STATISTICAL ANALYSIS PLAN

Protocol Number: A-101-SEBK-402

AN OPEN-LABEL STUDY ASSESSING SUBJECT SATISFACTION WITH A-101 HYDROGEN PEROXIDE TOPICAL SOLUTION, 40% (W/W) TREATMENT FOR SEBORRHEIC KERATOSES OF THE FACE, NECK, AND DECOLLETAGE (SK-FAN)

STATISTICAL ANALYSIS PLAN - TEXT

Title: AN OPEN-LABEL STUDY ASSESSING SUBJECT SATISFACTION WITH A-101 HYDROGEN PEROXIDE TOPICAL SOLUTION, 40% (W/W) TREATMENT FOR SEBORRHEIC KERATOSES OF THE FACE, NECK, AND DECOLLETAGE (SK-FAN)

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List of Abbreviations

Abbreviations/Acroynms

AE	adverse event
ATC	antomical therapeutic chemical
CS	clinically significant
CSR	clinical study report
CRF	case report form
Max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
mm	millimeters
NCS	non-clinically significant
NDA	new drug application
PLA	physician's lesion assessment
PT	preferred term
SAE	serious adverse event
SK	seborrheic keratosis
Std Dev	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event

1 STUDY OBJECTIVES AND SAMPLE SIZE RATIONALE

1.1 STUDY OBJECTIVES

The rationale for this study is to assess subject satisfaction after treatment with A-101 solution 40% (w/w) on Seborrheic Keratosis (SKs) of the face, neck, and décolletage. Subjects will be naive to A-101 (Hydrogen Peroxide) Topical Solution, 40% (w/w) treatment. Dermatologists identify 3 eligible target SKs on each subject; 2 target SKs must be on the face, and the additional 1 target SK must be on the neck or décolletage. Up to 4 additional non-target SKs may be identified on the face, neck or décolletage. This study is the first post-marketing study after the successful New Drug Application (NDA) and product launch for A-101 solution applied to SK lesions. Protocol provides a more detailed description of the study. Primary and Secondary Objectives are summarized below.

1.1.1 Primary Objective

Subject satisfaction after treatment with A-101 (Hydrogen Peroxide) topical solution, 40% (w/w) at Day 85 and Day 113.

1.1.2 Secondary Objectives

- Effectiveness of treatment as measured by the Physician's Lesion Assessment (PLA) at Day 85 and Day 113.
- Comparison of the PLA score(s) to treatment satisfaction at Day 85 and Day 113.

1.1.3 Safety Assessments

Safety assessments include adverse events, change in vital signs, and concomitant medication use.

1.2 SAMPLE SIZE

A total of 30 subjects are planned to enroll in the study.

2 STUDY DESIGN SUMMARY

This study is an open-label study designed to evaluate subject's satisfaction after treatment of seborrheic keratoses with A-101 40%. Dermatologists (investigators) identify 3 eligible target SKs on each subject; 2 target SKs must be on the face, and the additional 1 target SK must be on the neck or décolletage. Up to 4 additional non-target SKs may be identified on the face, neck or décolletage. Each target and non-target SK will be treated during up to 3 separate treatment visits: Visit 2, Visit 5, and Visit 7. Each SK must be treated by a study trained healthcare provider at the site. Retreatment of identified target and non-target SKs will be determined by the physician using the PLA. Each application will last up to 20 seconds with about 60 seconds between applications.

2.1 VISITS

Subjects will be required to complete a total of 11 study visits. The protocol defined study visits are:

- Visit 1 (Day -13 - 0) Screening
- Visit 2 (Day 1) Study Medication Treatment
- Visit 3 (Day 2) Follow-up Visit
- Visit 4 (Day 8) Follow-up Visit
- Visit 5 (Day 15) Study Medication Treatment (if PLA ≥ 1)
- Visit 6 (Day 22) Follow-up Visit
- Visit 7 (Day 29) Study Medication Treatment (if PLA ≥ 1)
- Visit 8 (Day 36) Follow-up Visit
- Visit 9 (Day 57) Follow-up Visit
- Visit 10 (Day 85) Follow-up Visit
- Visit 11 (Day 113) Follow-up Visit; End of Study

Study flow chart is as below.

Study Design and Schedule of Assessments

Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**
Treatment Day	**Day -13 - 0**	**Day 1**	**Day 2**	**Day 8**	**Day 15**	**Day 22**	**Day 29**	**Day 36**	**Day 57**	**Day 85**	**Day 113**
Visit Window	N/A	N/A	N/A	± 1 day	± 1 day	± 1 day	± 1 day	± 1 day	± 7 days	± 7 days	± 7 days
Informed Consent	X										
Inclusion/ Exclusion[1]	X	X									
Subject Identifier[2]	X										
Dermatological Medical History	X										
Demographics	X										
Fitzpatrick Skin Type Assessment[3]	X										
Vital Signs[4]	X	X			X		X			X	X
Prior Medications/Therapies[5]	X										
Target and Non-Target SK Identification[6]	X										
Physician's Lesion Assessment[7]	X	X	X	X	X		X			X	X
SK Dimensions[8]	X	X	X	X	X		X			X	X
SK Photography[9]	X	X[10]	X[11]	X	X[10]	X	X[10]	X	X	X	X
Study Medication Application[12]		X			X		X				
Subject Satisfaction Assessment[13]		X	X			X		X		X	X
Concomitant Therapies[14]	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[15]		X	X	X	X	X	X	X	X	X	X

[1] Subject inclusion/exclusion criteria will be reassessed prior to enrollment during Visit 2.

[2] Investigational sites will assign a unique five-digit subject identifier to each subject at Visit 1, formatted as NN-NNN where the first 2 digits are the site number, and the final 3 digits are the subject number that must be assigned in ascending numerical order (using leading zeroes, as appropriate). This subject identifier will be used in all study documentation for the duration of the study.

[3] Each subject's skin must be assessed during Visit 1 using the Fitzpatrick Skin Type Assessment. Refer to Table 6 for the scale.

[4] Vital signs [including temperature, pulse, respiratory rate, blood pressure, height and weight (Visit 1 only)] will be measured by a qualified staff member at Visit 1, Visit 2, Visit 5, Visit 7, Visit 10, and Visit 11.

[5] Prior medications/therapies will be collected for a time-period of 13 days prior to Visit 1. Refer to Section 8.4 for a list of permitted and restricted concomitant medications.

[6] The treating investigator will identify 3 target SKs and up to 4 non-target SKs. Two (2) target SKs must be on the face, and the additional 1 target SK must be on the neck or décolletage. The 4 non-target SKs may be located on the face, neck, or décolletage.

[7] The investigator will use the Physician's Lesion Assessment (PLA) to assess the severity of each target and non-target SKs at Visits 1, 2, 3, 4, 5, 7, 10, and 11. At Visit 2, Visit 5 and Visit 7, the investigator must assess each target and non-target SK prior to application of the study medication. In order to be eligible for enrollment to the study during Visit 2, the subject must have a PLA grade ≥ 2 for each target and non-target SK.

[8] The investigator will measure the dimensions of each target and non-target SK at Visits 1, 2, 3, 4, 5, 7, 10 and 11. At Visit 2, Visit 5 and Visit 7, the investigator must measure each target and non-target SK prior to application of the study medication. In order to be eligible for enrollment to the study during Visits 1 and 2, each target SK must have a diameter that is between ≥ 5 and ≤ 15 mm (inclusive) and be raised. In order to be eligible for enrollment to the study during Visits 1 and 2, each non-target SK must be a raised SK. At Visits 3, 4, 5, 7, and 10 the investigator must assess the thickness of each target and non-target SK above the surrounding skin. Additional target and non-target SK requirements are outlined in Protocol Section 10.1.

[9] Each target and non-target SK will be photographed at all study visits using the Aclaris Therapeutics, Inc. supplied photography equipment.

[10] During Visit 2 each target and non-target SK will be photographed prior to the application of A-101 40%, 10 minutes post application (+2 minutes), and 1-hour post application ($\pm$ 10 minutes). During Visit 5 and Visit 7, the target and non-target SKs will be photographed prior to the application of A-101 40%, if applicable.

[11] During Visit 3 each target and non-target SK will be photographed 24-hours post application during Visit 2 ($\pm$ 2 hours).

[12] A-101 40% will be applied to each target and non-target SK by a study trained healthcare provider at the site. Each target and non-target SK will be treated with A-101 40% following confirmation of subject eligibility and study enrollment at Visit 2. If a target or non-target SK meets the criteria for retreatment as defined in Section 9.5, the SK will be retreated at Visit 5 and Visit 7. Following application of A-101 40%, subjects must NOT wash/submerge a target and non-target SK for at least 6 hours and they must NOT apply any topical products to any target or non-target SK for at least 6 hours.

[13] Subjects will be asked to assess how satisfied they are with the treatment experience they received for the target and non-target SKs at the specified visits. On Visit 2 the subject will complete the assessment prior to application of A-101 40%. On Visit 3 the subjects will complete the assessment approximately 24 hours after the treatment. On Visit 6 and Visit 8 the subjects will complete the assessment approximately 1 week after the treatment, only if the subject received treatment on Visit 5 or Visit 7. The subject will complete the assessment during the Visit 10 and Visit 11.

[14] All concomitant therapies including (topical and oral) prescription medications, over the counter medications, natural supplements and non-drug therapies including chiropractic, physical therapy, and energy-based therapy must be documented in the subject CRF. Subjects must not apply any topical products *(e.g.*, moisturizers, sunscreen, etc.) to their target and non-target SKs within 12 hours prior to any study visit.

[15] The reporting period for SAEs begins when the subject signs the informed consent form. Refer to Protocol Section 11.6 for instructions on the reporting of SAEs. Non-serious clinical adverse events will be collected following the application of the study medication at Visit 2 and continue through Visit 11. All safety reporting (AEs and SAEs) will conclude at Visit 11.

2.2 SUBJECTS

2.2.1 Number of Subjects

A total of 30 subjects will be treated on the study at 3 investigational sites in US.

2.2.2 Diagnosis and Main Criteria for Inclusion

Subjects will be SK treatment naïve males and females between age of 30 and 75 years old with stable clinically typical SK. For each subject, 3 eligible target SKs; 2 target SKs must be on the face, and the additional 1 target SK must be on the neck or décolletage. Up to 4 additional non-target SKs may be identified on the face, neck or décolletage.

2.2.3 Study Population Characteristics

Subjects with a clinical diagnosis of SK who meet all the inclusion criteria and none of the exclusion criteria will be eligible to enroll in the study. Detailed inclusion and exclusion criteria, see protocol sections 7.1 and 7.2.

2.2.4 Replacement Subjects

If a subject is enrolled to the study but does not receive a dose of study drug, then the subject may be replaced. Subjects that are determined to be screen failures may be rescreened for the study and if determined to be eligible for the study they may be enrolled under using the same subject identifier and must sign a new informed consent form.

2.3 TREATMENT AND RANDOMIZATION

2.3.1 Study Medications, Treatment, and Mode of Administration

A-101 Solution, 40% (w/w), external topical.

2.3.2 Randomization

Not applicable.

2.3.3 Administration of Treatment

At Visits 2, 5, and 7, each target and non-target SK must be treated by a study trained healthcare provider at the site.

At Visits 5 and 7, all identified target and non-target SKs that have a PLA grade of ≥ 1 will be retreated with the solution. If in the investigator's opinion, the lesion is not appropriate for re-treatment, treatment will be withheld.

2.3.4 Duration of Treatment

The duration of the study participation is anticipated to be a maximum of 134 days per subject. The final visit (Visit 11), has a maximum allowable visit window of 7 days.

2.4 ASSESSMENTS

2.4.1 Evaluators

The investigator, a designated and appropriately trained staff member (e.g., sub investigator) or the subject will perform the study assessments according to the defined schedules.

Similar lighting conditions and subject positioning should be used for all evaluations for a given subject.

2.4.2 Evaluations – Efficacy

2.4.2.1 Physician's Lesion Assessment (PLA)

The PLA is the investigator's assessment of the severity of the target and non-target SK at a particular time point. The investigator may refer to other evaluations (*e.g.,* prior photographs) to assist with these assessments.

At Visits 1, 2, 3, 4, 5, 7, 10, and 11 the investigator will assess the target and non-target SK using the scale below and report the one integer that best describes the severity of the target or non- target SK. At Visit 2 and if applicable at Visit 5 and Visit 7, the investigator must complete the PLA prior to the study medication treatment. The description of PLA grade is as shown in the table below.

Grade	Descriptor
0	Clear: no visible seborrheic keratosis lesion
1	Near Clear: a visible seborrheic keratosis lesion with a surface appearance different from the surrounding skin (not elevated)
2	Thin: a visible seborrheic keratosis lesion (thickness ≤ 1mm)
3	Thick: a visible seborrheic keratosis lesion (thickness > 1mm)

In order for a subject to be eligible for screening and enrollment to the study, each target and non-target SK must have a PLA grade of ≥ 2.

2.4.2.2 SK Dimensions

At Visit 1 and Visit 2 prior to study enrollment, the investigator will measure the diameter and thickness of each target and non-target SK using the ruler provided.

The investigator must measure the diameter of the longest axis of each target and non-target SK in millimeters (mm) as follows:

- Diameter (i.e., the length of the longest axis)
- Thickness (height above the surrounding skin)

The PLA (the thickness) of the target and non-target SKs will be measured by the investigator at Visits 3, 4, 5, 7, 10, and 11. When the visit coincides with treatment (Visits 2, 5 and 7), the thickness must be measured prior to the application of study medication.

2.4.2.3 Subject Satisfaction Assessment

Subjects will be asked to assess their level of satisfaction regarding the study medication treatment experience. The subject survey will be completed at Visits 2, 3, 6 (only if treated at Visit 5), 8 (only if treated at Visit 7), 10, and 11.

The subject satisfaction assessments contain single and multiple choice questions. Three sets of questionnaires are designed for assessments at Day 1/Visit 2 prior to treatment, assessments for treatment experience after each treatment, and assessments at the end of study.

2.4.3 Evaluations – Safety

2.4.3.1 Adverse Events

Non-serious AEs will be recorded starting with the subject's first study medication treatment at Visit 2 and continuing through Visit 11. All SAEs regardless of relationship to study medication will be collected and reported from the time the Informed Consent is signed through Visit 11.

2.4.3.2 Vital Signs

Vital signs will be measured by a qualified staff member at Visit 1, Visit 2, Visit 5, Visit 7 Visit 10, and Visit 11. The following items will be measured:

- Body temperature
- Pulse rate

- Respiration rate
- Blood pressure (systolic and diastolic) after the subject sits quietly for at least 5 minutes
- Height (at Visit 1 only)
- Weight (at Visit 1 only)

Any measure that is, in the opinion of the investigator, abnormal AND clinically significant (CS) must be recorded as history if found prior to the first study medication treatment or as an AE if found after the first study medication treatment begins.

A systolic blood pressure >140mm Hg or a diastolic blood pressure >90mm Hg is considered abnormal and therefore must be defined as CS or non-clinically significant (NCS) on the Case Report Forms (CRFs).

2.4.4 Other Evaluations

At Visit 1, the investigator or designee will collect demographic information including date of birth, sex at birth, race, ethnicity, and Fitzpatrick Skin Type for each subject.

Skin Type Classification	Description
Type I	Always burns, never tans (pale white; blond or red hair; blue eyes; freckles)
Type II	Usually burns, tans minimally (white; fair; blond or red hair; blue, green, or hazel eyes)
Type III	Sometimes mild burn, tans uniformly (cream white; fair with any hair or eye color)
Type IV	Burns minimally, always tans well (moderate brown)
Type V	Very rarely burns, tans very easily (dark brown)
Type VI	Never burns, never tans (deeply pigmented dark brown to darkest brown)

3 STATISTICAL METHODOLOGY

This plan describes methods planned for the analysis and display of efficacy (PLA-based analyses only) and safety endpoints. Summaries will be based on mainly descriptive summaries for each assessment. A separate analysis plan will detail the analysis methods used for analyzing subject satisfaction assessments and its relationship with PLA.

3.1 GENERAL STATISICAL CONSIDERATIONS

Descriptive statistics (mean, standard deviation [Std Dev], median, minimum [Min], and maximum [Max]) will be used for continuous variables; number and percentage of subjects will be used for discrete variables. In general, the last measurement prior to the first dose of study treatment will be used as the baseline value. Nominal visits will be used for by-visit summaries.

All tabulations of summary statistics, graphical presentations, and statistical analyses will be performed using SAS® Version 9.2 or higher.

3.2 ANALYSIS POPULATION AND DISPOSITION OF SUBJECTS

3.2.1 Data Sets Analyzed

Intent-to-Treat (ITT) analysis set includes all enrolled subjects. This is the analysis set for all analyses. A subject is considered enrolled if at least one study treatment is applied.

3.2.2 Disposition of Subjects

The numbers of subjects screened (ie, signed informed consent), enrolled, discontinued from treatment (by reason), and replaced will be presented.

3.3 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be summarized. Gender, race, ethnicity, and Fitzpatrick skin type will be summarized with number and percentage presented for each category. Age, height, weight will be described with summary statistics (n, mean, Std Dev, median, minimum, and maximum).

3.4 MEDICAL HISTORY

Medical history will be summarized by body system class.

3.5 PRIOR/CONCOMITANT MEDICATIONS

The number and percentage of prior medications, and concomitant medications will be summarized by Antomical Therapeutic Chemical (ATC) and preferred term (PT) separately.

Medications taken any time prior to the first study treatment are counted as prior medications. Those taken any time on or after the first application of study medication through 30 days after the last application of study are counted as concomitant.

Subject will be counted only once within each classification. The same subject may contribute to two or more preferred terms within the same ATC classification.

3.6 STUDY DRUG EXPOSURE AND COMPLIANCE

Duration of treatment (Last study treatment application date – First study treatment application date + 1) will be summarized descriptively. Number and percentage of subjects at each visit will be summarized by the number of target/non-target lesions being treated. In addition, number and percentage of subjects with re-treatment will be summarized for the applicable visits.

3.7 EFFICACY ANALYSIS – PLA ANALYSES

PLA related parameters will be summarized at lesion level and at subject level.

At each visit or applicable visit, the following analyses will be performed:

- Number and percentage of lesions by PLA score categories (clear, near-clear, thin, and thick), overall and by target/non-target lesions; separately for face target lesions, and for neck target lesions;
- Summary statistics on PLA score (mean of all lesions, mean of target lesions, and non-target lesions, respectively);
- Summary statistics on percentage of lesions that are clear (PLA=0); separately for face target lesions, and for neck target lesions;
- Summary statistics on percentage of lesions that are clear or near clear (PLA=0 or 1); separately for face target lesions, and for neck target lesions;
- Number and percentage of lesions by location (face, neck, or décolletage), overall and by target/non-target lesions;

3.8 SAFETY ANALYSIS

The safety and tolerability of the investigational products will be determined by reported AEs, and vital signs.

3.8.1 Adverse Events

All subjects will be assessed regularly for the potential occurrence of adverse events (AEs) from the date of informed consent to 30 days after the last study treatment. The incidence of treatment-emergent AEs (TEAEs) will be summarized and tabulated using MedDRA (version 22.0), by System Organ Class (SOC) and Preferred Term (PT).

An overview of adverse events for the ITT analysis set will be provided, summarizing the incidence of the following:

- Count of TEAEs;
- Subjects with TEAEs;
- Count of Treatment-emergent serious AEs (TESAE);
- Subjects with TESAE;
- TEAE by maximum severity;
- TESAE by maximum severity;
- Subjects with TEAEs that lead to discontinuation of study;
- Subjects with TESAEs that lead to discontinuation of study;
- Subjects with Related TEAEs;
- Subjects with Related TESAEs.

3.8.2 Vital Signs

Vital signs measurements include pulse rate, temperature, systolic blood pressure, and diastolic blood pressure. Measures at baseline and changes from baseline to visit will be summarized. In addition, the maximum and minimum post-treatment values and their changes from baseline will be summarized. The number and percentage of subjects with abnormal blood pressure will be summarized.