CCI [redacted]

GALDERMA R&D

RD.06.SPR.204245

AkLief Evaluation in Acne-induced Post-Inflammatory Hyperpigmentation (LEAP)Evaluation of acne-induced hyperpigmentation during treatment of acne vulgaris subjects with trifarotene 50 µg/g cream versus vehicle cream over 24 weeks

Statistical Analysis Plan

Version: 1.0

CCI [redacted]

SPONSOR SIGNATURE PAGE

Approved by: _____ _____

PPD *Date*

Principal Biostatistician

Galderma R&D

Parexel SIGNATURE PAGE

Signature(s) below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

	Signatory
Author	PPD Project Role: Biostatistics Lead

TABLE OF CONTENTS

REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	[dd Mmm yy]	New document

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomic Therapeutic Class
CMH	Cochran-Mantel-Haenszel
CR	Copy Reference
CRF	Case Report Form
dE76	Color Distance
eCRF	Electronic Case Report Form
e.g.	For Example (Latin: exempli gratia)
ET	Early Termination
etc.	*Et cetera*
FST	Fitzpatrick Skin Type
i.e.	That is (Latin: *id est*)
CCI [redacted]	
ITA	Individual Typology Angle
ITT	Intent-to-treat
LOCF	Last Observation Carried Forward
MCMC	Markov Chain Monte Carlo
MAR	Missing At Random
MI	Multiple Imputation
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	Missing Not At Random
OC	Observed Case
OTC	Over-the-Counter
CCI [redacted]	
PIE	Post-Inflammatory Erythema
PIH	Post-Inflammatory Hyperpigmentation
PMM	Pattern-Mixture Model
PP	Per Protocol
PT	Preferred term

Abbreviation / Acronym	Definition / Expansion
CCI [redacted]	
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SPF	Sun Protection Factor
TEAE	Treatment-Emergent Adverse Event
UPT	Urine Pregnancy Test
UV	Ultraviolet
WHODD	World Health Organization Drug Dictionary

1 INTRODUCTION

Acne is one of the most common skin disorders treated by dermatologists. While acne is highly prevalent in youth with around 85% of teenagers affected at some point in time.

Acne may resolve with sequalae of Post-Inflammatory Hyperpigmentation (PIH), Post-Inflammatory Erythema (PIE) or atrophic scars. PIE is distinct from PIH because PIE describes residual erythema, while PIH describes subsequent pigment change. PIH can persist for months or years, causing considerable disfigurement and distress in the meantime. The psychological impact of PIH can be devastating, and many patients resort to extreme measures to try to eradicate it (Grimes, 2006).

As acne is a chronic and relapsing disease, normalizing follicular desquamation is then the key to achieve and maintain control of acne. Today it is established that retinoids such as trifarotene acts in the pathology of Acne vulgaris. Trifarotene is active and stable in keratinocytes but rapidly metabolized by human hepatic microsomes compared to other topical retinoids, leading to improved safety.

Acne can persist for years and may seriously affect psychosocial development, resulting in emotional problems, withdrawal from society, and depression (Koo, 1991). If not treated, acne may cause serious physical and emotional scarring and can significantly impact the quality of life of those affected by the disease (Usatine, 1998). Therefore, this study aims to evaluate efficacy of Trifarotene in acne lesions and Acne-induced hyperpigmentation in all skin phototype subjects. The local tolerance of the treatment regimen in terms of erythema, scaling, dryness, stinging/burning will also be evaluated.

This double-blind, randomized, vehicle-controlled clinical trial is the first to evaluate the clinical potential of trifarotene in treating Acne-induced hyperpigmentation in patients with acne.

No invasive methods are planned to be used during this trial.

Subjects are to be followed regularly during the trial, especially for adverse events (AEs), approximately once a month for 6 months.

The analyses described in this Statistical Analysis Plan (SAP) are based upon the following study documents:

- Study Protocol, Version 00 (August 18, 2021)
- electronic Case Report Form (eCRF), Version 2.0 (October 21, 2021)

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

The primary objective of this trial is to demonstrate the superiority of trifarotene 50 µg/g cream vs. its vehicle, in terms of absolute change from Baseline in the overall disease severity of PIH grade on the face at Week 24.

2.2 Secondary Objective(s)

The objective of this study is to evaluate the efficacy and safety of trifarotene 50 µg/g cream compared to its vehicle cream in the treatment of moderate acne vulgaris with acne PIH in subjects with Fitzpatrick Skin Types (FST) I-VI.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a phase IV, multi-center, randomized (1:1), double-blind, vehicle-controlled, parallel-group study evaluating trifarotene cream in treating acne-induced hyperpigmentation in subjects with acne.

The primary objective of this trial is to demonstrate the superiority of trifarotene 50 µg/g cream vs. its vehicle, in terms of absolute change from Baseline in the overall disease severity of PIH grade on the face at Week 24. It will be evaluated based on hyperpigmentation scores (9-point scale) from 0 (Clear) to 8 (Severe) at Screening, Baseline, Week 12, 16, 20 and 24 or early termination visits.

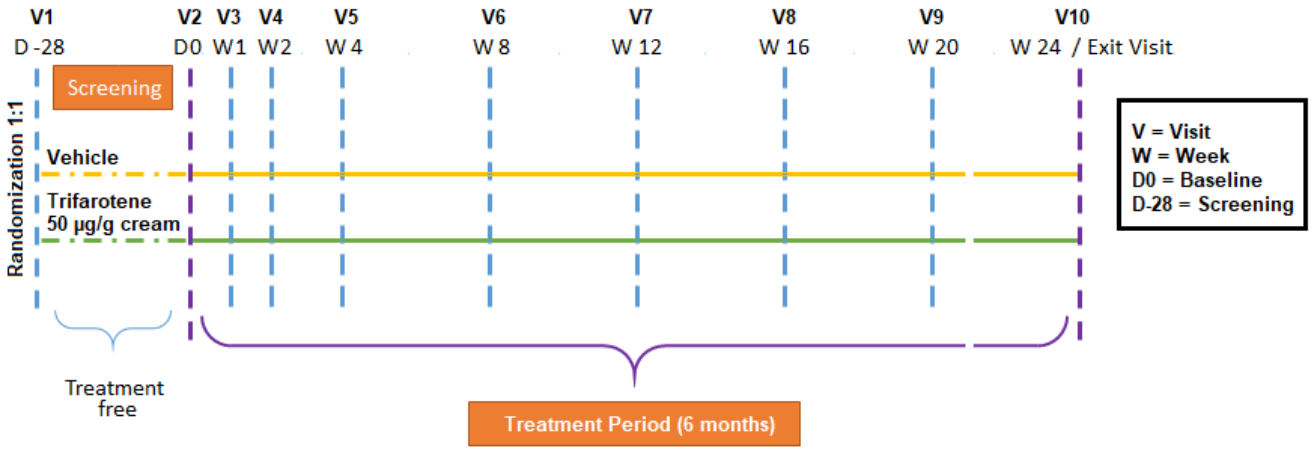
Approximately 120 subjects aged 13-35 are planned to be randomized, at approximately 20 study centers in the United States and Europe. Target enrollment should include an approximate distribution of FST, 30% light skin (I-III) and 70% dark skin (IV-VI).

The expected duration for each subject's participation in the study is 7 months. Subject eligibility is evaluated over a 28-day screening period. Qualifying subjects who complete Baseline assessments are randomized CCI to trifarotene or Vehicle for a 24-week treatment period.

Subjects who do not require a washout period might complete the Screening and Baseline assessments on the same day. Subjects who fail screening might be re-screened once, if the reason is not related to acne severity (Investigator's Global Assessment [IGA]) or lesion counts.

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

Study Schema



No interim analysis is planned for this study.

Table 1 Study Assessment Schedule

PROCEDURES	CLINICAL TRIAL VISITS									
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**
	Screening (Up to 28 days prior to Baseline)	**Baseline**	**Week 1** (±1 d)	**Week 2** (±1 d)	**Week 4** (±3 d)	**Week 8** (±3 d)	**Week 12** (±3 d)	**Week 16** (±3 d)	**Week 20** (±3 d)	**Week 24** (±5 d) or ET
Informed consent/Photography Consent	X									
Inclusion/Exclusion Criteria	X	X								
Demographics/ Relevant medical history/ Prior therapies [a]	X									
Urine Pregnancy test (UPT) [b]	X	X			X	X	X	X	X	X
Efficacy Assessments										
Overall Disease Severity PIH Score assessed by the investigator	X	X					X	X	X	X
3 prominent target lesions identified by the investigator (largest and darkest) [f]		X								
CCI										

PROCEDURES	CLINICAL TRIAL VISITS									
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**
	Screening (Up to 28 days prior to Baseline)	**Baseline**	**Week 1** (±1 d)	**Week 2** (±1 d)	**Week 4** (±3 d)	**Week 8** (±3 d)	**Week 12** (±3 d)	**Week 16** (±3 d)	**Week 20** (±3 d)	**Week 24** (±5 d) or ET
CCI [redacted]										
Safety Assessments										
Local tolerability assessment of face		X	X	X	X	X	X	X	X	X
Adverse events [c]	X	X	X	X	X	X	X	X	X	X
Concomitant therapies	X	X	X	X	X	X	X	X	X	X
Investigational Product Administration										
Dispensation of investigational products and subject diary		X			X	X	X	X	X	
Dispensation of non-investigational products		X			X	X	X	X	X	
Return of investigational products and accountability					X	X	X	X	X	X
Subject Diary/Compliance [d]			X	X	X	X	X	X	X	X
Exit form										X

a. Only prior therapies that were stopped within 6 months of the Baseline visit and that may have an impact on inclusion/exclusion criteria should be recorded. Treatment that continues after Baseline should be recorded on the Concomitant Treatment Form of the CRF.
b. For Subject of childbearing potential: UPT should be conducted if no menstrual period in the preceding four weeks. **Urine Pregnancy Tests are mandatory at Baseline and at Week 24 / ET (early termination).**
c. Adverse event onsets after subject signature of the informed consent form should be recorded on the AE Form of the CRF.
d. Subject diary is a diary which will be given to the subject to report the treatment application.
e. Comedones (open and closed), Papules, pustules, nodules will be counted.
f. For assessments where 3 target lesions are mentioned, the same 3 target lesions on the subject's face should be used throughout the study.
g. To be performed between Week 24 and Week 26 by Evidera (CRO), if consented.

3.2 Endpoints

3.2.1 Efficacy Variables

- Primary Efficacy Variable: PIH Overall Disease Severity scores at Week 24
- Secondary Efficacy Variables:
  - Post-inflammatory Hyperpigmentation:
    - PIH Overall Disease Severity scores at Week 12, 16 and 20.

CCI [redacted]

CCI [redacted]

CCI [redacted]

3.2.3 Safety Variables

- Incidence of AEs
- Local tolerability (erythema, scaling, dryness and stinging/burning)

CCI [redacted]

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures, and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard Parexel procedures.

4.2 General Presentation Considerations

4.2.1 Baseline and End of Study

Baseline is defined as the last non-missing measurement prior to the first treatment for subjects randomized and 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:

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

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

'End of Study' is defined as the last available assessment.

4.2.2 Reference Start Date and Analysis Day

For all randomized and treated subjects, the first treatment date will be the reference start date. For subjects 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 relative to the reference start date (i.e., first treatment date or date of randomization), as Analysis Day = Assessment Date – First Treatment Date + 1 for randomized and treated subjects and as Analysis Day = Assessment Date - Randomization Date + 1 for subjects randomized but not treated.

4.2.3 Descriptive Statistics

Continuous data will be summarized in terms of the mean, standard deviation (SD), median, lower quartile, upper quartile, minimum, maximum and number of observations, unless otherwise stated. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only.

Proportions will be reported as percentages (not as fraction of unit).

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

4.2.4 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, when applicable, the secondary endpoints.

P-values greater than or equal to 0.0001, in general, will be presented to four decimal places. P-values less than 0.0001 will be presented as "<0.0001", P-values more than 0.9999 will be presented as ">0.9999".

The following flagging conventions will be applied for the p-values of all statistical testing:

- 0.01 ≤ p-values < 0.05 will be flagged with one asterisk (e.g. "0.0499 *")
- 0.001 ≤ p-value < 0.01 will be flagged with two asterisks (e.g. "0.0099 **")
- 0.0001 ≤ 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 ****")

Confidence intervals (CIs) will be two-sided with 95% coverage for the primary endpoint and the secondary endpoints and will be presented to one more decimal place than the raw data.

4.2.5 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.

4.2.6 Analysis Visits

Efficacy, safety and subject reported outcomes 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

Analysis Visit	Target Study Day	Analysis Visit Window
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 any 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, excluding colorimetry data: the assessment taken closest to the target study day will be used for the summaries and analyses. If there are multiple assessments with same difference from target day, the latest assessment 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. If there are multiple assessments with same difference from target day, the latest assessment will be used for the summaries and analyses;
- Clinical laboratory tests: the latest assessment will be used for the summaries and analyses;
- Subject Reported Outcome: the assessment taken closest to the target study day will be used for the summaries and analyses. If there are multiple assessments with same difference from target day, the latest assessment will be used for the summaries and analyses;
- Colorimetry data: data derived from the latest photograph will be used for the summaries and analyses.

4.3 Software

All report outputs will be produced using SAS® version 9.4 or a later version in a secure and validated environment.

4.4 COVID-19 Impact

Some 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.

Nevertheless, subjects must be present in the office for the following assessments:

- CCI [redacted]
- PIH assessments (ODS, CCI [redacted])
- CCI [redacted]
- CCI [redacted]

- CCI [redacted]

Global COVID-19 pandemic ongoing during the course of the study can potentially impact the study. This section describes how the impact of COVID-19 will be reported.

4.4.1 *COVID-19 Impact on Subject Disposition*

Subjects who experience either screen failure or study treatment discontinuation or study discontinuation due to COVID-19 have the reason captured in the eCRF respectively on Randomization/Reason for Not Randomizing, End of Treatment form and End of Study form. Cases of screen failure or study treatment discontinuation or study discontinuation due to COVID-19 will be included in the summary of subject disposition and flagged in listings.

4.4.2 *COVID-19 Impact on Visit Modality and Missed Visits*

For each subject, eCRF Visit forms capture whether the missed visit or remote visit is due to COVID-19.

The number of subjects with missed visits or alternate visit modality (remote visit) due to COVID-19 will be summarized by visit and overall and will be listed.

4.4.3 *Protocol Deviations due to COVID-19*

Protocol deviations due to the COVID-19 pandemic will be collected per the study specific Protocol Deviation Specification. Major and minor pandemic related protocol deviations are identified within by using the term “COVID-19”. Major COVID-19-related protocol deviations will be summarized as sub-categories under existing categories of protocol deviations (see Section 4.5.2). All major COVID-19 related protocol deviations will appear in the listing of protocol deviations and will be flagged. All PDs will be reviewed during the Data Review Meeting.

4.4.4 *Prior/Concomitant Medications and Procedures related to COVID-19*

Prior and Concomitant Medications and Procedures related to COVID-19 are captured in the eCRF respectively on Prior/Concomitant Medications form and Procedures form.

Medications and therapies used to treat COVID-19 associated medical history and adverse events will be flagged in the listing of prior and concomitant medications.

Procedures used to treat COVID-19 associated medical history and adverse events will be flagged in the listing of prior and concomitant procedures.

4.4.5 *COVID-19 Impact on Efficacy Variables*

Number of missing assessments due to COVID-19 will be reported in respective summary tables described in section 4.10 for the following parameters:

- Overall disease severity hyperpigmentation

CCI [redacted]

4.4.6 *Adverse Events related to COVID-19*

Adverse events associated with COVID-19 are reported by investigators on Adverse Events form. All COVID-19 associated adverse events will be included in standard AE tables described in section 4.11.

An overview summary table of COVID-19 associated treatment-emergent adverse events (TEAEs) as described in section 4.11.3 will be provided for the Safety Population.

Listing of COVID-19 associated adverse events will be provided for all subjects in the Safety Population.

4.4.7 *COVID-19 Impact on Local Tolerability Scores*

Number of missing Local Tolerability Scores due to COVID-19 will be reported in the global summary table described in section 0.

4.4.8 *COVID-19 Impact on Subjects Reported Outcomes*

Number of missing subjects reported outcomes due to COVID-19 will be reported in respective summary tables described in section 4.12.1.

4.4.9 *Overview of COVID-19 Impact*

A by-subject listing with the following information:

- COVID-19 related study disruptions? [Yes/No]
- COVID-19 related study disruptions impacting efficacy? [Yes/No]
- COVID-19 related study disruptions impacting safety? [Yes/No]
- Description of how the individual's participation was altered by COVID-19 related study disruption

will be provided.

Number and percentages of subjects with at least one study disruptions due to COVID-19 will be included in the summary of subject disposition as follows:

- Subjects affected by COVID-19 related study disruptions
- Subjects affected by COVID-19 related study disruptions impacting efficacy
- Subjects affected by COVID-19 related study disruptions impacting safety

4.5 Study Subjects

4.5.1 Disposition of Subjects

A clear accounting of the disposition of all subjects who enter the study will be provided, from screening to study completion and will include the following summaries:

- Number of subjects screened for entry into the study (Analysis set: All Screened Subjects)
- Number and percentage of subjects excluded prior to randomization and major reason (Analysis set: All Screened Subjects)

- Number and percentage of subjects excluded prior to randomization due to COVID-19 and major reason (Analysis set: All Screened Subjects)
- Number and percentage of subjects randomized by treatment group and overall (Analysis set: All Screened Subjects)
- Number and percentage of subjects randomized who discontinued before treatment and major reason by treatment group and overall (Analysis set: All Subjects Randomized)
- Number and percentage of subjects randomized who discontinued before treatment due to COVID-19 and major reason by treatment group and overall (Analysis set: All Subjects Randomized)
- Number and percentage of subjects treated with at least one dose of study medication by treatment group and overall (Analysis set: All Subjects Randomized)
- Number and percentage of subjects withdrawing from study drug and reasons as specified on the eCRF for drug withdrawal per treatment group and overall (Analysis set: All Subjects Randomized)
- Number and percentage of subjects withdrawing from study drug due to COVID-19 and reasons as specified on the eCRF for drug withdrawal per treatment group and overall (Analysis set: All Subjects Randomized)
- Number and percentage of subjects completing the study by treatment group and overall (Analysis set: All Subjects Randomized)
- Number and percentage of subjects withdrawing from the study and reasons as specified on the eCRF for study withdrawal by treatment group and overall (Analysis set: All Subjects Randomized)
- Number and percentage of subjects withdrawing from the study due to COVID-19 and reasons as specified on the eCRF for study withdrawal by treatment group and overall (Analysis set: All Subjects Randomized)
- Number and percentage of subjects affected by COVID-19 related study disruption, affected by COVID-19 related study disruptions impacting efficacy and affected by COVID-19 related study disruptions impacting safety.

A by-subject listing of subjects' disposition details will be provided.

4.5.2 Accounting of Subjects

Number and percentage of subjects will be summarized by clinical visit and by analysis visit (Analysis set: All Subjects Randomized).

A by-subject listing of scheduled visits and a by-subject listing of unscheduled visits will be provided.

4.5.3 Protocol Deviations

Major protocol deviations and any action to be taken regarding the exclusion of subjects or affected data from specific analyses are defined in the project-specific Protocol Deviation Specification.

Number and percentage of subjects with at least a major protocol deviation by treatment group and overall and by type of deviation will be summarized (Analysis set: All Subjects Randomized)

A by-subject listing of all protocol deviations will be provided.

4.6 Analysis Sets

The efficacy summaries and analyses will be based on the **Intent-to-Treat (ITT) population** defined as all randomized subjects. If a subject is allocated the incorrect study drug as per the study randomization list, subjects will be summarized and analyzed 'as randomized' i.e., by randomized treatment group.

For the primary efficacy variable, a sensitivity analysis will be performed on the **Per Protocol (PP) Population** to assess the robustness of the study conclusions to the choice of population. The PP Population is defined as any subjects in the ITT population who had compliance to the study drug between 80% and 120% and assessments of the primary endpoint at Baseline and Week 24, without any major deviations that could have a significant effect on the efficacy of the study drug (e.g., errors in drug assignment, use of prohibited medications). Subjects will be summarized and analyzed 'as randomized' i.e., by randomized treatment group.

The safety summaries and analyses will be based on the **Safety Population**. The Safety Population is defined as comprising the ITT population subjects who applied/took the study drug at least once. If a subject is allocated the incorrect study drug as per the study randomization list, subjects will be summarized and analyzed 'as treated' i.e., by allocated treatment group.

Upon database release, protocol deviation and analysis populations outputs will be produced and reviewed. An analysis set classification meeting will be arranged to discuss the outputs and to decide which subjects and/or subject data will be excluded from certain analyses. Decisions made regarding the exclusion of subjects and/or subject data from analyses will be made prior to unblinding and will be documented and approved by Sponsor.

Number and percentage of subjects in each analysis population will be summarized by treatment group and overall, (Analysis set: All Randomized Subjects)

A by-subject listing of analysis populations details will be provided. This listing will be presented by treatment group and will include center, subject identifier, inclusion/exclusion flag for each population and reason for exclusion from each population. All subjects screened will appear on this listing. If subject data has been partially excluded, visit will also appear on this listing.

4.7 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized by treatment group and overall. All summaries will be produced based upon the ITT population. Additional summaries of demographic and baseline characteristics will be produced based upon the Safety population if the ITT population and the Safety population do not include the same subjects.

4.7.1 Demographic characteristics

A summary of demographic characteristics will be presented and will include the following variables:

- age in years as a continuous variable
- age in years by class :<18, ≥18
- gender

- ethnicity
- race

A by-subject listing of demographic characteristics details will be provided.

4.7.2 Baseline characteristics

A summary of baseline characteristics will be presented and will include the following variables:

- Fitzpatrick Skin Type score
- PIH Overall Disease Severity at Baseline

CCI [redacted]

A by-subject listing of baseline characteristics details will be provided.

4.7.3 Childbearing Potential Status, Methods of Contraception and Reproductive Status

A summary and a by-subject listing of Childbearing Potential Status, Methods of Contraception and Reproductive Status will be provided.

4.7.4 Medical History

Relevant medical history (past and current) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 or higher.

Previous and concomitant relevant or major illness will be summarized by system organ class (SOC) and preferred term (PT).

A by-subject listing of medical history will be provided and present the primary SOC, PT and verbatim text. The listings will be sorted by treatment group, subject, primary SOC, PT and verbatim text.

4.8 Prior and Concomitant Therapies

The following two categories will 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.

Prior and ongoing therapies started before the study and concomitant therapies will be coded using World Health Organization Drug Dictionary (WHODD) September 2021 Global B3. The therapeutic class will correspond to the second level of Anatomic Therapeutic Class (ATC) code.

Prior and ongoing medical and surgical procedures started before the study and concomitant medical and surgical procedures will be coded using MedDRA Version 24.1 or higher.

Therapies start and stop dates will be compared to the date of first application of study medication to allow therapies to be classified as either Prior or Concomitant.

Therapies that start and stop prior to the date of first application of study medication will be classified as Prior.

Therapies that start before the date of first application of study medication and stops on or after the date of first application of study medication, as well as therapies that start after first application of study medication will be classified as Concomitant.

Therapies with missing or incomplete start dates will be classified on the basis of the imputed start date (see imputation rules of section 4.2.5). Therapies will be assumed to be Concomitant, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started and stopped prior to the first dose of study medication.

Prior medications and concomitant medications will be summarized separately by therapeutic class and preferred name. These summary tables will be presented for each treatment group and overall based upon the ITT population.

Procedures will be classified as either Prior or Concomitant and summarized similarly to prior and concomitant medication by SOC and PT.

By-subject listings of prior and concomitant medications and of prior and concomitant procedures will be presented. Listings will be sorted by treatment group, subject, chronological start date, therapeutic class, preferred name and verbatim name.

4.9 Treatment Compliance

4.9.1 Study Duration and Treatment Duration

For randomized and treated subjects, study duration will be calculated relative to the reference start date (i.e., first treatment date) as Study Duration = End of Participation Date – First Treatment Date + 1.

For randomized but not treated subjects, study duration will be calculated relative to the reference start date (i.e., date of randomization) as Study Duration = End of Participation Date - Randomization Date + 1.

For randomized and treated subjects, treatment duration will be calculated relative to the date of first treatment as Treatment Duration = Last Treatment Date - First Treatment Date + 1.

Study duration and treatment duration will be summarized for each treatment group and overall based upon the ITT population.

4.9.2 Compliance and Drug Accountability

The compliance will be calculated for each visit and globally as:

$$\frac{\text{Actual applications}}{\text{Planned Applications} - \text{Missed Applications due to Prescribed Dose Reductions}} \times 100$$

For the overall compliance:

- Overall actual applications will be derived as the sum of actual applications at each visit. For treated subjects with no drug accountability information, overall actual applications will be calculated as Date of Last Treatment as collected in the End of Treatment form minus Date of First Treatment as collected in the End of Treatment form plus 1. If Date of Last Treatment is not collected in the End of Treatment form, overall actual applications will be set to 1.
- Overall planned applications will be derived as date of study completion/discontinuation minus date of baseline visit.
- Overall missed applications due to prescribed dose reductions will be derived as the sum of missed applications due to prescribed dose reductions at each visit.

Number and percentage of subjects compliant defined as having a compliance between 80% and 120% will be summarized by treatment group and overall.

Additionally, compliance expressed in percentage and by category (<80%; 80%-120%; >120%) will be summarized by visit and globally and will be presented for each treatment group and overall based upon the ITT population.

By-subject listings will be presented for compliance and drug accountability. .

4.9.3 Prescribed Dose Reductions

The following information will be summarized for each treatment group and overall based upon the ITT population:

- 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

A by-subject listing of Prescribed Dose Reductions will be presented.

4.10 Efficacy Evaluation

Summaries based on observed cases (OC) will be provided for all primary and secondary efficacy endpoints. For these summaries, no data will be imputed. All primary and secondary efficacy summaries will be based upon the ITT population.

Line plots and bar charts over time based on observed cases (OC) will be provided for PIH Overall Disease Severity scores and IGA scores. Line plots over time based on observed cases (OC) will be provided for total, inflammatory and non-inflammatory lesions. These plots and charts will be based upon the ITT population and no data will be imputed.

Moreover, line plots over time based on imputed data will be provided for PIH Overall Disease Severity scores. These plots will be based upon the ITT population and data will be imputed using Multiple Imputation (MI) under the Missing At Random (MAR) assumption (see section 4.10.1.3).

4.10.1 Analysis and Data Conventions

This study is designed to test for superiority. The null hypothesis for the treatment comparison will be that there is no difference between Trifarotene 50 µg/g cream and vehicle cream in Absolute change from Baseline in PIH Overall Disease Severity scores at Week 24. The alternative hypothesis will be that there is a difference.

$$\begin{cases} H_0: \mu_{\text{Trifarotene 50 µg/g}} - \mu_{\text{Vehicle}} = 0 \\ H_a: \mu_{\text{Trifarotene 50 µg/g}} - \mu_{\text{Vehicle}} \neq 0 \end{cases}$$

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

4.10.1.1 Multi-center Study

Prior to database lock, a review of the blinded data will be performed to determine the size of each center. If there are centers with less than 8 randomized subjects, then these centers will be pooled in order to carry out the analyses. The process of combining centers will be based on the ITT population, and same pooling will be repeated for PP population.

Pooling will be country based. First, centers of each country will be sorted by latitude zone (based on geographic and climatic similarities), number of randomized subjects (descending order) and center number (ascending order). Pooling will start with combining the largest of the set of small centers of a latitude zone of a country with the smallest center within the same latitude zone of that country. If there is a further need to combine data (the size of the pooled centers includes less than 8 subjects), the next smallest center will be combined with the next largest of the small centers, until the criterion of a minimum of 8 subjects is met. The process will continue until all pooled centers have a minimum of 8 subjects within the same latitude zone of a country. Any remaining small centers of a latitude zone of a country will be pooled with the last pooled center within the same latitude zone of that country. The pooled centers and the remaining original unpooled clinical centers will be referred to as 'analysis centers' and will be used as stratification factor in the statistical analyses.

If at the start of pooling any latitude zone of a country has less than 8 subjects in the ITT population in total, then centers will be added to the list of small centers in another latitude zone of that country and then combined as above. This decision will be documented in clinical report.

4.10.1.2 Adjustments for Covariates

The primary efficacy analysis and secondary efficacy analyses will be adjusted for the following baseline covariates:

1. Analysis Center
2. Baseline score

4.10.1.3 Handling of Dropouts or Missing Data

Distinct missing data patterns of PIH Overall Disease Severity scores, total lesion counts, inflammatory lesion counts, non-inflammatory lesion counts and Investigator Global Assessment (IGA) scores with their corresponding number and percentage of subjects will be presented in order to establish whether they are monotone or non-monotone.

The primary method of imputation for missing data of primary and secondary efficacy endpoints will be Multiple Imputation (MI) under the Missing At Random (MAR) assumption.

For the primary MAR based multiple imputation, the MI procedure of the SAS system will be used to generate sets of data with missing values imputed from observed data. 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 MI procedure.

The following steps will be followed:

1. For PIH Overall Disease Severity scores, CCI [redacted]. If the pattern is not 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. For PIH Overall Disease Severity scores only, the maximum value for imputed variables will be set to 8, in order to force PROC MI to redraw another value for imputation when an intended imputed value is greater than the 8. CCI [redacted]
Imputed values will be rounded to the nearest integer. The seed number will be set to 204245 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 204245. These imputations will use the following models:
    2.1. For total, inflammatory and non-inflammatory lesion counts, a predictive mean matching method will be used with covariates for non-missing total, inflammatory and non-inflammatory lesion count from earlier scheduled time points including baseline. The number of closest observations to be used in the selection of the imputed values will be set to 5. 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 total, inflammatory and non-inflammatory lesion counts will be derived from the corresponding imputed lesion counts.
    2.2. For ordinal PIH Overall Disease Severity scores and CCI [redacted], a logistic regression model based on fully conditional specification method with 200 burn-in iterations will be used with covariates for non-missing ordinal PIH Overall Disease Severity scores or CCI [redacted] from earlier scheduled time points including baseline. Separate imputations by treatment group will be carried out. CCI [redacted].
3. The imputed datasets will be analyzed as specified in sections 4.10.2.
4. The resulting analysis on the imputed datasets will then be combined to produce a single set of statistics as follows:

4.1. For PIH Overall Disease Severity scores, CCI [redacted], results from the ANCOVA analysis will be combined using the SAS PROC MIANALYZE.

4.2. For binary outcome, the results from the Cochran-Mantel-Haenszel (CMH) analysis will be combined using the Wilson-Hilferty transformation to produce a pooled CMH statistic and p-value. The differences in proportions and standard errors will be combined using the SAS PROC MIANALYZE. The resulting pooled difference and standard error will be used to produce the confidence interval based on the large-sample approximation method for binary data without using continuity correction. These methods will be used as described in the Bohdana Ratitch, et al. [Bohdana Ratitch, et al., 2013].

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

To assess the robustness of the primary efficacy results, sensitivity analyses of the primary endpoint will be conducted as follows:

1. Missing data of primary endpoint will be imputed using a Pattern-Mixture Model (PMM) for implementing a Copy Reference (CR) under the Missing Not At Random (MNAR) assumption, by using the profiles from Vehicle subjects with observed data to impute missing data. The process will be the same described for the MAR analysis, only the assumption about missing mechanism will be changed.
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.

4.10.1.4 Multiple Comparisons/Multiplicity

In order to maintain the overall type I error rate at 0.05, a predefined hierarchal testing procedure will be implemented to test the Trifarotene 50 µg/g cream treatment against vehicle cream treatment on primary endpoint and PIH related secondary endpoints.

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 PIH related secondary endpoints are conditional on the success of the primary endpoint.

The hypothesis tests for the 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) Percent change from Baseline in PIH Overall Disease Severity scores at Week 24
2) Absolute change from Baseline in PIH Overall Disease Severity scores at Week 20
3) Percent change from Baseline in PIH Overall Disease Severity scores at Week 20
4) Absolute change from Baseline in PIH Overall Disease Severity scores at Week 16
5) Percent change from Baseline in PIH Overall Disease Severity scores at Week 16

6) Absolute change from Baseline in PIH Overall Disease Severity scores at Week 12

7) Percent change from Baseline in PIH Overall Disease Severity scores at Week 12

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 other efficacy endpoints. p-values and 95% confidence intervals will be presented for descriptive purposes only.

4.10.1.5 Interim Analyses

Not Applicable.

4.10.1.6 Examination of Subgroups

There is no planned subgroup analysis.

4.10.2 Primary Efficacy Variable –Absolute change from Baseline in PIH Overall Disease Severity scores at week 24

4.10.2.1 Primary Efficacy Analysis

The analysis of Primary efficacy endpoint will be based upon ITT population.

The primary variable for the assessment of efficacy is the Absolute change from Baseline in PIH Overall Disease Severity scores of the face assessed by the investigator at Week 24 (or ET).

Overall Disease Severity Hyperpigmentation Score is graded from 0 to 8 as follows:

- Grade 0 Normal
- Grade 1 Present, but <mild
- Grade 2 Mild (slightly noticeable)
- Grade 3 Between mild and moderate
- Grade 4 Moderate
- Grade 5 Between moderate and marked
- Grade 6 Marked (distinctive)
- Grade 7 Between marked and severe
- Grade 8 Severe (very distinctive)

Missing data will be imputed as per primary method of imputation for missing data described in section Handling of Dropouts or Missing Data

The effect of treatment in terms of the absolute change from Baseline to Week 24 in PIH Overall Disease Severity scores of the face will be analyzed using analysis of covariance (ANCOVA). The statistical model will assess the main effect of treatment, adjusted for center and baseline score as fixed effects. The treatment effect will be estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups will be presented.

4.10.2.2 Primary Efficacy Sensitivity Analyses

Four sensitivity analyses will be conducted to assess the robustness of the primary efficacy results.

Imputation using a PMM

Missing data of primary endpoint will be imputed using a PMM for implementing a CR under the MNAR assumption, by using the profiles from Vehicle subjects with observed data to impute missing data. The analysis will be based upon the ITT population.

Last Observation Carried Forward (LOCF) analysis.

Missing post-Baseline data of primary endpoint will be carried forward from the last non-missing post-Baseline value. The analysis will be based upon the ITT population.

Observed Case (OC) analysis

The ANCOVA analysis will be performed on data without any imputation. The analysis will be based upon the ITT population.

Per Protocol (PP) analysis

Missing data will be imputed using the same imputation method as for the primary analyses (MI under the MAR assumption). The analysis will be based upon the PP population.

By-subject listings of the primary efficacy data will be provided.

4.10.3 Secondary Efficacy Variables

All secondary efficacy endpoint analyses will be based upon ITT population.

Percent change from Baseline in PIH Overall Disease Severity scores at week 24

Missing data will be imputed as per primary method of imputation for missing data described in section Handling of Dropouts or Missing Data

The same analysis as described for primary efficacy variable will be repeated for percent change from Baseline to Week 24.

Absolute and percent change from Baseline in PIH Overall Disease Severity scores will be analyzed at Week 12, 16 and 20

Absolute and percent change from Baseline in PIH Overall Disease Severity scores at Week 12, 16 and 20 will be calculated as for Week 24.

Missing data will be imputed as per primary method of imputation for missing data described in section Handling of Dropouts or Missing Data

The same analysis as described for primary efficacy variable will be repeated for:

- Absolute change from Baseline to Week 20
- Percent change from Baseline to Week 20
- Absolute change from Baseline to Week 16

- Percent change from Baseline to Week 16
- Absolute change from Baseline to Week 12
- Percent change from Baseline to Week 12

PIH Overall Disease Severity scores

PIH Overall Disease Severity scores assessed by the investigator will be summarized descriptively by treatment group based upon the ITT population in terms of absolute values at Baseline, Week 12, 16, 20 and 24, absolute changes and percent changes from baseline at Week 12, 16, 20 and 24.

Proportions of subjects across PIH Overall Disease Severity scores at Baseline, Week 12, 16, 20 and 24 will also be summarized by treatment group using tables of frequency.

CCI

CCI

[redacted]

CCI

CCI

[redacted]

4.11 Safety Evaluation

Summaries based on observed cases (OC) will be provided for all safety measures. For these summaries, no data will be imputed. All safety summaries will be based upon the Safety population.

Line plots and bar charts over time based on observed cases (OC) will be provided for each local tolerability parameter. These plots and charts will be based upon the Safety population and no data will be imputed.

4.11.1 Extent of Exposure

The mean daily amount of topical 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 sites - the nominal fill weight of topical 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 topical drug applied will be listed and summarized at each visit and overall by treatment group and overall in the Safety population.

Mean daily amount of topical drug applied by each subject will be presented in the by-subject listing of drug accountability.

4.11.2 Adverse Events

Adverse events will be coded using the MedDRA Version 24.1 or higher.

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 4.2.5), unless there is clear evidence (through comparison of partial dates) to suggest that the AE started prior to the first application of study drug.

Pre-Treatment Adverse Events (PTAEs) are defined as the adverse events that are not TEAEs.

Separate by-subject listings will be provided for TEAEs and PTAEs.

Adverse Events of Special Interest (AESI) are pre-defined as:

- Erythema, scaling, dryness, stinging/burning, and other related cutaneous AEs which lead to permanent treatment discontinuation
- Suspicion of allergic contact reaction related to the study drug

For the aim of the analysis, TEAEs whose relationship to study drug is assessed as “Reasonable Possibility” will be classified as “Related” and TEAEs whose relationship to study drug is assessed as “No Reasonable Possibility” will be classified as “Not Related”

Missing relationships to study drug 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. Number and percentage of subjects with any TEAE and number of TEAEs will be summarized by treatment group 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 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 leading to Study Drug Discontinuation;
- Subjects with any Serious TEAE leading to Study Discontinuation;
- Subjects with any Serious TEAE leading to Death.

Number and percentage of subjects with any TEAE and number of TEAEs will be summarized by treatment group and overall in the Safety population. The following tables will be provided:

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

Number and percentage of subjects with any Serious TEAE and number of Serious TEAEs will be summarized by treatment group and overall in the Safety population. The following tables will be provided:

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

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

The following by-subject listings based on 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.

4.11.4 Clinical Laboratory Evaluation

A by-subject listing of pregnancy test results will be provided.

4.11.5 Local tolerability scores on the face

Scores at each analysis visit, worst post-baseline score and final score during treatment of each local tolerability parameter (i.e. erythema, scaling, dryness and burning/stinging) will be summarized by treatment group and overall in the Safety population.

Number and percentage of subjects for each score at each analysis visit, worst post-baseline score and final score during treatment of each local tolerability parameter will be summarized by treatment group and overall in the Safety population.

Worst post-baseline score is defined as the worst score assessed at any post-baseline visit (including unscheduled ones) and final score during treatment is defined as the last score assessed up to 7 days after the last treatment at any post-baseline visit (including unscheduled ones).

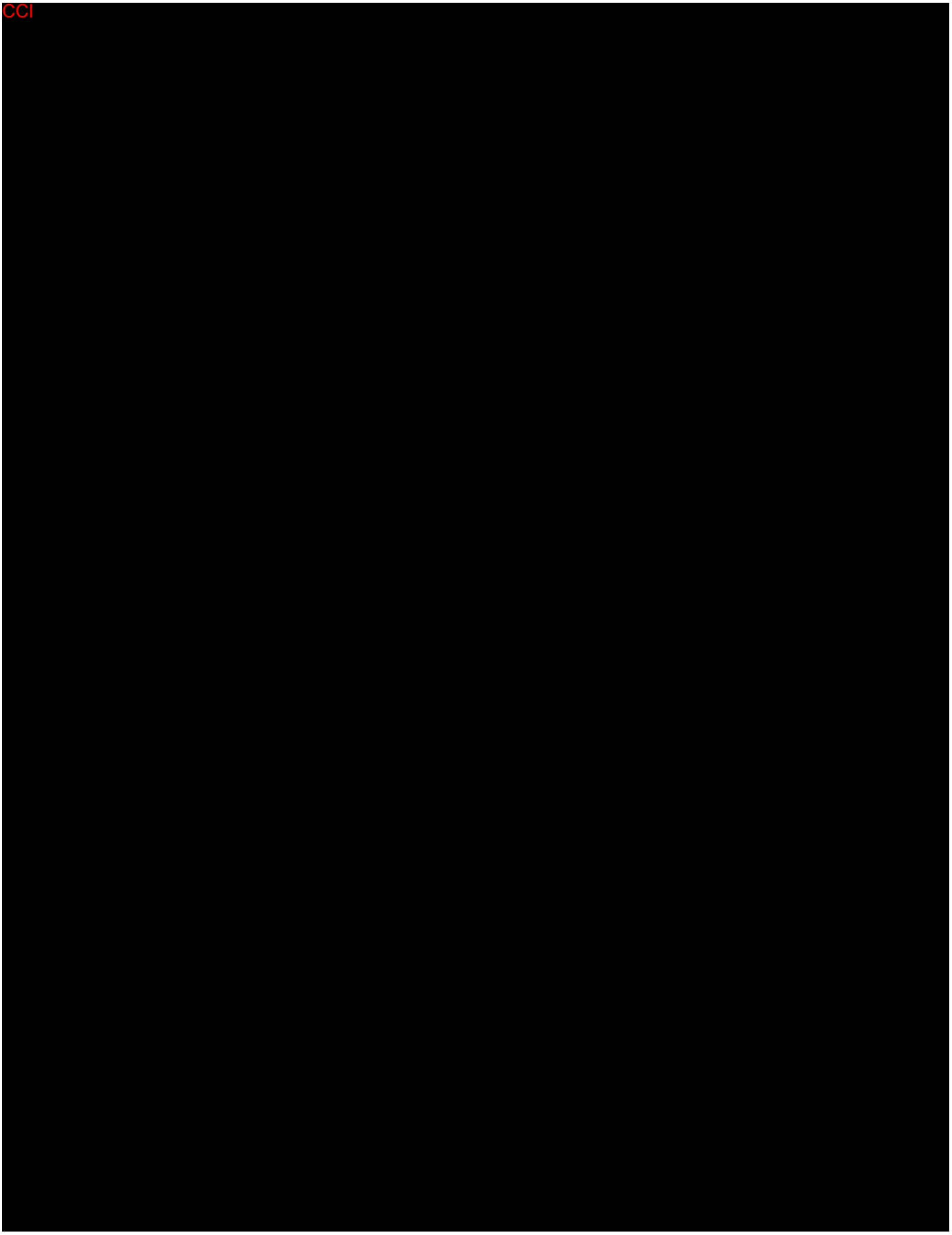
A by-subject listings of local tolerability scores on the face data will be provided.

4.11.6 Safety Monitoring (Independent Data Monitoring Committee, Data Monitoring Committee, Data and Safety Monitoring Board)

Not Applicable.

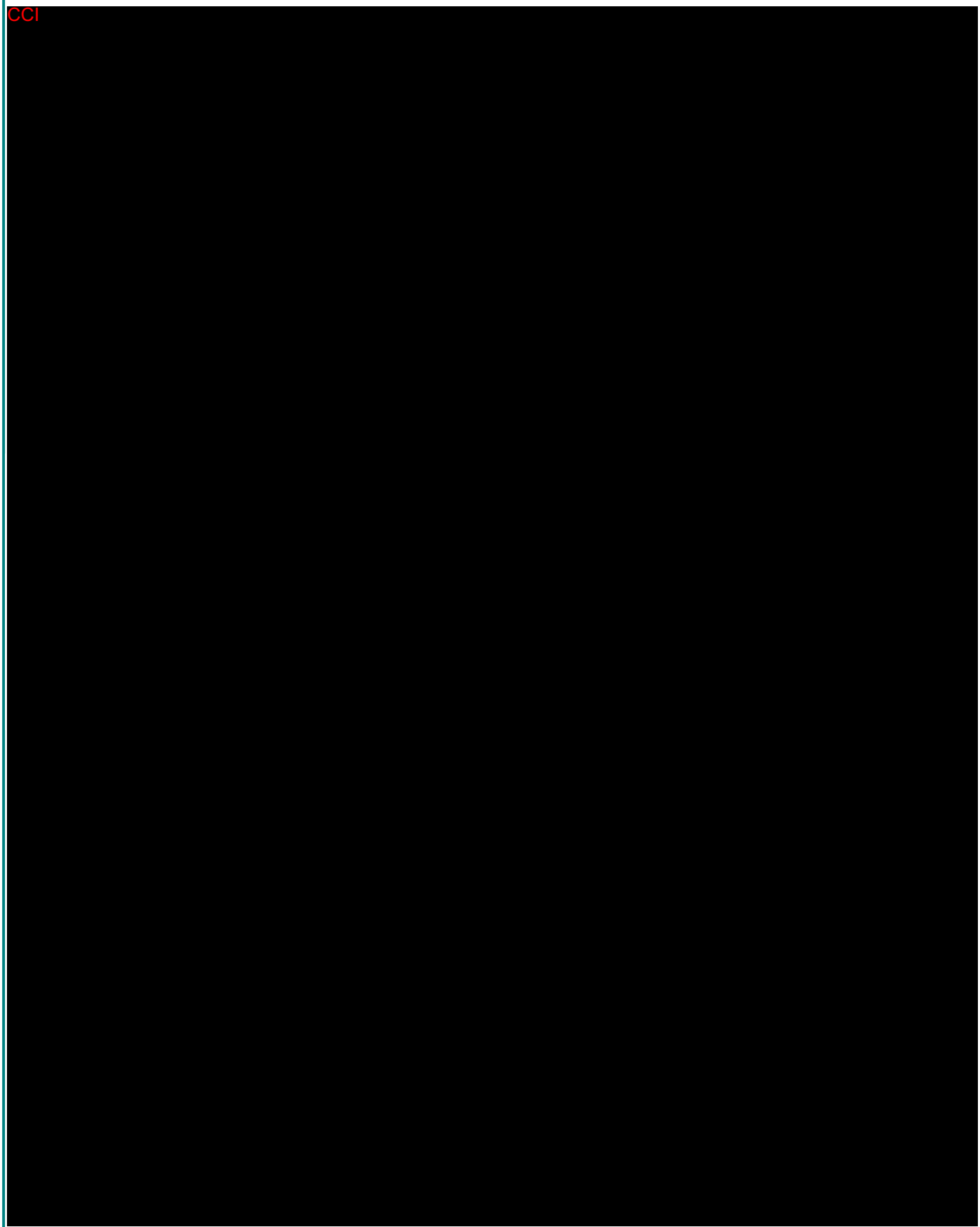
4.12 Other Analyses

CCI [redacted]

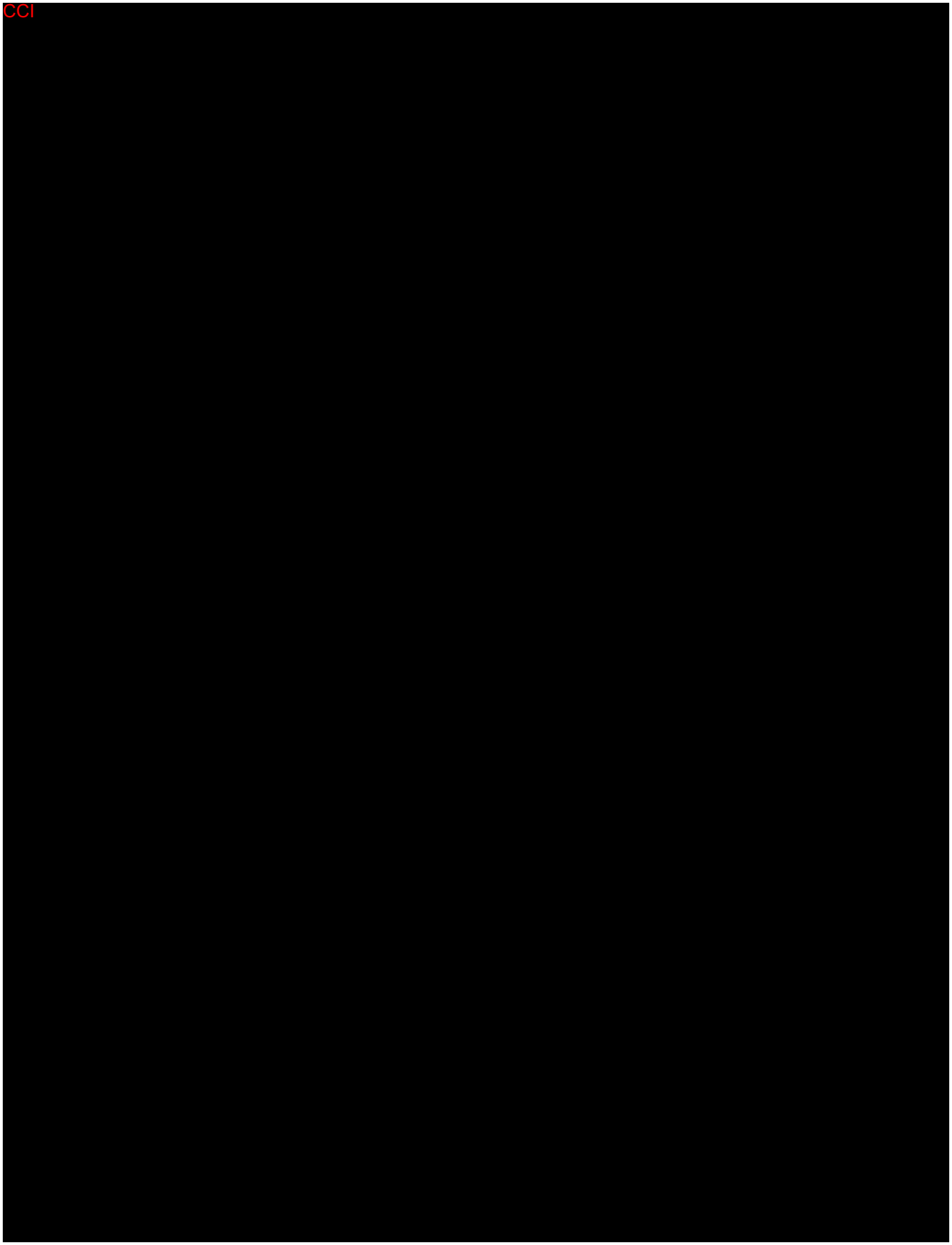


CCI

CCI



CCI



CCI

[redacted]

4.13 Determination of Sample Size

The sample size calculation is based on the results of the paper "Tazarotene Cream for Post-Inflammatory Hyperpigmentation and Acne Vulgaris in Darker Skin: A Double-Blind, Randomized, Vehicle-Controlled Study" (Grimes, 2006).

Trifarotene cream and tazarotene cream are both products indicated for the topical treatment of acne and have similar profiles in terms of tolerability. The study above was used as a basis for comparison in order estimate sample sizes for this study.

α (2-sided)	Power (%)	μ_{Diff}	σ_{Diff}	Sample Size		Drop out (%)	Randomised		
				Trifa	Vehicle		Trifa	Vehicle	Total
0.05	90%	-1.0	1.4	42	42	~30%	60	60	120

Considering a two-sided α=0.05, 90% power, a difference in the sample means of -1.0, a standard deviation of difference of 1.4, a 1:1 allocation ratio between trifarotene cream and vehicle cream and a proportion of drop-outs around 30%, approximately 120 subjects (60+60) are planned to be randomized.

4.14 Changes in the Conduct of the Study or Planned Analysis

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.

4.15 Shells of Tables, Figures and Listings and Reporting Output (General Features)

Tables, Figures and Listings 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 as needed.

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.

5 REFERENCES

[1] Grimes P and Callender VD. Tazarotene Cream for Post-inflammatory Hyperpigmentation and Acne Vulgaris in Darker Skin: A Double-Blind, Randomized, Vehicle-Controlled Study. Cutis. 2006; 77:45-50.

[2] Koo JY, et al. Psychologic aspects of acne. Pediatr Dermatol. 1991; 8:185-8.

[3] Usatine R, Quan M, and Strick R. Acne vulgaris: a treatment update. Hosp Prac 1998; Feb15:111-127.

[4] Bohdana Ratitch, et al. "Combining Analysis Results from Multiply Imputed Categorical Data", 2013, PharmaSUG Proceedings, Paper SP-03

CCI [redacted]

Approval Signatures

Document Name: Statistical Analysis Plan 03 Feb 2023 RD.06.SPR.20424

Document Number: VV-TMF-1272874

CCI [redacted]:

System Version Number: 1 .0

Document Approvals

Reason for signing: Approved	Name: PPD Role: Biostatistics Date of signature: PPD
Reason for signing: Approved	Name: PPD Role: Biostatistics Date of signature: PPD