Statistical Analysis Plan

Study Title:

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

Revision History

Revision	Revision Date	Reason for Revision/Change Request	Revised By
1.0	28-DEC-2016	Original Release	David Israel, BST
2.0	21-MAY-2017	Comments from VidacPharma	David Israel, BST

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1. DEFINITIONS AND/OR ABBREVIATIONS

AE	Adverse event
AK	Actinic keratosis
AUC	Area under the plasma concentration-time curve from time zero (t0) to the time of the last measured sample (t_{last})
BL	Baseline
BLQ	Below Level of Quantification
BMI	Body Mass Index
Cmax	Peak plasma concentration
CRF	Case Report Form (may be paper or electronic representation of the data collection tool)
CRO	Contract Research Organization
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
Hr(s)	Hour(s)
ICF	Informed Consent Form
I.e.	Id est, in other words
ITT	Intent-to-Treat
MedDRA	Medical Dictionary of Regulatory Affairs.
mITT	Modified ITT

NA	Not applicable
PI	Primary Investigator
PK	Pharmacokinetic
PT	Preferred Term
QTcB	QTc interval corrected using Bazett's formula
QTcF	QTc interval corrected using Fridericia's formula
SD	Standard Deviation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-emergent adverse event
t½	Terminal plasma half-life
Tmax	Time of the peak plasma concentration
ULN	Upper limit of normal
WHODRUG	World Health Organization coding system for medications

2. PURPOSE

2.1 The purpose of this document is to describe in detail the Statistical Plan Analysis of clinical trials procedure carried out by Medistat Ltd.

2.2 This procedure serves Medistat Ltd. as a guiding document for all statistical analyses performed at the end of each clinical study.

2.3 This SAP is adjusted for Vidac Pharma, VDA-CP-03, phase II.

2.4 This SAP aims to provide details on: sample size calculation, efficacy analyses, safety analyses, exploratory analyses and PK analysis.

3. SCOPE

3.1 This document applies to all members of the statistical & data management units in Medistat Ltd.

3.2 This document includes both the main study trial analysis and interim analyses when applicable.

4. RESPONSIBILITIES

4.1 Medistat Responsibilities

The following personnel are responsible for these activities:

Activities	**Responsible and accountable**	**Title**
Statistical Analysis Plan (SAP)	David Israel	Senior Biostatistician, SAS & EDC Programmer
Statistical Report and listing appendix	David Israel	Senior Biostatistician, SAS & EDC Programmer
Quality Assurance (QA) of SAP and programs	Daphna Goffer	Senior Biostatistician & SAS Programmer
Quality Assurance (QA) of final report	Nia Hen	Quality & Data Assurance Manager

4.2 Vidac Pharma's Responsibilities

4.2.1 To review and approve the SAP and related documents prior to database lock.

4.2.2 To review and approve the draft and final statistical report and listing appendix

5. PROCEDURE

5.1 Study Objectives and Endpoints

5.1.1 Study Objectives

5.1.1.1 Primary Objectives:

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

5.1.1.2 Secondary Objectives:

5.1.1.2.1 To evaluate the systemic and local (skin) safety and tolerability of once-daily topical application of 5% or 10% VDA-1102 ointment or placebo for 28 days in adult subjects with AK.

5.1.1.2.2 To assess the systemic exposure of VDA-1102 and jasmonic acid, its primary metabolite, at selected time points during topical application of 5% or 10% VDA-1102 ointment or placebo for 28 days in adult subjects with AK.

5.1.1.3 Exploratory Objectives:

5.1.1.3.1 To compare the proportion of subjects receiving 28 days of 5% or 10% VDA-1102 who on Day 56 had complete clearance of AK lesions to subjects receiving placebo.

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

5.1.2 Study Endpoints

5.1.2.1 Primary Efficacy Endpoints:

5.1.2.1.1 Change from baseline in the number of AK lesions within the Treatment Field of each subject on Day 56.

5.1.2.2 Safety Endpoints:

5.1.2.2.1 Assessment of:

5.1.2.2.1.1 AEs

5.1.2.2.1.2 Vital signs

5.1.2.2.1.3 Physical examinations

5.1.2.2.1.4 Clinical laboratory parameters

5.1.2.2.1.5 Local Skin Reaction (LSR) Scores (individual and total)

5.1.2.2.1.6 Electrocardiograms

5.1.2.3 Pharmacokinetic Endpoints:

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

5.1.2.4 Exploratory Endpoints:

5.1.2.4.1 The percentage of subjects achieving complete clearance of AK lesions within the Treatment Field on Day 56

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

5.2 Overall study design and plan

5.2.1 Study Design

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

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

5.2.1.3 To qualify for the study, subjects aged 18 (inclusive) or older must have signed informed consent and met the study enrollment criteria that include having 4-8 discrete Grade 1 or 2 AK lesions within a contiguous 25 cm^2 area on the scalp or face ("the Treatment Field"). Subjects will be randomly assigned in a double-blind fashion to 1 of 3 parallel treatment cohorts (5%, or 10% VDA-1102, or placebo, respectively) in a ratio of 1:1:1. Randomized subjects will apply a single thin application of the study drug to their Treatment Field for 28 days.

5.2.1.4 This clinical trial will include 3 study periods:

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

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

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

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

5.2.1.4.2 Treatment Period (Day 1 Dosing through Day 28):

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

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

5.2.1.4.3 Observation Period (Day 29 through 84):

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

Figure 1: Study Design Schematic

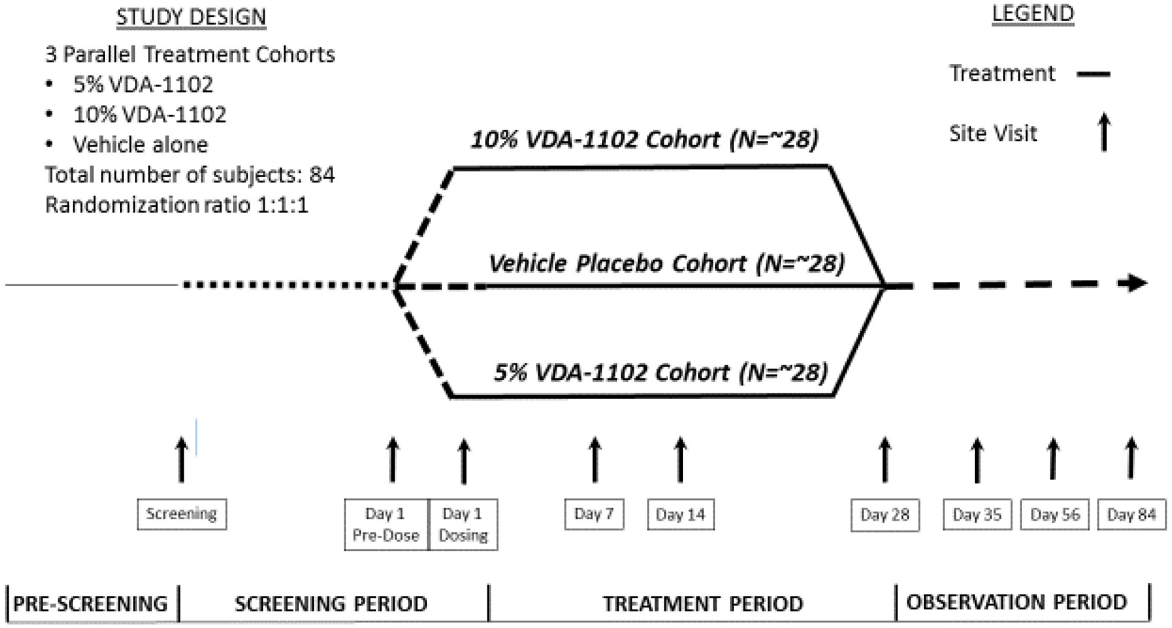

Table 1. Periods, Study Day, and Visits

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

5.2.2 Table of Study Assessments

5.2.2.1 Table 2 displays Schedule of Assessments for all subjects enrolled in the trial.

5.2.2.2 Table 3 displays Schedule of Assessments for subjects enrolled in the PK Study Sub-Cohort.

Table 2: Schedule of Assessments for all subjects:

Period	SCREENING PERIOD		TREATMENT PERIOD			OBSERVATION PERIOD		
Study Day	Day -21 to Day -1	Day 1		Day 7±2	Day 14±2	Day 28±4	Day 35±2	Day 56±4	Day 84±4
Procedure\Visit	Screening	Day 1 Pre-Dose	Day 1 Dosing	Day 7	Day 14	Day 28	Day 35	Day 56	Day 84
ICF procedures, signature, dating confirmed	√								
Enrollment criteria and/or safety data review	√	√							
Demographics and Medical History	√								
Adverse events reporting	√	√		√	√	√	√	√	√
Concomitant medications recorded	√	√		√	√	√	√	√	√
Vital signs	√	√		√	√	√	√		
Physical examination	√	√		√ [1]	√	√	√		
Height / Weight / BMI calculated	√								
12-Lead ECG	√	√		√ [1]	√	√			
Clinical laboratory testing	√	√		√ [1]	√	√			
Fitzpatrick skin type		√							
Treatment Field Selection	√	√							
AK lesions in the Treatment Field count and grade	√	√		√	√	√	√	√	√
Local Skin Reaction Score		√		√	√	√	√	√	√
Study drug measurement & application review	√	√ twice		√	√				
Pregnancy test (urine) at the site	√	√				√		√	
Subject randomization		√							
Application of the study drug each evening			√ Day 1 through Day 27						

Period	**SCREENING PERIOD**	**TREATMENT PERIOD**				**OBSERVATION PERIOD**		
Study Day	**Day -21 to Day -1**	**Day 1**		**Day 7±2**	**Day 14±2**	**Day 28±4**	**Day 35±2**	**Day 56±4**	**Day 84±4**
Procedure\Visit	**Screening**	**Day 1 Pre-Dose**	**Day 1 Dosing**	**Day 7**	**Day 14**	**Day 28**	**Day 35**	**Day 56**	**Day 84**
Supervised study drug application at the site			√						
Trial instruction review / Closure procedure	√		√	√	√	√	√	√	√
Telephone contact by study staff		Once-weekly communication between site visits							
Photographs of Treatment Field (at selected sites only)		√						√	√
Study drug & tools given subject, as needed			√	√	√				
Study drug accountability/dosing compliance [2]		√		√	√	√			

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

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

Table 3: Schedule of Assessments for PK Study Sub-Cohort:

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

5.2.3 Nested Phase 1b Safety Sub-Cohort

The first 15 (PK and non-PK) subjects enrolled in the trial will undergo on Day 7 the safety examinations planned for all other subjects plus a physical examination, clinical laboratory tests, and an ECG assessment. Once all 15 subjects in this Nested Phase 1b Safety Sub-Cohort have completed their Day 7 Visit, available blinded safety data (including AEs, LSR scores, clinical laboratory results, and ECG data) from Day 1 through Day 7 will be reviewed within 10 business days by a safety committee consisting of 3 Board-certified physicians not involved in the trial and the Study Medical Monitor. During this blinded interim safety review, enrolled subjects will continue dosing the study drug and study enrollment will remain open.

5.2.4 PK Study Sub-Cohort

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

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

5.2.5 Randomization, Blinding and Un-blinding

5.2.5.1 Assignment of study drug will be performed using a web-based Interactive Responsive Technology (IRT)-based randomization system (TrialMaster, OmniComm Systems, Fort Lauderdale, FL USA) . On Day 1 Pre-dose Visit, after confirming the subject's eligibility, the Investigator (or his designee) may approve the subject's blinded randomization.

5.2.5.2 The web-based IRT will randomize subjects in a fashion that will maintain a balance among the 3 treatment groups (5% and 10% VDA-1102, and placebo) across all subjects enrolled (not per site) and within the PK Study Sub-Cohort. (For further details see "VDA-CP-03 final randomization plan v1.1 15-06-2016.docx")

5.2.5.3 Subjects who withdraw or are terminated after the first study dose has been applied will not be replaced in the trial. Subjects who withdraw or are terminated before the first study dose has been applied due to error or violation of an enrollement criterion will be replaced and not included in the Intent-To-Treat (ITT) population.

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

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

5.3 Selection of Study Population

5.3.1 Study Population

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

5.3.2 Sample Size Justification

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

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

5.4 Statistical Analysis Software

5.4.1 Data manipulation, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed using SAS® version 9.3 or higher for Windows. If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

5.4.2 Data Management

5.4.2.1 The EDC system that will be used in the study is TrialMaster® (OmniComm Systems, Inc., Fort Lauderdale, FL, USA). It is a web-based software solution that allows clinical trial Sponsors and investigative sites to easily and securely collect, validate, transmit and analyze clinical study data. The system will be developed using OmniComm TrialMaster® EDC platform version: 4.2.1.23. OmniComm TrialMaster® EDC platform is compliant with the Food and Drug Administration (FDA) 21 CFR Part 11 regulations - electronic records; electronic signatures (last revised 01-Apr-2014)

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

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

5.4.3 Coding

5.4.3.1 Concomitant medications entered into the database will be coded using the WHO (World Health Organization) Drug Public Website Dictionary named WHOCC-ATC/DDD index, which employs the Anatomical Therapeutic Chemical classification system.

5.4.3.2 Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1 terminology or higher.

5.4.4 Handling of Missing Data

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

5.4.5 Protocol Violations and Deviations

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

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

5.4.5.2.1 A major deviation is one that will definitely, probably or possibly significantly impact the subject safety or the quality of the trial data. Major deviation includes:

5.4.5.2.1.1 Subject was reduced to every other day dose by investigator at any point during the study

5.4.5.2.1.2 Subject who received study drug dosing on fewer than 20 days. The number of days of dosing will be based upon: (a) the "start dose date" and "stop dose date" days and (b) the compliance data reported in the EDC from the subject diaries and coordinator telephone calls. Subjects who received 1 or 2 doses of study drug on Day 1 Dosing will both be considered having been dosed once, not twice, for this calculation only.

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

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

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

5.5 Subject Population for Analyses

5.5.1 Intent-to-Treat Population

5.5.1.1 The ITT population will be defined as all subjects who are randomized and who receive at least one dose of study drug. This is an appropriate population for the primary analysis and for exploratory analyses because this is a blinded trial and the 1st dose will be applied in the clinic by the research clinic staff per protocol.

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

5.5.2 Modified ITT (mITT) Population

5.5.2.1 The mITT population includes all ITT patients who completed the study and have protocol deviations or protocol violations that are not expected to significantly impact efficacy (e.g. the total treatment area > or < 25 cm^2).

5.5.2.2 The mITT population will also be used for the primary efficacy endpoint analysis.

5.5.2.3 The mITT population will also be used for exploratory analyses. Analyses on Day 56 will include mITT subjects who completed Day 56 regardless of whether or not they also completed Day 84, and analysis on Day 84 will include mITT subjects who completed Day 84.

5.5.3 Per-Protocol Population

5.5.3.1 The PP population includes all ITT patients who have no violations or major protocol deviations.

5.5.3.2 The PP population will also be used for the primary efficacy endpoint analysis.

5.5.3.3 The PP population will also be used for exploratory analyses. Analyses on Day 56 will include PP subjects who completed Day 56 regardless of whether or not they also completed Day 84, and analysis on Day 84 will include PP subjects who completed Day 84.

5.5.4 Pharmacokinetic Population

5.5.4.1 The subjects (maximum of 18) enrolled in the PK Study Sub-Cohort at approximately 3 sites will constitute the PK population.

5.6 Statistical Analysis

5.6.1 General

5.6.1.1 All measured variables and derived parameters will be listed individually and, if appropriate, tabulated by descriptive statistics. For categorical variables summary tables will be provided giving sample size, absolute and relative frequency and 95% CI (Confidence Interval) for proportions (if appropriate) by treatment group. For continuous variables summary tables will be provided giving sample size, arithmetic mean, standard deviation, coefficient of variation CV% (if appropriate), median, minimum and maximum and 95% CI (Confidence Interval) for means of variables (if appropriate) by treatment group. The data will be analyzed using the SAS ® version 9.3 or higher (SAS Institute, Cary North Carolina). Analyses presented in the clinical report but not mentioned in the SAP are unplanned or ad-hoc analyses.

5.6.1.2 Statistical methods presented in the SAP may be slightly different from those that are presented in the protocol. Differences are clearly stated in this SAP which supersedes the protocol only with regard to the way data will be handled and analysed.

5.6.2 Derived Data

5.6.2.1 Definition of baseline

5.6.2.1.1 Baseline is defined as the last non-missing value prior to the patient start of treatment (i.e., Day1 Pre-dose, if available, otherwise Screening). All tabulations involving change from baseline data will only include patients with data at baseline and at follow-up.

5.6.2.2 End of Study

5.6.2.2.1 The end-of-study visit is defined as Day 56 for protocol Version 1 and protocol amendment 1 and as Day 84 for protocol Amendment 2.

5.6.2.3 Early Termination

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

5.6.2.4 Incomplete dates

5.6.2.4.1 All incomplete dates will be entered in the database as they were recorded in the CRF. Thereafter, for calculation purposes, the incomplete dates will be completed using pre-defined rules. If a day or month is recorded as UNK it will be replaced by the first day of the month or January respectively, provided this does not contradict any other dates recorded.

5.6.3 Disposition of subjects (Table 14.1-1 – 14.1-2)

5.6.3.1 The number of subjects that randomized into the study, the number of subjects in the ITT, mITT and PK populations, and the number of study completers will be presented.

5.6.3.2 The reasons for early termination/ withdrawal and any randomization errors will be summarized.

5.6.4 Demographic and Baseline data (Tables 14.1-3 -14.1-6)

5.6.4.1 Baseline and demographic data will be summarized in appropriate tables by treatment group and overall using the ITT population. These data includes demographic characteristics (age, gender, ethnicity and race), weight, height, BMI, medical history and disease-related information.

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5.6.5 Efficacy Primary Analysis

5.6.5.1 The efficacy analysis will be performed with the ITT, mITT and PP populations (see Tables 14.2-1 - 14.2-9). The primary efficacy endpoint is the decrease from baseline in number of AK lesions. The within-group decrease in number of AK lesions from baseline to each visit will be analyzed using paired t-test or signed rank test for two means (paired observations, as is appropriate).

5.6.5.2 Comparative analysis of the decrease at Day 56 (mentioned above) will be applied between each of the active groups versus the placebo group using the two-sample t-test, the non-parametric Wilcoxon-Mann-Whitney rank sum test for independent samples, or the Median test (as appropriate) and using the Analysis of Covariance (ANCOVA), after optionally ranking transformation of the variable, with adjustment for sites and for other covariates suspected as affecting the outcome and which will be found different between the treatment groups.

5.6.5.3 Figures depicting the number of lesions by visit and by treatment group and depicting the reduction in number of lesions from Baseline to Day 56 will be generated

5.6.5.4 Binary variable will be defined based on the decrease in number of AK lesions at Day 56 according to a relevant cutoff (first quartile, median, third quartile or other cutoff computed by ROC curve sensitivity analysis). Comparative analysis of this variable will be applied between each of the active groups versus the placebo group using Chi-square test or Fisher's Exact test and using logistic regression with adjustment for site and for other covariates suspected as affecting the outcome and which will be found different between the treatment groups.

5.6.5.5 If the two active VDA-1102 groups trend similarily then these two groups may be pooled and compared to the placebo group in order to achieve higher statistical power.

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

5.6.5.7 For the ANCOVA analysis, logistic regression and mixed-effect model for repeated measures detailed above, if necessary, grouping of sites will be done based on similarities and differences observed between sites by post-hoc contrasts of ANOVA.

5.6.6 Exploratory Analysis

5.6.6.1 Two new variables will be defined and all comparative analyses that were done for the primary analysis above will be repeated for these two new variables:

5.6.6.1.1 The number of grade ≥ 2 lesions

5.6.6.1.2 An adjusted number of lesions weighted by grade. The weighted grade will be computed as follows: (Number of grade I lesions) + (2 × Number of grade II lesions) + (3 × Number of grade III lesions).

5.6.6.2 Comparative analysis of the decrease in number of grade ≥ 2 lesions will be applied on a sub-group of subjects with at least one grade ≥ 2 lesion at baseline.

5.6.6.3 Figures displaying the reduction in number of grade ≥ 2 lesions and the reduction of adjusted number of lesions weighted by grade from Baseline to Day 56 will be generated.

5.6.6.4 Chi-square test or Fisher's exact test (as is appropriate) will be used for analyzing the difference in percent of subjects with complete clearance of study AK lesions at Day 56 between each of the active groups versus the placebo group. Logistic regression will be applied for analyzing the difference in proportions of complete clearance with adjustment for site and for other covariates suspected as affecting the outcome and which will be found different between the treatment groups.

5.6.6.5 All analyses mentioned above on complete clearance will be performed on ≥75% clearance, ≥50% clearance and ≥ overall median% clearance as well.

5.6.6.6 Analyses mentioned above on complete clearance will be performed on clearance of grade ≥ 2 lesions as well.

5.6.6.7 The within-group decrease in number of AK lesions from baseline to each visit will be analyzed using paired t-test or signed rank test for two means (paired observations, as is appropriate) on the Day 84 completers subgroup.

5.6.6.8 Comparative analysis of the decrease in number of AK lesions from baseline to day 84 will be applied between each of the active groups versus the placebo group using the two-sample t-test, the non-parametric Wilcoxon-Mann-Whitney rank sum test for independent samples, or the Median test (as appropriate).

5.6.6.9 The effect of compliance (e.g. days dosed and tube weight) on the primary endpoint will be tested by sensitivity analysis. If the effect of compliance will be found significant, two additional analyses will be performed:

5.6.6.9.1 Analysis of Covariance (ANCOVA) will be applied in order to test the differences in change in number of AK lesions between the treatment groups adjusted for subject compliance. This analysis is included in primary analysis (see 5.6.3.2)

5.6.6.9.2 A relevant compliance cutoff will be computed and a stratified analysis will be performed according to this cutoff.

5.6.7 Safety analysis

5.6.7.1 All safety data will be summarized for the ITT population.

5.6.7.2 Adverse events will be coded according to coding dictionaries (MedDRA version 19.1 or higher) and presented in tables by System Organ Class (SOC) and Preferred Term (PT) and by treatment group.

5.6.7.3 Secondary analysis

5.6.7.3.1 The within-group changes from baseline to each visit in the Composite Local Skin Reaction score and in all of its components will be analyzed using Paired t-test or Signed- rank test for two means (paired observations, as is appropriate).

5.6.7.3.2 The within-group changes from baseline to each visit in the Composite Local Skin Reaction score and in all of its components will be analyzed using Paired t-test or Signed- rank test for two means (paired observations, as is appropriate) on the Day 84 completers subgroup.

5.6.7.3.3 A figure of the Composite Local Skin Reaction score, of the erythema component, and of the edema component by visit and by treatment group will be generated.

5.6.7.4 The incidence of AEs and TEAEs, as well as the intensity and relationship to study drug will be summarized by treatment group.

5.6.7.5 Safety will also be assessed by evaluating findings of physical examinations, vital signs, clinical laboratory test results, 12-lead ECG tracings, concomitant medications, and withdrawals/terminations/drug holiday/dosing adjustment by treatment group.

5.6.7.6 ECG data will be derived from 12-lead ECG tracings (and from cardiac Holter monitoring recordings, if appropriate).

5.6.7.7 Summary statistics for observed measures and changes from pre-dose in the following ECG variables will be tabulated at each post-baseline visit:

5.6.7.7.1 Heart rate (bpm)

5.6.7.7.2 PR interval (ms)

5.6.7.7.3 QRS complex (ms)

5.6.7.7.4 QT interval (ms)

5.6.7.7.5 QTcF interval (ms)

5.6.7.7.6 QTcB interval (ms)

5.6.7.8 The mean from Day 1 Pre-dose will serve as the ECG baseline to which all post dose ECG data will be compared. If the Day 1 value is missing, the Screening Visit value will be used as baseline.

5.6.7.9 For QT, QTcB and QTcF, absolute and relative frequency of patients with absolute result ≥ 500 ms at each visit will be displayed.

5.6.7.10 The changes from baseline in vital signs, ECG derived variables, clinical laboratory tests results will be analyzed by treatment group, using the Paired T-test if data is considered normally distributed or using the non-parametric Signed rank test (paired observations) if considered non-normal.

5.6.7.11 For QT, QTcB and QTcF (ECG data), absolute and relative frequency of increase above baseline divided into three categories < 30 ms, 30-60 ms and > 60 ms at each visit will be displayed.

5.6.7.12 Concomitant medication verbatim terms (as recorded on the CRFs) will be coded to Anatomical Therapeutic Chemical (ATC) Level 2 and 4 using the World Health Organization (WHO) dictionary.

5.6.8 PK Analysis

5.6.8.1 Non-compartmental PK will be calculated where applicable, if there are sufficiently high concentrations of VDA-1102 and/or its main metabolite for consistent calculations, using appropriate software. The PK sub-cohort including up to 18 subjects will be used.

5.6.8.2 The following PK parameters will be calculated:

5.6.8.2.1 C_0 – Pre-dose plasma concentration;

5.6.8.2.2 C_{max} - Maximum plasma concentration;

5.6.8.2.3 T_{max} - Time to reach the maximum plasma concentration;

5.6.8.2.4 AUC_{last} - Area under the plasma concentration-time curve from time of administration up to the last time point with a measurable concentration post dosing, calculated by linear up-logarithmic down trapezoidal summation.

5.6.8.2.5 AUC_{∞} - Area under the plasma concentration-time curve extrapolated to infinity, calculated as: $AUC\infty = AUClast + Clast/\lambda z$, where Clast is the last measurable concentration.

5.6.8.2.6 λ_z - Elimination rate constant, determined by linear regression of the terminal points of the ln-linear plasma concentration-time curve;

5.6.8.2.7 $T_{1/2}$ - Terminal elimination half-life, defined as $0.693/\lambda z$;

5.6.8.3 Total AUC is calculated by summation of partial AUCs using the trapezoidal rule.

5.6.8.4 An individual segment (AUC_i) is calculated using the following formulation:

$$AUC_1 = ((C_0 + C_1) \text{ X } Time_{1-0}) / 2$$

5.6.8.5 Where:

5.6.8.5.1 C_0 is the concentration measured on time 0

5.6.8.5.2 C_1 is the concentration measured on time point 1 (the next time point)

5.6.8.5.3 $Time_{1-0}$ is the time difference between time 1 and time 0.

5.6.8.6 The total AUC equals a summation of all partial AUC segments.

5.6.8.7 The calculated PK parameters as well as the raw data used for the calculations will be transferred to MediStat for generating a statistical report.

5.6.8.8 Medistat will further QA the data before generating the report. The QA will include checking for outlier measures and missing data.

5.6.8.9 MediStat will prepare a statistical report based on the raw data and the calculated PK parameters.

5.6.8.10 The data will be treatment blinded. Following data lock the treatment codes will be exposed and merged into the data and to be included in the statistical report

5.6.8.11 The report will include:

5.6.8.11.1 Summary tables of VDA-1102 and jasmonic acid plasma concentration by treatment and time point

5.6.8.11.2 Summary tables of PK parameters by treatment.

5.6.8.11.3 Individual listings of VDA-1102 and jasmonic acid plasma concentration

5.6.8.11.4 Individual listings of PK parameters

5.6.8.11.5 Graphical displays presenting mean concentration by time point

5.6.8.11.6 Individual figures presenting concentration by time point

5.6.8.12 Summary tables will be presented including sample size (N), mean, standard deviation, standard error, median, minimum and maximum values and 95% confidence intervals by treatment.

5.6.8.13 The data will be analysed using the SAS ® version 9.3 (SAS Institute, Cary North Carolina).

6. RELATED DOCUMENTS

6.1 Internal Documents

Not Applicable

6.2 External documents

6.2.1 VDA-CP-03 P2a 09June2016_DI,pdf

6.2.2 VDA-CP-03 Listing appendix of 029-BST-SOP-002

6.2.3 VDA-CP-03 Tables appendix of 029-BST-SOP-002

7. RELATED FORMS

Not Applicable

8. REFERENCES

Not Applicable

9. APPENDICES

APPENDIX I: TABLE SHELLS

Table 14.1-1: Subject Disposition

Table 14.1-2: Demographic Data

Table 14.1-3: Frequency of Medical History (except Actinic Keratosis) by Category

Table 14.1-4: Any Medications within 30 Days Prior to Screening

Table 14.1-5: Any Medications between Screening and Day 1 Dosing Visit

Table 14.1-6: Disease-related information

Table 14.1-7: Dermatological Evaluation at Pre-dose

Table 14.1-8: Compliance Data

Table 14.2-1: AK Lesions Count in ITT Population

Figure 14.2-1: Total Number of Lesions by Visit and by Study Group in ITT Population

Figure 14.2-2: Number of AK Grade ≥ 2 lesions by Visit and by Study Group in ITT Population

Figure 14.2-3: Adjusted Number of Lesions by Visit and by Study Group in ITT Population

Table 14.2-2: AK Lesions Count in mITT Population

Table 14.2-3: AK Lesions Count in PP Population

Table 14.2-4: AK Lesions Number: Absolute Changes from Baseline in ITT Population

Table 14.2-5: AK Lesions Number: Changes from Baseline in mITT Population

Table 14.2-6: AK Lesions Number: Changes from Baseline in PP Population

Table 14.2-8: AK Lesions Number: Changes from Baseline for Day 84 Completers

Table 14.2-9: AK Lesions Number: Relative Changes from Baseline in ITT Population (%)

Table 14.2-10: AK Lesions Number: Relative Changes from Baseline in mITT Population (%)

Table 14.2-11: AK Lesions Number: Relative Changes from Baseline in PP Population (%)

Table 14.2-12: AK Lesions Number: Relative Change from Baseline for Day 84 Completers

Table 14.2-13: Frequency of Decrease in AK lesions at Day 56 ≥ Cutoff Computed by Sensitivity Analysis/ Relevant Quartile in ITT Population

Table 14.2-14: Frequency of Decrease in AK lesions at Day 56 ≥ Cutoff Computed by Sensitivity Analysis/ Relevant Quartile in mITT Population

Table 14.2-15: Frequency of Decrease in AK lesions at Day 56 ≥ Cutoff Computed by Sensitivity Analysis/ Relevant Quartile in PP Population

APPENDIX II: LISTINGS SHELLS

Listing 16.2.1-1 Subject Disposition

Listing 16.2.1-2 Visit Dates per Subject

Listing 16.2.1-3 Unscheduled Visits per Subject

Listing 16.2.1-4 Phone Contact with Subject

Listing 16.2.2-1 Inclusion and Exclusion Criteria Violated

Listing 16.2.2-2: Protocol Deviations

Listing 16.2.3-1 Analysis Populations

Listing 16.2.4-1: Demographic data

Listing 16.2.4-2: Medical History Data

Listing 16.2.4-3: Disease-related Information

Listing 16.2.4-4: Dermatologic Assessment at Baseline

Listing 16.2.5-1 Exposure Data (Day 1)

Listing 16.2.5-2 Compliance Data (Days 7, 14, 28)

Listing 16.2.5-3 Accountability data

Listing 16.2.6-1: AK lesion count

Listing 16.2.6-2: PK parameters from Jasmonic Acid

Listing 16.2.6-3: PK parameters from VDA-1102

Listing 16.2.6-4: Jasmonic Acid concentrations (ng/mL) by time

Listing 16.2.7-1 Treatment Emergent Adverse Events

Listing 16.2.7-2 Other Adverse Events

Listing 16.2.8-1: Laboratory Tests

Listing 16.2.8-2: Hematology Results

Listing 16.2.8-3: Abnormal Hematology Results

Listing 16.2.8-4: Chemistry Results

Listing 16.2.8-5: Abnormal Chemistry Results

Listing 16.2.8-6: Urinary Results

Listing 16.2.8-7: Abnormal Urinary Results

Listing 16.2.8-8: Pregnancy tests (females only)