn, prepared, maintained, and shipped as per the study Clinical/PK Laboratory Manual. Blood sampling for all clinical laboratory tests should be performed following the fasting period prescribed in the manual.

The following tests will be performed at part of the Clinical Laboratory Tests:

a) ***Hematology:*** The hematology analysis will consist of the following tests:

- White Blood Cell Count
- White Blood Cell Differential in absolute numbers
- Hemoglobin
- Hematocrit
- Mean Corpuscular Volume
- Mean Corpuscular Hemoglobin Concentration
- Red Blood Cell Count
- Platelet Count

b) ***Coagulation Profile:*** The coagulation parameter analysis consists of the following tests:

- Prothrombin Time (PT) and/or International Normalized Ratio (INR)
- Activate Partial Thromboplastin (aPTT)

c) ***Complete Clinical Chemistry:*** The Complete Clinical Chemistry consists of the following tests:

- ALT
- AST
- Albumin
- Alkaline phosphatase
- Direct bilirubin
- Total bilirubin
- Blood urea nitrogen or urea
- Calcium
- Total cholesterol
- Chloride
- Creatinine
- Glucose
- Lactate dehydrogenase
- Inorganic phosphorus
- Potassium
- Total protein
- Sodium
- Triglycerides
- Uric acid
- Total CPK
- Glomerular filtration rate*

*Estimated glomerular filtration rate will be calculated using the SOPs of CRL, the central clinical laboratory.

d) ***Urinalysis:*** The urinalysis consists of the following tests:

- Glucose
- Protein
- pH
- Ketones
- Erythrocytes
- Leucocytes
- Nitrites

Note: Urine with abnormal protein, erythrocyte, leucocyte, or nitrite results will undergo a reflex automated examination.

10.1.1 Pregnancy Testing

The pregnancy testing will be performed on urine samples to be processed, assayed, and reported by site personnel as per the study Clinical/PK Laboratory Manual. The urine test must have a minimum sensitivity of 25 mIU for β-hCG per mL.

All women enrolled in the trial must have a negative urine pregnancy test at Screening and Day 1 Pre-Dose.

10.1.2 Toxicology and Drug Screen (PK Study Sub-Cohort only)

The toxicology, drug, and alcohol testing will be performed on urine samples to be processed, assayed, and reported by site personnel as per the study Clinical/PK Laboratory Manual.

10.1.3 Electrocardiogram

A standard, surface 12-lead ECG will be obtained as per the ERT manual at the time points listed in the Schedule of Assessments (Section 7.2).

ECGs will be interpreted by a Board-Certified cardiologist at ERT (Philadelphia, PA, USA). The QT interval results will be adjusted for rate using the Bazett (QTcB) and Fridericia (QTcF) corrections.

Cardiac dysrhythmias will be documented by occurrence (date and time), severity, type, and duration. Isolated premature ventricular contractions and supraventricular extra-systolic waveforms will not be considered clinically significant.

Two printouts (original copies) of each electrocardiogram will be stored in the subjects' medical records. ECGs will be assessed, signed, and dated by the Investigator (or designee).

All ECGs will be electronically transmitted to the central ECG laboratory for interpretation.

10.1.4 Holter Monitoring (PK Study Sub-Cohort only)

Subjects in the PK Study Sub-Cohort will undergo approximately 24-hours of continuous multi-lead cardiac telemetric monitoring from Day 28 (approximately 12 hours after the Day 27 dosing) through Day 29. Subjects will remove the monitors on Day 29, approximately 24 hours after they are attached, and return the Holter recorder at the Day 35 Visit.

ERT's instruction manual describes proper use and placement of these monitors. Site personnel will be trained regarding proper placement of the electrodes and recorders.

The purpose of the 24-hour cardiac Holter monitor recording is to allow ECGs to be extracted based upon the plasma PK findings.

10.1.5 Local Skin Reaction Score

The Investigator (or designee) will use the Local Skin Reaction (LSR) Score (see Section 22.1) to numerically assess the overall degree of erythema, edema, weeping / exudate, vesicles, erosions / ulcerations, scaling / dryness, scabbing / crusting, itching, or pain) in the Treatment Field on a 5-point scale, from 0 (none) to 4 (severe). This assessment will be performed on Day 1 Pre-Dose (baseline) and repeated at each subsequent visit. The individual scores for each potential finding will be recorded in the respective cells by the assessor.

In this trial LSRs will be collected independently of AEs. Details regarding reporting are included in Section 15.1.

10.1.6 Once-Weekly Subject Contact

Site personnel will contact each subject once-weekly during the Treatment Period. The goals of this contact are: (a) to review the Dosing Instruction Packet and Dosing Diary with each subject; (b) to answer any questions raised by the study participants; (c) to remind subjects of their upcoming site visit and any related activities; and (d) to remind subjects to bring their study drug to each site visit.

10.2 Pharmacokinetic Measures (PK Study Sub-Cohort only)

A maximum of eighteen subjects will participate in the PK Study Sub-Cohort. Blood samples for measurement of plasma VDA-1102 and its primary metabolite jasmonic acid (JA) will be taken at Day 1 Pre-dose. Post-dose blood sampling will occur at the Days 7, Day 14, and Day 28 Visits at approximately 12 hours after the Day 6, Day 13, and Day 27 evening doses, respectively. On Day 28, the sample should be drawn as close to 12 hours after the previous evening's dose as possible, and additional samples should be drawn at approximately 15, 18, and 21 hours (±30 mins) after the Day 27 evening dose. A final sample will be collected on Day 35. The exact time of each blood sampling will be recorded in the EDC.

Further details regarding the PK blood sampling as well as PK sample handling, processing, storage, and shipping are included in the study Clinical/PK Laboratory Manual.

Non-compartmental PK parameters (e.g., AUC, C_{max}, T_{max}, $t_{1/2}$) will be calculated, if possible.

11. PROCEDURES FOR EFFICACY EVALUATIONS

11.1 AK Lesions

11.1.1 AK Lesion Grading

This trial will use the AK lesion clinical grading established by Olsen *et al* and as recommended by the International League of Dermatologic Societies and the European Dermatology Forum:

Grade 1 – mild (slightly palpable AK that are felt better than seen)

Grade 2 – moderate (moderately thick AK that are easily seen and felt)

Grade 3 - severe (very thick and/or obvious AK). Treatment Fields selected for this trial must not contain any Grade 3 AK lesions (see Section 11.1.2, below).

11.1.2 AK Lesion Eligibility

In order to be eligible for this trial, the AK lesions must meet each of the following criteria:

a. Grade 1 or Grade 2 AK lesions (Section 11.1.1);

b. located on the subject's forehead, cheeks, or scalp but not on the lips, submandibular area, or neck;

c. discrete (i.e., no borders are clearly touching one another);

d. a maximum diameter 10 mm (inclusive) in any direction;

e. non-hypertrophic and non-hyperkeratotic (i.e., no thick scale, horn, or > 1 mm raised above background skin); and

f. not atrophic, acantholytic, pigmented, or Bowenoid.

11.1.3 Treatment Field Selection

Any 25 cm^2 contiguous area on the face or scalp of the subject that contains 4-8 AK lesions that meet the requirements stated in AK Lesion Eligibility criteria (section 11.1.2) may be selected as the study Treatment Field. The Treatment Field will be selected at Screening and confirmed on Day 1 Pre-Dose. If the Treatment Field selected at Screening is no longer eligible at Day 1 Pre-Dose, a new Treatment Field may be selected on Day 1 Pre-Dose.

It is recommended that the Treatment Field be a square or rectangle and that is visible to the subject when looking in the mirror. Treatment Fields not visible to the subject when looking in the mirror are best managed by having a dosing partner help with the dosing. Dosing partners must accompany the subject on Day 1 so as to undergo training and testing like all the subjects who self-dose.

The Treatment Field or its outer border must **not** be:

a) Within 2.5 cm (~1 inch) of either labial commissure of the mouth, lip vermilion border, palpebral fissure or a suspected or proven malignancy;

b) Close to another active dermatologic process that could spread to the Treatment Field and interfere with the proper assessment of the Treatment Field and/or its included AK lesions; or

c) So close to the eyebrows, beard, or other area with hair as to interfere with proper application of the study drug or assessment of the Treatment Field.

NOTE: Ideally other AKs should NOT be adjacent to the border of the Treatment Field which could confound the AK lesion counting or identification of the Treatment Field at subsequent study visits.

11.1.4 Study Tools

The following 3 study tools will be used for Treatment Field selection, AK Lesion counts, Study Drug measurement, and Study Drug Application. The preliminary tools will be supplied by the Sponsor; Investigators (or designee) will prepare the final tools for use by the sites and the subject.

Examples of the 3 study tools appear in Section 22.2 (Treatment Field Map), Section 22.4 (Treatment Field Template), and Section 22.6 (Subject Dosing Card).

1. **Treatment Field Map** - This flexible, 8.5 x 11 inch plastic transparency with 1 cm x 1 cm grid printed on the surface will be used by the Investigator (or designee) to: (a) define a Treatment Field at Screening and Day 1 Pre-Dose Visits; (b) count AK lesions in the Treatment Field; and (c) to create the Treatment Field Template. Instructions regarding use of this tool appear in the Treatment Field Map Instructions (Section 22.3).
2. **Treatment Field Template –** The tool consists of a clear, thin, flexible, 8.5 x 11 inch plastic transparency sheet supplied by the Sponsor marked by the Investigator (or designee) with landmarks (e.g. eyebrows, ear helix, and/or nevi) to guide the subject to the proper placement of the sheet. The template also includes a cut-out hole that will act as a stencil, guiding the Subject (or dosing partner) to the precise Treatment Field for application of the study drug. This template (stencil) will be used by the:
    a. Investigator (or designee) (a) to train the subject in proper identification of their unique Treatment Field; and (b) to train the subject in precise study drug application to their unique Treatment Field.

b. Subject (or dosing partner): (a) to identify their unique Treatment Field and (b) to apply the study drug precisely to their Treatment Field. Instructions regarding use of this tool appear in the Treatment Field Template Instructions (Section 22.5).

3. **Dosing Card –** a clear, thin, flexible plastic transparency with a rectangle printed on the back side. A strip of ointment expressed from the study drug tube that fits the clear portion of the rectangle is the correct approximate dose of study drug to be applied to the Treatment Field. A new previously unused Dosing Card will be used each evening by the subject to measure their proper study drug dose, and will be discarded after use. A sample of the Dosing Card is included in Section 22.6. Instructions regarding use of the Dosing Card are included in the Subject Instruction Packet.

11.1.5 AK Lesion Count

At the Screening and Day -1 Pre-Dose Visits, the selected Treatment Field must include at least four (4) and no more than eight (8) visible and discrete non-hyperkeratotic, non-hypertrophic AK lesions.

All AK lesions in the selected contiguous 25 cm^2 Treatment Field will be identified, counted, graded, and recorded at each visit.

If the subject has a LSR that prevents the investigator or designee from performing the AK count at a visit, the investigator or designee should document in the source document and CRF that the AK count was unable to be obtained due to a LSR.

11.1.6 Photography

Photography will be performed at designated study visit(s) at selected sites participating in this study as specified per protocol. The selected study sites will be provided with suggested guidelines to assist them in taking standardized photographs. However, it should be noted that all study sites, at the discretion of the investigator, may elect to photograph the subject under various magnification and lighting conditions to document the effects of treatment, adverse events or other findings during the trial. All photographs taken as part of this study are for informational purposes only and are not to assist in grading or for any other assessment.

Note: Subjects may decline to have photographs taken during the conduct of the study. If a subject initially consents to photographs, then declines further photography, the Sponsor may use the photographs taken under consent for the purposes noted.

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12. CONDUCT OF THE STUDY

12.1 Study Blinding and Randomization

12.1.1 Randomization

Assignment of study drug will be performed using a web-based Interactive Responsive Technology (IRT)-based randomization system. On Day 1 Pre-Dose, after confirming the subject's eligibility, the Investigator (or his designee) may approve the subject's blinded randomization.

The web-based IRT will randomize subjects in a fashion that will maintain a balance among the 3 treatment groups (5% and 10% VDA-1102, and placebo) across all subjects enrolled (not per site) and within the PK Study Sub-Cohort.

Subjects who withdraw or are terminated after 1 study dose has been applied will not be replaced in the trial.

Should a subject lose or destroy a tube, the IRT is capable of assigning additional study drug to each subject with the appropriate treatment assignment.

12.1.2 Blinding

All site staff at the investigative sites, Sponsor, CROs, and vendors as well as all enrolled subjects will be masked to the study drug assignments throughout the trial. One pre-designated statistician will have access to the blinded treatment assignments and be responsible for all activities that require unblinding, including the per protocol Interim Efficacy Analysis (Section 17.4).

12.1.3 Unblinding

In the event of an emergency, the Investigator (or designee) should contact the Study Medical Monitor to discuss the case before unblinding of an individual subject's treatment code is broken by the site. If the medical condition of the subject warrants immediate unblinding, the treatment assignment of the subject may be obtained from the IRT without first consulting the Study Medical Monitor. However, the site must contact the Study Medical Monitor as soon as possible after the unblinding.

An interim efficacy analysis will performed after approximately 50% of the enrolled subjects have completed their Day 56 Visit and their data have been recorded. The single pre-designated unblinded statistician described above in Section 12.1.2 will perform this analysis. The specifics of this interim analysis will be included in the Statistical Analysis Plan.

12.2 Subject Informed Consent

Written consent will be obtained from the subject prior to any study-specific procedure or investigation.

Information about the study, explaining the objectives and potential risks and benefits, will be given to the subject in writing and verbally in a language that is understood by the subject. The subject should have adequate time to read the information and to ask the Investigator any questions. The Investigator must be satisfied that the subject has understood the information provided before written consent is obtained.

If a subject agrees to participate, he/she will be asked to sign and date an informed consent form (ICF), the original copy of which will be kept by the Investigator. A copy of the signed ICF will be given to the subject.

12.3 Study Periods

The clinical trial will consist of the following periods:

- Screening: Days -21 through Day 1 Pre-dose
- Treatment: Day 1 Dosing through Day 28
- Observation: Day 29 through Day 84

12.4 Study Procedures per Period and Visit

❖ ***Procedures that relate only to the PK Study Sub-Cohort will be denoted by a diamond similar to the one at the beginning of this paragraph.***

12.4.1 Screening Period

The Screening Period begins immediately following the ICF signing (see Section 12.2 for a description of the informed consent procedures).

✓ ***Screening Visit (Day -21 to Day -1)***

The following procedures are to be performed during the Screening Visit:

- Site personnel confirm that the ICF: (a) is the most current ICF; (b) was signed and dated by the subject, (c) was witnessed; and (d) was copied with one copy given to the subject for their personal records
- Demographics recorded
- Medical history recorded
- Concomitant medications documented
- Adverse events that occur following ICF signing will be recorded
- Height and weight recorded

- Vital Signs: oral temperature, peripheral blood pressure, heart rate, and respiratory rate will be recorded
- Physical examination
- Clinical laboratory tests: Fasting status will be recorded
- Urine pregnancy test will be performed in all females and the results will be recorded
- 12-lead ECG tracing recorded as per the ERT manual. An original (duplicate) copy of the ECG is required for trial documentation. This ECG will also be transmitted to the central ECG laboratory.
- Scalp and face examination by PI (or designee) with selection of a Treatment Field that meets the criteria stated in Section 11.1. The Treatment Field Map and Template will be prepared as per the Investigator
- AK lesions count (11.1.5) and grading (11.1.1)
- Study Drug Measurement and Application review (see Section 13.6.3). Subject will be trained to measure (using placebo ointment on the Dosing Card) and to accurately apply the study drug, without actually applying placebo ointment to their Treatment Field
- Subject instructions review will be reviewed including appointment for the next visit
- Inclusion and exclusion (enrollment) criteria applied by Investigator and recorded
- Investigator may declare of subject's potential eligibility for PK Study Sub-Cohort

Subjects who are eligible for the **PK Study Sub-Cohort** will undergo the following additional safety assessments:

- ❖ Review additional Exclusion Criteria for PK subjects
- ❖ Toxicology and drug screen
- ❖ Alcohol level

✓ ***Day 1 Pre-Dose Visit***

Subjects who have completed all screening procedures and continue to meet the study enrollment criteria will return to the investigative site on Day 1 Pre-Dose. During this visit, the following procedures will be performed:

- Vital signs: oral temperature, peripheral blood pressure, heart rate, and respiratory rate will be recorded
- Adverse event(s): volunteered, elicited, and observed AEs will be recorded

- Concomitant medications documented
- Study Drug Measurement and Application review (see Section 13.6.3) should be one of the first procedures performed upon arrival at the site. The Treatment Field Map and Template will be prepared as per the Investigator instruction sheet.
- Subject will be trained to measure (using placebo ointment on the Dosing Card) and to accurately apply the study drug, without actually applying placebo ointment to their Treatment Field
- Physical examination
- Fitzpatrick skin typing (Section 9.3.2)
- Local Skin Reaction Score (baseline)
- AK Lesions in the Treatment Field: baseline count (11.1.5) and grading (11.1.1)
- Urine pregnancy test will be performed in all females and results recorded.
- 12-lead ECG tracing will be recorded as per the ERT manual. An original (duplicate) copy of the ECG is required for trial documentation. This ECG will also be transmitted to the central ECG laboratory
- Study Drug Application: Training and Testing (see Section 13.6.3) should be repeated after all the above activities have been completed. Subject will be trained to measure (using placebo ointment on the Dosing Card) and to accurately apply the study drug, without actually applying placebo ointment to their Treatment Field.
- Safety data from Screening, all available data from the Day 1 Pre-Dose Visit, as well as the Enrollment Criteria will be reviewed and approved by the Investigator (or designee)

Subjects who meet the study enrollment criteria will undergo the following procedures:

- Randomization of subjects
- Clinical laboratory tests: Fasting status will be recorded.
- Photographs of Treatment Field at designated sites
- Study drug weighed and recorded

Subjects enrolled in the **PK Study Sub-Cohort** will undergo the following additional procedure:

- ❖ Notify IWRS that the subject was enrolled in the PK Study Sub-Cohort to enable proper randomization and treatment assignment
- ❖ Blood sampling for (baseline) PK

12.4.2 Treatment Period

✓ ***Day 1 Dosing Visit***

The following procedures will be performed on subjects selected to proceed to the Treatment Period.

- Study drug application and completion of the Dosing Diary by the subject under the supervision of the site personnel.
- Subject Instruction Packet will be reviewed including appointment for the next visit.
- Study drug and study tools will be given to the subject.

✓ ***Day 1 Post-Dose through Day 6***

- Subjects will dose at home each evening, beginning with Day 1 and record the application in the Dosing Diary.

  Note: Subjects will receive 2 doses of the study drug on Day 1: once at the site after randomization and once in the evening at home.
- Site personnel will communicate with the subjects once a week (Section 10.1.6) in order to review the Subject Instruction Packet and Dosing Diary as well as to remind each subject of their next site visit.

✓ ***Day 7 Visit***

On Day 7 (±2) the following procedures will be performed:

- Adverse event(s) recorded
- Concomitant medications documented
- Study drug accountability and dosing compliance: study drug tubes will be weighed, the results recorded, and diaries reviewed and photocopied. Study drug and/or tools will be replenished, as needed.
- Vital signs: oral temperature, peripheral blood pressure, heart rate, and respiratory rate will be recorded.
- Local Skin Reaction Score in the Treatment Field
- AK Lesions in the Treatment Field: count (11.1.5) and grading (11.1.1)
- Study Drug Measurement and Application review (see Section 13.6.3)

- **The first 15 subjects randomized (Nested Phase 1b Safety Cohort) will undergo:**
  - **12-lead ECG tracing will be recorded as per the ERT manual. An original (duplicate) copy of the ECG is required for trial documentation. This ECG will also be transmitted to the central ECG laboratory**
  - **Clinical laboratory tests: fasting status will be recorded**
  - **Physical examination**

The following additional procedures will only be performed on the Day 7 Visit only in subjects enrolled in the subjects enrolled in the **PK Study Sub-Cohort**:

❖ PK blood sampling approximately 12 hours after the Day 6 dose

- Subject Instruction Packet will be reviewed including appointment for the next visit.
- Study drug and study tools will be given to the subject, as needed.

✓ ***Day 7 through Day 13***

- Subjects will dose at home each evening approximately 2 hours before bedtime and record the application in the dosing diary.
- Site personnel will communicate with the subjects once a week (Section 10.1.6) in order to review the Subject Instruction Packet and Dosing Diary as well as to remind each subject of their next site visit.

✓ ***Day 14 Visit***

On Day 14 (±2) the following procedures will be performed:

- Adverse event(s) will be recorded
- Concomitant medications documented
- Vital signs: peripheral blood pressure, respiratory and heart rates, and oral temperature will be recorded
- Physical examination
- Clinical laboratory tests: Fasting status should be recorded
- 12-lead ECG tracing will be recorded as per the ERT manual. An original (duplicate) copy of the ECG is required for trial documentation. This ECG will also be transmitted to the central ECG laboratory

- Local Skin Reaction Score in the Treatment Field
- AK Lesions in the Treatment Field: count (11.1.5) and grading (11.1.1)
- Study Drug Measurement and Application review (see Section 13.6.3)
- Study drug accountability and dosing compliance: study drug tubes will be weighed, the results recorded, and diaries reviewed and photocopied
- Study drug and study tools will be given to the subject, as needed

The following additional procedures will be performed on the Day 14 Visit only in subjects enrolled in the subjects enrolled in the PK Study Sub-Cohorts:

❖ PK blood sampling approximately 12 hours after the Day 13 dose

- Subject Instruction Packet will be reviewed including an appointment for the next visit will be given

✓ ***Day 14 through Day 27***

- Subjects will dose at home each evening approximately 2 hours before bedtime and record the application in the Dosing Diary.
- Site personnel will communicate with the subjects once a week (Section 10.1.6) in order to review the Subject Instruction Packet and Dosing Diary as well as to remind each subject of their next site visit

✓ ***Day 28 Visit***

On Day 28 *(±4)* the following procedures will be performed:

- Adverse event(s) AEs will be recorded
- Concomitant medications documented
- Vital signs: peripheral blood pressure, respiratory and heart rates, and oral temperature will be recorded
- Physical examination
- Local Skin Reaction Score in the Treatment Field
- AK Lesions in the Treatment Field: count (11.1.5) and grading (11.1.1)
- Study drug accountability and dosing compliance: study drug tubes will be weighed and the results recorded. Dosing Diaries will be collected and not returned

- 12-lead ECG tracing recorded as per the ERT manual. An original (duplicate) copy of each ECG is required. This ECG will also be transmitted to the central ECG laboratory
- Complete clinical laboratory tests: Fasting status to be recorded
- Urine pregnancy test will be performed at the investigative site in all females and the results will be recorded

The following Procedure will only be performed on the Day 28 Visit in subjects enrolled in the **PK Study Sub-Cohort**:

❖ PK blood sampling approximately 12 hours after the Day 27 dose. Additional blood samples will be collected at approximately 15, 18, and 21 hours post dose

❖ 24-hour ambulatory cardiac Holter monitor will be connected to the subject

- Trial instruction review including an appointment for the next visit will be given.

12.4.3 Observation Period

✓ ***Day 29 through Day 34***

- No procedures will be performed on these days.

❖ Subjects in the **PK Study Sub-Cohort** will remove the Holter on Day 29 approximately 24 hours after it was attached and will be returned by the subject to the site on Day 35.

✓ ***Day 35 Visit***

On Day 35 (±2) the following procedures will be performed:

- Adverse event(s) will be recorded
- Concomitant medications documented
- Vital signs: peripheral blood pressure, respiratory and heart rates, and oral temperature will be recorded
- Physical examination
- Local Skin Reaction Score in the Treatment Field
- AK Lesion in the Treatment Field: count (11.1.5) and grading (11.1.1)
- Trial instruction review including appointment for the next visit will be given

The following Procedure will only be performed on the Day 35 Visit in subjects enrolled in the PK Study Sub-Cohort:

- ❖ PK blood sampling

✓ ***Day 36 through Day 55***

From Day 36 through Day 55 no procedures will be performed.

✓ ***Day 56 Visit***

On Day 56 (±4) the following procedures will be performed:

- Adverse event(s): volunteered, elicited, and observed AEs will be recorded
- Concomitant medications documented
- Local Skin Reaction Score in the Treatment Field
- AK Lesions in the Treatment Field: count (11.1.5) and grading (11.1.1)
- Urine pregnancy test will be performed in all females and the results will be recorded
- Photographs of Treatment Field at selected sites
- Trial instruction review including appointment for the next visit will be given

✓ ***Day 57 through Day 83***

From Day 57 through Day 83 no procedures will be performed

✓ ***Day 84 Visit***

On Day 84 (±4) the following procedures will be performed:

- Adverse event(s): volunteered, elicited, and observed AEs will be recorded
- Concomitant medications documented
- Local Skin Reaction Score in the Treatment Field
- AK Lesions in the Treatment Field: count (11.1.5) and grading (11.1.1)
- Photographs of Treatment Field at selected sites
- Visit Closure Procedures: Subjects will be thanked for their participation and completion of the study will be noted in the subject's record

12.5 Unscheduled Visits

Investigators will invite subjects to attend an unscheduled visit to the investigative site (a) if during the course of the trial a subject's medical condition warrants more frequent observations than prescribed by the clinical protocol and/or (b) if a subject has an AE that has not stabilized or resolved and requires additional visits or follow-up beyond Day 84.

12.6 General Restrictions

12.6.1 Medication and Other Therapeutic Restrictions

- Topical creams, lotions, makeup or gels of any kind within the selected Treatment Field and the surrounding 2 cm border area from Screening through Day 84 are prohibited unless prescribed by the site Investigator and documented in the subject's file.
- Topical medications within the region of the head that contains the selected Treatment Field (i.e., left face, right face or scalp) are prohibited from Screening through Day 84:
  - Topical skin corticosteroids;
  - Keratolytic-containing therapeutic products or medicated or irritant topical salves, including, but not limited to, alpha-hydroxy acids (e.g., glycolic acid, lactic acid etc. >5%), beta-hydroxy acid (salicylic acid >2%), and urea >5%;
  - Topical retinoids (e.g., tazarotene, adapalene, tretinoin).
- Topical AK treatments including, but not limited to, 5-fluorouracil, diclofenac, imiquimod, or ingenol mebutate, and other at-home AK treatments **at any body site** are prohibited from Screening through Day 84**.**
- Any AK therapy including, but not limited to, topical medications, cryo-destruction or chemo-destruction, surgical excision, curettage, photodynamic therapy, dermabrasion, chemical peel, or laser resurfacing **on the head** are prohibited from Screening through Day 84.
- Systemic medications:
  - Immuno-modulatory medications including corticosteroids, interferon or interferon inducers, cytotoxic drugs, or immunosuppressive therapies
  - Retinoid therapy
- Investigation drug or devices.
- Any prescription medications or medicinal products that might obscure, impact, or interfere with proper evaluation of the test product and the Treatment Field are prohibited during the study.
- Starting any new systemic therapy during the trial is prohibited without prior approval of the Study Medical Monitor.

Allowed medications or therapies during the study must be documented and include:

- Subjects taking prescription medication, vitamins, or medical product not specifically prohibited above, may continue taking those products as long as the subject has been taking them continually for at least 2 months prior to Screening with no change in dose, manufacturer, or dosing interval. These medicinal products must be recorded on the appropriate Concomitant Medication pages. All other prescription medications, medicinal products, and vitamins are prohibited without prior approval of the Investigator and the Medical Monitor. The only exceptions to this rule are ≤ 1000 mg

acetaminophen, ≤ 550 mg naproxen, ≤ 400 mg ibuprofen or aspirin 325 mg once daily without prior consultation.

- Intranasal, inhaled, and ophthalmic corticosteroids used in the past for the management of allergies, pulmonary disorders, or other conditions.
- Light bodied bland moisturizer (e.g., Cetaphil, Lubriderm [without alpha-hydroxy acid]) in the selected Treatment Field as an aid to managing AEs with the approval of the site Investigator. Moisturizers must not be applied within six hours of test article application and the Treatment Field must be washed with soap prior to the next dosing.
- Medications used as prn (e.g. bronchodilators, antihistamines, sleep medications) listed as concomitant medications at Screening and/or Day 1 Pre-Dose Visits are permitted.
- Physical AK therapies including, but not limited to, topical cryo-destruction, surgical excision, curettage, dermabrasion, or laser resurfacing **on areas other than the head** are permitted at any time during the trial.

12.6.2 Topical Product Restrictions

Subjects should be instructed not to change their soaps, shampoos, laundry detergents, deodorants, etc. from Screening Visit through completion of the Day 84 Visit.

12.6.3 Sun Protection and Tanning

Subjects must avoid purposeful direct exposure to the sun or ultra-violet light from Screening Visit through completion of the Day 84 Visit activities. Subjects who go outdoors should wear proper clothing and hats that protect their skin from sunlight.

Purposeful tanning and application of tanning agents are prohibited at any time during the trial.

NOTE: Subjects should be encouraged to apply sunscreens that the subject has applied previously without developing a reaction. However, no topical sunscreens, creams, lotions, or gels of any kind may be applied within the selected Treatment Field or the surrounding 2 cm border area from Screening through Day 84 unless prescribed by the site Investigator and documented in the subject's file. Therefore, at Screening, subjects should be carefully instructed regarding this restriction as well as use of proper headwear to protect the Treatment Field and the surrounding skin.

12.6.4 Dietary Restrictions

Subjects may not ingest any product containing jasmine (e.g. jasmine tea).

Subjects may not drink any spiced, herbal, scented, or flavored teas from Screening until completion of all Day 35 procedures since these often contain jasmine without necessarily appearing on the label.

Subjects not included in the PK Study must limit their daily alcohol consumption to ≤ 24 ozs (ounces) of beer; ≤ 8 ozs of wine; or ≤ 2 ozs of any distilled alcoholic beverage from Day 1 through completion of the Day 35 Visit.

Dietary restrictions for the subjects in the PK Study are discussed in Section 12.6.5.

12.6.5 Special Restrictions for the PK Study Sub-Cohort

Subjects enrolled in the **PK Study Sub-Cohort** may not smoke, use nicotine products, or drink any alcohol from the Screening Visit until they complete Day 35 Visit. All medications taken between Screening and Day 84 must be pre-approved by their site Investigator.

12.6.6 Physical Exercise Restrictions

There are no restrictions placed upon physical exercise.

12.7 Childbearing Potential

12.7.1 Definitions

Childbearing Potential: Female subjects with at least one of the following medical conditions will be considered lacking childbearing potential:

a) aged ≥50 years and last normal menstrual period was at least 12 months prior to Screening;

b) undergone removal of her entire uterus (total hysterectomy); bilateral tubal ligation at least 6 months prior to Screening and/or bilateral oophorectomy

Females who do not meet at least 1 of the above criteria and have that criterion documented in the Medical History will be considered capable of childbearing and must be willing and able to use an acceptable form of contraception. Any subject who considered childbearing and who cannot use an acceptable form of contraception, must be excluded from the study under Exclusion Criterion #3 (Section 8.2).

Acceptable forms of contraception are: a) hormonal contraceptives [e.g., oral, transdermal, injectable, or intravaginal], b) barrier methods [condom and spermicidal or diaphragm/cervical cap and spermicidal], c) partner vasectomy (performed at least six months prior to study entry), or d) total abstinence. Subjects who become sexually active or begin to have relations with a partner who is not sterile during the study must agree to use an effective form of birth control for the duration of the study.

Urine Pregnancy test: All women enrolled in the trial must have a negative urine pregnancy test at Screening and Day 1 Pre-Dose. The urine dipstick test must have a minimum sensitivity of 25 mIU for β-hCG/mL.

12.7.2 Contraception

Nursing mothers, pregnant females, and women with childbearing potential (as defined in Section 12.7.1) must be able and willing to use a contraceptive method describes in that section, **until 1 month following the final study drug application (i.e., until the Day 56 Visit).**

Non-vasectomized male subjects with female partners without childbearing potential (as defined in Section 12.7.1) are not required to use contraception.

Non-vasectomized male subjects with female partners with childbearing potential (as defined in Section 12.7.1) must agree to use an acceptable form of contraception (as defined in Section 12.7.1) from Screening until 3 months after the last dose of study drug and must refrain from sperm donation for 3 months after the last dose of study drug.

Vasectomized males require no contraception.

13. STUDY MEDICATION

13.1 Description of Study Medication

The study drug will be manufactured, packaged, and labeled under GMP.

VDA-1102 is formulated as a milky-white ointment, with the drug substance being dissolved in a water-free ointment base. There are no discernable differences in color between VDA-1102 ointment and placebo.

5% and 10% VDA-1102 topical ointments and placebo ointment are supplied in 10 gm aluminum tubes with plastic caps, and stored refrigerated at 2-8 °C (36-46°F). Placebo will be identical to VDA-1102 minus the API (Active Pharmaceutical Ingredient).

13.2 Drug Packaging

The study drug tubes are enclosed in an aluminum envelope with an enclosed desiccant. The pouch is packaged in a protective container.

13.3 Drug Labeling

Each tube will be labeled with the following information:

1. Study number
2. Name of the Sponsor
3. Drug name (or placebo)
4. Lot numbers for placebo, 5% VDA-1102, and 10% VDA-1102
5. Directions for use
6. The statement, “Caution: New drug - limited by United States law to investigational use”
7. Storage conditions (degrees C and F)
8. Quantity: 10 grams

13.4 Study Drug Distribution

Sites in the U.S. will receive their drug from a depot located in the United States, while sites located in Israel will receive their drug from an Israeli depot. Study drug will be shipped under refrigerated conditions with temperature loggers.

13.5 Study Drug Storage

Site Pharmacy

All study drug will be stored at the investigative site (or their institutional pharmacy) at 2-8 °C (36-46°F) in a secured area with access limited by coded keypads and/or locks.

Home Storage

Subjects will be instructed to keep the study drug tube in the accompanying container and to keep this unit in their home refrigerator.

Travel

If a subject needs to transport the study drug (while travelling on vacation or business, or to the site), they will be instructed to protect the study drug from heat in the supplied cooler pack. The drug should not be placed in the trunk of a car or in checked luggage on a plane.

Subjects planning to travel away from home should contact their site in order to receive instructions how to properly care for the study drug.

13.6 Study Drug Dispensing and Administration

13.6.1 Study Drug Dispensing

Following conclusion of the Day 1 Pre-Dose procedures, the Investigator (or designee) will assure that the subject still meets all the study enrollment criteria. The investigator may then approve subject randomization.

Based on the randomization number generated by the IVRS, the site personnel (or institutional pharmacist) will allocate the appropriate study drug for each subject. The tube with its aluminum envelope will be removed from its container in the refrigerator. The envelope will be opened by site personnel and the tube removed. The aluminum envelope will be retained at the site for monitoring purposes and the tube will be placed in the container until dosing time.

13.6.2 Study Drug Dosing Cards

Study Drug Dosing Cards will be distributed to all the sites. These cards will be used: (a) by site personnel to train and to test subjects in the proper length of the study drug ointment strip to be expressed and applied to the Treatment Field, and (b) by enrolled subjects to measure the appropriate length of study drug ointment to be applied each evening to their Treatment Field.

A sample of the Dosing Card is included in Section 22.6. Instructions regarding proper use of the Dosing Card are included in the Subject Instruction Sheet.

13.6.3 Study Drug Measurement and Application Review

All sites will receive tubes of placebo with which to train all subjects to measure the appropriate quantity of study drug to be applied. These training tubes will be clearly marked.

Using the Treatment Field Template, placebo training ointment, and a Study Drug Dosing Card, the subject will be trained and tested in proper and precise dosing techniques.

Note: Training tubes containing placebo ointment will only be used to practice measurement of the proper study drug dose on the Dosing Card and <u>not</u> for application to the face during training and testing.

Screening Visit

Subjects will be trained and tested by site personnel at the Screening Visit. The subject will be taught to measure the study drug using placebo tubes supplied by the Sponsor. The subjects will also be taught how to apply the study drug, but they will not use the placebo for this part of the training. In other words, placebo should not be applied to their skin during the training.

Subjects who have difficulty measuring the dose or applying the study drug to the precisely may be asked to bring a dosing partner with them to the Day 1 Pre-Dose Visit. This dosing partner must be willing and able to assist the subject with study drug application once every evening for 28 days.

If the subject (or dosing partner) is unlikely to apply the study drug appropriately, the subject should be terminated from the study based on Inclusion#4 (Section 8.1).

Day 1 Pre-Dose Visit

Subjects who continue to meet the study enrollment criteria following Screening will be trained and tested twice by site personnel during the Day 1 Pre-Dose Visit: once at the beginning of the visit and once again at the end of the visit before randomization. If the subject (or dosing partner) is unlikely to apply the study drug appropriately, the subject should be excluded from the study based on Inclusion #4 (Section 8.1).

Day 1 Dosing Visit

Dosing at this visit will occur under the supervision of the site personnel. If at this visit the subject is unable to precisely prepare the study drug or is unable to properly locate the Treatment Field, they should be withdrawn before the study drug is applied. Application of the study drug during this visit will be the same as described in Section 13.6.4, below.

13.6.4 Study Drug Administration at Home

The study drug will be applied to the Treatment Field by the subject (or dosing partner) each evening approximately 2 hours before bedtime. If the subject would like to shower, wash their face, shampoo their hair, etc. before bedtime, these should be performed prior to study drug application.

At the dosing time, the subject should check the Treatment Field in the mirror to assure it is clean and dry.

The study drug tube will be removed from the container, the tube cover unscrewed, and the study drug ointment expressed as a strip into the rectangle printed on the supplied Dosing Card.

Using a mirror, photographs, and/or the landmarks drawn on the Treatment Field Template, the template will be appropriately positioned on the subject's face or scalp. The subject (or

dosing partner) will apply the study drug to the Treatment Field on their skin that corresponds to the 25 cm^2 area cut out of the template. Subjects (or their dosing partners) will apply the study drug with one finger to the center of the Treatment Field and spread the ointment evenly over the entire field. The Treatment Field will **not** be occluded. The subject will remove the Treatment Field Template from their face. With the same finger, the subject will spread ointment at the periphery of the Treatment Field approximately ¼ inch beyond the Treatment Field perimeter in order to insure that the whole Treatment Field was covered with study drug.

The subject will be instructed not to wet or touch the Treatment Field from the time of dosing until the following morning.

13.7 Study Drug Accountability and Dosing Compliance

The CRO will request the Investigator or their designee to sign a receipt for the study drugs on the day of arrival at the site. The site pharmacist and/or the assigned site personnel will be responsible for drug accountability. A drug accountability record should be maintained by the person responsible for dispensing the study drug to the subject. This should record which supplies arrived at the site and which container(s) is issued to each subject. The Medical Monitor should be notified of details of any supplies which are inadvertently damaged. Details of any supplies which are inadvertently damaged or unaccountable for any reason should be given on this drug accountability record, which will be collected at the end of the study.

All drugs will be inventoried by the monitor during and at the conclusion of the study. Secure disposal or return of unused supplies to the Sponsor at the end of the study will be arranged.

A single 10 mL tube of study drug will be assigned to each subject. Each tube will be weighed prior to the first dosing and at Day 7, 14, and 28 Visits. Subjects will also be asked during the once-weekly communication with the site and at each site visit whether they missed any doses and responses will be appropriately documented in the subject's medical record. In addition, subjects will complete a Dosing Diary, following each evening dose, with the date and time of dosing.

14. CONCOMITANT MEDICATION

Any prescription or non-prescription medication, alternative medication, herbal product, homeopathic substance, etc. used by the subject from 30 days prior to Screening until the subjects leaves the trial will be referred to as a Concomitant Medication. The Investigator is to record the use of all concomitant medications, both prescribed and over-the-counter, in the CRF.

Subjects should be advised against taking any new medication, both prescribed and over-the-counter, without consulting the Investigator, unless the new medication is urgently required for emergency use. Subjects taking medication other than those listed as prohibited in Section 12.6.1 may continue taking their routine medications and vitamins so long as they have been taking them for at least 2 months prior to Screening with no change in dose, manufacturer, or dosing interval.

At Screening and Day -1 Pre-Dose Visits, the study site personnel will check each subject's concomitant medications to ensure that subjects are not taking any prohibited medications listed in Section 12.6.1.

The Investigator and his designees are obligated to ensure the well-being of all subjects during this study. Consequently, no medication or treatment should be withheld from a subject requiring medical intervention. This may include treatments received by the subject prior to enrollment as well as in response to any new medical conditions that developed during the study. The Investigator (or designee) must inform a subject when concomitant medical intervention or treatment is indicated and report this in the appropriate section of the CRF.

15. ADVERSE EVENTS

15.1 Adverse Event Definition

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product, which does not necessarily have to have a causal relationship with the pharmaceutical product treatment. Any worsening of the subject's disease under study or other medical conditions will also be considered to be an AE, unless it is within the normal range of disease fluctuation for that subject.

In this trial LSRs will be collected independently of AEs. Any LSR that occurs within the selected Treatment Field and extends to adjacent surrounding skin (defined as within a 2 cm border around the Treatment Area) will be considered LSRs and will not be recorded as AEs. LSRs that require medical intervention (prescription medication) or extend beyond the 2 cm surrounding skin should be documented as an AE.

Clinically meaningful (for a given subject) changes in physical examination and test findings should also be recorded as AEs. The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

1. Test result is associated with accompanying symptoms, and/or
2. Test result requires additional diagnostic testing or medical/surgical intervention, and/or
3. Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
4. Test result leads to any of the outcomes included in the definition of a SAE.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not meet Condition 2 above for reporting as an AE.

Any abnormal test result that is determined to be an error does not require reporting as an AE.

Treatment Emergent Adverse Events (TEAEs) are AEs that occur *de novo* or worsen following the initiation of study treatment.

Surgical procedures themselves are not AEs; they are therapeutic measures taken for the AE, and should be documented as such.

Planned hospital admissions documented in the subject's CRF prior to randomization and study-related procedures are also not AEs.

Overdoses of the study drug will not be reported as an AE. However, any AEs or SAEs, as defined in Section 15, associated with an overdose will be reported as such.

15.2 Clarification of the Difference between "Severe" and "Serious"

Severity describes the intensity of an event, irrespective of its medical significance (such as severe headache). This is not the same as seriousness, which is based on regulatory definitions. Seriousness (not severity) defines SAE reporting obligations. The severity of all AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in detail on the CRF.

- Mild: Discomfort noticed but no disruption of normal daily activity.
- Moderate: Discomfort sufficient to reduce or affect daily activity.
- Severe: Inability to work or perform normal daily activity.

15.3 AE Reporting

Specific instructions regarding the reporting of AEs, including start and stop dates, relationship to study drug, outcomes, expectedness, etc. will be detailed in the Safety Monitoring Plan.

15.4 Relationship to Study Treatments

"Causality" refers to the relationship of the AE to the study drug. The investigator must include assessment of causality (whether there is a reasonable possibility the drug caused the event) for each AE. Causality will be categorized according to the following criteria:

- **Not Related:** There is no medical evidence to suggest that the AE may be related to study drug usage and other causes are much more likely.
- **Unlikely Related:** There is no medical evidence to suggest that the AE may be related to study drug usage, but a relationship cannot be completely ruled out. There are other more likely causes.
- **Possibly Related:** There is weak medical evidence to suggest that the AE may be related to study drug usage and a relationship cannot be completely ruled out.
- **Likely Related:** There is good medical evidence to suggest that the AE may be related to study drug usage but other causes cannot be ruled out completely.
- **Related:** There is a strong and convincing medical evidence to suggest that the AE is related to study drug usage and other possible causes are highly unlikely.

15.5 Laboratory Test and Diagnostic Procedure Abnormalities

An abnormal result will not be recorded as an AE unless one or more of the below occurs:

- The abnormal test is accompanied by symptoms.
- The test result leads to an alteration or interruption in study medication.
- The test result requires medical or surgical intervention

- The test result is considered clinically significant by an Investigator.

If such an event occurs, the test should be repeated within 10 days to confirm the finding and appropriately monitored.

15.6 Follow-up of Adverse Events

All AE related symptoms and/or signs will be followed until there is a return to the baseline status, all associated parameters have returned to normal (or are no longer considered clinically significant), or no further improvement is anticipated. Follow-up is mandatory, irrespective of causal relationship to the study drug(s). SAEs will be monitored until resolution, as medically indicated.

Any subject who has received at least 1 dose of the study drug and has experienced an AE that has not resolved or stabilized, may be invited to attend and unscheduled visits. Subjects with AEs that have not resolved or stabilized should be followed until resolution of the AE or for a minimum of 30 days after the subject's last application of the study medication.

15.7 Documentation and Reporting of Adverse Events by Investigator

Instructions for the completion of AE reports in a clinical study are provided by the Sponsor in the Safety Monitoring Plan.

16. SERIOUS ADVERSE EVENTS

16.1 Definition

An SAE is any AE that, at any dose, results in at least one of the following outcomes:

1. Death. Death is an outcome, not an event. Where the cause of death is uncertain, the reported SAE should be the same as the term on the subject's death certificate.
2. Is life-threatening. Life-threatening means that the subject was at immediate risk of death at the time of the SAE; it does not refer to an SAE that hypothetically might have caused death if it were more severe.
3. Requires or prolongs inpatient hospitalization.
4. Persistent or significant disability or incapacity. "Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.
5. A congenital anomaly or birth defect.
6. A medically serious event based upon appropriate medical judgment. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

16.2 Reporting of Serious Adverse Events

Full details of SAE reporting will appear in the Safety Monitoring Plan.

16.2.1 Reporting of Serious Adverse Events by Investigators

If the AE is serious, the Investigator must complete an SAE Report form, in addition to the AE page in the CRF.

Any SAE, whether or not related to the study treatment, must be reported within 24 hours to the Study Medical Monitor and the CRO responsible for the site. The following contact and communication methods may be used. The Medical Monitor and CRO will confirm receipt upon receiving the notification.

Chaim M. Brickman, Study Medical Monitor (Sponsor)

Telephone (mobile): 1-646-757-1062

E-mail: cbrickman@vidacpharma.com

Office Fax: 011-972-2-595-2091 from US

Home fax: 011-972-9-743-7061 from US

Chris Jones, Project Manager (U.S. CRO; Therapeutics, Inc.)

Telephone (mobile): 1-858-232-6969

E-mail: cjones@therapeuticsinc.com

Office: 1-858-571-1800 x169

Fax: 1- 858-571-1234

Samuel Kalderon, Monitor (Israel CRO; CTA Clinical Research Ltd.)

Telephone (mobile): +972-504233110

E-mail: samuelk@tca.co.il

Office: +972-9-966-2857

Fax: +972-9-894-3445

The SAE Report Form must be completed in accordance with instructions provided by the Sponsor or designee. The completed form must be faxed or emailed to the Study Safety Monitor within 24 hours of discovery of the SAE.

If, for any reason, the Investigator cannot notify the Study Safety Monitor via the appropriate form or if the Investigator suspects that using this method will delay the notification (e.g., during a holiday period), the Investigator must verbally notify the Sponsor Medical Monitor (or designee) via telephone. The SAE Report form must still be relayed at the earliest possible opportunity. SAEs must be reported to the IRB according to IRB guidelines.

The initial report must be as complete as possible, including details of the current illness and the SAE, and an assessment of the causal relationship between the event and the investigational product(s) or the study procedures.

Information not available at the time of the initial report (e.g., an end date for the AE or laboratory values received after the report) must be documented as a follow-up on the SAE Report form.

In addition, when a non-serious event becomes serious, details must be forwarded, within 24 hours of Investigator awareness that an AE has become serious, to the Sponsor or designee on an SAE Report form, with the date of the seriousness upgrade as the SAE start date.

All ancillary documentation (e.g. discharge letters, laboratory reports and consultations) must be sent to the Sponsor or designee. In the event of an SAE resulting in death, post-mortem reports should be routinely sent to the Sponsor or designee.

Any serious adverse events (SAEs) including death due to any cause, which occurs in any subject through Day 84, whether or not related to the investigational product, must be reported to the Sponsor within 24 hours. All subjects with SAEs must be followed-up for outcome.

17. STATISTICAL PLAN

17.1 Sample Size Rationale and Justification

The primary objective of the trial is to compare the reduction on Day 56 in the number of the AK lesions (or % reduction if baseline measure will be found different between the groups) in the Treatment Field of subjects receiving 5% or 10% VDA-1102 ointment to the reduction in the number of AK lesions in subjects receiving placebo. The sample size calculation was based on demonstrating an effect size of 0.83 using a two group t-test with a 0.045 two-sided significance level. The total significance level of 5% was divided between the interim analysis 0.5% (0.005) and the final analysis 4.5% (0.045). The sample size calculation was based on the final significance. The spending function calculation for alpha will be performed using the O'Brien-Fleming approach. Assuming a drop-out rate of 10%, approximately 84 subjects will be recruited in order to complete the study with a sample of approximately 75 evaluable subjects.

A sample size of 25 in each group will have 80% power to detect an effect size of 0.83 using a two group T-test with a 0.045 two-sided significance level.

17.2 Statistical analysis

All measured variables and derived parameters will be listed individually and, if appropriate, tabulated by descriptive statistics. For categorical variables summary tables will be provided giving sample size, absolute and relative frequency and 95% CI (Confidence Interval) for proportions by treatment group. For continuous variables summary tables will be provided giving sample size, arithmetic mean, standard deviation, coefficient of variation (CV%), median, minimum and maximum and 95% CI (Confidence Interval) for means of variables by treatment group. The data will be analyzed using the SAS ® version 9.3 or higher (SAS Institute, Cary North Carolina).

17.2.1 Efficacy Analysis

The efficacy analysis will be performed with the ITT, mITT, and PP populations (see Section 17.5.2). The primary efficacy endpoint is the change from baseline in number of AK lesions. If the baseline lesions number will be found different between the treatment groups, then relative change (%) will be analyzed as well. The within-group absolute changes (decrease) in AK number of lesions from baseline to each visit will be analyzed using paired t-test or signed rank test for two means (paired observations, as is appropriate).

Comparative analysis of the above changes will be applied between each of the active groups versus the placebo group using the two-sample t-test, the non-parametric Wilcoxon-Mann-Whitney rank sum test for independent samples, or the Median test (as appropriate).

If no statistically significant differences are observed between the two active VDA-1102 groups then these two groups will be pooled and compared to the placebo group in order to achieve higher statistical power.

The overall effect and trend of differences in the changes over time between the groups will be analyzed using a mixed-effect model for repeated measures. The model will include changes from baseline at any time, the fixed effect time, and the interaction of treatment and time. Contrast will be calculated for each time point (Days 7, 14, 28, 35 and 56) versus baseline and the overall effect. The model will be adjusted for baseline measure and for other covariates suspected as affecting the outcome and which will be found different between the treatment groups.

In case the baseline number of lesions differs between the groups, analysis of relative change (%) will be applied as well.

Chi-square test or Fisher's exact test (as is appropriate) will be used for analyzing the difference in percent of subjects with complete clearance of study AK lesions at the end of the treatment. Logistic regression will be applied for analyzing the difference in proportions with adjustment for baseline measure and for other covariates suspected as affecting the outcome and which will be found different between the treatment groups.

17.2.2 Safety Assessments

The safety end point data will be summarized for the ITT population. AEs will be categorized by System Organ Class (SOC) and Preferred Terms (PT) using the Medical Dictionary for Regulatory Activities (MedDRA version 19.1 or higher). The incidence of AEs, as well as the intensity and relationship to study drug will be summarized by treatment group. Safety will also be assessed by evaluating findings of physical examinations, vital signs, dermatologic assessments, clinical laboratory test results, 12-lead ECG tracings, Local Skin Reaction Score, drug exposure, concomitant medications, and withdrawals/terminations. These findings will be summarized and compared between treatments and within treatment group compared to findings from baseline evaluations.

Local Skin Reaction scores (LRS) will be summarized by treatment.

17.2.3 Pharmacokinetic Parameters

Non-compartmental PK parameters (e.g., AUC, C_{max}, T_{max}, $t_{1/2}$) will be calculated, if possible.

17.2.4 Exploratory Endpoints Assessment

Chi-square test or Fisher's exact test (as is appropriate) will be used for analyzing the difference in percent of subjects with complete clearance of study AK lesions at the end of the treatment. Logistic regression will be applied for analyzing the difference in proportions with adjustment for baseline measure and for other covariates suspected as affecting the outcome and which will be found different between the treatment groups.

Sensitivity analysis will be applied for identifying the cut-off of the change (or relative change) from baseline in number of lesions on Day 56. Analysis of the difference in the binary change will be applied using Chi-square test or Fisher's exact test. Logistic regression will be applied for analyzing these differences with adjustment for baseline measure and for other covariates suspected of affecting the outcome and which will be found different between the treatment groups.

Additional exploratory endpoint assessments will be described in the Statistical Analysis Plan.

17.3 Missing Data

Assuming the scope of missing data of the primary efficacy endpoint will be significant, data imputation will be applied. Missing data at random imputation (MAR) will be performed for those subjects with missing data. Multiple imputation will be applied using SAS PROC MI to perform the imputations. Sensitivity analysis will be used for detecting differences between the analyses with and without data imputation.

17.4 Interim Efficacy Analysis

An interim efficacy analysis will be conducted as soon as approximately 50% of the subjects have completed the study. The objective of the interim analysis is to evaluate the probability to achieve the primary efficacy endpoint.

The data for the interim analysis sub-set will be collected and analyzed for effect size and t-value. Effect size will be calculated based on the difference in the change from baseline in AK lesions for each of the active groups as compared to the placebo group. Relative change (%) will be used if baseline measure will be found different between the groups.

Futility will be based on O'Brien-Fleming boundaries. If the t-value with 22 degrees of freedom is below 0.34, then the study is unlikely to succeed when taken to completion. In case the distribution of the outcome variable will not be found with approximation to normality, then appropriate non-parametric methods will be considered for the interim analysis.

17.5 Data Sets

17.5.1 Intent-to-Treat Population

The ITT population will be defined as all subjects who are randomized and who receive study drug. This is an appropriate population for the primary analysis because this is a blinded trial and the dose will be applied in the clinic by the research clinic staff.

All safety analyses will be performed on the ITT population. Subjects will be analyzed according to the treatment actually received, not the treatment they were supposed to have received.

17.5.2 Modified ITT (mITT) Population

The mITT population includes all ITT patients who completed the study and have protocol deviations that do not significantly impact efficacy. The mITT population will also be used for the primary efficacy endpoint analysis.

17.5.3 Per-Protocol Population

The PP population includes all ITT patients who have no major protocol deviations. The PP population will also be used for the primary efficacy endpoint analysis.

17.5.4 Pharmacokinetic Population

A maximum of 18 subjects enrolled in the PK Study Sub-Cohort will constitute the PK population.

17.5.5 Definitions of the Terms Violation and Deviation

Violation – Any enrolled subject who does not meet the study enrollment criteria (see Inclusion and Exclusion Criteria in Section 8) will be considered a violation.

Deviation – Any activity that diverges from the procedures defined by this clinical protocol will be considered a deviation.

A **major deviation** is one that will definitely, probably or possibly significantly impact the subject safety or the quality of the trial data. An example of a major deviation is a subject who missed dosing >7 consecutive days of study drug.

A **minor deviation** is one that does not, or is unlikely to, significantly impact subject safety or the quality of the trial data.

All violations and deviations must be recorded in the study site's electronic system and signed by the Investigator (or designee).

It is the Sponsor's responsibility to determine whether the event will be considered a violation, major deviation, or minor deviation.

17.5.6 Subject Compliance Definitions

Subjects in the Treatment Period will be contacted by site personnel once-weekly. During that telephone conversation, subject compliance with the study drug dosing will be obtained and recorded.

17.6 Demographic and Baseline Characteristics

The comparability of the dose groups will be summarized by the evaluation of the demographic information, including age, gender, and country.

18. STUDY MANAGEMENT AND DATA COLLECTION

18.1 Data Collection Methods

An Electronic Data Capture (EDC) system will be utilized in this trial. The EDC system is fully validated and conforms to Title 21 Code of Federal Regulations (CFR) Part 11 and the Guidance for Industry on Computerized Systems Used in Clinical Trials requirements. The system has capabilities such as on-line data review via the browser, tracking review status of eCRFs with built-in flagging, issuance and tracking of electronic Data Clarification Forms (queries), and real-time viewing of entered subject's data. If the EDC is not ready to accept data by the time the trial begins enrollment, data may be entered on paper CRFs and transferred to the EDC as soon as it is ready to accept data.

The trained Investigational site staff will enter the data required by the protocol into the eCRFs from source documents into the EDC system. All information on the eCRFs must be traceable to these source documents. Instances of missing or uninterpretable data will be discussed with the study site for resolution. The study site is responsible for providing missing data and resolutions to the data queries and for correcting the eCRFs as appropriate. Electronic CRFs must be reviewed, signed, and dated by the Investigator. All original laboratory, and ECG reports will be kept with the subject source documentation and a copy will be transmitted to the Sponsor (or designee), if required.

Cardiac data should be transferred to eRT (eResearch Technology, Inc., Philadelphia, PA) the same day the data are obtained, if possible. Central Laboratory samples should be shipped on a daily basis, if possible, unless specific holiday or weekend schedules are in effect.

Data should be entered into the EDC (or paper CRF) within 5 business days of the study visit; queries should be appropriately addressed within 3 business days of receipt. During data cleaning and preparations for data lock, queries must be appropriately addressed by the site in a timely manner (2-3 business days).

18.2 Monitoring

Vidac Pharma (or their designee) will conduct site visits to the investigation facilities for the purpose of monitoring all aspects of the study.

18.3 Data Retention

All relevant correspondence (e.g. with the Sponsor, CRO, IRB, etc.) relating to this clinical study conduct should be maintained in the appropriate file at the site.

The Investigator must retain all records, including the source documents, ICFs, central laboratory reports including ECGs, and all other study-related documentation for a period of at least 2 years following the date the last marketing application is approved for the study drug for the indication for which it is being investigated, or 2 years after the date that the

FDA has been notified that all clinical investigation of the drug has been discontinued, whichever is greater, unless notified otherwise in writing by the Sponsor. These documents should, however, be retained for a longer period if required by the applicable regulations or if requested by the Sponsor. The Investigator must contact the Sponsor and gain written approval prior to destroying any records. No study documents will be destroyed or moved to a new location without prior written approval of the Sponsor. If the Investigator relocates, retires, or withdraws from a clinical study for any reason, all records required for the study should be transferred to an agreed-upon designee, e.g. another Investigator.

19. CLINICAL STUDY ADMINISTRATION, ETHICS, AND CONDUCT

19.1 Good Clinical Practice

GCP is an important ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of study subjects are protected.

19.2 Confidentiality

19.2.1 Study Confidentiality

All information regarding the nature of the investigation provided by the Sponsor or its designee to the Investigator and his / her staff or designees (except for information required by law or regulations to be disclosed to the IRB, the subject, and/or the appropriate regulatory authorities) must be maintained in confidence by the Investigator and his / her staff or designees.

19.2.2 Subject Anonymity

The anonymity of participating subjects must be maintained. Subjects will be identified by their initials and subject number on eCRFs and other documents submitted to the Sponsor. Documents not submitted to the Sponsor include those that identify the subject (eg, the signed ICF), and must be maintained in strict confidence by the Investigator, except as necessary to allow auditing by the IRB, Sponsor or its designee, FDA, and/or equivalent authorities.

19.3 Subject Information and Informed Consent

Before being enrolled in the clinical study, subjects must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to them.

An informed consent document that includes information about the study will be prepared and given to the subject. This document will contain all the elements required by the ICH E6 Guideline for GCP and any additional elements required by local regulations. The document must be in a language understandable to the subject and must specify who informed the subject. Where required by local law, the person who informs the subject must be a physician.

All ICFs must contain the minimum elements as mandated by the FDA and ICH guidelines and will be subject to the Sponsor's (or designee's) approval as well as the IRB's approval.

The Sponsor (or designee) may submit ICFs to a central IRB for review and approval or favorable opinion contingent upon the prior Investigator permission and review.

The Investigator will not undertake any measures or procedures specifically required of a subject for the clinical study until valid consent has been obtained.

The Investigator should inform the subject's primary physician about the subject's participation in the study if the subject has a primary physician and if the subject agrees to the primary physician being informed, as per the site's standard operating procedures.

If an amendment to the protocol changes the subject participation schedule in scope or activity, or increases the potential risk to the subject, the ICF must be revised, submitted to the IRB for review and approval or favorable opinion. The revised ICF must be used to obtain consent from a subject currently enrolled in the study only if he or she is affected by the amendment. The revised ICF must be used to obtain consent from any new subjects who are enrolled into the study after the date of the approval or favorable opinion of the amendment.

19.4 Study Closure

Completion or premature termination of the study will be reported by the Sponsor to the regulatory agency and by the Sponsor or by the Investigator to the IRB as required by local regulations or by the IRB.

Once the database is locked, and all efforts are made to settle all outstanding queries, site closeout will occur. Study materials must be returned, disposed of, or retained, as directed by the Sponsor.

19.5 Early Termination of the Clinical Trial

If, in the opinion of the Investigator, the clinical observations in the study suggest that it may be unwise to continue, the Investigator may terminate the study after consultation with the Sponsor. A written statement fully documenting the reasons for such a termination will be provided to the Sponsor. In addition, the Sponsor may terminate the study at any time.

If it becomes apparent that subject enrollment is unsatisfactory with respect to quality or quantity, or that data recording is inaccurate or incomplete on a chronic basis, the Sponsor has the right to terminate the study and remove all study materials from the investigational site. A written statement will be provided to the Investigator, the IRB, and regulatory authorities, if required. In the event any SAEs or non-SAEs are reported, all documentation relating to the event(s) must be obtained.

20. INVESTIGATOR'S OBLIGATIONS

20.1 General

The Investigator agrees that the study will be conducted in accordance with the clinical protocol, FDA's GCP guidelines, ICH guidelines, and the Declaration of Helsinki. The Investigator will conduct all aspects of this study in accordance with all governmental, state and local laws.

20.2 Institutional Review Board

Before initiation of the study at any site, the PI or designee must obtain approval of the clinical protocol and ICF from the IRB complying with the provisions specified in FDA CFR, Title 21, Part 56, ICH Guidelines, and all governmental, state and local laws.

A copy of the written IRB approval of the protocol, ICF and any other documentation (such as advertising) as appropriate must be provided to the Sponsor or its designee prior to initiation of the study. The approval letter must identify the IRB name and address, the clinical protocol by title and/or protocol number, and the date approval was granted. Furthermore, the approval letter must contain a statement that the IRB complies with the FDA CFR, Title 21, Part 56, and ICH Guidelines for a study conducted under an IND, or other applicable government regulations for studies not conducted under an IND.

The Investigator is responsible for supplying the IRB with the data required for continued review of this study at intervals not exceeding one year, or at intervals otherwise specified by the IRB. The Investigator shall supply the Sponsor with written documentation of this continued review. When necessary, an extension or renewal of the IRB approval must be obtained and this shall also be forwarded to the Sponsor. A list of the IRB members should be forwarded to the Sponsor in accordance with local regulations.

The IRB and the regulatory authorities will be provided with any amendments for their review and/or approval. A yearly status report on the progress of the study will be submitted by the Investigator to the IRB per their regulations.

20.3 Investigator Protocol Adherence

The Investigator and his/her designees are required to adhere to the protocol. While deviations from the protocol are discouraged, they may be necessary in order to eliminate an immediate hazard to subjects or to facilitate adherence to protocol procedures.

Emergency deviations from the protocol that eliminate an apparent immediate hazard to a subject and that are deemed crucial for the safety and well-being of a particular subject may be instituted for that subject only. The Investigator or other attending physician will contact the Sponsor as soon as possible in the case of such a deviation. These deviations do not

require pre-approval by the IRB; however, the Sponsor and the IRB must be notified in writing as soon as possible after the departure has been made. In addition, the Investigator will document in the subject's eCRF the reasons for protocol deviation and the ensuing events.

20.4 Protocol Amendments

Any additions or changes to the clinical protocol will require a protocol amendment. The Amended Clinical Protocol Signature Page will be signed by the protocol signatories. Protocol amendments must undergo IRB approval prior to implementation. Should the ICF require changes, the revised ICF must be approved also according to the same procedure.

20.5 Audits and Inspections

The Investigator will permit study-related monitoring, audits and inspections by the IRB, the Sponsor or its designee, government regulatory bodies, and quality assurance groups of all study-related documents. This includes direct access to source documents, regulatory documents, data collection instruments, study data, etc. The Investigator will ensure that all study-related facilities (e.g., pharmacy, laboratories, etc.) are maintained in accordance with GCP guidelines.

Participation as an Investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable quality assurance offices.

21. REFERENCES

Chetty C, Choi F, and Mitchell T (2015), "Primary care review of actinic keratosis and its therapeutic options: a global perspective", *Dermatol Ther (Heidelb)* 5:19-25.

Cohen J.L. et al. (2010), "Actinic keratosis as a key component of preventive strategies for nonmelanoma skin cancer", *Journal of Clinical and Aesthetic Dermatology* 3(6):39-44.

Heaphy M.R. Jr. and A.B. Ackerman (2000), "The nature of solar keratosis: a critical review in historical perspective", *Journal of the American Academy of Dermatology* 43(1):138-150.

Hurwitz R.M. and L.E. Monger (1995), "Solar keratosis: an evolving squamous cell carcinoma. Benign or malignant?", *Dermatologic Surgery* 21(2):184.

Kanellou P. et al. (2008), "Genomic instability, mutations and expression analysis of the tumour suppressor genes p14 ARF, p15 INK4b, p16 INK4a and p53 in actinic keratosis", *Cancer letters* 264(1): 145-161.

Kanjilal S. et al. (1995), "p53 mutations in nonmelanoma skin cancer of the head and neck: molecular evidence for field cancerization", *Cancer research* 55(16): 3604-3609.

Krawtchenko N. et al. (2007), " A randomised study of topical 5% imiquimod vs. topical 5-fluorouracil vs. cryosurgery in immunocompetent patients with actinic keratoses: a comparison of clinical and histological outcomes including 1-year follow-up", *British Journal of Dermatology* 157(s2): 34-40.

Mittelbronn et al. (1998), "Frequency of pre-existing actinic keratosis in cutaneous squamous cell carcinoma", *International Journal of Dermatology* 37(9): 677-681.

Olsen et al. (1991), "A double-blind, vehicle-controlled study evaluating masoprocol cream in the treatment of actinic keratosis on the head and neck: A double-blind, vehicle-controlled study evaluating masoprocol cream in the treatment of actinic keratoses on the head and neck", *J Am Acad Dermatol* 24(5 Pt 1): 738-43.

Oppel T. and H.C Korting (2004), "Actinic keratosis: the key event in the evolution from photoaged skin to squamous cell carcinoma. Therapy based on pathogenetic and clinical aspects", *Skin Pharmacol Physiol.* 17:67–76.

Ortonne J.P. (2002), "From actinic keratosis to squamous cell carcinoma", *British Journal of Dermatology* 146(s61): 20–23.

Padilla R. S. et al. (2010), "Gene expression patterns of normal human skin, actinic keratosis, and squamous cell carcinoma: a spectrum of disease progression", *Archives of Dermatology* 146 (3): 288-293.

Röwert-Huber J. et al. (2007)," Actinic keratosis is an early in situ squamous cell carcinoma: a proposal for reclassification", *British Journal of Dermatology* 156(s3): 8–12.

Shergill B, Zokaie S, and Carr AJ (2014), "Non-adherence to topical treatment for actinic keratosis", *Patient Prefer Adherence* 8:35-41.

Stockfleth, E. (2012), "The paradigm shift in treating actinic keratosis: a comprehensive strategy", *Journal of Drugs in Dermatology: JDD* 11(12):1462-1467.

Warino L. et al. (2006), "Frequency and cost of actinic keratosis treatment", *Dermatologic Surgery* 32(8):1045–1049.

Werner R.N. et al (2015), "Evidence- and consensus-based (S3) guidelines for the treatment of actinic keratosis – International League of Dermatological Societies in cooperation with the European Dermatology Forum - Short–Version", *Journal of the European Academy of Dermatology and Venerology* 29: 2069-2079.

Ziegler A. et al. (1994), "Sunburn and p53 in the onset of skin cancer", *Nature* 372(6508): 773-776.

22. APPENDICES

22.1 Local Skin Reaction Score

This score has been modified from a score published in Lebwohl M et al (2012), "Ingenol Mebutate Gel for Actinic Keratosis", *N Engl J Med* 2012;366:1010-9).

The Local Skin Reaction Score is an assessment of **all** the skin in the Treatment Field (not of the AK lesions). At each study visit the Investigator (or designee) will assign a severity score to each of the objective and subjective findings listed in the table. For example, if the Treatment Field contains vesicles of moderate severity, the number 3 would be placed under the field labelled "Vesicles".

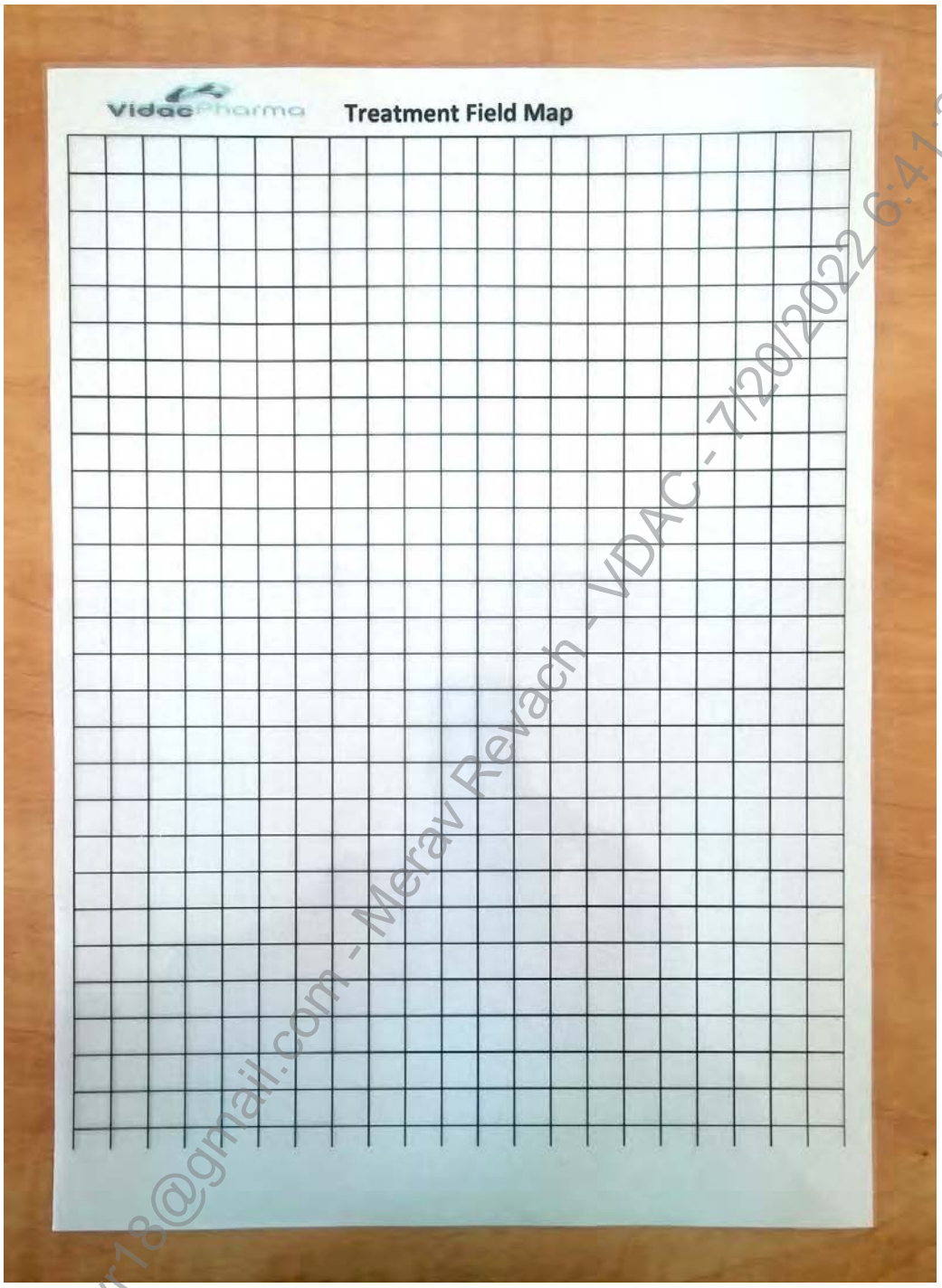
The Investigator will assess the selected Treatment Field and rate the findings on a 5 point scale. The LSR score will consist of the sum of all the individual severity scores.

Treatment Field Findings	**Erythema**	***Edema***	**Weeping or Exudate**	**Vesicles**	**Erosion or Ulceration**	**Scaling or Dryness**	**Scabbing or Crusting**	**Itching**	**Pain**
Severity Score [1]									

The 5 point LSR Score is: **0 = No reaction, 1=Trace reaction, 2= Mild reaction, 3=Moderate reaction, and 4=Severe reaction.**

22.2 Treatment Field Map

Below is a picture of the Treatment Field Map on a white piece of paper on a brown platform.



22.3 Treatment Field Map Instructions

This thin, flexible, plastic transparency sheet (Section 22.2), with a grid of 1cm x 1cm squares printed on the surface, will be used by the Investigator (or designee) to outline the Treatment Field, enabling consistent counting the AK lesions within the Treatment Field. It is also used to prepare the Treatment Field Template (see Treatment Field Template instructions Section 22.5).

This tool should be used in the following manner:

1. Affix a label that includes the subject's identifier(s) and the visit date near the top of the sheet.
2. Place this transparency over the Treatment Field selected on the subject's face or scalp.
3. With a supplied marker, draw the outline of several facial landmarks (e.g. eyebrows, ear helix and/or lobule, moles, scars) on this map. These landmarks will be transferred
4. Write at the top of the map any additional information that helps orient placement of the map. For example, "Left Face" or "Center Scalp".
5. Identify the 25 squares that make up the 25 cm^2 contingent area (that includes 4 to 8 discrete non-hyperkeratotic and non-hyperkeratotic AK lesions)
6. With the supplied marker, outline the outer border of the 25 squares that defines the chosen Treatment Field.

22.4 Treatment Field Template

Below is a picture of the Treatment Field Template on a white piece of paper on a brown background.

22.5 Treatment Field Template Instructions

This thin, flexible, plastic blank transparency (Section 22.4) will be used by the Investigator (or designee) to prepare a template (stencil) outlining the Treatment Field. This template will be used by the subject to precisely locate the Treatment Field and to properly apply the study drug. This tool should be prepared in the following manner by the Investigator (or designee):

1. Take one of the supplied clear Treatment Field Templates and affix a label to the top that includes the subject's identifiers and the date of the visit.
2. Lay the template on top of the Treatment Field Map of this subject.
3. Trace all the identifying landmarks from the Treatment Field map onto the clear template using the supplied marker.
4. After the template is removed from the map, the Treatment Field should be precisely cut out of the Treatment Field Template using the supplied safety blade.
5. At least 4 templates should be made by repeating steps 1-4.
6. The map and the templates should each be checked for accuracy on the subject's Treatment Field. Make sure the template delineates the Treatment Field precisely and doesn't include a wider area (and different AK lesions) when it is laid flat.
7. **Use this opportunity to demonstrate to the subject the proper positioning of the template on the Treatment Field.** If possible, let the subject use a mirror to observe the position of the template over the Treatment Filed.
8. The Treatment Field Map and one copy of the template should be stored at the site in a protective envelope. The template should be used at each visit for counting AK lesions, **not the map** since the grip marks on the map might obscure or distort the AK lesions.
9. At each visit, at least 2 copies of the Treatment Field Template should be given to the subject for practicing and dosing purposes.

22.6 Subject Dosing Card

Below is a picture of the Dosing Card on a white piece of paper on a brown background.

22.7 Subject Instruction Packet

Below is a copy of the Subject Instruction Packet.

VidacPharma 1 of 4

SUBJECT INSTRUCTION PACKET

Please follow these instructions carefully. Contact the study staff at the telephone number below, if you have any questions or concerns.

Name: _____ Phone: _____

A. Your study kit contains the following materials:

1. **One study drug tube in a single container**. The study drug should be kept REFRIGERATED at all times in its container.
2. **Dosing Cards** – plastic cards with a small rectangle. These will be used to measure the correct amount of ointment to apply each night to your Treatment Field (the area on your face or scalp where you will apply the study drug).
3. **Treatment Field Template** – a plastic sheet with a cut out. This stencil will be used as a guide to assist in applying the study drug to your Treatment Field on your face or scalp.

B. Travelling with the study drug:

1. Place the study drug in your REFRIGERATOR (not freezer) as soon as you get home from your study visits.
2. When travelling, try to keep the study drug and container cool. Keep the study drug in the passenger area of the car and away from any sources of heat.
3. If you plan to travel away from home overnight, discuss proper care of the study drug with the study staff.
4. When travelling, NEVER place your study drug in the trunk of your car or in checked luggage on a plane. Keep the drug with you.
5. Don't leave the study drug in your car. Take it with you.

C. When to Apply the Study Drug:

1. The study drug should be applied every evening approximately **2 hours** before bedtime to a clean and dry Treatment Field.
2. If you plan to shower or wash up in the evening, to wash your face, to shower, or to shampoo your hair before bedtime, always do so *before* you apply the study drug to your face or scalp.
3. After you apply the study drug, do not touch or wash the Treatment Field until the following morning.

Subject #: _ _ _ _ _ _ _ _ Subject Initials: _ _ _

D. Measuring the Correct Dose of the Study Drug:

1. Place the Dosing Card on a white piece of paper. Find the clear rectangle in the middle of the Dosing Card.
2. Remove the study drug container from the refrigerator. Take the study tube out of its container and remove the cap.
3. Dispense a strip of the study drug so that it fills the clear portion of the rectangle, from one end of the clear part of the rectangle to the other end of that clear space.
4. Replace the cap on the tube and place the tube back in its container. Return the container to the refrigerator.

E. Applying the Study Drug to the Correct Part of your Face or Scalp:

1. Remove the Treatment Field Template from its envelope.
2. Find a mirror that doesn't require you to hold it in your hand. A wall mirror or a free-standing mirror on a stand is fine.
3. Using the mirror and **the landmarks drawn on the Treatment Field Template**, place the template on your face or scalp. If you've positioned the template properly using the landmarks, the hole in the template should be over the Treatment Field.
4. Hold the template in place with one hand so that the other hand is free. Check in the mirror to be sure that the landmarks are still lined up properly.
5. Using one finger on your free hand, remove the study drug from the Dosing Card.
6. Spread the study drug evenly over the entire Treatment Field via the hole in the template.
7. Use the same finger to remove any study drug left on the Dosing Card. Apply the remaining ointment to the Treatment Field and spread it evenly.
8. Put down the template.
9. While looking in the mirror, use the same finger to spread the study drug approximately ¼ inch beyond the borders of the Treatment Field so as to ensure that you covered the entire Treatment Field. Make sure you covered all areas of the field.
10. Wash your hands with tap water and soap.
11. Fill out the Dosing Diary immediately. Don't wait.

Subject #: _ _ _ _ _ _ _ **Subject Initials:** _ _ _

F. Dripping of the Study Drug

1. Should the study drug begin to run or drip outside the Treatment Field, gently wipe the area with a clean, dry tissue.
2. Never wipe the Treatment Field itself.

G. Proper Care of the Treatment Field

1. When washing the Treatment Area the next morning, wash gently using your usual soap. Do not cover the Treatment Area with bandages or other dressings. Never rub the Treatment Field with a wash cloth.
2. If your eyes are exposed to the study drug, wash the eye region thoroughly with warm tap water.
3. Avoid excessive sun exposure (e.g., sunbathing, tanning booths) and wear protective loose head wear over the Treatment Area when exposed to sunlight throughout the duration of the study.
4. Do not apply any moisturizers, sunscreen, make-up, creams, lotions, powders or any topical product other than the study drug to the Treatment Field unless instructed to do so by your study doctor.

H. Visits to the Study Site

The study staff will arrange an appointment for your next study site visit.

Remember to bring 2 things to each study visit:

a. The **study drug** – bring the container and the tube
b. This **Subject Instruction Packet** - bring all pages with you. The study staff will want to review the instructions and your diary with you.

I. Food and Medication Restrictions

1. Do not change your soaps, shampoos, laundry detergents, deodorants, etc. while you are in the study.
2. Do not drink jasmine tea or any spice, herbal, scented, or flavored teas at any time during the study since they may include jasmine.
3. If you are not included in the PK Study must limit their daily alcohol to less than 24 ozs (ounces) of beer, 8 ozs of wine; or 2 ozs of whisky, whiskey or brandy from the first time you apply the study drug until the end of the study.
4. If you are included in the PK study, you cannot smoke, use any nicotine products, or drink any alcoholic beverages while you are in study. You cannot take any medications without first consulting with your study staff.

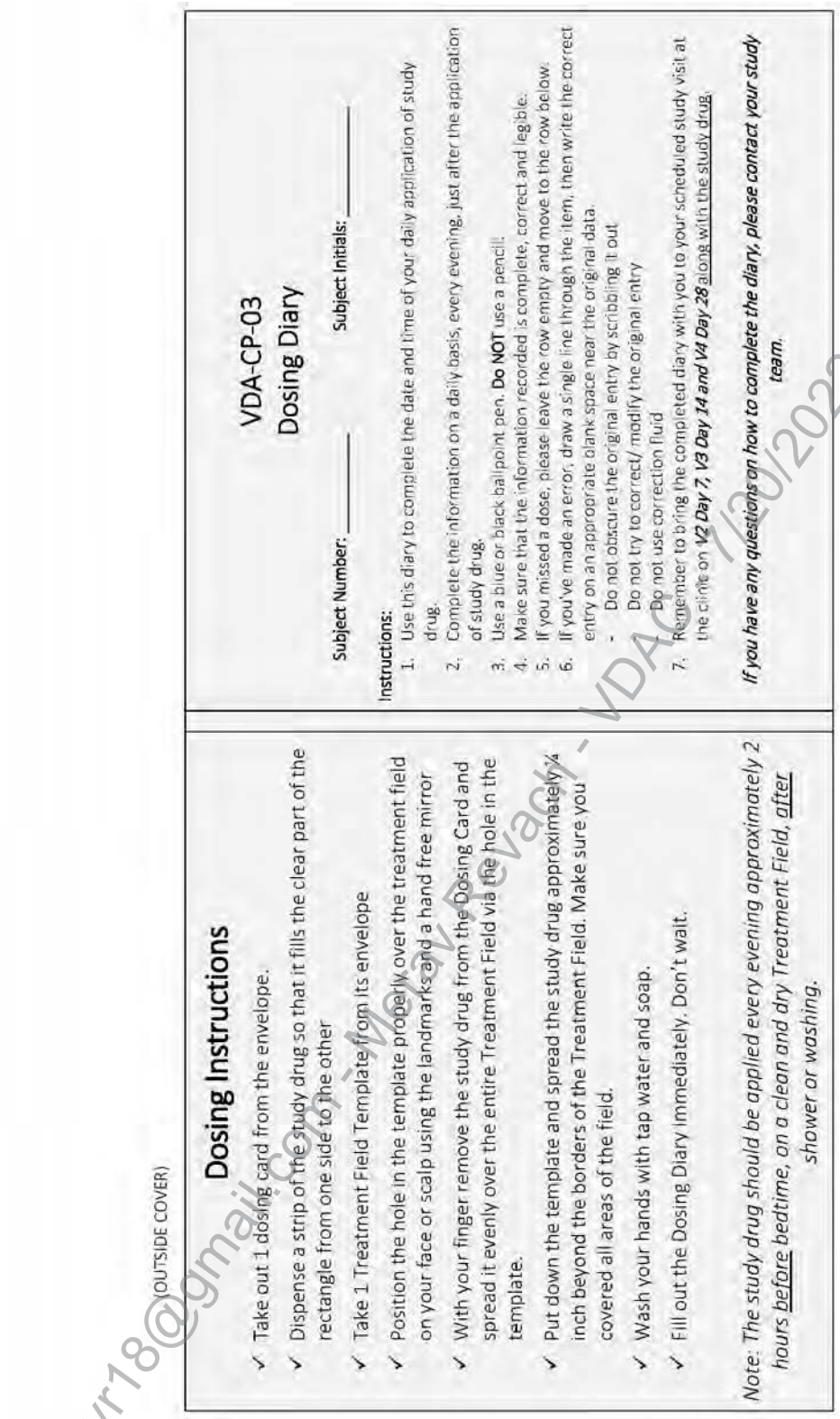
Subject #: _ _ _ _ _ _ _ Subject Initials: _ _ _

5. If you are taking medication, vitamins, or medical product, you may continue taking those products as long as you have been taking them continually for at least 2 months prior to starting the study as long as there has been no change in dose, manufacturer, or dosing interval during those 2 months. All other prescription medications, medicinal products, and vitamins are prohibited without prior approval of the Investigator and the Medical Monitor. The only exceptions to this rule without prior consultation are once daily doses of less than 1000 mg acetaminophen, or 550 mg naproxen, or 400 mg ibuprofen or aspirin 325 mg.
6. Nasal, inhaled, and eye steroids drop or sprays used in the past for the management of allergies, pulmonary disorders, or other conditions are permitted.

If you ever have any questions or issues, please call the number on the first page of this packet.

Subject #: _ _ _ _ _ _ _ _ Subject Initials: _ _ _

22.8 Dosing Diary



(OUTSIDE COVER)

Dosing Instructions

- ✓ Take out 1 dosing card from the envelope.
- ✓ Dispense a strip of the study drug so that it fills the clear part of the rectangle from one side to the other
- ✓ Take 1 Treatment Field Template from its envelope
- ✓ Position the hole in the template properly over the treatment field on your face or scalp using the landmarks and a hand free mirror
- ✓ With your finger remove the study drug from the Dosing Card and spread it evenly over the entire Treatment Field via the hole in the template.
- ✓ Put down the template and spread the study drug approximately ¼ inch beyond the borders of the Treatment Field. Make sure you covered all areas of the field.
- ✓ Wash your hands with tap water and soap.
- ✓ Fill out the Dosing Diary immediately. Don't wait.

Note: The study drug should be applied every evening approximately 2 hours before bedtime, on a clean and dry Treatment Field, after shower or washing.

VDA-CP-03
Dosing Diary

Subject Number: _____ Subject Initials: _____

Instructions:

1. Use this diary to complete the date and time of your daily application of study drug.
2. Complete the information on a daily basis, every evening, just after the application of study drug.
3. Use a blue or black ballpoint pen. **Do NOT** use a pencil!
4. Make sure that the information recorded is complete, correct and legible.
5. If you missed a dose, please leave the row empty and move to the row below.
6. If you've made an error, draw a single line through the item, then write the correct entry on an appropriate blank space near the original data.
   - Do not obscure the original entry by scribbling it out
   - Do not try to correct/ modify the original entry
   - Do not use correction fluid
7. Remember to bring the completed diary with you to your scheduled study visit at the clinic on ***V2 Day 7, V3 Day 14 and V4 Day 28*** along with the study drug.

If you have any questions on how to complete the diary, please contact your study team.

VDA-CP-03 Dosing Diary ENG v2 dated 05July16

DOSING DIARY

Treatment Day	Day of Week	Date of application (dd/MMM/yy)	Time of application (hh:mm am/pm)	Treatment Day	Day of Week	Date of application (dd/MMM/yy)	Time of application (hh:mm am/pm)
1				15			
2				16			
3				17			
4				18			
5				19			
6				20			
7				21			
8				22			
9				23			
10				24			
11				25			
12				26			
13				27			
14				28			

VDA-CP-03 Dosing Diary ENG v2 dated 05July16