CLINICAL STUDY PROTOCOL

1. COVER AND SIGNATURE PAGES

1.1. Title Page

Clinical Study Number:	VDA-CP-05
Original Clinical Protocol Date:	30 April 2018
Clinical Protocol Amendment	N/A
Clinical Protocol Amendment Date	N/A
Study Drug Identification:	VDA-1102
Clinical Protocol Version	1.0
Clinical Protocol Title:	A Phase 2B Open-Label Study to Evaluate the Efficacy, Safety, and Tolerability of Topical VDA-1102 Ointment in Subjects with Actinic Keratosis
Study Phase:	Phase 2B
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. Chief Medical Officer
Study Principal Investigator	Mark Lebwohl, M.D. Mount Sinai School of Medicine New York, New York USA

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) as set forth in the International Conference on Harmonization (ICH) guidelines on GCP (ICH E6), and applicable local regulatory requirements. The concepts and information contained herein are confidential and proprietary to Vidac Pharma Limited and shall not be distributed or disclosed in whole or in part without the expressed written permission of Vidac Pharma Ltd.

1.2. Signature Pages

1.2.1. Clinical Signature Page

Title: A Phase 2B Open-Label Study to Evaluate the Efficacy, Safety, and Tolerability of Topical VDA-1102 Ointment in Subjects with Actinic Keratosis

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

Signature: _____

Date: _____

Chaim M. Brickman, M.D.
Chief Medical Officer or designee
Sponsor Medical Monitor

Signature: _____

Date: _____

1.2.2. Investigator Signature Page

Clinical Study Number:	VDA-CP-05
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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 2B Open-Label Study to Evaluate the Efficacy, Safety, and Tolerability of Topical VDA-1102 Ointment in Subjects with Actinic Keratosis	
Study Center(s): Approximately 8 sites in the US	
Study Duration: Approximately 12 months	**Phases of Development:** Phase 2

Study Objectives

Primary Objectives:

- To assess the percent of subjects with complete clearance of the actinic keratosis (AK) lesions in their Treatment Field at Week 16
- To assess the percent of subjects who have facial Treatment Fields who have complete clearance of actinic keratosis (AK) lesions at Week 16
- To evaluate the systemic and local (skin) safety and tolerability of topical application of VDA-1102 ointment in adult subjects with AK.

Secondary Objectives:

- To assess the percent of subjects with partial (≥75%) clearance of the actinic keratosis (AK) lesions in their Treatment Field on Week 16
- To assess the percent of subjects with facial Treatment Fields who have partial (≥75%) clearance of the actinic keratosis (AK) lesions on Week 16
- To assess the reduction in the number of the actinic keratosis (AK) lesions in the Treatment Field on Week 16
- To assess the reduction in the number of the actinic keratosis (AK) lesions on Week 16 of subjects with facial Treatment Fields

Study Design

This Phase 2 clinical trial is a 3-part, open-label, multi-center study involving a non-occluded, daily topical dermal application of 1 of 2 strengths of VDA-1102 ointment for approximately 12 weeks (84 days) to an initial 2 cohorts of subjects. The first 40 eligible subjects will be enrolled into Cohort 1 (Part A). Cohort 1 subjects will be assigned to receive approximately 200 mg of 10% VDA-1102 twice-daily (BID). Once approximately 40 subjects have been enrolled in Cohort 1, Cohort 1 will be closed to enrollment and Cohort 2 (Part B) will be opened for enrollment. Cohort 2 subjects will be assigned to receive approximately 200 mg of 20% VDA-1102 once-daily (QD). Once approximately 40 subjects have been enrolled in Cohort 2, an additional 70 subjects will be randomly assigned to Cohort 1 or Cohort 2 (Part C) in a 1:1 ratio.

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 actinic keratosis (AK) lesions within an approximate 25 cm^2 area on the cheek, forehead, or hairless scalp (the "Treatment Field").

Parts A, B, and C of this clinical trial will each include the same 3 study periods, a Screening Period (Day -21 through Day 1 Pre-Dose), a Treatment Period (Day 1 Dosing through Week 12), and a Post-Treatment Follow-Up Period (Week 13 through Week 16).

During the **Screening Visit** (up to 21 days pre-dose) subjects who have given written informed consent will undergo safety assessments, Treatment Field identification, and 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. Subjects who continue to meet the enrollment criteria will be enrolled and will continue to the Day 1 Dosing Visit. The number of AK lesions within the Treatment Field will be recorded.

During the Treatment Period, enrolled subjects (or their dosing partner) will apply the first dose of the study drug on Day 1 under the supervision of the site personnel to assure proper application. After release from the research clinic on Day 1, subjects (or their dosing partner) will continue the prescribed VDA-1102 dosing regimen at home. Subjects will visit their respective investigative sites on **Week 4** and **Week 8** for safety and efficacy (AK lesion count) assessments, drug accountability, and re-training in proper application of the study drug. On the **Week 12 Visit**, subjects will return to the clinic for their final safety and efficacy assessments as well as final study drug accountability.

During the Post-Treatment Follow-up Period, subjects will visit their respective investigative sites on **Week 13** and **Week 16** for safety and efficacy assessments. Subjects will exit the study following completion of their Week 16 assessments. Subjects with continuing AEs will be scheduled for follow-up evaluation, as appropriate.

Subjects will have Post-Treatment Follow-Up visits to their respective investigative sites on **Week 13 and Week 16** for safety and efficacy assessments. All AK lesions within the Treatment Field will be counted. At the Week 13 Visit site personnel will review with each subject the study instructions and the date of their next study visit.

Subject Population:

Men or women 18 years of age or older with a diagnosis of Actinic Keratosis with between 4 and 8 Grade 1 or Grade 2 AK lesions within a single contiguous 25 cm^2 area of skin on their face or balding scalp.

Number of Enrolled Subjects (planned):

A maximum of approximately 150 subjects will be enrolled in this 2-cohort clinical trial. In each cohort, approximately 75 eligible subjects will be enrolled in order to complete each cohort with safety and efficacy data from at least 70 subjects who received study drug.

Maximum Time Subjects May Remain in the Study:

Subjects may participate in this study for a maximum of 143 days (21 days Screening Period + 89 days Treatment Period + 33 days Post-Treatment Follow-Up Period).

Study Endpoints:

Primary Efficacy Endpoints:

- Percentage of subjects achieving complete clearance of AK lesions within their Treatment Field on Week 16
- Percentage of subjects with facial Treatment Fields achieving complete clearance of AK lesions on Week 16

Secondary Efficacy Endpoints:

- Percentage of subjects achieving partial (≥75%) clearance of AK lesions within their Treatment Field on Week 16
- Percentage of subjects with facial Treatment Fields achieving partial (≥75%) clearance of AK lesions on Week 16
- Change from baseline in the number of AK lesions in the Treatment Field of each subject by Weeks 16
- Change from baseline in the number of facial AK lesions in the Treatment Field of each subject by Weeks 16

Safety Endpoints:

- AEs, clinical laboratory parameters, vital signs, physical examinations, Local Skin Reaction (LSR) Scores, electrocardiograms, and drug exposure.

Statistical Analyses:

Sample Size

The study is designed to evaluate the efficacy, safety, and tolerability of topical VDA-1102 ointment in subjects with actinic keratosis. Approximately 150 subjects will be enrolled in this 2-cohort clinical trial. In each cohort, approximately 75 eligible subjects will be enrolled in order to complete each cohort with safety and efficacy data from at least 70 subjects who received study drug. Considering the results from a previous Phase 2 parallel, randomized, placebo-controlled study with a sample size of 29 to 32 subjects per treatment group, this sample size is considered adequate to evaluate the stated objectives. A formal sample size calculation was not performed.

Efficacy Analyses

Efficacy endpoints will be summarized by cohort and visit on the modified Intent-to-Treat (mITT) population and Per Protocol (PP) population, as well as on pre-defined subgroups of the modified Intent-to-Treat population and Per Protocol population including subjects whose Treatment Field was on their face (i.e., cheek or forehead, not scalp).

Given that the study does not contain a control arm, formal statistical analyses of the efficacy data are not planned.

Safety Analysis

The safety endpoint data will be summarized for the Safety 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 cohort. Safety will also be assessed by evaluating findings of vital signs, physical examinations, Local Skin Reaction Scores, clinical laboratory test results, 12-lead ECG tracings, drug exposure/compliance, concomitant medications, pregnancy testing, dose adjustments, and withdrawals / terminations. These findings will be summarized and compared to findings from Baseline (Day 1 Pre-Dose) 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
aPTT	Activate Partial Thromboplastin
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
cSCC	Cutaneous Squamous Cell Carcinoma
D5W	5% Dextrose
dL	Deciliter
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDTA	Ethylenediamine tetra-acetic acid
eg	Exempli gratia, for example
EP	Electrophysiology
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
ICH	International Conference on Harmonisation
IEA	Interim Efficacy Analysis
I.e.	Id est, in other words
IID	FDA's database on Inactive Ingredients

Abbreviation	Definition
IND	Investigational New Drug
INR	International Normalized Ratio
IOP	Intraocular pressure
IRB	Institutional Review Board
IRT	Interactive Responsive Technology
ITT	Intent-to-Treat
IU	International Units
IV	Intravenous
IWRS	Interactive Web Randomization
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
NOAEL	No Observed Adverse Effect Level
NSAID	Non-steroidal anti-inflammatory drugs
OD	Right eye
Oz / ozs	Ounce / ounces
PBS	Phosphate buffered saline
PDT	Photodynamic Therapy
pg	Picogram
PI	Primary Investigator
pH	hydrogen ion concentration
PK	Pharmacokinetic
PM	Evening
prn	Pro re nata (as needed)
PSA	Prostate-Specific Antigen
PT	Prothrombin Time or Preferred term
QAM	Each morning
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

Abbreviation	Definition
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
UPT	Urine Pregnancy Test
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 AK's (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 four GLP toxicology studies performed were the 28-day and 13-week repeated dose oral toxicity studies in male and female rats (with a recovery phase and toxicokinetics), and the 28-day and 3-month topical dermal toxicity studies in male and female minipigs (with a recovery phase and toxicokinetics).

5.4.1. Oral toxicity studies in male and female rats

- *28-day repeated dose with a recovery phase and toxicokinetics*
  Oral administrations of 800 mg/kg/day of VDA-1102 once daily for 28 days to male and female SD rats was associated with clinical signs and intestinal-tract related inflammation in the non-glandular stomach (forestomach), cecum, and colon. These findings were either resolved or trending towards remission at the end of the 2-week recovery phase. These gastrointestinal effects may be related to irritant properties associated with repeated oral gavage administration of VDA-1102. The No Observed Adverse Effect Level (NOAEL) was 300 mg/kg/day (this approximately equates to a human equivalent dose (HED) of 48 mg/kg/day). Systemic exposure to VDA-1102 was not detected, but substantial blood levels of its metabolite jasmonic acid were found, suggestive of a rapid metabolism of VDA-1102 by this route of administration.

- *13-week repeated dose with a recovery phase and toxicokinetics*

  A 13-week study was conducted to evaluate the potential toxicity of VDA-1102 after daily oral administration of 75, 150, and 300 mg/kg/day (HED 12, 24, and 48 mg/kg/day, respectively) of VDA-1102 for 13 weeks to male and female SD rats with a 6 weeks recovery period and toxicokinetics. All the animals in this study have completed their 13-week dosing period and 6-week recovery period. There were no deaths, no observed changes in food consumption, nor decrease in body weight in any of the rats. No treatment-related changes were recorded in organ weights or macroscopic examinations in treated animals, when compared with controls. Laboratory investigation (i.e. hematology, coagulation, blood chemistry and urinalysis) failed to show toxicologically relevant modifications at any of the tested doses. The only clinical observation was salivation in most of the animals in the high-dose group and in some animals in the mid-dose group.

  Non-adverse histopathological changes were observed in the duodenum and spleen of male and female animals dosed at 300 mg/kg/day (high dose level). These findings were not observed at the end of a 6-week treatment-free recovery period. Therefore, the NOAEL (No Observed Adverse Effect Level) for this study was considered to be 300 mg/kg/day.

5.4.2. Topical dermal toxicity studies in male and female minipigs

- *28-day repeat dose with a recovery phase and toxicokinetics*

  In the 28-day minipig study, there were no noteworthy systemic toxicity effects observed following once-daily dermal application of VDA-1102 ointment to 10% of their body surface area, even at the highest strength tested of 20%, which is also the maximum feasible dose in this formulation. The NOAEL for systemic toxicity was thus 20% VDA-1102 ointment, corresponding to a topical dose level of 60 mg/kg/day (HED 43 mg/kg/day). The NOAEL for local application site effects was 5% VDA-1102 ointment. The only notable findings were observed in animals treated with 10% and 20% VDA-1102 ointment, where very slight to slight erythema was reported, that progressed after approximately 2 weeks to mild/moderate erythema, edema, desquamation, and/or scabs. These findings appeared to be reversible with cessation of the treatment. A maximum tolerated dose (MTD) for the local application of VDA-1102 was not reached even at the highest dose tested of 20%.

- *13-week repeat dose with a recovery phase and toxicokinetics*

  A 13-week study was conducted to evaluate the potential toxicity of VDA-1102 when administered on the skin in male and female minipigs after daily unoccluded topical administration to 10% of the body surface area at concentrations 2.5, 5 and 15% of VDA-1102 ointment (corresponding to 7.5, 15, and 45 mg/kg/day, HED 11, 21, and 32 mg/kg/day, respectively). No treatment-related changes of significance were observed in mortality, clinical signs of systemic toxicity, body weight, food consumption, ophthalmoscopy, electrocardiography, clinical pathology investigations, organ weights, or macroscopic/microscopic examinations apart from changes at the dermal application site.

  Erythema (sometimes multifocal) at the treatment site of similar magnitude and severity were observed in both VDA-1102-treated and vehicle control animals. Erythema was of similar magnitude and severity in all treatment groups with a mean severity score of “very slight” to “slight/well-defined.” In single cases and for a limited period of time, “moderate” erythema was observed. On occasion crust/scabs accompanied the erythema, particularly in animals receiving 15%VDA-1102. In addition, dose-related “very slight” edema was only occasionally observed in animals receiving VDA-1102.

  Skin reactions, in general, appeared within the first two weeks of the study, increased up to Week 4 and remained stable or showed a tendency to a slight improvement thereafter. During recovery a clear trend to recovery was observed and a complete recovery was noted at Week 4 of the recovery period.

  The undetectable (or very low) concentrations of VDA-1102 measured on Day 1 and the low blood levels detected on Week 13 along with the low concentrations of jasmonic acid detected on Day 1 and the large exposure to this metabolite measured on Week 13, suggest that VDA-1102 is slowly absorbed from the skin of the minipigs and rapidly metabolized. The Week 13 jasmonic acid systemic exposure in minipigs following dermal application of 5% VDA-1102 in the present study was comparable to that obtained in minipigs receiving 5% VDA-1102 for 4 weeks in a previous study (RTC Study A0608), suggesting that at this dose level, there is no accumulation with an increase in duration of topical application.

The NOAEL (No Observed Adverse Effect Level) for systemic toxicity was 15% VDA-1102, the highest concentration tested. The NOAEL for the local effects was 5% VDA-1102 (15.2 mg/kg/day).

As discussed below in Section 5.7, the relative doses of VDA-1102 fed to rats and applied to the skin of minipigs were significantly higher than the exposures in the current planned 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

Three clinical trial have been conducted with VDA-1102 topical (dermal) ointment, a first-in-human Phase 1a single-dose study in older-adult healthy volunteers, a Phase 2a study in which 93 subjects with actinic keratosis received a once-daily application of study drug (5% or 10% VDA-1102, or Placebo) for 4 weeks, and an ongoing Phase 1b multiple-dose preliminary safety trial in AK subjects to evaluate a more frequent applications, higher strength of VDA-1102, and longer treatment durations (8-12 weeks).

5.5.1. Phase 1A Clinical Trial (Completed)

Study VDA-CP-01 was a single-center, randomized, double-blinded, placebo-controlled, single-dose, dose-escalation study in 3 unique cohorts (4 active, 1 placebo randomized per cohort) of older healthy adult subjects. The objectives of the study were assessment of the local and systemic safety of the study drug as well and the pharmacokinetics of VDA-1102 and its primary metabolite (jasmonic acid) after application of VDA-1102 (5, 10 or 20%) or placebo to a 25 cm^2 area of the skin of each subject's forehead for 24 hours.

The conclusions of this study were as follows:

- Topical application of VDA-1102 at concentrations of 5%, 10%, and 20% versus placebo were well-tolerated following a single application of approximately 250 mg to a 25 cm^2 Treatment Field (forehead area) of healthy older-adult subjects.
- Detailed and frequent examination of the Treatment Field for local skin reactions did not reveal any treatment-emergent findings **at concentrations as high as 20% VDA-1102**.
- There were no TEAEs related to study drug in any subject with the exception of mild left eye pain that occurred approximately 4 hours after the drug was applied to the forehead in 1 subject receiving 10% VDA-1102. This event was short-lived and resolved without sequelae.
- There were no treatment emergent changes in any subject in clinical laboratory, vital signs, physical examination, or ECG evaluations.
- Undetectable plasma concentrations of VDA-1102 or its primary metabolite (jasmonic acid) at any time point (using a sensitive LC-MS/MS validated assay) during or after a 24-

hour topical exposure to up to 20% VDA-1102 suggest minimal systemic absorption of VDA-1102 under the conditions of this study.

5.5.2. Phase 2 Clinical Trial (Completed)

Study VDA-CP-03 was a Phase 2, multi-center, randomized, double-blind, placebo-controlled, multiple-dose, parallel-cohort study involving the once-daily non-occluded, topical dermal application of VDA-1102 ointment for 28 to subjects with AK. Eligible subjects were required to present with a minimum of 4 and a maximum of 8 discrete Grade 1-2 AK lesions within a single 25 cm^2 area of skin on their scalp or face that met specific criteria for the AK Lesions and Treatment Field. Ninety-three (93) eligible subjects in Israel and the United States were randomly assigned in a double-blind fashion to 1 of 3 parallel treatment groups (5%, or 10% VDA-1102, or placebo) in a ratio of 1:1:1. Randomized subjects applied approximately 200 mg of study drug each evening to a 25 cm^2 Treatment Field on their face or scalp. Subjects underwent safety and efficacy assessments during the Treatment Period on Days 7, 14, and 28 and during the Observation Period on Days 35 and 56 (and Day 84 for subjects who consented to Amendment 2). A sub-group of 12 subjects, who met additional more stringent enrollment criteria, participated in the PK Study Sub-Cohort.

The overall conclusions from this proof-of-concept study that included a relatively short 28-days of double-blind, placebo-controlled treatment with study drug are as follows:

- VDA-1102 at dosage strengths of 5% or 10% given as 200 mg topical doses daily for 28 days was well-tolerated both from a systemic as well as a local skin area (site of application) perspective. This is consistent with the good dosing compliance and low level of early discontinuations without the need to adjust the dosing regimen for any subject.
- There were no deaths, serious adverse events related to study drug, or early study discontinuations for AEs related to study drug in this study.
- In the AK patient population evaluated in this study, 28 days of once daily dosing of a predefined Treatment Field on the face or scalp with 200 mg of either VDA-1102 5% or 10% did not result in a statistically significant decrease in the number of AK lesions compared to placebo treatment. However, the mean decrease was greater in the VDA-1102 10% treatment group compared to the placebo treatment group.
- The differences between the VDA-1102 10% treatment group and the placebo treatment group on the 4 exploratory efficacy endpoints consistently favored VDA-1102 10% across all 3 analysis populations. These differences (ITT population) were statistically significantly different (versus placebo) for change from baseline in the number of lesions with a grade ≥ 2 ($P = 0.03$) and change from baseline in the adjusted number of lesions weighted by grade ($P = 0.02$).
- There were no statistically or clinically relevant differences on any exploratory endpoint between the VDA-1102 5% and placebo treatment groups.
- Post-hoc analysis of an efficacy subset of patients who were only treated for AK Treatment Field lesions on the face (ie, not scalp) and represented approximately 75% of enrolled patients demonstrated that the VDA-1102 10% treatment group (ITT population) had a statistically significant greater reduction in the number of AK lesions compared to the placebo treatment group ($P = 0.02$).

- The positive finding for VDA-1102 10% treatment group in the efficacy subset of patients with AK Treatment Fields only on the face was supported by similar treatment effect differences versus the placebo treatment group on the exploratory endpoints evaluated in the originally planned exploratory analyses.
- A post-hoc analysis of treatment group differences (ITT population) for progression of AK to Grade 3 indicated 2 subjects in the placebo treatment group progressed to grade 3 versus no subjects in the 2 VDA-1102 treatment groups.
- The inability to detect plasma concentrations of VDA-1102 or jasmonic acid using sensitive methodology in the subjects included in the PK sub-cohort suggests no systemic absorption of 200 mg VDA-1102 when applied once-daily topically for up to 28 days in a 25 cm^2 Treatment Field.

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

5.5.3. Phase 1B Clinical Trial (Ongoing)

Study VDA-CP-04 is an ongoing single-center, open-label, 2-cohort, dose-escalation study in patients with AK. Cohort 1 of the study is complete; Cohort 2 is ongoing. In the completed Cohort 1, five subjects applied 200 mg of 10% VDA-1102 twice-daily for 8 weeks to a 25 cm^2 Treatment Field located on their face, forehead, or balding scalp. Subjects underwent safety and efficacy assessments at Baseline and at Week 2, 4, 6, 8, 9, and 12 Visits. The following is a summary of the available safety data from the completed Cohort 1 of this study:

- There have been no systemic safety signals as demonstrated by a lack of clinically significant changes in vital signs, physical examinations, clinical laboratory results, and electrocardiographic data.
- There were no deaths or SAEs and no subject withdrew consent from the trial prematurely, although 1 subject described below prematurely stopped the study drug due to an AE.
- The mean maximum Local Skin Reaction (LSR) composite score was 1.2 (0=no reaction; 1=trace; 2=mild; 3=moderate; 4=severe).
- Three of the 5 subjects reported treatment-related AEs. For 2 of these subjects the AEs were mild in severity (conjunctivitis right eye and itchy and painful scalp). For 1 subject the AE of contact dermatitis was considered severe. For this latter subject, the Treatment Field was on their right forehead. The subject received topical 5-FU and photodynamic therapy (major deviations) to numerous AKs located over a large area of her upper chest during Week 3 and developed a severe facial dermatitis at Week 4 that involved the right forehead, ipsilateral periorbital area, and bilateral cheeks. Throughout, the individual LSR scores remained mild to moderate. The eruption completely resolved with cessation of the study drug 2 days after the Week 4 Visit (2 weeks) and application of a topical steroid cream (1 week).
- Neither the parent molecule VDA-1102 nor its primary metabolite jasmonic acid was detected in timed blood samples assayed with a validated and sensitive bioanalytical method.

In Cohort 2, six subjects will apply 200 mg of 20% VDA-1102 to their Treatment Field for 12 weeks. This cohort is currently enrolling.

5.6. Rationale for Study Design and Subject Population

5.6.1. 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 1–2 weeks of treatment initiation, although full clinical benefit was observed after 3-4 weeks.

In the Phase 2a study (Section 5.5.2, above) subjects treated once-daily with 10% VDA-1102 or placebo for 4 weeks (28 days) had a modest reduction from baseline in the total number of AK lesions (32.1% versus 27.8%, respectively). The decrement in the number of lesions of subjects in the per protocol population who had Treatment Fields located on their face (not scalp) was more impressive and statistically significantly (median 50%; mean 41.3% ±38.5% for the VDA-1102 10% treatment group versus median 10%; mean 29.4% ±32.5%, for the placebo treatment group, $P = 0.022$ adjusted for age, gender and site).

In the small (N=5) completed Cohort 1 of the Phase 1B trial summarized in Section 5.5.3, subjects treated with 10% VDA-1102 twice-daily for 8 weeks had a 74% reduction in the number of AK lesions in their Treatment Field. Aside from 2 subjects with reversible skin reactions, the drug was well-tolerated and safe. Together, these data suggest VDA-1102 has therapeutic effects and further evaluation of the dosing regimen/dose and longer duration of treatment is warranted.

In contrast to the aforementioned Phase 2a study where 200 mg of 10% VDA-1102 ointment was applied once-daily for 4 weeks and the completed Cohort 1 of the small ongoing Phase 1b study where 200 mg of 10% VDA-1102 ointment was applied twice-daily for 8 weeks, the dosing frequency in Part A (Cohort 1) of the current clinical trial remains 200 mg of 10% VDA-1102 ointment twice-daily; however, the treatment duration will be extended to 12 weeks.

In Part B (Cohort 2) of the current trial, the strength of the VDA-1102 ointment increases from 10% to 20% but the dosing frequency drops from twice-daily to once-daily. The treatment duration will be the same as in Part A, 12 weeks.

Subjects enrolled in Part C of the current trial will be randomized to receive approximately 200 mg of either 10% VDA-1102 BID as was given to Cohort 1 in Part A or 20% VDA-1102 QD as was applied by Cohort 2 in Part B.

5.6.2. Safety

The results from the toxicology studies and the estimated safety margins indicate that daily dermal application of 200 mg of VDA-1102 ointment for 12 weeks at doses as high as 20% to an area of 25 cm^2 does not pose an untoward risk for evaluation in the target patient population. Specifically, topical application once-daily for 13-weeks of approximately 5 grams of 2.5%, 5%, 15% VDA-1102 ointment to 10% of the minipigs body surface area in the nonclinical toxicology program resulted in no systemic safety findings. Only mild to moderate skin

findings (almost exclusively erythema; no ulceration, vesiculation or pustulation) were seen in the VDA-1102 treated groups as well as in the control groups. Transient mild edema and isolated scabs/crust were reported in a minority of 15% VDA-1102-treated animals. All lesions were self-limited and reversible.

In the completed Study VDA-CP-01 in healthy subjects (Section 5.5), 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 the completed Study VDA-CP-03 in AK patients (Section 5.6.1), 200 mg of 5% or 10% VDA-1102 ointment was applied once-daily for 4 weeks to an area of 25 cm^2 on the cheek, forehead, or scalp. No safety concerns were identified. VDA-1102 5% and 10% were well-tolerated when applied once-daily for 4 weeks. There was no clinically significant change in the Local Skin Reaction individual component scores or total scores. PK analyses of plasma from timed pre- and post-dose blood samples demonstrated that there were no detectable concentrations of VDA-1102 or its primary metabolite jasmonic acid.

In the competed Cohort 1 of the ongoing Study VDA-CP-04 (Section 5.5.3) in AK patients, subjects applied 200 mg of 10% VDA-1102 twice-daily to their facial or scalp Treatment Field for 8-weeks. No significant systemic safety findings were reported. Two subjects experienced reversible skin eruptions attributed to the study drug: one of whom underwent extensive prohibited treatments (topical 5FU and photodynamic therapy) to AK lesions on her upper chest during the Treatment Period coincident with the initiation of the facial eruption and a second subject who experienced a mild, self-limited scalp eruption. PK analyses of plasma from timed pre- and post-dose blood samples demonstrated that there were no detectable concentrations of VDA-1102 or its primary metabolite jasmonic acid in the plasma samples.

In the current study, 10% VDA-1102 will be applied twice-daily for 12 weeks in Cohort 1 and 20% VDA-1102 will be applied once-daily for 12 weeks in Cohort 2. Given the lack of systemic absorption in subjects treated with 10% VDA-1102 BID for 8 weeks in Study VDA-CP-04 (Section 5.5.3), we believe that any potential safety concerns in either of these 2 cohorts would not be systemic and will be limited to the Treatment Field and perhaps the surrounding skin. To date, all adverse reactions in and around the Treatment Field have been reversible and the great majority were mild, short-lived, and self-limited.

5.6.3. Pharmacokinetics

In preclinical PK studies, VDA-1102 was rapidly metabolized, forming jasmonic acid (JA) 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 13-week topical dermal toxicity study performed in minipigs, low levels of both VDA-1102 and the major metabolite JA were detected on Day 1. However, by Week 13 high concentrations of JA (C_{max}= 954 and 1830 ng/mL for male and female minipigs, respectively) were found in plasma while VDA-1102 concentrations remained low which suggested a slow absorption of VDA-1102 and rapid metabolism of the parent drug to JA.

In the completed Phase 1a, 1b, and 2a clinical trials, plasma levels of VDA-1102 and its primary metabolite jasmonic acid (JA) were below the lowest level of detection at all timepoints sampled.

5.6.4. Study Design Rationale

The results from the Phase 2a (VDA-CP-03; Section 5.5.2) clinical trial support the safety and tolerability of 200 mg of 10% VDA-1102 ointment when applied once-daily for 4 weeks (28 days), but the efficacy was moderate. In the completed Cohort 1 of the ongoing Phase 1B trial (VDA-CP-04; Section 5.5.3) subjects treated with 10% VDA-1102 twice-daily for 8 weeks the efficacy was improved, while safety and tolerability were maintained. These studies suggest that higher study drug concentrations, more frequent dosing, and/or a longer treatment duration are likely to improve efficacy. The non-clinical and clinical data support the safety of this approach as well.

In Cohort 1 (**Part A**) of the current study 40 subjects will apply approximately 200 mg of 10% VDA-1102 twice-daily, the same dose applied in Cohort 1 of trial VDA-CP-04. However, subjects enrolled in the current study (VDA-CP-05) will apply the study drug to their Treatment Field for 12 weeks instead of 8 weeks.

Once approximately 40 subjects have been enrolled in Cohort 1 (Part A), this cohort will be closed to enrollment and Cohort 2 (Part B) will be opened for enrollment.

The reason for the initial split into Part A and Part B is due to the drug product manufacturer's schedule (i.e., drug supply).

In Cohort 2 (**Part B**) approximately 40 subjects will apply approximately 200 mg of 20% VDA-1102 once-daily to their Treatment Field for 12 weeks.

Following completion of enrollment of approximately 40 subjects into Cohort 2 (Part B), **Part C** will be opened to enrollment wherein 70 subjects will be randomized in a 1:1 ratio to either Cohort 1 or Cohort 2. Thus, the trial will close with a total of approximately 75 subjects in each cohort.

The goals and rationale of this open-label, dose-escalation trial are to assess the tolerance, safety, and efficacy of two different dosing strategies for VDA-1102 ointment. The results of this study will be applied to the study design and dose selection for the pivotal Phase 3 trials.

5.7. Dose and Posology Justification

Vidac is assessing the dose-response curve and therapeutic index of VDA-1102 ointment in AK subjects to further determine the most appropriate treatment parameters to support a potential Phase 3 study. The Phase 2a trial (VDA-CP-03) involved once-daily 200 mg application of 10% VDA-1102 to a 25cm^2 Treatment Field on the face or balding scalp of subjects with AK for 4 weeks. The study drug was well-tolerated with hardly any LSRs reported. Neither VDA-1102 nor its major metabolite JA was detected in the plasma of treated subjects. The reduction in the number of AK lesions in this short, proof-of-concept trial was modest.

In the completed Cohort 1 of the ongoing dose-ranging Study VDA-CP-04, 5 AK subjects applied 200 mg of 10% VDA-1102 twice-daily for 8 weeks to a 25cm^2 Treatment Field on the face or balding scalp. In this small study, the reduction in AK lesions was considerably better (74%) than in the Phase 2a trial (32%) and no systemic exposure was found for VDA-1102 or its major metabolite, supporting an even longer (e.g., 12 week) treatment period in order to obtain clinically significant complete clearance.

The goals of the current study (VDA-CP-05) are to evaluate efficacy, safety, and tolerability of the same total daily dose of VDA-1102 already tested in a previous clinical study (VDA-CP-05). This total daily dose (1.67 mg/kg/day) will be given either as a divided dose of 10% VDA-1102 BID (Cohort 1) or a single dose of 20% VDA-1102 QD (Cohort 2) for a 12-week treatment period. This dose (1.67 mg/kg/day) is close to 20-fold lower than the HED of the NOAEL dose determined in the 13-week dermal toxicity study in minipigs (32 mg/kg/day) and is close to 30-fold lower than the HED of the NOAEL dose determined in the oral 13-week toxicology study in rats (48 mg/kg/day).

6. STUDY OBJECTIVES

Primary Objective:

- To assess the percent of subjects with complete clearance of the actinic keratosis (AK) lesions in their Treatment Field at Week 16
- To assess the percent of subjects with facial Treatment Fields who achieved complete clearance of actinic keratosis (AK) lesions at Week 16
- To evaluate the systemic and local (skin) safety and tolerability of topical application of VDA-1102 ointment in adult subjects with AK for 12 weeks

Secondary Efficacy Objectives:

- To assess the percent of subjects with partial (≥75%) clearance of the actinic keratosis (AK) lesions in their Treatment Field on Week 16
- To assess the percent of subjects with facial Treatment Fields who have partial (≥75%) clearance of the actinic keratosis (AK) lesions on Week 16
- To assess the reduction in the number of the actinic keratosis (AK) lesions in the Treatment Field on Week 16
- To assess the reduction in the number of the actinic keratosis (AK) lesions on Week 16 of subjects with facial Treatment Fields Study Description

7. STUDY DESIGN

7.1. Study Design: Study Weeks and Visits

This is a multi-center, open-label, 3-part, 2-cohort Phase 2b study involving daily non-occluded, topical dermal application of VDA-1102 ointment in subjects with actinic keratosis (AK). The study design is summarized in Figure 1.

To qualify for the study, male and female subjects aged 18 (inclusive) or older must have signed informed consent and have met the study enrollment criteria at the **Screening Visit** and Day 1 Pre-Dose Visit that include having 4-8 actinic keratosis (AK) lesion within an approximate 25 cm^2 area on the cheek, forehead or balding scalp (the "Treatment Field").

Part A / Cohort 1

A total of approximately 75 subjects will be consecutively enrolled in Cohort 1. Enrolled subjects will apply approximately 200 mg of 10% VDA-1102 twice-daily to their Treatment Field for approximately 12 weeks. Safety assessments will occur on the **Day 1 Pre-Dose** and **Day 1 Dosing Visits**. Safety and efficacy assessments will be repeated at the **Week 4, 8 and 12 Visits**. This portion of the study will be called the **Treatment Period**.

Subjects will return for safety and efficacy assessments at the **Week 13 and 16 Visits** (**Post-Treatment Follow-Up Period).**

Once approximately 40 subjects have been enrolled in Cohort 1, enrollment into this cohort will be closed and Cohort 2 will be opened to enrollment.

Part B / Cohort 2

Cohort 2 subjects will apply approximately 200 mg of 20% VDA-1102 to their Treatment Field each morning (QAM) for approximately 12 weeks.

The procedures and activities to be performed on subjects enrolled in Cohort 1 are the same as those to be performed on subjects in Cohort 2.

Part C / Cohorts 1 and 2

Once the number of subjects in Cohort 2 approximates the number in Cohort 1, Part C of the study will begin wherein approximately 70 eligible subjects will be randomly assigned to either Cohort 1 or Cohort 2. Thus, the trial will close with a total of approximately 75 subjects in each cohort.

7.2. Study Design: Periods

The study periods are the same for all 3 parts of the study. The study design is summarized in Figure 1 and further details for each study period are provided below.

7.2.1. Screening Period (Day -21 through Day 1 Pre-Dose)

During the Screening Visit (up to approximately 21 days pre-dose) subjects who have given written informed consent will undergo screening, safety assessments, Treatment Field identification, and study drug application training.

At the Day 1 Pre-Dose Visit, eligible subjects will return to the investigative site for baseline assessments, final eligibility screening, Treatment Field identification, and study drug application training. AK lesions within the Treatment Field will be counted.

Three times during the Screening and Day 1 Pre-Dose Visits, subjects will be trained and tested in proper measurement and application of the study drug to the Treatment Field with the help of a Dosing Card and 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 day.

Subjects who continue to meet the enrollment criteria will be enrolled and will continue to the Day 1 Dosing Visit.

7.2.2. Treatment Period (Day 1 Dosing Visit through Week 12)

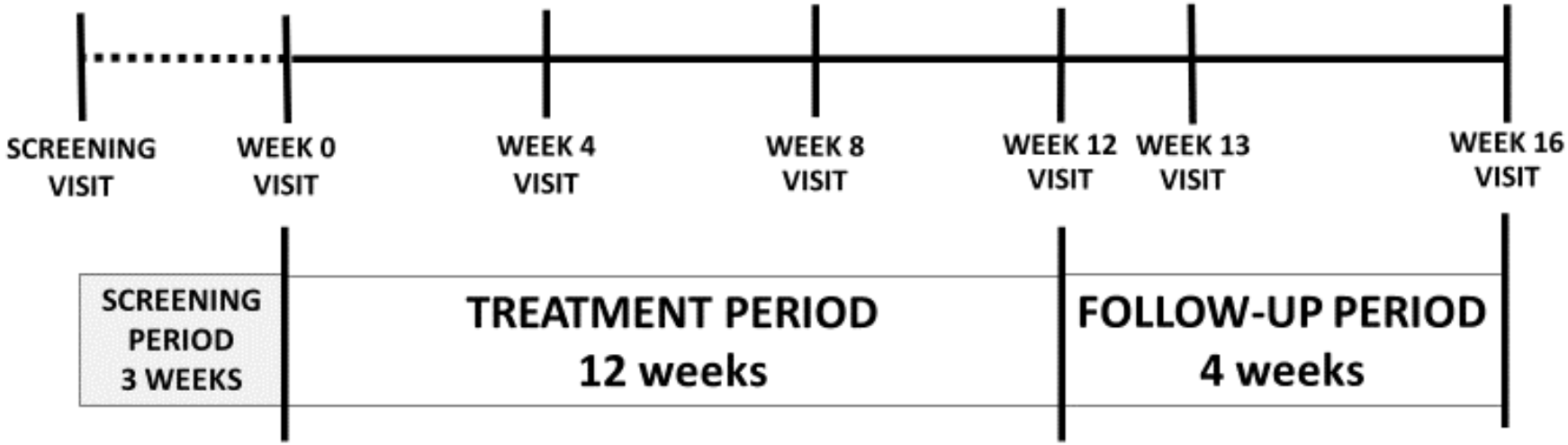
Subjects (or their dosing partner) will apply the first dose of the study drug during the Day 1 Dosing Visit under the supervision of the site personnel to further assure proper application. Subsequently, subjects will apply the study drug (10% VDA-1102 BID or 20% VDA-1102 QAM) to their respective Treatment Fields while at home for 12 weeks. Subjects will visit their respective investigative sites at Weeks 4, 8, and 12 for safety and efficacy assessments, drug accountability, and re-training in proper application of the study drug.

7.2.3. Post-Treatment Follow-Up Period (Week 13 through Week 16)

Subjects will undergo safety and efficacy assessments at Week 13 and 16 Visits. Subjects will exit the trial at the conclusion of the Week 16 Visit procedures.

Figure 1. Study Design Schematic – Cohort 1 and Cohort 2

- *Open-label, multi-center study*
- *150 subjects with AK*
- *3- part study (Parts A, B, and C)*
- *2 cohorts*
  - *200 mg 10% VDA-1102 BID*
  - *200 mg 20% VDA-1102 QAM*
- *12 week Treatment Period*



7.3. Study Assessments

The Table of Assessments appears below. The number preceding the √ denotes the number of times this procedure will be performed at that visit (e.g. 3√ means 3 times). If the √ is not preceded by a number, then the procedure will be performed only once.

Table 1: Schedule of Study Assessments

ASSSESSMENTS	STUDY PERIODS, STUDY VISITS, AND STUDY DAYS							
	SCREENING PERIOD	TREATMENT PERIOD					POST-TREATMENT FOLLOW-UP PERIOD	
	Screening Visit	Day 1 Visits		Week 4 Visit	Week 8 Visit	Week 12 / Early Termination Visit [1]	Week 13 Visit	Week 16 Visit
	Day -21 to Day -1	Day 1 Pre-Dose	Day 1 Dosing	Day 29 ±4	Day 57 ±5	Day 85 ±5	Day 92 ±5	Day 113 ±5
Informed Consent	√							
Enrollment criteria and safety data review	√	√						
Demographics & Medical History	√							
Adverse events recording	√	√		√	√	√	√	√
Concomitant medications recording	√ [2]	√		√	√	√	√	√
Vital signs	√	√		√	√	√		√

[1] Subjects attending an Early Termination Visit (Section 7.5) will undergo Week 12 Visit procedures. In addition, women will undergo a Urine Pregnancy Test.

[2] Prior concomitant medications will be recorded at Screening, which includes all ongoing medications and medicinal products or with a stop date within **2 months** preceding Screening. All topical skin treatments (i.e., medicinal or physical) received in the **4 months** prior to Screening will be recorded.

ASSSESSMENTS	STUDY PERIODS, STUDY VISITS, AND STUDY DAYS							
	SCREENING PERIOD			TREATMENT PERIOD			POST-TREATMENT FOLLOW-UP PERIOD	
	Screening Visit	Day 1 Visits		Week 4 Visit	Week 8 Visit	Week 12 / Early Termination Visit [1]	Week 13 Visit	Week 16 Visit
	Day -21 to Day -1	Day 1 Pre-Dose	Day 1 Dosing	Day 29 ±4	Day 57 ±5	Day 85 ±5	Day 92 ±5	Day 113 ±5
Physical examination		√		√	√	√		√
Height / Weight	√							
12-Lead ECG [3]	√	√				√	√	√
Clinical laboratory testing [3, 4]	√	√				√	√	√
Treatment Field Selection	√	√						
AK lesions numbering, counting and grading	√	√		√	√	√	√	√
Local Skin Reaction Score		√		√	√	√	√	√
Treatment Field photograph, Template, and Map prepared		√						
Urine Pregnancy Test (UPT) [5]	√	√				(√[6])	√	

[3] Clinical laboratory testing and 12-lead ECG will only be performed at Week 13 and/or Week 16 Visits if the results from the previous visit were abnormal and clinically significant.

[4] Hematology, Chemistry, Coagulation, and Urinalysis. A sample for coagulation will not be collected at Day 1. Blood sampling for all clinical laboratory tests should be performed following a fasting period of approximately 8 hours with the exception of the Screening blood sampling that may be performed randomly (i.e., with or without fasting). The fasting status will be noted.

[5] All women will be tested at the Screening, Day 1 Pre-Dose, and Week 13 Visits.

[6] Urine Pregnancy Test will be performed on females undergoing an Early Termination Visit only. All other women will undergo a UPT at the Week 13 Visit.

ASSSESSMENTS	STUDY PERIODS, STUDY VISITS, AND STUDY DAYS							
	SCREENING PERIOD		TREATMENT PERIOD				POST-TREATMENT FOLLOW-UP PERIOD	
	Screening Visit	Day 1 Visits		Week 4 Visit	Week 8 Visit	Week 12 / Early Termination Visit [1]	Week 13 Visit	Week 16 Visit
	Day -21 to Day -1	Day 1 Pre-Dose	Day 1 Dosing	Day 29 ±4	Day 57 ±5	Day 85 ±5	Day 92 ±5	Day 113 ±5
Supervised study drug measurement and application training at site [7]	√	2√						
Supervised study drug application at site			√	√	√			
Telephone contact by site personnel				√	√	√		
Study drug accountability / dosing compliance			√	√	√	√		
Study drug weighing [8]			√	√	√	√		
Subject instructions reviewed	√		√	√	√	√	√	√

[7] Subjects will be trained on study drug measurement and application using the study tools and a placebo demo kit; however, **NO** placebo ointment will be applied on the treatment field.

[8] New (unused) study drug tubes assigned to the subject at Day 1, Week 4, and Week Visits must be weighed **before** the first dosing. Used study drug returned by the subject at Week 4, Week 8, and Week 12 must also be weighed.

7.4. Dose Holidays and Dosing Adjustments

If for any reason a subject or an Investigator decides to alter the prescribed dosing of the study drug due to a local skin reaction and/or AE, subjects may be offered the following options at the Investigator's discretion.

a) Subjects may be offered to continue the study drug, adding a bland moisturizer. The bland 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.

b) Subjects may temporarily stop the study drug for up to 7 days and to re-assess within that period;

c) Subjects may be offered to reduce the dosage, for example from 200 mg to 150 mg per once-daily application;

d) Subjects applying the study drug BID may be offered to apply their medication once-daily while subjects applying the study drug QD may be offered to apply their study drug every other day; and/or

e) Subjects may be offered to stop the study drug permanently.

Subjects may be offered one of the above options or combinations thereof.

7.5. Study Withdrawals and Discontinuations

Subjects may **withdraw** their consent from participation in the study at any time. The date and reason for withdrawal should be recorded.

Subjects who wish to **withdraw** from the study due to an AE related to the study drug should be encouraged to remain in the study and consider the options offered in Section 7.4 instead of withdrawing completely from the study. Subjects who decide to **withdraw** from the study should be encouraged to undergo Early Termination Visit assessments (Section 12.6.4).

Subjects who permanently **discontinue** applying their study drug for any reason (whether on their own initiative or at the behest of the investigator) should be encouraged to remain in the trial (not to withdraw consent from participation) so they may undergo the remaining trial procedures and assessments. The date and reason for the study drug discontinuation should be recorded.

8. STUDY ENDPOINTS

Primary Efficacy Endpoints:

- Percentage of subjects achieving complete clearance of AK lesions within their Treatment Field on Week 16
- Percentage of subjects with facial Treatment Fields achieving complete clearance of AK lesions on Week 16

Secondary Efficacy Endpoints:

- Percentage of subjects achieving partial (≥75%) clearance of AK lesions within their Treatment Field on Week 16
- Percentage of subjects with facial Treatment Fields achieving partial (≥75%) clearance of AK lesions on Week 16
- Change from baseline in the number of AK lesions in the Treatment Field of each subject by Weeks 16
- Change from baseline in the number of facial AK lesions in the Treatment Field of each subject by Weeks 16

Safety Endpoints:

- AEs, clinical laboratory parameters, vital signs, physical examinations, Local Skin Reaction (LSR) Scores, electrocardiograms, and drug exposure.

9. SUBJECT ELIGIBILITY AND WITHDRAWAL CRITERIA

9.1. Inclusion Criteria

Subjects fulfilling all the 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. Male and female subject aged 18 years or older at Screening; and
3. Subject at the baseline Day 1 Pre-Dose Visit has between 4 and 8 Grade 1 or Grade 2 (see AK Lesion Eligibility, Section 11.1.3) AK lesions within a single contiguous 25 cm^2 area of skin on their face or balding scalp (the Treatment Field);

9.2. 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 or Day 1 results that (a) are clinically significant; (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 in the opinion of the Investigator.

   (Examples of laboratory and ECG results for which the Study Medical Monitor should be consulted are listed in Section 9.3.)
3. Subject (or their dosing partner) is unable to demonstrate adequate precision applying the study drug to the Treatment Field during the Screening and Day 1 Pre-Dose Visits.
4. Subject is: (a) pregnant; (b) lactating; (c) planning to become pregnant during the study, or (d) fertile (as defined in Section 12.10.1) and she or their fertile partner is unable or unwilling to use the contraceptive methods discussed in Section 12.10.2;
5. Subject has <u>any</u> skin pathology, known dermatologic disease, or medical condition that could interfere with the evaluation of the test product or requires the use of a prohibited topical or systemic therapy in the opinion of the Investigator (Section 12.9);
6. Subject has in the opinion of the Investigator (a) an unstable medical, psychiatric, social problem, self-reported alcohol or illicit drug dependency, or any similar condition that could (a) place the subject at a safety risk; (b) interfere with the subject's performance of the trial activities, completion of the trial, or attendance at scheduled site visits; (c) obfuscate the subject's data; or (d) threaten the proper interpretation of the trial safety data.

7. Subject has at any time been given a diagnosis or treatment associated with immunosuppression (e.g., organ transplant recipients, HIV, systemic chemotherapy, graft vs. host disease, dialysis, etc.);
8. Subject has participated in a clinical trial, received an investigational drug, or been treated with an investigational device within 1 month prior to Baseline (Day 1).
9. Subject is unable to comply with the sun protection techniques or the limitations placed on tanning, medicinal products, activities, alcoholic beverages, or foods listed in Section 12.9.
10. Subject is unwilling to avoid any form of therapy, emollients, moisturizers, makeup, sunscreens, etc. to the Treatment Field from Screening through completion of all study visits.
11. Subject has a known sensitivity to propylene glycol, caprylic acid, dimethyl sulfoxide (DMSO), petrolatum, or paraffin wax.
12. Subject had any type of allergic reaction or rash that resulted from application of a topical medicament (e.g. cream, ointment, oil, spray, lotion, moisturizer, sunscreen, makeup, etc.).
13. Subject has used any of the following topical medicinal or physical treatments in the Treatment Field within 4 months of Day 1 Visit: topical retinoids (e.g. tazarotene, adapalene, tretinoin), microdermabrasion, laser ablative treatments, photodynamic therapy, chemical peels, 5-FU, diclofenac, imiquimod, ingenol, cryotherapy, or other topical treatments for AK or that might impact AK.
14. Subject has used systemic retinoid therapy within 6 months of Day 1 Visit.
15. Subject has a history of malignancy within 5 years of Day 1 other than adequately-treated carcinoma in-situ of the cervix, non-metastatic basal cell carcinoma or non-metastatic cutaneous squamous cell carcinoma;
16. Subject had major surgery within 60 days of Baseline, hospitalization, or plans to have major surgery during the study;
17. Subject has received VDA-1102 in the past.

9.3. Study Medical Monitor Enrollment Consultation

The Investigators are encouraged to consult with the Study Medical Monitor in cases where the Screening or Day 1 Visit findings suggest that the subject may have a medical condition that is unstable or liable to obfuscate the safety data collected. Below are examples of such laboratory and ECG findings.

1. Clinical laboratory findings:
    a. Both ALT and AST are above the upper limit of normal
    b. Hemoglobin <11 gm/dL, platelet count <125,000/mL, or a low neutrophil or lymphocyte count

c. Microscopic hematuria, proteinuria, or pyuria

d. Glucose >250 mg/dL

2. Electrocardiographic findings:

a. Left bundle branch block

b. Bifascicular block – right bundle branch block with either left anterior or left posterior hemiblock

c. PR interval >220 msecs

d. QTcF >470 msecs

e. Atrial fibrillation

9.4. Subject Replacement

Enrolled subjects who prior to completion of the Week 8 Visit are: (a) terminated by the PI or completely withdraw themselves from the study, (b) declared a violator or major deviator, or (c) lost to follow-up, may be replaced at the discretion of the Sponsor.

9.5. Subjects Leaving the Trial

Subjects who are terminated or who withdraw from the trial will be asked to complete Week 12 assessments (see Early Termination Visit, Section 12.6.4). Women will also be asked to undergo β-HCG testing at that time.

9.5.1. 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. Terminations must be reported verbally and in writing to the Study Medical monitor within 24 hours.

In addition, if an Investigator (or designee) believes that the current dosing may be detrimental to a subject's well-being, that subject may be offered any of the options discussed in Section 7.4 (Dose Holidays and Adjustments) following consultation with the Safety Medical Monitor.

9.5.2. Subjects Who Wish to Withdraw

If a subject who received at least 1 dose of the study drug wishes to withdraw from the trial, that subject may be offered any of the options discussed in Section 7.4 (Dose Holidays and Adjustments). These options may be offered without prior consultation with the Study Medical Monitor.

Subject withdrawals must be reported verbally and in writing to the Study Medical Monitor within 24 hours.

If a subject withdraws consent from the study, all data and samples (blood, urine, ECGs, etc.) collected prior to the time of withdrawal will be analyzed and the data will be included in the trial data base.

9.5.3. 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.

10. PROCEDURES FOR SAFETY EVALUATIONS

10.1. Medical History

Medical history, including any diseases, all past surgeries including skin procedures, and psychiatric illnesses will be documented.

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.

10.2. Prior Concomitant Medications

All medications or medical products taken by the subject within 2 months prior to Screening, whether the subject has stopped the medication or whether the subject has continued taking the medication, will be recorded as a Prior Concomitant Medication. This also includes medications taken prn.

All topical skin treatments (i.e., medicinal or physical) received in the 4 months prior to Screening will be recorded.

10.3. Safety Measures

10.3.1. Adverse Events

The investigator will determine at each study visit whether any AEs have occurred. Sections 15 and 16, respectively, contain additional information regarding AEs and SAEs.

10.3.2. Vital Signs, Weight, and Height

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 during the Screening visit.

10.3.3. Physical Examination

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

The investigator will also be asked to assess whether the following neurologic functions are normal / abnormal.

1. Mentation: appropriate behavior; logical thought processes

2. Motor: use of all 4 extremities
3. Cerebellar: gait; balance standing and sitting
4. Cranial nerves: speech, facial symmetry, and hearing

If any of these is abnormal or changed from baseline, the Investigator will be asked to describe the findings.

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

AK lesions that are outside the Treatment Field must be recorded in the physical examination. This applies to AK lesions on the head or on any other part of the body. However, only lesions that require treatment at the time of the examination should be considered clinically significant. Please refer to Section 12.9.1 regarding which AK treatments are allowed and prohibited during the trial.

All other skin lesions must be reported on the physical examination. However, only skin lesions that require treatment at the time of the examination should be considered clinically significant.

10.3.4. Clinical Laboratory Tests

Blood and urine sampling will be collected and sent for analysis to CRL the central laboratory and will occur as listed in Section 12.6 and the Table of Study Assessments (Section 7.3). All blood samples will be drawn, prepared, and maintained as per central laboratory manual. Blood sampling for all clinical laboratory tests should be performed following a fasting period of approximately 8 hours with the exception of the Screening blood sampling that may be performed randomly (i.e., with or without fasting). The fasting status of the subject will be recorded.

The following tests will be performed as 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 only (not percent)
   - Hemoglobin
   - Hematocrit
   - Mean Corpuscular Volume (MCV)
   - Mean Corpuscular Hemoglobin Concentration (MCHC)
   - Red Blood Cell Count
   - Platelet Count

b) ***Coagulation Profile:*** The coagulation parameter analysis will consist 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 (as per the clinical laboratory's SOPs)

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

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

10.3.5. Urine Pregnancy Test

Pregnancy testing will be performed on urine samples to be processed, assayed, and reported by site personnel.

All women enrolled in the trial must have a negative urine pregnancy test at their Screening and Day 1 Pre-Dose Visits before they can proceed to Day 1 Dosing.

10.3.6. Electrocardiogram

A standard, surface 12-lead ECG will be obtained as per the central ECG laboratory's manual at the time points listed in the Schedule of Assessments (7.3).

ECGs recorded, transmitted to the central ECG laboratory, and interpreted by that laboratory. 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). The Investigator's initial assessment is for purposes of screening and safety follow-up only.

The Investigator's findings will be included in the final data base for insertion into listings. However, these findings will **not** be tabulated, included in summary statistics, or considered the official reading of record for purposes of study safety assessments.

All ECGs will be electronically transmitted to the central ECG laboratory for interpretation. The central ECG interpretation overrides the investigator's and will be considered the official reading of record for purposes of study safety assessments.

10.3.7. 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 as well as the Subjective LSR Score (Section 0) to assess itching and pain in the Treatment Field. The assessments will use a 5-point scale, from 0 (none/trace) to 4 (extreme). This assessment will be performed on Day 1 Visit and repeated at each subsequent visit. The individual scores for each potential finding will be recorded in the respective cells by the assessor.

Whenever possible, the same investigator should perform all of these assessments.

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

11. PROCEDURES FOR EFFICACY EVALUATIONS

11.1. AK Lesions

11.1.1. AK Lesion Count

At the Screening and Day 1 Pre-Dose Visits, the selected Treatment Field must include 4-8 discrete qualifying AK lesion and no disqualifying lesions (Section 11.1.3).

At the Day 1 Pre-Dose Visit, all AK lesions in the selected contiguous 25 cm^2 Treatment Field will be identified, counted, and recorded. The approximate outline of each AK lesion will be transcribed on the Treatment Field Map on Day 1. A photograph of the subject's Treatment Field will be taken and a copy given to the Subject to assist the subject in locating their Treatment Field.

At visits after Day 1 specified below, the investigator will be given the Day 1 Treatment Map and Photograph of the Treatment Field for reference and asked to count the number of AK lesions identified within the Treatment Field.

If new AK lesions appear in the Treatment Field after Day 1, they **will** be counted.

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 not obtained due to LSR local effects.

11.1.2. Definition of AK Lesion Clearance

A prior AK lesion that is no longer seen **OR** no longer palpable is to be considered cleared and will not be counted, **even if a residual color or skin texture change remains in the skin.**

11.1.3. AK Lesion Eligibility

To be eligible for this trial, the Treatment Field must contain **4-8 AK lesions** that meet each of the following criteria:

a. Grade 1 or 2 AK lesions only - not Grade 3; The definitions of AK Grades to be used for eligibility purposes are as follows:
   - 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, obvious, and/or hyperkeratotic AK). Treatment Fields selected for this trial must **not** contain any Grade 3 AK lesions.

b. located on the subject's head including the face or balding scalp but not on the lips, ears, submandibular area, or neck;

c. located in an area of the subject's head that easily visible to the subject in a mirror;

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

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

f. not atrophic, pigmented, or Bowenoid.

AK lesions grades will not be recorded in the CRF since the AK lesion grades are not an endpoint in this study.

11.2. 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 11.1.3) 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 must be selected on Day 1 Pre-Dose.

The Treatment Field must be a single, contiguous 25 cm^2 area that is easily visible to the subject when looking in the mirror. The Treatment Field should include at least 4 but not more than 8 AK lesions all of which must be Grade 1 or 2 AK lesions. The ideal Treatment Field should optimally be square or rectangular and not irregular, to simplify study drug application by the subject.

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

a) An area of skin that received any AK or other medical or physical treatment within 4 months of the Day 1 Visit (Exclusion Criterion #14);

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

c) 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;

d) 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.

11.3. Study Tools

The following four (4) 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 based upon the instructions provided by the Sponsor.

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 will be distributed to the site.

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 will be distributed to the site.

3. **Dosing Card –** a, thin plastic card with a rectangle printed on the middle of the card. 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 for each application by the subject to measure their proper study drug dose and will be discarded after use.

Instructions regarding use of this tool will be distributed to the site.

4. **Treatment Field Photograph –** At least 1 standard facial photograph that includes the Treatment Field and its surrounding landmarks may be taken of each subject. The sole purpose of this photography to supplement the use of the Treatment Field Template in guiding the site and the subject to the subject's precise Treatment Field. The photograph that best represents the Treatment Field will be printed. The site personnel will label the photograph with "left" and "right" as well as point out landmarks on the picture to subject (e.g. moles, eyebrows, or nose) in order to properly orient the subject. The subject will be given the labelled photograph for use with the template and retention in the subject's source documentation.

12. CONDUCT OF THE STUDY

12.1. Study Blinding and Randomization

12.1.1. Study Blinding

This is an open-label study. Therefore, no one will be blinded.

12.1.2. Randomization

Subjects who pass screening and are eligible for enrollment will be consecutively enrolled into Part A (Cohort 1) and Part B (Cohort 2). There will be no need for randomization in Part A or Part B.

Subjects enrolled into Part C will be randomly assigned to Cohort 1 or to Cohort 2 at a ratio of 1:1 to allow for equal expansion of the number of subjects into each of these cohorts. Details regarding the randomization technique(s) will be detailed in the SAP. On Day 1 Pre-Dose, after confirming the subject's eligibility, the Investigator (or his designee) will approve the subject's unblinded randomization. Subjects will be randomized in a fashion that will maintain a balance between the 2 cohorts across all subjects enrolled (not per site) and notify the site of the result.

12.2. 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.

12.3. Subject Informed Consent

No activities other than pre-screening procedures (including Screening activities) may be performed before a fully executed IRB approved current informed consent form (ICF) has been obtained, with a copy of the ICF given to the subject and another copy placed in the subject's medical records.

Information about the study, explaining the objectives, procedures, and potential risks versus 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 in the ICF before written consent is obtained.

12.4. General Considerations

12.4.1. Demographics

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

12.5. Study Periods

This study will consist of the following periods:

- Screening Period: Days -21 through Day 1 Pre-dose
- Treatment Period: From Day 1 Dosing through Week 12 Visit (Day 1 Dosing - Day 85)
- Post-Treatment Follow-Up Period: Between Week 13 and Week 16 Visits (Day 85 – Day 113)

12.6. Study Procedures per Period and Visit

12.6.1. Screening Period

The Screening Period begins immediately following the ICF signing (see Section 12.3 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 both by the subject and investigator or designee; and (d) was copied with one copy given to the subject for their personal records. The process of the informed consent should be documented in the subject's medical records.
- Demographics recorded
- Medical (and surgical) history recorded
- Prior concomitant medications
- 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
- Clinical laboratory tests including hematology, chemistry, coagulations, and urinalysis: Fasting status will be recorded.
- Urine beta-HCG will be performed on all women
- 12-lead ECG tracing recorded. An original duplicate copy of the recorded ECG is required for trial documentation. This ECG will also be transmitted electronically to the central ECG laboratory.
- Scalp and face examination by PI (or designee) with selection of a Treatment Field that is anticipated to meet the criteria stated in Section 11.2 at the Day 1 Visit
- AK lesion count (Section 11.1.1)
- Supervised study drug measurement and application training (see Section 13.6.3). The Treatment Field Map and Template will be prepared as per the Investigator. 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 will be reviewed including appointment for the next visit
- Inclusion and exclusion (enrollment) criteria applied by Investigator and recorded

✓ ***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
- Treatment Field selection/confirmation
- The Treatment Field photograph, Map, and Template will be prepared.
- Supervised study drug measurement and application training (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.
- Physical examination (Section 10.3.3)
- Local Skin Reaction Score of the skin around the AK lesions in the Treatment Field (baseline)
- AK Lesions in the Treatment Field: baseline count (Section 11.1.1)
- Clinical Laboratory tests including hematology, chemistry, and urinalysis. Fasting status should be recorded.
- Urine beta-HCG test will be performed on all women and results recorded.
- 12-lead ECG tracing will be recorded. An original (duplicate) copy of the ECG is required for trial documentation. This ECG will also be transmitted to the central ECG laboratory
- Repeat supervised study drug measurement and application training (see Section 13.6.3) will occur a 2nd time at the end of the Day 1 Pre-Dose Visit. Subject will be tested as to whether they can measure (using placebo ointment on the Dosing Card) and to accurately apply the study drug, without actually applying placebo ointment to their Treatment Field. Subjects (or their dosing partners) who fail to measure and/or apply the study drug properly will be screen failed.
- Enrollment criteria and safety data (from Screening and all available data from the Day 1 Pre-Dose Visit) will be reviewed and approved by the Investigator (or designee)

12.6.2. Treatment Period

✓ *Day 1 Dosing Visit*

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

- Study drug accountability and dosing compliance: Study drug tube will be designated and a Dosing Diary will be provided to the subjects.
- Used and new study drug tubes will be weighed and the results recorded.
- Study drug application and completion of the Dosing Diary by the subject under the supervision of the site personnel.
- Subject instructions 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 Week 4 Visit***

- Subjects will dose at home and record each application in the Dosing Diary.
- Study drug application:
  - Subjects in Cohort 1 will apply study drug twice daily. On Day 1 subjects in Cohort 1 will apply the second dose at home in the evening.
  - Subjects in Cohort 2 will apply study drug once daily.
- Site personnel will communicate with the subjects approximately 2 weeks after Day 1 (Section 12.7) to review the trial instructions and Dosing Diary as well as to remind each subject of their next site visit. Subjects will be reminded to bring all study drug with them to the next visit.

✓ ***Week 4 Visit***

On Day 29 (±5 days) 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 (Section 11.1.1)
- Study drug accountability and dosing compliance: Used study drug tube will be collected and new tubes designated. Dosing Diaries will be collected and reviewed with the subject, and a new diary will be provided to the subjects.
- Used and new study drug tubes will be weighed and the results recorded.

- Study drug application and completion of the Dosing Diary by the subject under the supervision of the site personnel.
- Trial instruction review including an appointment for the next visit will be given. Study drug and study tools (as required) will be re-supplied to the subject, as needed. Subjects will be reminded to bring all study drug with them to the next visit.

✓ ***Week 5 through Week 8 Visit***

- Subjects will dose at home and record each application in the Dosing Diary.
- Study drug application:
  - Subjects in Cohort 1 will apply study drug twice daily.
  - Subjects in Cohort 2 will apply study drug once daily.
- Site personnel will communicate with the subjects approximately 2 weeks after the Week 4 Visit (Section 12.7) to review the trial instructions and Dosing Diary as well as to remind each subject of their next site visit. Subjects will be reminded to bring all study drug with them to the next visit.

✓ ***Week 8 Visit***

On Day 57 (±5 days) 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 (Section 11.1.1)
- Study drug accountability and dosing compliance: Used study drug tube will be collected and new tubes designated. Dosing Diaries will be collected and reviewed with the subject, and a new diary will be provided to the subjects.
- Used and new study drug tubes will be weighed and the results recorded.
- Study drug application and completion of the Dosing Diary by the subject under the supervision of the site personnel.
- Trial instruction review including an appointment for the next visit will be given. Study drug and study tools (as required) will be re-supplied to the subject, as needed. Subjects will be reminded to bring all study drug with them to the next visit.

✓ ***Week 9 through Week 12 Visit***

- Subjects will dose at home and record each application in the Dosing Diary.

- Study drug application:
  - Subjects in Cohort 1 will apply study drug twice daily.
  - Subjects in Cohort 2 will apply study drug once daily.
- Site personnel will communicate with the subjects approximately 2 weeks after the Week 8 Visit (Section 12.7) to review the trial instructions and Dosing Diary as well as to remind each subject of their next site visit. Subjects will be reminded to bring all study drug with them to the next visit.

✓ ***Week 12 Visit***

On Day 85 (±5 days) 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 (11.1.1)
- 12-lead ECG tracing recorded pre-dose. An original (duplicate) copy of each ECG is required. This ECG will also be transmitted to the central ECG laboratory
- Clinical laboratory tests including hematology, chemistry, coagulations, and urinalysis: Fasting status to be recorded
- Study drug accountability and dosing compliance: Used study drug tube will be collected. Dosing Diaries will be collected and reviewed with the subject**. Neither study drug nor Dosing Diaries will be returned to the subject.**
- Used study drug tubes will be weighed and the results recorded.
- Trial instructions will be reviewed including an appointment for the next visit will be given.

12.6.3. Post-Treatment Follow-Up Period

✓ ***Week 12 through Week 13 Visit***

- No procedures will be performed on these days.

✓ ***Week 13 Visit***

Note: *Despite the overlap between the windows for the Week 12 and Week 13 Visits, the Week 13 Visit should occur at least 5 days after the Week 12 Visit.*

On Day 92 (±5 days) the following procedures will be performed on all subjects:

- Adverse event(s) will be recorded

- Concomitant medications documented
- Urine Pregnancy Test will be performed on all women and results recorded.
- Local Skin Reaction Score in the Treatment Field
- AK lesion in the Treatment Field: count (11.1.1)
- Trial instruction review including an appointment for the next visit will be given.

✓ ***Week 14 through Week 16 Visit***

- Site personnel will communicate with the subjects on Week 15 (Section 12.7) to review the trial instructions and to remind each subject of their next site visit. Subjects will be reminded to bring all unreturned study drug with them to the next visit.

✓ ***Week 16 Visit***

On Day 113 (±5) the following procedures will be performed on all subjects:

- 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 (11.1.1)

Subjects will be thanked for their participation in the trial and exit the study.

12.6.4. Early Termination Visit

Subjects exiting the study before completion of the Treatment Period should undergo Early Termination Visit assessments. The following assessments will be performed during such a visit.

- 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 (11.1.1)
- 12-lead ECG tracing recorded pre-dose. An original (duplicate) copy of each ECG is required. This ECG will also be transmitted to the central ECG laboratory

- Clinical laboratory tests including hematology, chemistry, coagulations, and urinalysis: Fasting status to be recorded
- Study drug accountability and dosing compliance: study drug tubes will be weighed and the results recorded. Dosing Diaries will be collected. **Neither study drug nor Dosing Diaries will be returned to the subject.**
- Urine Pregnancy Testing will be performed on all women and results recorded.

12.7. Once-Monthly Subject Contact

Site personnel will contact each subject between study visits. These phone calls should be made, whenever possible, approximately 2 weeks after the Day 1, Week 4, Week 8, and Week 13 Visits. The goals of this contact are: (a) to review the dosing instructions 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; (d) to remind subjects to bring their study drug to each site visit; and/or (e) to ask subjects not to take their dose on site visit days since the study drug dose on those days will be applied under the supervision of site personnel.

12.8. Unscheduled Visits

Investigators will invite subjects to attend an unscheduled visit to the investigative site (a) if during 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 the standard study days.

12.9. General Restrictions

12.9.1. Medication and Other Therapeutic Restrictions

Prohibited **Products and Procedures**

All prescription medications, vitamins, medicinal products, and AK therapies (including chemical peels and photodynamic therapy) are prohibited from Day 1 through the subject's exit from the study unless explicitly permitted below or approved in writing by the Investigator and Study Medical Monitor.

Topical creams, lotions, makeup, or gels of any kind are prohibited within the selected Treatment Field and the 3-inch area around the border of this field from Day 1 through the subject's exit from the study unless prescribed by the site Investigator and documented in the subject's file.

Permitted **Products and Procedures**

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

- Daily medications: Subjects taking vitamins, prescription medications, or medical products daily 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 significant change in dose or dosing interval. These medicinal products must be recorded on the appropriate Concomitant Medication pages. All other prescription medications, medicinal products, and vitamins (with exceptions noted in the bullets below) are prohibited without prior approval of the Investigator and the Medical Monitor.
- Non-prescription prn medications: The following non-prescription medications are allowed without prior consultation: ≤ 1500 mg acetaminophen, ≤ 1650 mg naproxen, or ≤ 1200 mg ibuprofen within a 24-hour period for not more than 2 consecutive days.
- Prescription prn medications: Prescribed medications taken prn including antihistamines, bronchodilators, sleep medications, and intranasal, inhaled, and ophthalmic corticosteroids that are listed as concomitant medications at Screening and/or Day 1 Pre-Dose Visits are permitted. PRN medication taken daily are to be considered "daily medications."
- Physical treatments or procedures such as cryo-destruction, surgical excision, curettage, dermabrasion, or laser resurfacing more than 3 inches from the border of the Treatment Field are permitted.
- Topical creams, lotions, makeup, or gels applied outside the 3-inch border area of the selected Treatment Field is permissible. Subjects, however, should not change such products between and screening and their exit from the trial.
- Light bodied bland moisturizer (e.g., Cetaphil or Lubriderm without alpha-hydroxy acid) may be applied to 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 the last study drug application and the Treatment Field must be washed with soap prior to the next dosing.

12.9.2. Topical Non-Medicinal Product Restrictions

Subjects should be instructed not to change their cosmetics, soaps, shampoos, laundry detergents, deodorants, moisturizers, sunscreens, etc. from Day 1 through their exit from the trial.

12.9.3. Sun Protection and Tanning

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

Subjects must avoid purposeful direct exposure to the sun or ultra-violet light from Day 1 through their trial exit. Subjects who go outdoors should wear proper clothing and hats that protect their skin from sunlight.

NOTE: Subjects should be encouraged to apply sunscreens that the subject has applied previously without untoward effects. Sunscreen products that have not been used previously by the subject must be avoided.

No topical sunscreens, creams, lotions, or gels of any kind may be applied within the selected Treatment Field or within the surrounding 3-inch border area from Day 1 through the subject's exit from the trial 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.

12.9.4. Dietary Restrictions

Since this study does not include PK, subjects have no food restrictions.

12.9.5. Nicotine and Alcohol Restrictions

Subjects enrolled in the study have no smoking restrictions. Social drinking of alcoholic beverages is also not restricted.

12.9.6. Physical Exercise Restrictions

There are no restrictions placed upon physical exercise. However, subjects should not swim or perform strenuous activities within 6 hours after applying the study drug. If the subject would like to perform such activities, the study drug application should be postponed until after the activity has been completed.

12.10. Childbearing Potential

12.10.1. 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 or do not have at least 1 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 meets this definition for childbearing and who cannot use an acceptable form of contraception, must be excluded from the study under Exclusion Criterion #3 (Section 9.2).

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 (UPT): All women enrolled in the trial must have a negative UPT at Screening and on Day 1 Pre-Dose before first study drug dosing. In addition, all women must also undergo a UPT testing approximately one week after the final study drug application.

12.10.2. Contraception

Women with childbearing potential (as defined in Section 12.10.1) must be able and willing to use a contraceptive method describes in that section, from Screening **until 1 month following the final study drug application.**

Non-vasectomized male subjects with female partners without childbearing potential (as defined in Section 12.10.1) are not required to use contraception.

Non-vasectomized male subjects with female partners with childbearing potential (as defined in Section 12.10.1) must agree to use an acceptable form of contraception (as defined in Section 12.10.1) 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 ≥ 6 month post the vasectomy procedure, 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.

– 10% VDA-1102 topical ointment is supplied in 15 grams (gm) aluminum tubes with plastic caps and stored refrigerated at 2-8 °C (36-46°F).

– 20% VDA-1102 is supplied in 10 grams (gm) aluminum tubes with plastic caps and stored refrigerated at 2-8 °C (36-46°F).

13.2. Drug Packaging

The study drug tubes are enclosed in an aluminum pouch with an enclosed desiccant. The pouch is packaged in a protective cardboard 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
4. Lot numbers
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

13.4. Study Drug Distribution

Study drug will be shipped under refrigerated conditions with temperature loggers from the drug depot to the site pharmacy.

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. The aluminum pouch and desiccant may be discarded once the pouch is opened at the site for the first study drug application.

Home Storage

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

Travel

If a subject must transport the study drug (for example, while travelling on vacation, on 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 enrolment.

Site personnel (or institutional pharmacist) will allocate the appropriate study drug for each subject. The tube with its aluminum envelope will be removed from the cardboard container in which it was stored while refrigerated. The aluminum 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 returned to the container until dosing time.

Subjects will receive a new tube of the study drug at Day 1 Dosing, Week 4, and Week 8 Visits and tubes will be returned by the subjects at Week 4, Week 8, and Week 12 Visits.

13.6.2. Study Drug Dosing Cards

Study Drug Dosing Cards will be distributed to the site. 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 to their Treatment Field.

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 photograph and 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 not 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 84 days.

If the subject (or their dosing partner) is unlikely to apply the study drug appropriately, the subject should be terminated from the study based on Inclusion #3 (Section 9.1).

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 #3 (Section 9.1).

Day 1 Dosing Visit

Dosing at this visit will occur under the supervision of the site personnel. If at this visit the subject (or their dosing partner) 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 and considered a screening failure.** 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 their dosing partner. Subjects in Cohort 1 will apply approximately 200 mg of 10%VDA-1102 each morning before 10:00 am and each evening at least 3 hours prior to bedtime. Subjects in Cohort 2 will apply approximately 200 mg of 20%VDA-1102 each morning before 10:00 am.

Cohorts 1 and 2: The morning dose should be applied before 10 am. **If a subject knows that they will perspire, shower, vigorously exercise, etc. before 10 am, application of the study drug should be delayed until completion of those activities.**

Cohort 1 only: The evening dose should be applied each day **at least 3 hours** before bedtime.

If the subject would like to shower, wash their face, shampoo their hair, etc., 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, Treatment Field photograph, 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 to ensure that the whole Treatment Field was covered with study drug.

After each study drug application, the subject's hands should be very carefully washed with warm water and soap.

The subject will be instructed not to wet or touch the Treatment Field. Subjects should not perform activities that might cause wetting or excessive sweating of the Treatment Field, for approximately 6 hours after dosing.

After each dosing, the Dosing Diary must be completed.

13.7. Study Drug Accountability and Dosing Compliance

13.7.1. Study Drug Site Accountability

Study sites will be asked to acknowledge receipt of 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 inventory. A drug inventory 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 Sponsor 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 documented on the drug inventory record, which will be collected at the end of the study.

All study drug 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. Sufficient study drug will be given to each subject to allow for proper dosing between site visits.

13.7.2. Study Drug Accountability and Dosing Compliance

Study drug distributed to each subject and returned by each subject will be documented in the Drug Accountability Log.

Dosing cards will be distributed and collected with study drug. Subjects will complete a Dosing Diary with the date and time of each dosing. Missed doses will be recorded. Dosing cards will be used to assess subject compliance.

13.7.3. Study Drug Weighing

Each new (unused) study drug tube will be weighed before the first dose is dispensed. As part of study drug accountability, study tubes returned by the subjects at Weeks 4, 8, and 12 will be weighed. Study drug weights will be recorded and these data will be used to assess subject compliance.

14. CONCOMITANT MEDICATION

Any prescription or non-prescription medication, alternative medication, herbal product, homeopathic substance, etc. that the subject receives while they are enrolled in the trial or that was taken within 2 months of Screening 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 subject medical record.

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 12.9.1 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 or dosing interval.

At Screening and Day 1 Pre-Dose Visits, the study site personnel will review each subject's concomitant medications to ensure that subjects are not taking any prohibited medications listed in Section 12.9.1.

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 Definitions

15.1.1. General

An AE is any untoward medical occurrence 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.

Abnormal clinically significant changes in physical examination or vital signs should be recorded as AEs.

15.1.2. Local Skin Reactions

In this trial Local Skin Reactions (LSRs) will <u>not</u> be recorded as AEs unless they (a) require treatment with a prescribed medication; (b) extend >2 centimeters beyond the border of the Treatment Field; or (c) require a study drug dose adjustment.

15.1.3. Laboratory and ECG Data

Abnormal clinical laboratory or ECG findings should be reported as an AE are as follows:

1. Test result is associated with accompanying symptoms;
2. Test result requires additional diagnostic testing or medical/surgical intervention;
3. Test result leads to a change in study dosing, discontinuation from the study, initiation of a prescription medication, or surgical intervention; and
4. Test result leads to any of the outcomes included in the definition of a SAE.

If such an event occurs, the test should be repeated within approximately 7 days to confirm the finding and appropriately monitored. The mere repetition of an abnormal test, in the absence of any of the above conditions, does not fulfil 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.

15.1.4. Miscellaneous Definitions

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 due to an AE and they should be documented as such.

Planned hospital admissions documented in the subject's medical record prior to enrolment and study-related procedures are also not to be reported as AEs.

Overdoses of the study drug will <u>not</u> 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. 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), stabilized, 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 or stabilized 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.

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. 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. Congenital anomaly or birth defect.
6. 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 be based on the ICH guidelines for reporting SAEs and will appear in the study Safety Monitoring Plan.

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

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

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.

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

Marietta Radona, Project Manager (Therapeutics, Inc.)

Telephone (mobile): 1-973-979-3307

E-mail: mradona@therapeuticsinc.com

Office: 1-858-571-1800 x171

Fax: 1- 858-571-1234

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.

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.

All subjects with SAEs must be followed-up for outcome.

17. STATISTICAL PLAN

17.1. Sample Size Rationale and Justification

The study is designed to evaluate the efficacy, safety, and tolerability of topical VDA-1102 ointment in subjects with actinic keratosis. Approximately 150 subjects will be enrolled in this 2-cohort clinical trial. In each cohort, approximately 75 subjects will be enrolled in order to complete each cohort with safety and efficacy data from at least 70 subjects who received study drug. Considering the results from a previous Phase 2 parallel, randomized, placebo-controlled study with a sample size of 29 to 32 subjects per treatment group, this sample size is considered adequate to evaluate the stated objectives. A formal sample size calculation was not performed.

17.2. Statistical analysis

All measured variables and derived parameters will be listed individually and, if appropriate, tabulated by descriptive statistics. Data will be summarized by cohort and visit, if appropriate. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects (n), mean, median, standard deviation (SD), minimum, and maximum for continuous data and frequencies and percentages for categorical data. The data will be analyzed using the SAS® version 9.4 or higher (SAS Institute, Cary North Carolina). Details of all statistical analyses to be performed will be included in the Statistical Analysis Plan (SAP).

17.3. Secondary Efficacy Analyses

17.3.1. Primary Efficacy Analyses

The proportion of subjects achieving complete clearance of AK lesions within their Treatment Field will be summarized by cohort and visit. The 95% confidence interval for the percentage will be calculated using the Clopper-Pearson method for binomial proportions. The analysis will be conducted on the modified Intent-to-Treat (mITT) population, mITT Face (mITT-Face) subpopulation, Per Protocol population (PP), and PP Face (PP-Face) subpopulation.

17.3.2. Secondary Efficacy Analyses

The proportion of subjects achieving partial (≥75%) clearance of AK lesions within their Treatment Field will be summarized by cohort and visit. The 95% confidence interval for the percentage will be calculated using the Clopper-Pearson method for binomial proportions.

The number of facial AK lesions in the Treatment Field, change from baseline values, and percent change from baseline values will be summarized by cohort and visit.

These analyses will be conducted on the modified Intent-to-Treat (mITT) population, mITT Face (mITT-Face) subpopulation, Per Protocol population (PP), and PP Face (PP-Face) subpopulation.

17.4. Safety Assessments

The safety endpoint 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 cohort. Safety will also be assessed by evaluating findings of physical examinations, vital signs, clinical laboratory test results, 12-lead ECG tracings, Local Skin Reaction Score, drug exposure, concomitant medications, Urine Pregnancy Test results, withdrawals/terminations, and dose adjustments. These findings will be summarized and compared to findings from baseline evaluations.

Local Skin Reaction (LSR) Scores will be summarized.

17.5. Pharmacokinetic Parameters

Not applicable.

17.6. Missing Data

Every effort will be made to obtain required data at each scheduled visit from all subjects who have been enrolled. Details regarding the handling of missing data will be presented in the SAP.

17.7. Data Sets

17.7.1. Safety Population

The Safety population will be defined as all subjects who are randomized and who receive study drug. Safety analyses will be performed on the Safety population.

17.7.2. Modified ITT (mITT) Population

The modified Intent-to-Treat (mITT) population will be defined as all subjects who are enrolled into the study, received any study drug, and did not fail Exclusion Criterion #2. Subjects in this population will be analyzed according to the cohort to which they were allocated. All efficacy analyses will be performed on the mITT population.

17.7.3. Per Protocol Population

Subjects without violations or major deviations will be included in the Per Protocol Population. All efficacy analyses will be repeated on this population.

17.7.4. Face Subpopulation

Subjects whose Treatment Fields are located on their face (i.e., cheeks or forehead) will constitute the ITT-Face, mITT-Face, and PP-Face populations.

17.7.5. Pharmacokinetic Population

Not applicable.

17.8. 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 9) 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).

A Violation and Deviation Review Meeting that includes members of the study team from the Sponsor and the Statistical Management CRO will determine which subjects meet the above definitions. Details of this meeting will be included in the Statistical Analysis Plan. It is the Sponsor's responsibility to determine whether the event will be considered a violation, major deviation, or minor deviation.

17.9. Subject Compliance

Subjects will record administered and missed doses in their Dosing Diaries. Study drug tubes will also be weighed at each site visit.

17.10. Demographic and Baseline Characteristics

The comparability of the cohorts 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

Trained investigational site staff will enter the data required by the protocol into the eCRFs from source documents. 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. eCRFs 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.

ECGs should be transmitted to the central laboratory the same day the data are obtained, if possible.

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, 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 CRFs and other documents submitted to the Sponsor. Documents not submitted to the Sponsor include those that identify the subject (e.g., 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 Investigator will not undertake any measures or procedures specifically required of a subject for the clinical study until valid consent has been obtained.

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 (including used and unused study drug) 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 an Investigator, the clinical observations in the study suggest that it may be unwise to continue, that Investigator may terminate their site's participation after consultation with the Sponsor. A written statement fully documenting the reasons for such a termination will be provided to the Sponsor.

The Sponsor may terminate the study at any time for any reason.

If it becomes apparent that subject enrollment at a particular site 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 participation of that site and remove all study materials from that investigational site. A written statement will be provided to the Investigator, the IRB, and regulatory authorities, if required.

20. INVESTIGATOR'S OBLIGATIONS

20.1. General

The Investigator agrees that the study will be conducted in accordance with the clinical protocol, ICH-GCP 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 Investigator 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.

In general, protocol deviations will not be granted. However, if a minor protocol deviation is necessary in order to eliminate an immediate hazard to a subject or to facilitate a subject's adherence to protocol procedures, such a deviation request may be communicated to the Study Medical Monitor in writing for their consideration. Such a request should include a clear, complete, and compelling written description and justification. A copy of this request and the written response of the Study Medical Monitor must also be placed in the appropriate file at the site.

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. If time allows, the Investigator must consult with the Study

Medical Monitor. If time does not allow, the Investigator may approve the deviation without prior consultation with the Study Medical Monitor. The Investigator 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 CRF 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 Sponsor (or designee) quality assurance personnel.

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

The Local Skin Reaction Score is an assessment of the skin in the Treatment Field. At each study visit the Investigator (or designee) will assign a severity score to each of the objective findings listed in the table. **Whenever possible, the same investigator should perform all the LSR assessments.**

The Investigator will assess the selected Treatment Field and rate the findings on a 5-point scale (0-4). The composite LSR score will consist of the sum of all the individual LSR scores.

Local Skin Reaction	**0 NONE**	**1 MILD**	**2 MODERATE**	**3 SEVERE**	**4 EXTREME**
Erythema	None or Pinkish-red over isolated portions of the Treatment Field	Pinkish-red over most of the Treatment Field	Red	Intense redness (beet red)	Very intense redness that extends >2 cm beyond the Treatment Field
Edema / Swelling	None or Trace edema	Slightly palpable or barely visible edema	Visible and easily palpable edema	Gross edema	Gross edema that extends >2 cm beyond the Treatment Field
Weeping / Exudate / Crust	None	Mild weeping or exudate	Moderate weeping, exudate or crust	Thick exudate or crust over >50% of the Treatment Field	Heavy exudate or crust that extends >2 cm beyond the Treatment Field
Vesicles / Pustules	None	Vesicles with limited coalescing	Vesicles over >50% of the Treatment Field with majority coalescing	Pustulation	Coalesced pustules
Flaking / Scaling	None or Trace flaking/scale	Mild flaking or light scale	Moderate flaking and/or scaling over >50% of Treatment Field	Severe, thick scale	Severe, thick scale that extends >2 cm beyond the Treatment Field
Erosion / Ulceration	None	Scattered shallow erosions	Deep erosions over >50% of the Treatment Field or limited areas of ulcerations	Small eschar or extensive ulcerations	Eschar that covers the entire Treatment Field

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

In this trial Local Skin Reactions (LSRs) will not be recorded as AEs unless they (a) require treatment with a prescribed medication; (b) extend >2 centimeters beyond the border of the Treatment Field; or (c) require a study drug dose adjustment.

22.2. Subjective Local Skin Reaction Score

Itching and pain will be reported as a Subjective LSR Score. The same 5-point (0-4) scale listed above for the LSR Score will be used for these parameters.