STATISTICAL ANALYSIS PLAN

Study Number:	202395
Study Title:	Evaluation of the risk of atrophic acne scar formation during treatment of acne vulgaris subjects with trifarotene 50 µg/g cream versus vehicle cream over 24 weeks
Study Short Name:	START
CD Number:	CD5789
IND Number:	Not Applicable
EudraCT Number:	Not Applicable
Study Phase:	IV
Protocol Version and Date of Issue:	Amended Protocol 01/Global 9Jul2021
Sponsor:	Galderma S.A. Avenue d'Ouchy 4 1006 Lausanne Switzerland
Contract Research Organization:	Advanced Clinical 6 Parkway North, Suite 100 Deerfield, IL 60015 United States
CRO Study Number:	GAL 1914
Author:	PPD
Version and Date of Issue:	Final version 2.0, 27FEB2023

This study is conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for current Good Clinical Practice (GCP) and applicable regulatory requirements.

DOCUMENT HISTORY

Version	Date of Issue	Reason for Change
Draft 0.1	29JUN2021	PPD issued the first draft of the SAP
Draft 0.2	24AUG2021	PPD implemented the changes required by PPD and issued the second draft of the SAP
Draft 0.3	05OCT2021	PPD implemented the changes required by PPD, PPD and PPD and issued the third draft of the SAP
Draft 0.4	07DEC2021	PPD implemented the changes required by PPD and set SAP to stable
Draft 0.5	14DEC2021	PPD removed line plots of acne lesion counts, removed line plots and bar charts of Investigator Global Assessment of facial acne and issued the fifth draft of the SAP
Draft 0.6	14FEB2022	PPD implemented the changes required by PPD and issued the sixth draft of the SAP
Final 1.0	27APR2022	PPD issued the final version 1.0 of the SAP
Draft 1.1	14DEC2022	PPD implemented the changes required by PPD and issued the draft version 1.1 of the SAP
Final 2.0	27FEB2023	PPD issued the final version 2.0 of the SAP

GALDERMA APPROVAL AND ACKNOWLEDGEMENT SIGNATURES

Galderma Study Biostatistician (for approval and acknowledgement)

PPD, PPD

PPD	DocuSigned by: PPD BE3F4107B2644F5...
Date (ddMMMyyyy)	Signature

CRO APPROVAL AND ACKNOWLEDGEMENT SIGNATURES

CRO Study Biostatistician (for approval and acknowledgement)

PPD

PPD	DocuSigned by: PPD 707B5AEA7FDB428...
Date (ddMMMyyyy)	Signature

CRO Reviewer Statistician (for approval and acknowledgement)

PPD, Manager Biostatistics

PPD	DocuSigned by: PPD 2FFE70722CE5417...
Date (ddMMMyyyy)	Signature

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
CI	Confidence Interval
CRO	Contract Research Organization
CSR	Clinical Study Report
ECG	Electrocardiogram
ET	Early Termination
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
CCI	[redacted]
IRT	Interactive Response Technology
ITT	Intent-To-Treat
LOCF	Last Observation Carried Forward
MAR	Missing At Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputations
MNAR	Missing Not At Random
OC	Observed Case
PP	Per Protocol
PTAE	Pre-treatment Adverse Event
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
TEAE	Treatment-emergent Adverse Event
TLF	Tables, Listings and Figures
WHO	World Health Organization

1 INTRODUCTION

This Statistical Analysis Plan (SAP) of the study 202395 is based on the global amendment of the study protocol dated 09JUL2021. This document describes all the analyses and reporting that will be required for a clinical report purpose and any resulting publications. This SAP has been developed prior to any examination of study data. The analyses and reporting will be performed after the completion of study. Any post hoc, or unplanned, exploratory analyses performed, if included, will be clearly identified as such in the final Clinical Study Report (CSR).

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

The purpose of this study is to evaluate the effect of trifarotene 50 µg/g cream versus vehicle cream on the risk of formation of atrophic acne scars in facial acne subjects.

2.2 Study Endpoints

2.2.1 Primary Endpoint

- Absolute change from Baseline in total atrophic acne scar count per half-face at Week 24

2.2.2 Secondary Endpoints

- Absolute change in total atrophic acne scar count per half-face from Baseline to Week 20;
- Total atrophic acne scar count per half-face from Baseline to Week 24

CCI

[redacted]

CCI

[redacted]

2.2.4 Safety

- Local tolerability parameters (erythema, scaling, dryness and stinging/burning) will be evaluated per half-face at each visit on a 4-point scale ranging from 0 (none) to 3 (severe). Local tolerability scores will be summarized using frequency tables for worst post-baseline score, the final score during treatment, as well as scores for each visit;
- Incidence of all TEAEs including any dermatologic AEs per half-face, AESIs, SAEs and TEAEs leading to discontinuation.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a multi-center, randomized, double-blind, vehicle-controlled study using intra-individual comparison (right half-face versus left half-face) to evaluate the safety and efficacy of trifarotene (CD5789) cream for preventing the risk of atrophic scar formation. For the purposes of this protocol, the "left" or "right" side of the face is always defined as the subject's left or right.

An initial sample size of 118 subjects is planned to be randomized. To account for unknown treatment variability associated with trifarotene vehicle, a blinded sample size re-estimation will be performed after 40 subjects complete/discontinue the study (i.e. after ~33% of the initial planned subjects complete/discontinue the study) in order to evaluate the need for additional subjects to be randomized. Site enrollment strategies should include outreach plans with a goal for approximate even distribution of male to female subjects, to the extent possible.

Subject eligibility is evaluated over a 28-day screening period. Qualified subjects will complete baseline assessments and be randomized (left face versus right face) to apply trifarotene (CD5789) and trifarotene vehicle over a 24-week treatment period, for an intra-individual, split face comparison. Subjects will apply study medication under site supervision, at the Baseline visit, and will be reminded not to dose on the first evening. Subjects will be provided skin care products including Cetaphil® Gentle Skin Cleanser for washing the face twice daily (morning and evening); Cetaphil® PRO Oil Absorbing Moisturizer with SPF 30 for daily use on the face (morning) and to be re-applied to face when sun exposure is expected; and Cetaphil® Moisturizing Lotion for supplemental moisturizer use, as needed. Use of an equivalent available skincare product per country is permitted as well as the subject's preferred or investigator's recommended non-comedogenic cleanser, moisturizer and sunscreen (SPF ≥30 or equivalent). If a subject experiences persistent dryness or irritation, the investigator may consider a reduced application frequency for the study drug, up to a maximum of 2 weeks, within the first four (4) weeks of the treatment period.

Subjects will receive an electronic tablet at baseline for daily recording of study medication use (electronic dosing calendar), as well as for capturing daily videos of applying study medication to each side of the face. Study medication dosing data will be uploaded for remote assessment by the clinical site and will serve as the primary means for recording dosing compliance. All videos will remain on the local drive of the study electronic tablet and reviewed by site staff at scheduled office visits for supportive evidence of treatment compliance.

Subjects who do not require a washout period may complete the Screening and Baseline assessments on the same day. Subjects who initially fail screening may be re-screened once, provided the reason for screen failure is not due to acne severity (IGA) or lesion counts.

Subjects will return to the clinic for safety and efficacy assessment at Weeks 1, 2, 4, 8, 12, 16, 20 and 24. Study procedures and assessments are performed according to the schedule of assessments (see Section 3.1.2).

3.1.1 Study Schema

Figure 1 Study Schema

T: trifarotene (CD5789) cream
TV: trifarotene vehicle
R Randomization (split-face design)

BL: Baseline visit

W: Scheduled visit week

Note: For the purposes of this protocol, the "left" or "right" side of the face is always defined as the subject's left or right

3.1.2 Schedule of Assessments

3.1.2.1 Study Assessments Considerations Pertaining to the COVID-19 Pandemic

Subjects who are wearing a face mask should continue to do so until seated in an exam room, in accordance with local guidelines. The general sequence of examinations should begin with a wellness assessment, review of dosing calendar/compliance and completion of subject questionnaires prior to performing scar and acne assessments, local tolerability assessment and imaging (for designated imaging centers).

The following study procedures are permitted, within the protocol defined visit windows, to ensure safety of enrolled subjects and continuity of the follow-up visit schedule, due to circumstances when a subject is unable to return to the clinic due to the COVID-19 pandemic. These circumstances include, but are not limited to: shelter in place guidelines, quarantines, travel restrictions, clinical site closures, etc. As with all study procedures, clear and complete documentation in source records is required in these circumstances.

- Remote visits (phone, etc) in lieu of scheduled office visits:
  - for safety and wellness assessment (concomitant medications, AEs, etc).
- Subject questionnaire completion:
  - sent to subject by email or mail;

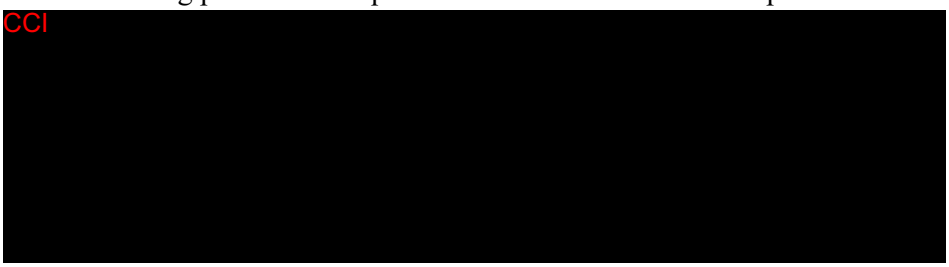
- subject signs, dates and returns, by email of mail.

- Collection of previously dispensed study drugs, from an adult family member along with the study electronic tablet:
  - Weighing of returned study drug is required;
  - A follow-up phone call with the subject is required to review the dosing calendar and returned study drugs, for appropriate clarification in study medication use.
- Dispensing of new study drugs and non-investigational supplies (a new dosing calendar, non-IP supplies, etc) to an adult family member:
  - Weighing of study drug is required, before dispensing;
  - A follow-up phone call with the subject is required to convey reminders on proper instructions for study medication and other supplies use, and to use the newly dispensed study drugs beginning that evening (and to stop using previously dispensed medication, if not returned).
- FDA COVID-19 guidance allows for secure delivery for self-administered study medication. In cases where a family member is not available for dispensing study medication and other supplies, delivery using an express courier with appropriate temperature control capability is permitted. A follow-up phone call is required in these circumstances to confirm receipt and provide the subject with appropriate reminders and proper instructions for study medication and other supply use.

  Note: The decision to ***dispense additional study drug should be based on the investigator's*** clinical judgement that ongoing dosing does not pose undue safety risks to the subject, and that the subject is willing to continue using the study drug. In all cases for maintaining study drug availability to subjects, existing requirements for maintaining study supply accountability remain.

The following procedures require an in-office examination to perform:

CCI



3.1.2.2 Study Assessments Schedule

Table 1 Study Assessments Schedule

Procedures	Screening[g]	Baseline	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24/ET[i]
	≤28 days	--	±2 days	±2 days	±3 days	±3 days)	±7 days	±7 days	±7 days	±7 days
Informed Consent [including daily videos (all subjects); static images (designated imaging centers only)]	X	X[h]								
Demographics / Medical History	X	X								
Previous Therapies and Medications[a]	X	X								
Concomitant Medications / Therapies / Procedures	X	X	X	X	X	X	X	X	X	X
Inclusion / Exclusion Criteria	X	X								
Urine Pregnancy Test[k]	X	X	X	X	X	X	X	X	X	X

CCI [redacted]

Procedures	Screening[g]	Baseline	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24/ET[i]
	≤28 days	--	±2 days	±2 days	±3 days	±3 days)	±7 days	±7 days	±7 days	±7 days
Subject Dosing Calendar (electronic tablet)		D	R/D	R/D	R/D	R/D	R/D	R/D	R/D	C/R
Video Review of IP Use (electronic tablet)			R/D	R/D	R/D	R/D	R/D	R/D	R/D	C/R
Exit Form										X

For study drug and/or dosing calendar: W=Weigh; D=Dispense; R=Review; C=Collect and I=Inspect (includes returning all study drug; the study drug dispensed at Baseline are inspected/weighed and re-dispensed at Week 1 and Week 2)

a. Acne treatment for the previous 6 months and all other therapies for the previous 4 weeks. Therapy that continues after baseline should be recorded on the concomitant medication CRF
b. Global assessment of severity is conducted on the face (SGA and IGA), **and should be performed before scar/lesion counts**
c. Inflammatory lesions (papules, pustules), non-inflammatory lesions (open and closed comedones) and other lesions (nodules, cysts) will be counted, on each half-face.
d. The Investigator must record and grade the severity of the signs and record the assessment of symptoms of local tolerability (erythema, dryness, scaling, and stinging/burning) on the face, at each visit. Severity grading is based on signs/symptoms occurring after the last dose of topical study drug before the visit. A sign/symptom which requires concomitant medication/therapy or results in permanent discontinuation of topical study drug should be recorded as an AE.
e. AE onset after subject signature of the ICF should be recorded on the AE CRF.
f. All subjects will complete the SCARS questionnaire, at the designated times.
g. Screening may be completed over several visits, over a 28-day period. Screening and Baseline may be completed on the same day, provided the subject meets eligibility requirements and does not require a washout period. Subjects may be re-screened one time, provided the reason for re-screening is not due to atrophic scar counts, acne severity or lesion counts.
h. If Screening and Baseline occur as separate visits, the ICF does not have to be signed again at Baseline.
i. Week 24 visit procedures are to be performed for early termination/exit visit.
j. These assessments exclude the nose and the middle zone of the face (approximately 2 cm). These assessments are to be performed by the same evaluator throughout the study, for a given subject. If it is not possible to use the same evaluator to follow a given subject, evaluations between the primary and subsequent evaluator should overlap (both evaluators should examine the subject together and discuss findings) for at least one prior visit. At Week 24 or Early Termination, attempts should be made to complete assessments by the same rater as Baseline, to the extent possible.
k. For WOCBP only. Mandatory at Screening, Baseline, Week 24 and ET visits. UPT is required at other visits if no menstrual period has occurred in the preceding four weeks. For prepubertal subjects, reconfirm pre-menses status at every visit and, in case of status change, collect information on contraceptive measures and perform a UPT according to the schedule for WOCBP. Sites will provide UPT supplies (hCG sensitivity ≤25 mIU/mL).
l. Study drug refers to trifarotene (CD5789) cream or trifarotene cream vehicle. First application of study drug occurs under site staff supervision, at the clinic, at the Baseline visit. Subjects are reminded not to dose that evening.
m. Consent to facial photography for visual evidence of treatment effect is mandatory to study participation, but only applies to designated imaging centers. Consent to photographs of patch testing results (suspected contact allergic reaction) and daily video recording of IP use on electronic tablet is mandatory for all subjects to participate in the study.

3.2 Selection of Study Population

3.2.1 Number of Planned Subjects

An initial number of 118 subjects is planned to be randomized. A blinded sample size re- estimation will be performed after 40 subjects complete/discontinue the study (i.e. after ~33% of the initial planned subjects complete/discontinue the study) in order to evaluate the need for additional subjects to be randomized. Site enrollment strategies should include outreach plans with a goal for approximate even distribution of male to female subjects, to the extent possible.

Refer to section 4 for the statistical considerations on which the sample size is based.

3.2.2 Inclusion Criteria

Refer to section 5.3.2 of the study protocol.

3.2.3 Exclusion Criteria

Refer to section 5.3.3 of the study protocol.

3.2.4 Removal of Subjects from Therapy or Assessments

Although the importance of completing the entire clinical study will be explained to the subjects, any subject is free to discontinue his/her participation in the study at any time and for whatever reason, specified or unspecified, and without any prejudice. No constraints are to be imposed on the subject, and when appropriate, a subject may be treated with other conventional therapy when clinically indicated. Investigators or the Sponsor can also withdraw subjects from the clinical study if deemed to be necessary.

For discontinuation due to an AE, the Investigator should ensure that the subject receives suitable therapy for his/her AE.

Possible reasons for discontinuing the study are summarized in Table 2:

Table 2 Possible Reasons for Study Discontinuation

Pregnancy:	Withdraw the Subject from the clinical study and follow the procedure described in Section 6.11.2.2.5 of the study protocol
Lack of Efficacy:	Investigator judgment only: based on therapeutic/disease-state expectations. If subject opinion only, mark "subject request" and document it in the comment section of the Exit Form.
Adverse Event:	Complete an Adverse Event Form.
Death:	Death of the subject.
Withdrawal by Subject [a]:	Includes consent withdrawal, subject relocation, schedule conflicts. Explain the reason for withdrawal in the comment section of the Exit Form.
Withdrawal by Parent / Guardian [a]	An indication that a study participant has been removed from the study by the parent or legal guardian. Explain the reason for withdrawal in the comment section of the Exit Form.
Protocol Violation:	Explain the violation in the comment section of the Exit Form.
Lost to Follow-up:	Confirmed with two documented phone calls and a certified letter (delivery receipt requested) without answer. Explain in the comment section of the Exit Form.
Non-Compliance with Study Drug:	An indication that a subject has not agreed with or followed the instructions related to the study medication.
Physician Decision [a, b]:	A position, opinion or judgment reached after consideration by a physician with reference to subject. Explain the reason in the comment section of the Exit Form.
Site Terminated by Sponsor:	An indication that the clinical study was stopped at a particular site by its sponsor.

Study Terminated by Sponsor:	An indication that the clinical study was stopped by its sponsor.
Sponsor Request:	An indication that the study subject was removed from the study at the sponsor's request.
Other [a]:	This category is to be used for a subject who discontinues due to a reason other than as specified in the predefined categories above. Explain the reason for discontinuation in the comment section of the Exit Form.

a) If reason for discontinuation is "withdrawal by subject", "withdrawal by parent/guardian", "physician decision" or "other", the subject will be questioned to rule out the possibility of an AE (this should be documented in the comment section of the Exit Form).
b) Investigator may withdraw a subject for dramatic, clinically significant differences in appearance between the right and left sides of the face where full face treatment may be indicated, based on the investigator's clinical judgment.

The reason(s) for withdrawal will be documented in the CRF. Subjects who have been randomized will not be replaced by another subject.

Subjects who prematurely discontinue study drug will be encouraged to complete the scheduled study visits for safety purposes and for collecting at least the data for the primary endpoint, before study exit.

When a subject discontinues the study, he/she will be fully assessed whenever possible, and followed according to guidelines presented in section 3.4.1.
Reasonable efforts will be made to contact subjects who are lost to follow-up (e.g., non-response/contact after 2 phone calls and a certified letter with return receipt). These efforts must be documented in the subject's file.

The Sponsor has the right to terminate the study at any time in case of SAEs or if special circumstances concerning the investigational product or the company itself occur, making further treatment of subjects impossible. In this event, the investigator(s) will be informed of the reason for study termination

3.3 Investigational Products

Investigational products include trifarotene (CD5789) cream and trifarotene vehicle.

3.3.1 Treatments Administered

Refer to section 5.4.1 of the study protocol.

3.3.2 Method of Assigning Subjects to Treatment Sides

Upon signature of the ICF, each subject will be assigned a Subject Identification Number (SIN) to be used throughout the study. Once a SIN has been assigned, that number must not be used again for any other subject. Subjects may be re-screened once provided the reason for re- screening is not related to atrophic scar counts, acne severity (IGA) or lesion counts.

Prior to the start of the clinical study, a randomization list will be generated and transmitted to the clinical packaging organization for study drug labeling. The randomization will assign the trifarotene (CD5789) cream or trifarotene vehicle cream to the right or left side of the face, for each study drug kit, and study drug instructions will include which study drug should be applied on which side of the face.

NOTE: For the purposes of this protocol, the "left" or "right" side of the face is always defined as the subject's left or right.

Upon chronological order of confirming subject eligibility, subjects are assigned a study drug kit in ascending numerical order of kit ID.

Refer to section 3.1.1 for an illustration of the study design and treatment allocation.

3.3.3 Allocation Concealment and Blinding

Allocation concealment is ensured as the kits will be assigned in chronological order on the basis of the confirmed subject eligibility. Randomization will occur individually, each kit will be assigned to a unique randomized subject and the simultaneous randomization of groups of subjects will be prevented.

All attempts will be made to keep the study team, site staff and subjects blinded to study treatment throughout the study, including:

Members of the study team or site staff will not have access to the randomized treatment assignment.

Study drug will have similar appearance, packaging and use instructions as the corresponding vehicle.

3.3.4 Prior and Concomitant Therapy

3.3.4.1 Definition

Information on previous and concomitant therapies will be collected and recorded in the CRF.

Previous therapies are defined as medications or procedures that have been stopped before the Screening visit and includes all acne therapies (within 6 months) and all other therapies (within 1 month).

Concomitant therapies are defined as:

- any existing therapies ongoing at the Screening visit;
- any changes to existing therapies (such as changes in dose or formulation) during the course of the clinical study, or

- any new therapies received by the subject since the Screening visit

Any new concomitant therapy or modification of an existing therapy may be linked to an adverse event (AE). A corresponding AE form must be completed to account for the change in therapy, except in some cases such as therapy used for prophylaxis, dose modification for a chronic condition, etc. In these cases, the medication will be linked to an item in the medical history.

3.3.4.2 Categories

The following two categories are to be considered for previous and concomitant therapies:

- Drugs/therapies including, but not limited to, prescription, over-the-counter (OTC), birth control pills/patches/hormonal devices, vitamins, cleansers, moisturizers, sunscreens, herbal medicines/supplements, and homeopathic preparations.
- Medical and surgical procedures including, but not limited to, laser/radiation procedures, dermal fillers, X-rays (excluding dental X-rays), etc.

3.3.5 Treatment Compliance - Primary Source Data

Subjects will be instructed by study personnel on the importance of being compliant with the use of the study drug and non-study products.

Subjects will receive an electronic tablet at baseline for recording study medication use on each half-face (electronic dosing calendar) with clear instructions for daily use throughout the study (see Section 3.1.2). The subject-reported data in the dosing calendar will be used as the primary source data for calculating treatment compliance, per each half-face.
Results are uploaded to a secure portal for remote monitoring, with subject counseling, as needed, throughout the study.

Subjects will be instructed to return the study electronic tablet and all study medication at each study visit. Site personnel will review dosing compliance data since the last visit, derive treatment compliance for each half-face and counsel/re-train subjects, if needed. Treatment compliance will be derived from the total expected doses and number of actual doses recorded, over a given visit interval.

Any missed dose will be considered a protocol deviation, based on recordings in the dosing calendar. Subjects should be appropriately counseled on the importance of following study drug dosing instructions and daily recordings in the dosing calendar. Subjects should be reminded and encouraged to follow guidelines for non-study product use, throughout the study.

3.3.6 Treatment Compliance - Supportive Video Evidence

The assigned electronic tablet will also be used by subjects to capture videos of study drug application, for each half-face, on a daily basis (Protocol section 5.4.3 - Study Drug Application with Video Collection). The study drug label will be apparent in the video to confirm which product was applied to each side of the face (e.g., red label = right side of face, etc). All videos are collected

and stored locally and securely on the electronic tablet. There are no video uploads or transfer from the local device. Only designated site staff will have access to view these videos on the electronic tablet.

Even though no videos will be uploaded to a central portal for remote viewing, the electronic dosing calendar will include a question whether the subject is collecting daily videos, which site staff can reference for remote monitoring and counseling.

While the dosing calendar data will be the primary source for reporting treatment compliance, daily videos are used for site staff to spot-check for proper use of study medication, and appropriately counsel and re-train subjects on the importance of following proper study drug instructions.

At each visit, the subject will return the electronic tablet. Site staff will review videos and provide subject counseling and reminders on the importance of following study drug dosing instructions, throughout the study. At least two videos since the prior visit should be reviewed. Subjects who display repeated non-compliance based on video evidence, despite repeated counselling and re-training, should be discontinued from the study, based on investigator discretion.

Note: Subjects will be informed that videos will be reviewed to ensure proper use of study drug throughout the study; however, they will not be told how many videos will be reviewed. This non-disclosure allows subjects to be appropriately informed with sufficient detail of what study procedures will be performed and does not create any added risks to the subjects by withholding this level of detail. Preserving the notion that someone is watching is considered critical to maintaining the integrity of the split-face study design, as it provides motivation to remain compliant, while attempting to balance the administrative burden of daily video review by site staff, over a total treatment period of approximately 170 days, for each subject. The subject-reported dosing compliance data recorded on the electronic dosing calendar will be used to derive compliance, which is a common procedure used in clinical studies to reliably assess daily product use. Repeated non- compliance observed by video evidence should result in subject termination, based on investigator discretion.

At the end of the study, the electronic tablet will be collected, and all collected information fully removed by the clinical site and confirmed by the equipment vendor.

3.4 Duration of Subject Participation

The expected duration for each subject's participation in the study is approximately 28 weeks (including a 4-week screening period and a 24-week treatment period).

3.4.1 Early Termination Visit

When a subject does not complete the clinical study, he/she will be fully assessed, if such assessment is possible. The procedures designated for the Week 24/Early Termination visit should be completed for all subjects discontinuing the study and the appropriate CRF page should be completed.

Refer to section 3.2.4 for reasons for study discontinuation.

3.4.2 Unscheduled Visit

The subject should be reminded to adhere to the study visit schedule. Unscheduled visits are unplanned and may include examinations for safety or repeat study assessments. Visits occurring outside of the visit window are not considered unscheduled visits.

Assessments to be conducted at the unscheduled visit will depend on the reason for the visit. Any of the procedures/assessments listed in section 3.1.2 in may be conducted, as appropriate.

3.5 Efficacy and Safety Assessments

3.5.1 Efficacy Assessments

Efficacy measurements should be conducted by the investigators (or designees) or by subjects (for subject-reported assessments) according to section 3.1.2.

Evaluators must complete standardized training prior to performing the following assessments: atrophic scar severity (SGA), atrophic scar counts, acne severity (IGA), inflammatory lesion counts (papules and pustules), non-inflammatory lesion counts (open and closed comedones), and other lesion counts (nodules and cysts).

Notes:

1) Scar severity grading (SGA) and scar counts will be performed separately. The scar severity assessment will be performed before the scar counting.
2) Acne severity grading (IGA) and acne lesion counts will be performed separately. The acne severity assessment will be performed before the acne lesion counting.

Throughout the study when possible, the same evaluator should perform the SGA, scar counts, IGA and acne lesion counts, for each subject. In the event there is a change in the assigned evaluator for a given subject, the reason for change should be documented. If it is not possible to use the same evaluator to follow a given subject, evaluations between the primary and subsequent evaluator should overlap (both evaluators should examine the subject together and discuss findings) for at least one prior visit. At the final study visit (Week 24 or Early Termination), attempts should be made for the rater to be the same as baseline for the following assessments, to the extent possible:

For all efficacy assessments, the zone in the middle of the face (approximately 2 cm wide and inclusive of the nose) should be excluded for clinical efficacy evaluation because subjects may apply a mix of investigational products in this area (Figure 2).

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

- [redacted]

CCI

[redacted]

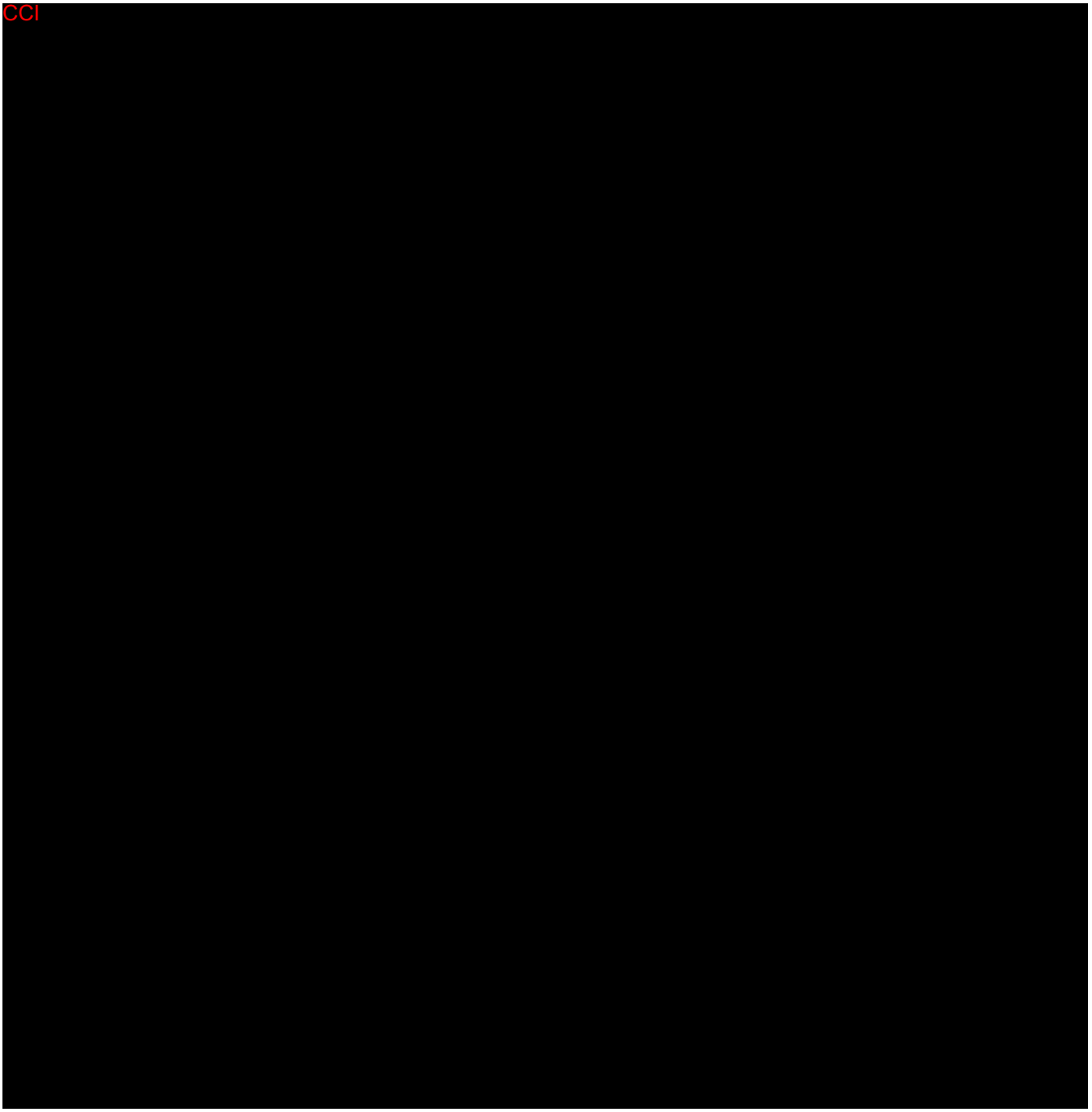
3.5.2 Safety Assessments

Safety assessments include the recording of adverse events and local tolerability scores.

3.5.2.1 Adverse Events

Adverse events (AEs) are to be monitored throughout the course of the clinical study. All AEs are to be reported on the Adverse Event Form with complete information as required. If AEs occur, the main concern will be the safety of the subjects. At the time of the ICF signature, each subject must be provided with the name and phone number of clinical study center personnel for reporting AEs and medical emergencies.

CCI



4 SAMPLE SIZE CONSIDERATION

The sample size calculation is based on the results of the study RD.06.SPR.118295 "A Multi-Center Study to evaluate Subject Reported Outcomes with use of trifarotene 50 µg/g cream in the treatment of moderate facial and truncal acne vulgaris" and of the study RD.03.SPR.105061 "Effect of Adapalene 0.3% - Benzoyl Peroxide 2.5% gel versus vehicle gel on the risk of formation of atrophic acne scars in moderate to severe acne subjects".

In study RD.06.SPR.118295, the following results were obtained for the absolute change from baseline in total atrophic acne scar count at week 24:

These results refer to a whole face treatment whilst in the current study a split-face design is used. Moreover, due to the lack of a Vehicle arm, it is not possible to estimate the mean value and the variability of the difference in mean absolute change from baseline in total atrophic acne scar between treatment arms.

It is possible to hypothesize that the mean reduction in trifarotene 50 µg/g cream arm when only half-face is treated is -1.7 but there are no data for estimating the variability of the difference between trifarotene 50 µg/g cream and vehicle cream.

In study RD.03.SPR.105061 a split-face design was used and the following results were obtained for the absolute change from baseline in total atrophic acne scar count at week 24:

CCI

[redacted]

Under the following hypotheses:

- Mean absolute change from baseline in total atrophic acne scar count at week 24 for trifarotene 50 µg/g cream is -1.7
- Mean absolute change from baseline in total atrophic acne scar count at week 24 for Vehicle cream is zero
- Difference absolute change from baseline in total atrophic acne scar count at week 24 between trifarotene 50 µg/g cream and vehicle cream is -1.7
- Variability of the difference between trifarotene 50 µg/g cream and vehicle cream is 6.0 (derived by supposing an increase of about 35% of the variability observed in study RD.03.SPR.105061)

the sample size for a Student's t-test for paired samples can be calculated according to the following formula:

$$n \geq \frac{\left(t_{1-\frac{\alpha}{2},n-1} + t_{1-\beta,n-1}\right)^2 \sigma_{Diff}^2}{\left(\mu_{Trifarotene} - \mu_{Vehicle}\right)^2}$$

where $t_{p,\nu}$ is the Student's t distribution quantile with ν degrees of freedom and probability p (n is rounded up to the closest integer).

Table 8 Sample Size Calculation

α (2-sided)	β	Power (%)	$\mu_{Trifarotene} - \mu_{Vehicle}$	σ_{Diff}	n	Drop-out and Non-evaluable Proportion (%)	Subjects to be Randomized
0.05	0.2	80	-1.7	6.0	100	15	118

An initial number of 118 subjects is planned to be randomised. Due to the uncertainty of the estimation of the variability, a blinded sample size re-estimation will be performed after 40 subjects complete/discontinue the study (i.e. after 33% of the initial planned subjects complete/discontinue the study) in order to evaluate the need for additional subjects to be randomized.

4.1 Blinded Sample Size Re-estimation

A blinded sample size re-estimation will be performed after 40 subjects complete/discontinue the study (i.e. after ~33% of the initial planned subjects complete/discontinue the study) in order to evaluate the need for additional subjects to be randomized.

Given the paired-sample problem of testing the following two-sided hypothesis

$$\begin{cases} H_0: \mu_{Diff} = 0 \\ H_a: \mu_{Diff} \neq 0 \end{cases}$$

for the mean of difference between paired samples with unknown variance of difference σ^2_{Diff}, the initial sample size per group N_{init} is determined on the basis of the anticipated estimate of variance of difference S_{init} and the expected mean of difference $\mu_{Diff}=\delta$ under H_a as follows:

$$N_{init}(S_{init}) \geq \left(t_{1-\frac{\alpha}{2},N_{init}-1} + t_{1-\beta,N_{init}-1}\right)^2 \frac{S^2_{init}}{\delta^2}$$

After $n_1<N_{init}$ pairs of observations, the sample size is recalculated by replacing the initial estimate of variance of difference S_{init} with the variance estimate S_{recalc} from the subsample in the sample size formula:

$$N_{recalc}(S_{recalc}) \geq \left(t_{1-\frac{\alpha}{2},N_{recalc}-1} + t_{1-\beta,N_{recalc}-1}\right)^2 \frac{S^2_{recalc}}{\delta^2}$$

with the restriction that the recalculated sample size should not be lower than the initially planned one (N_{init}) and should not be greater than a maximum predefined sample size (N_{max}):

$$N = min\left(N_{max}, max(N_{init}, N_{recalc})\right)$$

For this study, N_{max} is set to 160 subjects.

The response variable for each subject is the within-subject difference between the observations of each treatment

$$D_j = X1_j - X2_j$$

that cannot be calculated without unblinding the treatment assigned to each half face.

If treatments assignment were known, the observed variance after n_1 subjects would be calculated as follows:

$$S^2_{Obs} = \frac{1}{n_1 - 1}\left(\sum_{j=1}^{n_1}\left(D_j - \overline{D}\right)^2\right)$$

where

$$\overline{D} = \frac{1}{n_1}\sum_{j=1}^{n_1} D_j$$

The observed variance after n_1 subjects can be re-written as follows:

$$S^2_{Obs} = \frac{n_1}{n_1 - 1}\frac{1}{n_1}\left[\sum_{j=1}^{n_1}\left(D_j - \overline{D}\right)^2\right] = \frac{n_1}{n_1 - 1}\left(\overline{D^2} - \overline{D}^2\right)$$

where

$$\overline{D^2} = \frac{1}{n_1}\sum_{j=1}^{n_1} D_j^2$$

is the mean of squared differences. Without unblinding the treatment assigned to each half face, we can calculate the Left-Right difference as follows:

$$LR_j = XLeft_j - XRight_j$$

Since

$$|LR_j| = |D_j|$$

the mean of squared differences can be re-calculated as follows:

$$\overline{D^2} = \frac{1}{n_1}\sum_{j=1}^{n_1} D_j^2 = \frac{1}{n_1}\sum_{j=1}^{n_1} LR_j^2 = \overline{LR^2}$$

and the following conditions hold for the mean of differences and the squared mean of differences

$$-\overline{|LR|} \le \overline{D} \le \overline{|LR|}$$

and

$$0 \le \overline{D}^2 \le \overline{|LR|}^2$$

where

$$\overline{|LR|} = \frac{1}{n_1}\sum_{j=1}^{n_1} |LR_j|$$

is the average of the absolute values of the Left-Right differences.

According to the previous formulas, the following boundaries can be calculated for observed variance after n_1 subjects:

$$\frac{n_1}{n_1 - 1}\left(\overline{LR^2} - \overline{|LR|}^2\right) \le S_{Obs}^2 \le \frac{n_1}{n_1 - 1}\overline{LR^2}$$

The observed variance after n_1 subjects can be estimated as follows:

$$S_{Obs}^2 = \frac{n_1}{n_1 - 1}\overline{LR^2}$$

Missing squared differences of atrophic acne scar counts between the left and right sides of the face at Week 24 will be imputed using multiple imputation methodology (as specified in section 6.3.6.2). A linear regression model will be used with covariates for non-missing squared differences of atrophic acne scar counts between the left and right sides of the face from earlier scheduled time points including baseline.

5 POPULATIONS ANALYZED

For the purposes of this study, randomization (i.e., treatment assignment to left or right side of the face) is achieved by assigning available treatment kit IDs, in increasing sequential order, at the time subjects are confirmed to fully qualify for the study. This study will not use IRT technology to generate a randomization record.

5.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) population is defined as all randomized subjects and will be used for the analyses of efficacy endpoints on the face. Subjects of the ITT population will be summarized and analyzed according to the treatment they were randomized to.

5.2 Per Protocol Population

The Per Protocol (PP) population is defined as comprising the ITT population subjects who are compliant to the treatment application (i.e. with an overall compliance between 80% - 120% inclusive), whose Baseline and Week 24 total atrophic acne scar counts are performed and who have no major deviations from the protocol that could have a significant effect on the efficacy of the study treatment (e.g. errors in treatment assignment, use of prohibited medications).

5.3 Safety Population

The Safety (SAF) population is defined as comprising the ITT population subjects who applied/took the study drug) at least once and will be used for all safety analyses. Subjects of the Safety population will be summarized according to the treatment they actually received.

6 STATISTICAL METHODS AND DATA CONSIDERATIONS

6.1 General Considerations

6.1.1 Baseline

For statistical analyses purpose, baseline is defined as the last non-missing measurement prior to the first treatment for subjects treated and as the last non-missing measurement prior to randomization for subject randomized but not treated.

Absolute change from baseline and percent change from baseline will be calculated as follows:

$$\text{Absolute Change from Baseline} = \text{PostBaseline} - \text{Baseline}$$

$$\text{Percent Change from Baseline} = \begin{cases} \text{Baseline} \neq 0 \Rightarrow 100 \cdot \dfrac{\text{PostBaseline} - \text{Baseline}}{\text{Baseline}} \\ \text{Baseline} = 0 \Rightarrow \text{Missing} \end{cases}$$

6.1.2 Missing and Partial Dates Management

- Start Date Imputation of Adverse Events:
  - Imputation of adverse event end date has to be done before imputation of event start date.
  - Completely missing: For subjects treated, impute to the first treatment date. For subject randomized but not treated, impute to the randomization date. For subjects not randomized, impute to the date of informed consent.
  - Missing day and month: For subjects treated, impute to January 1st, unless year is the same as year of first treatment dose then impute to the first treatment date. For subject randomized but not treated, impute to January 1st, unless year is the same as year of randomization then impute to the randomization date. For subjects not randomized, impute to January 1st, unless year is the same as year of informed consent then impute to the informed consent date
  - Missing day: For subjects treated, impute to the 1st of the month, unless month and year are the same as month and year of first treatment dose then impute to the first treatment date. For subject randomized but not treated, impute to the 1st of the month, unless month and year are the same as month and year of randomization then impute to the randomization date. For subjects not randomized, impute to the 1st of the month, unless month and year are the same as month and year of informed consent then impute to the informed consent date.
  - If imputed event start date is after event end date (imputed or not), set the event start date to the imputed event end date.
- Start Date Imputation of Prior/Concomitant Therapies and Medical/Surgical Procedures:
  - Imputation of therapy/procedure end date has to be done before imputation of

therapy/procedure start date.

- Completely missing: For subjects treated, impute to the first treatment date. For subject randomized but not treated, impute to the randomization date. For subjects not randomized, impute to the date of informed consent.
- Missing day and month: For subjects treated, impute to January 1st, unless year is the same as year of first treatment dose then impute to the first treatment date. For subject randomized but not treated, impute to January 1st, unless year is the same as year of randomization then impute to the randomization date. For subjects not randomized, impute to January 1st, unless year is the same as year of informed consent then impute to the informed consent date
- Missing day: For subjects treated, impute to the 1st of the month, unless month and year are the same as month and year of first treatment dose then impute to the first treatment date. For subject randomized but not treated, impute to the 1st of the month, unless month and year are the same as month and year of randomization then impute to the randomization date. For subjects not randomized, impute to the 1st of the month, unless month and year are the same as month and year of informed consent then impute to the informed consent date.
- If imputed therapy/procedure start date is after therapy/procedure end date (imputed or not), set the therapy/procedure start date to the imputed therapy/procedure end date.

- Start Date Imputation of Medical History Diseases:
  - Imputation of disease end date has to be done before imputation of disease start date.
  - Completely missing: Leave it missing.
  - Missing day and month: Impute to January 1st.
  - Missing day: Impute to the 1st of the month.
  - If imputed disease start date is after disease end date (imputed or not), set the disease start date to the imputed disease end date.
- End Date Imputation of Adverse Events, Prior/Concomitant Therapies and Medical/Surgical Procedures, Medical History Diseases:
  - Completely missing and with outcome 'Not Recovered/Not Resolved' or 'Unknown' (Adverse Events): Leave it missing.
  - Completely missing and flagged as being ongoing (Prior/Concomitant Therapies and Medical/Surgical Procedures, Medical History Diseases): Leave it missing.
  - Completely missing and with an outcome different from 'Not Recovered/Not Resolved' and 'Unknown' (Adverse Events): Impute to the last contact date.
  - Completely missing and not flagged as being ongoing (Prior/Concomitant Therapies and Medical/Surgical Procedures, Medical History Diseases): Impute to the last contact date.
  - Missing day and month: Impute to December 31st, unless year is the same as last contact date then impute to the last contact date.
  - Missing day: Impute to the last day of the month, unless year and month are the same as

year and month of last contact date then impute to the last contact date.

6.1.3 Reference Start Date and Analysis Day

For subjects treated, the first treatment date will be the reference start date. For subject randomized but not treated, the randomization date will be the reference start date. For subjects not randomized, the reference start date will be set to missing.

Analysis day will be calculated from the reference start date and will be used to show start/end day of assessments, events, diseases, therapies or procedures.

In the situation where the assessment/event/disease/therapy/procedure date is fully missing and cannot be imputed (i.e. when an adverse event has outcome 'Not Recovered/Not Resolved' or 'Unknown' and when a disease, therapy or procedure is reported as being ongoing), analysis day will be missing.

6.1.4 Descriptive Statistics

For the descriptive statistics, unless otherwise noted, the categorical variables will be summarized by frequencies and proportions expressed as percentages (n, %) of subjects for each classification category and the continuous variables will be summarized using standard descriptive statistics (n, mean, standard deviation, median, first and third quartile, min and max).

6.1.5 Statistical Tests and Confidence Intervals

A two-sided type I error $\alpha = 0.05$ will be used to declare statistical significance for the primary endpoints and the secondary endpoints. Confidence intervals (CIs) will be two-sided with 95% coverage for the primary endpoint and the secondary endpoints. The following flagging conventions will be applied for the p-values of all statistical testing:

- $0.01 \leq$ p-values < 0.05 will be flagged with one asterisk (e.g. "0.0499 *")
- $0.001 \leq$ p-value < 0.01 will be flagged with two asterisks (e.g. "0.0099 **")
- $0.0001 \leq$ p-value < 0.001 will be flagged with three asterisks (e.g. "0.0009 ***")
- p-value < 0.0001 will be flagged with four asterisks (e.g. "< 0.0001 ****")

6.1.6 Decimal Precision

Unless otherwise noted, the following rounding conventions will be applied:

- means, medians, first and third quartiles will be rounded and presented to one more decimal digit than the source data;
- confidence intervals of means and medians will be rounded and presented to one more decimal digit than the source data;
- standard deviations and standard errors will be rounded and presented to two more decimal digits than the source data;

- minima and maxima will be presented to the same number of decimal digits as the source data;
- proportions will be reported as percentages (not as fraction of unit);
- percentages greater than or equal to 0.1 will be rounded and presented to one decimal digit, percentages lower than 0.1 and greater than 0 will be presented as '<0.1', percentages equal to 0 will not be presented;
- confidence intervals of percentages will be rounded and presented to one decimal digit;
- standard errors of percentages will be rounded and presented to two decimal digits;
- p-values greater than or equal to 0.0001 and lower than or equal to 0.9999 will be rounded and presented to fourth decimal digits;
- p-values lower than 0.0001 will be presented as '< 0.0001';
- p-values greater than 0.9999 will be presented as '> 0.9999';

6.1.7 Software Version

All analyses will be performed using SAS® software Version 9.4 or higher.

6.2 Study Subjects

6.2.1 Disposition of Subjects

Frequencies and proportions (n, %) of subjects will be summarized for the following categories:

- Subjects screened
- Screen failures/not randomized subjects
  - Reason for screen failure/not randomized
- Screen failures/not randomized subjects due to COVID-19
  - Reason for screen failure/not randomized due to COVID-19
- Subjects randomized
- Subjects randomized who discontinued before treatment
  - Reasons for study discontinuation before treatment
- Subjects randomized who discontinued before treatment due to COVID-19
  - Reasons for study discontinuation before treatment due to COVID-19
- Subjects randomized who underwent the treatment
- Subjects randomized who completed the treatment
- Subjects randomized who discontinued the treatment
  - Reasons for treatment discontinuation
- Subjects randomized who discontinued the treatment due to COVID-19

  - Reasons for treatment discontinuation due to COVID-19
- Subjects randomized who completed the study
- Subjects randomized who discontinued the study
  - Reasons for study discontinuation
- Subjects randomized who discontinued the study due to COVID-19
  - Reasons for study discontinuation due to COVID-19
- Subjects randomized affected by COVID-19 related study disruptions
- Subjects randomized affected by COVID-19 related study disruptions impacting efficacy
- Subjects randomized affected by COVID-19 related study disruptions impacting safety

Listing for subjects' disposition, screen failures, discontinued subjects, treatment completion status, discontinued treatment and subjects affected by COVID-19 related study disruptions will be provided.

6.2.2 Accounting of Subjects

Frequencies and proportions (n, %) of subjects will be summarized in the ITT population for each clinical visit and each analysis visit.

Listings for subject scheduled visits and subject unscheduled visits will be provided.

6.2.3 Protocol Deviations

Major protocol deviations, major protocol deviations leading to the exclusion from the PP population, major protocol deviations due to COVID-19 and minor protocol deviations will be summarized using frequencies and proportions (n, %) of subjects in the ITT population for each deviation coded term by treatment side (trifarotene 50 µg/g versus vehicle) and overall.

Local protocol deviations (localized to right or left side) will be presented by treatment side (trifarotene 50 µg/g versus vehicle) and overall. Protocol deviations that are subject specific will be presented overall only.

A listing of all protocol deviations will be provided.

6.2.4 Data Sets Analyzed

Frequencies and proportions (n, %) of subjects in each analysis population (ITT, PP, SAF) will be summarized.

Frequencies and proportions (n, %) of subjects will be summarized for each inclusion/exclusion criterion not met.

Listings for inclusion/exclusion criteria not met and analysis populations will be provided.

6.2.5 Demographic and Other Baseline Characteristics

Descriptive statistics (n, mean, standard deviation, median, first and third quartile, min and max) or frequencies and proportions (n, %) of subjects for each classification category (as applicable) will be presented using the ITT population for the following demographic data and baseline characteristics:

- Age (years)
- Age Groups
  - <18 years old
  - ≥18 years old
- Sex
  - Male
  - Female
- Ethnicity
  - Hispanic or Latino
  - Not Hispanic or Latino
  - Not Reported
- Race
  - White
  - Black or African American
  - Asian
  - American Indian or Alaska Native
  - Native Hawaiian or Other Pacific Islander
  - Other
  - Multiple
- Body weight at Screening (kg)
- Fitzpatrick Skin Type
  - Type I
  - Type II
  - Type III
  - Type IV
  - Type V
  - Type VI

- Baseline Investigator Scar Global Assessment (SGA) by treatment side (trifarotene 50 µg/g versus vehicle)
  - 0 - Clear
  - 1 - Almost Clear
  - 2 - Mild
  - 3 - Moderate
  - 4 - Severe
- Baseline Total Atrophic Acne Scar Counts by treatment side (trifarotene 50 µg/g versus vehicle)
- Baseline 2-4 mm Atrophic Acne Scar Counts by treatment side (trifarotene 50 µg/g versus vehicle)
- Baseline >4 mm Atrophic Acne Scar Counts by treatment side (trifarotene 50 µg/g versus vehicle)
- Baseline Investigator Global Assessment (IGA) by treatment side (trifarotene 50 µg/g versus vehicle)
  - 0 - Clear
  - 1 - Almost Clear
  - 2 - Mild
  - 3 - Moderate
  - 4 - Severe
- Baseline Total Lesion Counts by treatment side (trifarotene 50 µg/g versus vehicle)
- Baseline Inflammatory Lesion Counts by treatment side (trifarotene 50 µg/g versus vehicle)
- Baseline Non-Inflammatory Lesion Counts by treatment side (trifarotene 50 µg/g versus vehicle)

If ITT population and Safety population do not include the same subjects, the summary will be presented for the Safety population too.

Frequencies and proportions (n, %) of subjects will be summarized using the ITT population (females only) for the following classification category:

- Childbearing Potential
  - Strict Abstinence
  - Male/Female Condom
  - Cap, Diaphragm or Sponge with Spermicide
  - Combined (estrogen and progestogen containing) Oral, Intra-vaginal or Transdermal Hormonal Contraception

- Injectable or Implanted Hormonal Contraception
- Intra-Uterine Devices
- Vasectomized partner for at least 3 months prior to the Screening visit
- Other

- Non-childbearing Potential
  - Post-Menopausal
  - Hysterectomy or Bilateral Oophorectomy
  - Pre-Menses

Listings for demographic data, baseline characteristics and childbearing potential status (inclusive of methods of contraception and reproductive status) will be provided.

6.2.6 Medical History, Prior and Concomitant Therapies and Procedures

For statistical analysis purposes, prior therapies/procedures are defined as those ending before the first treatment day; concomitant therapies/procedures are defined as those starting before the first treatment day and ongoing on the first treatment day and as those starting on the first treatment day or after. If a subject does not undergo treatment, all therapies/procedures of that subject will be classified as prior.

Previous and concomitant therapies/medications will be coded using WHO Drug Dictionary (March 2021, B3 format). Medical history diseases and prior and concomitant medical/surgical procedures will be coded using MedDRA dictionary (version 24.0).

Summaries will be presented overall using the ITT population for the following:

- Frequencies and proportions (n, %) of subjects who had medical history diseases by System Organ Class and Preferred Term;
- Frequencies and proportions (n, %) of subjects who had prior therapies/medications by ATC levels 2, 3 and Active Ingredient(s);
- Frequencies and proportions (n, %) of subjects who had concomitant therapies/medications by ATC levels 2, 3 and Active Ingredient(s);
- Frequencies and proportions (n, %) of subjects who had prior medical/surgical procedures by System Organ Class and Preferred Term;
- Frequencies and proportions (n, %) of subjects who had concomitant medical/surgical procedures by System Organ Class and Preferred Term

Listings of all medical history diseases, prior and concomitant therapies/medications and medical/surgical procedures will be provided.

6.2.7 Measurements of Treatment Compliance

6.2.7.1 Study Duration and Treatment Duration

For randomized subjects who discontinued before treatment, study duration will be calculated as date of end of participation minus date of randomization plus one (1).

For randomized subjects who underwent treatment, study duration will be calculated as date of end of participation minus date of first treatment plus one (1).

Study duration will be summarized for all patients in the ITT population using descriptive statistics (n, mean, standard deviation, median, first and third quartile, min and max).

Treatment duration will be calculated as date of last treatment minus date of first treatment plus one (1) and will be summarized using descriptive statistics (n, mean, standard deviation, median, first and third quartile, min and max) by treatment side (trifarotene 50 µg/g versus vehicle) and overall in the ITT population.

Listings presenting study duration and treatment duration will be provided.

6.2.7.2 Compliance and Drug Accountability

For both trifarotene 50 µg/g and vehicle, treatment compliance will be calculated as follows:

$$\text{Treatment Compliance} = 100\frac{\text{Actual Applications}}{\text{Planned Applications} - \text{Missed Applications due to Prescribed Dose Reductions}}$$

Planned applications are calculated as the number of days between start date and stop date of each compliance evaluation period.

Subject's compliance is derived as the farthest from 100% in absolute value between trifarotene 50 µg/g compliance and vehicle compliance.

Video compliance will be calculated on a per-subject basis as follows:

$$\text{Video Compliance} = 100\frac{\text{Actual Videos}}{\text{Planned Videos} - \text{Missed Videos due to Prescribed Dose Reductions}}$$

Planned videos are calculated as the number of days between start date and stop date of each compliance evaluation period.

Treatment compliance will be summarized at each analysis visit and overall using descriptive statistics (n, mean, standard deviation, median, first and third quartile, min and max) by treatment side (trifarotene 50 µg/g versus vehicle) and overall in the ITT population.

Frequencies and proportions (n, %) of subjects with treatment compliance <80%, between 80% and 120% and >120% will be summarized at each analysis visit and overall by treatment side

(trifarotene 50 µg/g versus vehicle) and overall in the ITT population.

Video compliance will be summarized at each analysis visit and overall using descriptive statistics (n, mean, standard deviation, median, first and third quartile, min and max) in the ITT population.

Frequencies and proportions (n, %) of subjects with video compliance <80%, between 80% and 120% and >120% will be summarized at each analysis visit and overall in the ITT population.

Treatment compliance, video compliance and drug accountability will be presented in listings.

6.2.7.3 Prescribed Dose Reductions

Descriptive statistics (n, mean, standard deviation, median, first and third quartile, min and max) or frequencies and proportions (n, %) of subjects for each classification category (as applicable) will be presented at each analysis visit for drugs in the ITT population for the following:

- Subjects with Prescribed Dose Reduction since the Last Scheduled Visit
- Reasons for Prescribed Dose Reduction
- Application/Dose Frequency during the Prescribed Dose Reduction
- Duration of Prescribed Dose Reduction (days)
- Missed Applications due to Prescribed Dose Reductions

Duration of the prescribed dose reduction will be calculated as Dose Reduction End Date minus Dose Reduction Start Date plus one (1).

Listings for drugs prescribed dose reductions will be provided.

6.2.7.4 Non-Investigational Products

Frequencies and proportions (n, %) of subjects using any non-investigational products during the study will be summarized by treatment side (trifarotene 50 µg/g versus vehicle) in the ITT population.

All non-investigational products used during the study will be listed.

6.3 Efficacy Analysis

Primary inference for efficacy analysis will be based on the ITT population at week 24.

Subjects will be summarized and analyzed according to the treatment sides they were randomized to and all efficacy data (including efficacy data of incomplete treatments) will be listed.

6.3.1 Missing Data Pattern

Distinct missing data patterns of acne atrophic scar counts with their corresponding frequencies

and proportions (n, %) of subjects will be presented for each treatment side (trifarotene 50 µg/g versus vehicle) in order to establish whether they are monotone or non-monotone.

6.3.2 Efficacy Data Summary

A summary based on observed case (OC) will be provided for all primary and secondary efficacy endpoints and Quality of Life/Subject-Reported Outcomes. For these summaries, no data will be imputed.

CCI

CCI

[redacted]

CCI

[redacted]

6.3.3 Analysis of Primary Endpoint

The hypothesis test for the primary endpoint can be formally defined as follows:

$$\begin{cases} H_0: \mu_{Diff} = 0 \\ H_a: \mu_{Diff} \neq 0 \end{cases}$$

where μ_{Diff} is the mean of the differences in change from baseline in total atrophic acne scar count at Week 24 between the trifarotene 50 µg/g side and the vehicle side.

The hypothesis test for the primary endpoint will be evaluated on the ITT population at the two-sided significance level $\alpha = 0.05$. Efficacy will be claimed if the between treatment difference on the primary endpoint is statistically significant with a p-value < 0.05.

The bilateral difference between the trifarotene side and the vehicle side in absolute change from baseline in total atrophic acne scar counts at Week 24 will be analyzed on the ITT population using the Student's t-test for paired samples. The point estimate of the mean difference and the related 95% confidence interval will be presented. Assumption of normality will be checked. If normality assumption is not met, the appropriate non-parametric statistical method (Wilcoxon signed rank test, Hodges-Lehmann estimate of location shift and asymptotic confidence interval) will be used.

For analysis of change from baseline in total atrophic acne scar counts to Week 24, missing counts will be imputed using Multiple Imputation (MI) under the Missing At Random (MAR) assumption. It is expected that the pattern of missing data will be monotonic, with slight deviations being corrected by the Markov Chain Monte Carlo (MCMC) method of the SAS MI procedure. Separate imputations by treatment group will be carried out. Linear regression will be employed to model the missing acne counts, with the following covariates included in the imputation model: non-missing total atrophic acne scar counts from earlier time points (see Section 6.3.6.2 for further details).

6.3.4 Sensitivity Analysis of Primary Endpoint

To assess the robustness of the primary efficacy results, the following sensitivity analyses will be conducted:

1) Jump-to-Reference (J2R) approach under Missing Not At Random (MNAR) assumption, by imputing missing differences between treatments as zero (0);
2) Missing data of primary endpoint will be imputed using Last Observation Carried Forward (LOCF);
3) Observed Case (OC) analysis;
4) Per Protocol (PP) analysis.

6.3.5 Analysis of Secondary Endpoints

6.3.5.1 Atrophic Acne Scar Counts up to Week 20

The hypothesis test for the absolute change in total atrophic acne scar count per half-face from Baseline up to Week 20 can be formally defined as follows:

$$\begin{cases} H_0: \mu_{Diff} = 0 \\ H_a: \mu_{Diff} \neq 0 \end{cases}$$

where μ_{Diff} is the mean of the differences between the trifarotene 50 µg/g side and the vehicle side at Week 1, 2, 4, 8, 12, 16 and 20.

The hypothesis tests for the absolute change in total atrophic acne scar count per half-face from baseline up to Week 20 will be evaluated on the ITT population at the two-sided significance level $\alpha = 0.05$ (the management of multiplicity is described in Section 6.3.6.5).

No hypothesis test will be evaluated for the rest of the secondary efficacy endpoints. p-values and 95% confidence intervals will be presented for descriptive purposes only.

The bilateral difference between the trifarotene side and the vehicle side in absolute change from baseline in total atrophic acne scar counts at Week 1, 2, 4, 8, 12, 16 and 20 will be analyzed on the ITT population using the Student's t-test for paired samples. The point estimate of the mean difference and the related 95% confidence interval will be presented. Assumption of normality will be checked. If normality assumption is not met, the appropriate non-parametric statistical method (Wilcoxon signed rank test, Hodges-Lehmann estimate of location shift and asymptotic confidence interval) will be used.

The bilateral difference between the trifarotene side and the vehicle side in percent change from baseline in total atrophic acne scar count at each post-baseline visit will be analyzed on the ITT population using the Student's t-test for paired samples. The point estimate of the mean difference and the related 95% confidence interval will be presented. Assumption of normality will be checked. If normality assumption is not met, the appropriate non-parametric statistical method (Wilcoxon signed rank test, Hodges-Lehmann estimate of location shift and asymptotic confidence interval) will be used.

For analysis of change from baseline in total atrophic acne scar counts to Weeks 1, 2, 4, 8, 12, 16 and 20, missing counts will be imputed using Multiple Imputation (MI) under the Missing At Random (MAR) assumption. It is expected that the pattern of missing data will be monotonic, with slight deviations being corrected by the Markov Chain Monte Carlo (MCMC) method of the SAS MI procedure. Separate imputations by treatment group will be carried out. Linear regression will be employed to model the missing acne counts, with the following covariates included in the imputation model: non-missing total atrophic acne scar counts from earlier time points (see Section 6.3.6.2 for further details).

CCI

CCI

[redacted]

6.3.6 Statistical/Analytical Issues

6.3.6.1 Adjustments for Covariates

No adjustment for covariates is planned for the primary, secondary and exploratory efficacy analyses.

6.3.6.2 Handling of Dropouts or Missing Data

Missing data for atrophic acne scar counts will be imputed using Multiple Imputation (MI) under the Missing At Random (MAR) assumption. The following steps will be followed:

1. The missing data pattern of atrophic acne scar counts will be evaluated. If the pattern is non-monotone, the MCMC method of SAS PROC MI will be used to make it monotone. The single chain method will be used, with 200 burn-in iterations and 100 iterations between imputations. In case of lack of convergence with the single chain method, the multiple chain method will be used. Separate imputations by treatment group will be carried out. The minimum values for imputed variables will be set to 0, in order to force PROC MI to redraw another value for imputation when an intended imputed value is less than the 0. Imputed values will be rounded to the nearest integer. The seed number will be set to 202395 and fifty (50) imputations will be created.
2. SAS PROC MI will be used for imputing missing values of data with monotone missing pattern. If the MCMC method of step 1 was previously employed, one imputation will be made using each of the fifty (50) MCMC-imputed datasets. If the MCMC method of step 1 was not previously employed, fifty (50) imputations will be created assuming the data are Missing At Random. The seed number will be set to 202395. A linear regression model will be used with covariates for non-missing atrophic acne scar counts from earlier scheduled time points

including baseline. In case of lack of convergence with linear regression model, a predictive mean matching method will be used. Separate imputations by treatment group will be carried out. The minimum values for imputed variables will be set to 0, in order to force PROC MI to redraw another value for imputation when an intended imputed value is less than the 0. Imputed values will be rounded to the nearest integer. Absolute and percent change from baseline in atrophic acne scar counts will be derived from the corresponding imputed lesion counts.

3. The imputed datasets will be analyzed as specified in sections 6.3.3 and 6.3.5.
4. The resulting analysis on the imputed datasets will then be combined to produce a single set of statistics using PROC MIANALYZE.

The number of fifty (50) imputations was selected in order to prevent a power falloff due to choosing a number of imputations too small [1].

As sensitivity analysis of the primary endpoint, the primary analysis will be repeated on the ITT population by imputing atrophic acne scar counts on the basis of a Jump-to-Reference (J2R) approach under the Missing Not At Random (MNAR) assumption. Missing values of bilateral difference in atrophic acne scar counts between the trifarotene side and the vehicle side will be imputed as zero (0).

As additional sensitivity analysis of the primary endpoint, the primary analysis will be repeated on the ITT population by imputing missing data using Last Observation Carried Forward (LOCF). In case no post-baseline value is available, baseline value will be carried forward.

Missing values of acne lesion counts, SGA scores and IGA scores will be imputed using LOCF. In case no post-baseline value is available, baseline value will be carried forward. SGA/IGA success will be calculated from the imputed ordinal SGA/IGA scores. Moreover, SGA/IGA success will be imputed using Missing as Failure (MAF) method as additional analysis.

6.3.6.3 Interim Analyses and Data Monitoring

No interim analysis will be performed. A blinded sample size re-estimation will be performed after 40 subjects complete/discontinue the study (i.e. after ~33% of the initial planned subjects complete/discontinue the study) in order to evaluate the need for additional subjects to be randomized (see Section 4.1).

6.3.6.4 Multicenter Study

No analysis by center is planned for this study.

6.3.6.5 Multiple Comparison/Multiplicity

In order to maintain the overall type I error rate at 0.05, a predefined hierarchal testing procedure will be implemented.

The hypothesis test for the primary endpoint will be evaluated on the ITT population at the significance level $\alpha = 0.05$.

The hypothesis tests for the scar secondary efficacy endpoints will be evaluated on the ITT population according to the following predefined order, all at the same significance level $\alpha = 0.05$, moving to the next hypothesis test only after a success on the previous hypothesis test.

1) Absolute change from Baseline in total atrophic acne scar count at Week 20
2) Absolute change from Baseline in total atrophic acne scar count at Week 16
3) Absolute change from Baseline in total atrophic acne scar count at Week 12
4) Absolute change from Baseline in total atrophic acne scar count at Week 8
5) Absolute change from Baseline in total atrophic acne scar count at Week 4
6) Absolute change from Baseline in total atrophic acne scar count at Week 2
7) Absolute change from Baseline in total atrophic acne scar count at Week 1

This approach does not inflate the Type I error rate as long as the hypothesis tests for the secondary efficacy endpoints are conditional on the success of the primary, there is a prospective specification of the testing sequence and no further testing is performed once the sequence breaks, that is, further testing stops as soon as there is a failure of a hypothesis test in the sequence to show significance at the predefined alpha level.

No hypothesis test will be evaluated for the rest of the secondary efficacy endpoints. p-values and 95% confidence intervals will be presented for descriptive purposes only.

6.3.6.6 Use of an Efficacy Subset of Subjects

The classification of the protocol deviations and the exclusion of subjects from the Per Protocol (PP) population will be determined prior to breaking the study blind (see Section 5.2).

The analysis on the PP population will allow evaluating the impact of major protocol deviations on the estimation of the treatment effect.

6.3.6.7 Active-Control Studies Intended to Show Equivalence

Not applicable.

6.3.6.8 Examination of Subgroups

No subgroup analysis is planned for this study.

6.3.6.9 Analysis Visits Definition

Efficacy and safety by-visit summaries and analyses will use analysis visits. Both scheduled and unscheduled visits (including early termination visit) will be windowed based on the following analysis visit windows.

Analysis Visit	Target Study Day	Analysis Visit Window
Baseline	1	<= 1
Week 1	8	4 - 11
Week 2	15	12 - 19
Week 4	29	22 - 36
Week 8	57	50 - 64
Week 12	85	75 - 95
Week 16	113	103 - 123
Week 20	141	131 - 151
Week 24	169	>= 159

If two or more assessments (include both scheduled and unscheduled assessments) are available for the analysis visits then all assessments will be listed and the following rules will be applied for determining the values to be used for the summaries and analyses.

- Efficacy assessments: the assessment taken closest to the target study day will be used for the summaries and analyses;
- Safety assessments, excluding clinical laboratory tests: the assessment taken closest to the target study day will be used for the summaries and analyses;
- Clinical laboratory tests: the latest assessment will be used for the summaries and analyses.

6.4 Safety Analysis

6.4.1 Extent of Exposure

The mean daily amount of drug applied will be calculated as the difference between the weight (in grams) of dispensed pumps and the weight (in grams) of returned pumps (missing pumps not returned by the subjects are assigned a weight difference of 45.0 grams for US sites and 75.0 grams for EU and Canada sites - the nominal fill weight of drug - for the aim of this calculation, supposing their content was completely used) divided by the number of days of use of the pumps (calculated as the difference between the date of compliance assessment and the dispensing date of each pump). The date of compliance assessment will be used instead of the actual pumps return date in order to avoid an overestimation of the number of days of use in case of delayed return of the pumps and to estimate the number of days of use in case of pumps not returned. Small differences (up to 0.5 g) between weights of dispensed and returned pumps are deemed due to weighting errors and thus are ignored and handled as no differences.

The mean daily amount of drug applied will be listed and summarized at each analysis visit using descriptive statistics (n, mean, standard deviation, median, first and third quartile, min and max) by treatment side in the Safety population.

6.4.2 Adverse Events

All Adverse Events (AEs) will be coded using MedDRA dictionary (version 24.0). All local AEs (localized to right or left side) will be presented by side (trifarotene 50 µg/g versus vehicle) and overall. AEs that are subject specific will be presented overall only.

Treatment-Emergent Adverse Events (TEAEs) are defined as the adverse events that occurred, or worsened, on or after the first treatment date. AEs with missing or incomplete start dates will be classified on the basis of the imputed start date (see imputation rules of Section 6.1.2)

Pre-Treatment Adverse Events (PTAEs) are defined as the adverse events that are not TEAEs. Separate listings will be provided for TEAEs and PTAEs.

Missing relationships to study drug or study procedures will be imputed with the closest relationship (i.e. Related). Missing relationship to COVID-19 will be imputed with the closest relationship (i.e. Related). Missing severities will be imputed with the greatest severity (i.e. Severe).

An overall summary of TEAEs will be presented. Frequencies and proportions (n, %) of subjects with any TEAE and frequencies (n) of TEAEs will be summarized by treatment side (trifarotene 50 µg/g versus vehicle) and overall in the Safety population according to the following categories:

- Subjects with any TEAE;
- Subjects with any TEAE that occurred in >1% of Subjects of the Safety Population;
- Subjects with any TEAE of Special Interest;
- Subjects with any TEAE due to COVID-19;
- Subjects with any TEAE by Closest Relationship to Study Drug:
  - Subjects with any TEAE whose closest relationship to Study Drug is Related;
  - Subjects with any TEAE whose closest relationship to Study Drug is Not Related;
- Subjects with any TEAE by Closest Relationship to Study Procedures:
  - Subjects with any TEAE whose closest relationship to Study Procedures is Related;
  - Subjects with any TEAE whose closest relationship to Study Procedures is Not Related;
- Subjects with any TEAE by Greatest Severity:
  - Subjects with any TEAE whose greatest severity is Mild;
  - Subjects with any TEAE whose greatest severity is Moderate;
  - Subjects with any TEAE whose greatest severity is Severe;
- Subjects with any TEAE leading to Study Drug Discontinuation;
- Subjects with any TEAE leading to Study Discontinuation;
- Subjects with any Serious TEAE;

- Subjects with any Serious TEAE of Special Interest;
- Subjects with any Serious TEAE due to COVID-19;
- Subjects with any Serious TEAE by Closest Relationship to Study Drug:
  - Subjects with any Serious TEAE whose closest relationship to Study Drug is Related;
  - Subjects with any Serious TEAE whose closest relationship to Study Drug is Not Related;
- Subjects with any Serious TEAE by Closest Relationship to Study Procedures:
  - Subjects with any Serious TEAE whose closest relationship to Study Procedures is Related;
  - Subjects with any Serious TEAE whose closest relationship to Study Procedures is Not Related;
- Subjects with any Serious TEAE leading to Study Drug Discontinuation;
- Subjects with any Serious TEAE leading to Study Discontinuation;
- Subjects with any Serious TEAE leading to Death.

Frequencies and proportions (n, %) of subjects with any TEAE and frequencies (n) of TEAEs will be summarized by treatment side (trifarotene 50 µg/g versus vehicle) and overall in the Safety population. The following tables will be provided:

- Summary of Subjects with any TEAE and Frequency of TEAEs by System Organ Class and Preferred Term;
- Summary of Subjects with any TEAE and Frequency of TEAEs that occurred in >1% of Subjects of the Safety Population by System Organ Class and Preferred Term;
- Summary of Subjects with any TEAE of Special Interest and Frequency of TEAEs of Special Interest by System Organ Class and Preferred Term;
- Summary of Subjects with any TEAE due to COVID-19 and Frequency of TEAEs due to COVID-19 by System Organ Class and Preferred Term;
- Summary of Subjects with any TEAE related to Study Drug and Frequency of TEAEs related to Study Drug by System Organ Class and Preferred Term;
- Summary of Subjects with any TEAE related to Study Procedures and Frequency of TEAEs related to Study Procedures by System Organ Class and Preferred Term;
- Summary of Subjects with any TEAE and Frequency of TEAEs by Greatest Severity, System Organ Class and Preferred Term;
- Summary of Subjects with any TEAE leading to Study Drug Discontinuation and Frequency of TEAEs Leading to Study Drug Discontinuation by System Organ Class and Preferred Term;
- Summary of Subjects with any TEAE Leading to Study Discontinuation and Frequency of TEAEs Leading to Study Discontinuation by System Organ Class and Preferred Term;

Frequencies and proportions (n, %) of subjects with any serious TEAE and frequencies (n) of serious TEAEs will be summarized by treatment side (trifarotene 50 µg/g versus vehicle) and overall in the Safety population. The following tables will be provided:

- Summary of Subjects with any Serious TEAE and Frequency of Serious TEAEs by System

Organ Class and Preferred Term;

- Summary of Subjects with any Serious TEAE of Special Interest and Frequency of Serious TEAEs of Special Interest by System Organ Class and Preferred Term;
- Summary of Subjects with any Serious TEAE due to COVID-19 and Frequency of Serious TEAEs due to COVID-19 by System Organ Class and Preferred Term;
- Summary of Subjects with any Serious TEAE related to Study Drug and Frequency of Serious TEAEs related to Study Drug by System Organ Class and Preferred Term;
- Summary of Subjects with any Serious TEAE related to Study Procedures and Frequency of TEAEs related to Study Procedures by System Organ Class and Preferred Term;
- Summary of Subjects with any Serious TEAE leading to Study Drug Discontinuation and Frequency of Serious TEAEs Leading to Study Drug Discontinuation by System Organ Class and Preferred Term;
- Summary of Subjects with any Serious TEAE Leading to Study Discontinuation and Frequency of Serious TEAEs Leading to Study Discontinuation by System Organ Class and Preferred Term.

6.4.3 Deaths, Other Serious Adverse Events and Other Significant Adverse Events

The following listings for all subjects included in the Safety population will be provided:

- Adverse Events leading to Death;
- Serious Adverse Events;
- Treatment-Emergent Adverse Events of Special Interest;
- Adverse Events due to COVID-19;
- Treatment-Emergent Adverse Events leading to Study Drug Discontinuation;
- Treatment-Emergent Adverse Events leading to Study Discontinuation.

6.4.4 Clinical Laboratory Evaluation

A listing of pregnancy test results will be provided.

6.4.5 Vital Signs

Not applicable.

6.4.6 Physical Findings

Not applicable.

CCI

CCI

6.4.10 Re-Challenge Patch Test and Ingredient Patch Test

Listing of re-challenge patch test and ingredient patch test results will be provided.

7 CHANGES FROM THE PROTOCOL ANALYSIS PLAN

Any change from the protocol will be justified and fully documented.

If the blind review suggests changes to the principal features stated in the protocol, these have to be documented in a protocol amendment. Otherwise, it will suffice to update the statistical analysis plan with the considerations suggested from the blind review.

8 SHELLS OF TABLES, FIGURES AND LISTINGS AND REPORTING OUTPUT (GENERAL FEATURES)

TLF have to be printed in A4 page size with landscape orientation and with the following margins:

- Top: 2.0 cm (i.e. headers at 2.0 cm from page edge)

- Bottom: 2.0 cm (i.e. footers at 2.0 cm from page edge)
- Left: 0.8 cm
- Right: 0.8 cm

Courier New, 8-point font will be used for TLF contents (excluding column headers) and TLF footnotes.

Courier New, 8-point, bold font will be used for page headers and footers, TLF title, TLF headers, column headers and figures' axis labels.

A clear, accurate and complete programming code will be developed to generate the statistical analyses, summary tables, figures and listings to be integrated in the report. Fluent use of precise titles and footnotes will be made to improve the understanding of summaries and document any assumption. Details of analysis specifications including but not limited to the SAS code will be documented on the shells.

The final list of tables, figures and listings and their shells for the reporting of this study will be available in a separate document that will be developed and will be finalized before database lock.

9 REFERENCES

1. John W. Graham, Allison E. Olchowski, Tamika D. Gilreath, "How Many Imputations are Really Needed? Some Practical Clarifications of Multiple Imputation Theory", Prev Sci (2007) 8:206-213 DOI 10.1007/s11121-007-0070-9