STATISTICAL ANALYSIS PLAN

Study Number:	202394
Study Title:	A Multi-Center, Randomized, Double-Blind, Placebo Controlled Study To Compare Efficacy and Safety of Trifarotene (CD5789) Cream When Used with an Oral Antibiotic for the Treatment of Severe Acne Vulgaris
Study Short Name:	DUAL
CD Number:	CD5789
IND Number:	Not Applicable
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Study Phase:	IV
Protocol Version and Date of Issue:	V2 21AUG2020
Sponsor:	Galderma R&D, LLC 14501 North Freeway Fort Worth, TX 76177 United States
Contract Research Organization:	CCI [redacted]
CRO Study Number:	GAL 1907
Author:	PPD
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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	05AUG2020	PPD issued the first draft of the SAP
Draft 0.2	04SEP2020	PPD updated the SAP on the basis of the comments provided by PPD and PPD and issued the second draft
Draft 0.3	09SEP2020	PPD updated the SAP on the basis of the comments provided by PPD and issued the third draft
Draft 0.4	14SEP2020	PPD updated the SAP on the basis of the comments provided by PPD and PPD and issued the fourth draft
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GALDERMA APPROVAL AND ACKNOWLEDGEMENT SIGNATURES

Galderma Study Biostatistician (for approval and acknowledgement)

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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 ET	Early Termination
GCP	Good Clinical Practice
ICF	Informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IGA	Investigator Global Assessment
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 202394 is based on the study protocol final version 2 dated 21AUG2020. 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 demonstrate that a daily treatment regimen of topical trifarotene 50µg/g (CD5789) cream when used in association with oral doxycycline hyclate delayed-release tablets (DORYX MPC, 120mg) is safe and effective for the treatment of severe facial Acne Vulgaris.

2.2 Study Endpoints

2.2.1 Primary Endpoint

- Absolute Change in facial total lesion counts from Baseline to Week 12.

2.2.2 Secondary Endpoints

- Absolute Change in facial inflammatory and non-inflammatory lesion counts from Baseline to Week 12;
- IGA Facial Success Rate at Week 12, defined as the proportion of subjects who achieve an IGA score of 1 (Almost Clear) or 0 (Clear) and at least a 2-grade improvement from Baseline to Week 12.

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2.2.4 Safety

- Local tolerability parameters (erythema, scaling, dryness and stinging/burning) will be evaluated 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 TEAEs including AESIs, SAEs and TEAEs leading to discontinuation.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a multi-center, randomized (2:1), double-blind, placebo-controlled study evaluating the safety and efficacy of topical trifarotene 50µg/g (CD5789) cream associated with oral doxycycline 120mg (T+D) compared to trifarotene vehicle and doxycycline placebo (TVeh+DPbo) for the treatment of severe facial Acne Vulgaris (see section 3.1.1).

At least 198 randomized subjects aged 12 and older are planned, at approximately 30 study centers in the United States and Puerto Rico. Target enrollment should include an approximate even distribution of male to female subjects, and adult (≥18 years) and adolescent subjects (12-17 years).

Subject eligibility is evaluated over a 28-day screening period. Qualified subjects will complete baseline assessments and be randomized (2:1) to T+D or TVeh+DPbo for a 12 week treatment period. Subjects will be provided skin care products including Cetaphil® Gentle Skin Cleanser for washing the face twice daily (morning and evening); Cetaphil® PRO Oil Abosorbing Moisturizer with SPF 30 for use daily on the face (morning) and to be re-applied to face and other exposed skin when sun exposure is expected; and Cetaphil® Moisturizing Lotion for supplemental moisturizer use, as needed. Use of the subject's preferred or investigator's recommended non-comedogenic cleanser, moisturizer and sunscreen (SPF ≥30) is permitted. If a subject experiences persistent dryness or irritation, the investigator may consider a reduced application frequency for the topical

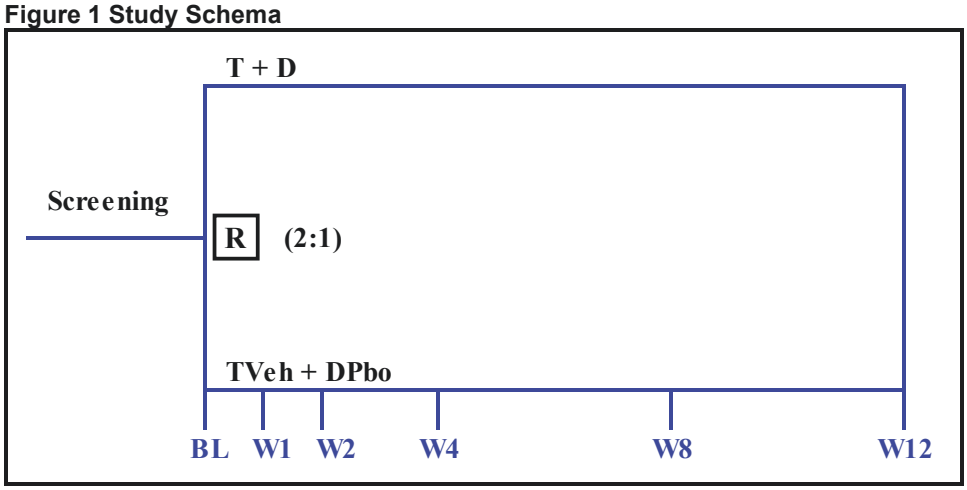
study drug, over a maximum of 2 weeks, within the first four (4) weeks of the treatment period (see section 5.4.8 of the study protocol). Dose modification for oral study drug is allowed for safety reasons only and should be based on individual investigator clinical judgment (see section 5.4.9 of the study protocol).

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 and 12. 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+D:	Topical trifarotene (CD5789) cream + oral doxycycline (DORYX MPC, 120mg) *
TVeh+DPbo:	Topical trifarotene vehicle + oral doxycycline placebo * 2:1 randomization (active/active to vehicle/placebo)
BL:	Baseline visit
W:	Scheduled visit week
*:	Doxycycline and placebo dosing: ▪ Day 1 - 1 tablet in the evening ▪ Day 2 - 1 tablet in the morning and evening ▪ Day 3 and beyond - 1 tablet in the evening

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 your 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 acne assessments (IGA, lesion counts), 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).
- Questionnaire completion:
  - sent to subject by email or mail;
  - subject signs, dates and returns, by email of mail.
- Collection of previously dispensed study drugs and dosing calendar, from an adult family member:
  - Weighing of returned topical 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 topical 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:

- Acne assessments (IGA, Lesion counts);
- Local Tolerability;
- Photographs (for subjects enrolled at designated imaging centers).

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/ET [i]
	(≤ 28 days)	--	(±2 days)	(±2 days)	(±3 days)	(±3 days)	(±3 days)
Informed Consent / Assent	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
Inclusion / Exclusion Criteria	X	X					
Urine Pregnancy Test [k]	X	X	X	X	X	X	X
Acne Severity Assessment (IGA) [b,j]	X	X	X	X	X	X	X
Lesion Counts [c,j]	X	X	X	X	X	X	X
Local Tolerability [d]		X	X	X	X	X	X
Adverse Events [e]		X	X	X	X	X	X
Subject Satisfaction Questionnaire with Assigned Study Treatment (study cream and study tablet)							X
Topical Study Drug Acceptability Questionnaire							X
Acne Specific QOL [f]		X					X
Photographs (face; at designated centers) [m]		X					X
Randomization		X					
Study Drug [l]		W/D	I/W	I/W	C/I/W/D	C/I/W/D	C/I/W
Subject Dosing Calendar		D	C/R/D	C/R/D	C/R/D	C/R/D	C/R
Exit Form							X

For study drugs and/or dosing calendar: W=Weigh; D=Dispense; R=Review; C=Collect and I=Inspect (includes returning all study drugs, for weighing bottle pumps and tablet counting; the study drugs dispensed at Baseline are 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 acne severity is conducted on the face (IGA), and should be performed before lesion counts

c) Inflammatory lesions (papules, pustules), non-inflammatory lesions (open and closed comedones) and other lesions (nodules, cysts) will be counted, on the 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) 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) Subjects aged 13-35 years at time of Screening will complete the Acne Specific QOL.

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 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 12 visit procedures are to be performed for early termination/exit visit.

j) 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, it is recommended that evaluations between the primary and subsequent evaluator overlap (both evaluators should examine the subject together and discuss findings) for at least one visit.

k) For WOCBP only. Mandatory at Screening, Baseline, Week 12 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 both topical and oral medications. Only topical study drug will be weighed (W). Oral study medication (tablets) will be inspected (I)/counted, upon return, for ongoing compliance counseling. For compliance calculations, tablets dispensed will be based on fill count.

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) is mandatory for all subjects to participate in the study.

3.2 Selection of Study Population

3.2.1 Number of Planned Subjects

At least 198 total subjects are planned to be randomized in a 2:1 ratio, active (T+D) to placebo (TVeh+DPbo). Target enrollment should include an approximate even distribution of male to female subjects, and adult (≥18 years) and adolescent subjects (12-17 years).

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.

Reasons for discontinuing the study are summarized hereinafter.

Table 2 Reasons for Study Discontinuation

Pregnancy:	Withdraw the Subject from the clinical trial and follow the procedure described in section 6.7.2.2.5 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]:	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).

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.

3.3 Investigational Products

Investigational products include trifarotene (CD5789) cream, trifarotene vehicle, doxycycline hyclate delayed-release tablets (DORYX MPC, 120mg) and doxycycline placebo for purposes of this double-blind study. The study design includes an active arm (T+D) and a comparator arm (TVeh+DPbo). See section 3.1.1.

3.3.1 Treatments Administered

Refer to section 5.4.1 of the study protocol.

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3.3.3 Allocation Concealment and Blinding

Subjects will be centrally randomized using a system based on Interactive Response Technology (IRT). Allocation concealment will be ensured, as the system will not release the randomization code until the subject has been recruited into the trial, which takes place after all inclusion/exclusion criteria have been evaluated. Randomization will occur individually, the randomization code will be assigned to the unique Subject Identification Number (SIN) of each randomized subject and the simultaneous randomization of groups of subjects will be prevented.

All attempts will be made to keep the study site staff and subjects blinded to study treatment throughout the study. Members of the site staff will not have access to the randomized treatment assignment. Active topical and oral study medications will have similar appearance, packaging and use instructions as the corresponding vehicle or placebo.

3.3.4 Prior and Concomitant Therapy

3.3.4.1 Definition

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

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

A dosing calendar will be provided to the subject with clear directions for completion at each dispensing visit (see section 3.1.2). Subjects will record daily use of topical study drug and oral study medication. Subjects will be instructed to return the dosing calendar and all study medication at each study visit, for review by study personnel in the presence of the subject.

The completed dosing calendar since the last visit will be collected, at each visit. The following guidelines pertain to treatment compliance assessment:

- Topical study drug (study cream): Treatment compliance will be assessed using the subject dosing calendar and derived from the total expected doses and number of actual doses recorded in the dosing calendar (based on CRF data entries), over a given visit interval.
- Oral study drug: Treatment compliance for oral study medication will be based on tablet counts, derived from the total expected doses and number of actual doses taken, over a given visit interval (assume total fill count per bottle = 30). The bottle fill count and number of remaining tablets are used to calculate actual doses taken, unless otherwise clarified by the subject or dosing calendar recordings. Oral study drug will be re-dispensed at Week 1 and Week 2 visits, after counting tablets for treatment compliance reporting. At Week 4 and Week 8, new bottles of study medication are dispensed.

Inadvertent missed doses of topical or oral study drug will be considered protocol deviations, as confirmed by discussions with the subject after reviewing tablet counts and dosing calendar, and subjects should be appropriately counseled on the importance of following study drug dosing instructions. Subjects should be reminded and encouraged to follow guidelines for non-study product use, throughout the study (see section 5.4.2 of the study protocol).

3.4 Duration of Subject Participation

The expected duration for each subject's participation in the study is approximately 16 weeks (including a 4-week screening period and a 12-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 12/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 trained 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: acne severity (IGA), inflammatory lesion counts (papules and pustules), non-inflammatory lesion counts (open and closed comedones), and other lesion counts (nodules and cysts). Refer to section 8.1 of the study protocol for further details on site personnel training. Acne severity grading (IGA) and lesion counts will be performed separately. The acne severity assessments will be performed before the lesion counting.

Throughout the study when possible, the same evaluator should perform the IGA and lesion counts, for each individual 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, it is recommended that evaluations between the primary and subsequent evaluator overlap (both evaluators should examine the subject together and discuss findings) for at least one visit.

3.5.1.1 Investigator Global Assessment (IGA) of Facial Acne

The IGA will be performed by trained evaluators. The areas defined for IGA assessment are forehead, each cheek, chin, and nose. The IGA is reported as a global assessment, considering all areas as a whole.

The Investigator's Global Assessment (IGA) is a snapshot, static assessment to be done prior to detailed lesion counts. The evaluator should make no reference to baseline or other previous visits when performing the IGA.

The IGA will be assessed according to the schedule of assessments (3.1.2) using the scale shown hereinafter.

Table 3 Investigator Global Assessment Scale

Score	Category	Description
0	Clear	Clear skin with no inflammatory or non-inflammatory lesions.
1	Almost Clear	A few scattered comedones and a few small papules.
2	Mild	Easily recognizable; less than half the surface is involved. Some comedones and some papules and pustules.
3	Moderate	More than half of the surface is involved. Many comedones, papules and pustules. One nodule may be present.
4	Severe	Entire surface is involved. Covered with comedones, numerous papules and pustules. Few nodules may be present.

3.5.1.2 Lesion Counts on the Face

Lesion Counts will be performed by trained evaluators. IGA will be performed before lesion counting. Lesion counting will be performed using both visual observation and palpation strictly at all visits.

The lesion counts will be performed separately on the face (forehead, left cheek, chin and right cheek). Lesions on the nose and under the jawline or along the hairline (including eyebrows) will not be included in the counts.

Inflammatory lesions

- Papule: A small, solid elevation less than 5 mm in diameter. Most of the lesion is above the surface of the skin.
- Pustule: A small, circumscribed elevation of the skin which contains yellow-white exudates.

Non-inflammatory lesions

- Open comedo: A mass of sebaceous material that is impacted behind an open follicular orifice (blackhead).
- Closed comedo: A mass of sebaceous material that is impacted behind a closed follicular orifice (white head).

Other lesions

- Nodule: A circumscribed, elevated, solid lesion at least 0.5 cm in diameter with palpable depth.
- Cyst: A smooth, dome-shaped, elevated, freely moveable, skin-colored, round-to-ovoid lesion.

Total Lesions

- Total lesions are calculated as the sum of Inflammatory lesions and Non-inflammatory lesions.

3.5.2 Subject Reported Outcomes

Subject-reported assessments should be completed prior to performing any acne assessments to minimize any impact on the subject responses. The questionnaires completed will be considered as source data and the answers will be entered into the CRF by the site.

3.5.2.1 Acne-Specific Quality of Life Questionnaire (Acne-QoL)

The Acne-QoL will be collected at Baseline and the Week 12/ET visit. The Investigator or designee should provide the subject (only subjects ages 13-35 years at Informed Consent) with the Acne-QoL Form (see Appendix 14.1 of the study protocol) and instruct the subject to read and answer all questions.

The questionnaire will measure the impact of facial acne on health-related quality of life. There are 19 questions, with multiple-choice responses on a 0-6 scale. Questions are separated into 4 domains: Self-perception (5 questions - total score range from 0 to 30), Role-emotional (5 questions

- total score range from 0 to 30), Role-social (4 questions - total score range from 0 to 24), and Acne symptoms (5 questions - total score range from 0 to 30).

3.5.2.2 Subject Satisfaction Questionnaire on Using the Assigned Study Treatment (Topical and Oral)

Prior to any acne assessment, subjects will complete a satisfaction questionnaire at Week 12/Early Termination visit regarding use of the assigned study treatment (topical study drug and oral study drug, see Appendix 14.2 of the study protocol).

3.5.2.3 Topical Study Drug (Study Cream) Acceptability Questionnaire

Prior to any acne assessment, subjects will complete a topical study drug (study cream) acceptability questionnaire at Week 12/Early Termination visit (see Appendix 14.3 of the study protocol). The designated study personnel should check the questionnaires for completeness prior to the subject leaving the office.

3.5.3 Safety Assessments

Safety assessments include the recording of adverse events and local tolerability scores and should be conducted by the investigators (or trained designees) according to section 3.1.2.

3.5.3.1 Adverse Events

Adverse events (AEs) are to be monitored throughout the course of the clinical trial. 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 trial center personnel for reporting AEs and medical emergencies.

Refer to section 6.6.2 of the study protocol for further details.

3.5.3.2 Local Tolerability

The local tolerability assessment is performed after a general wellness assessment, review of dosing calendar/compliance and subject completion of questionnaires.

Local tolerability assessment(s) on the face will include erythema, scaling, dryness and burning/stinging. At visits specified in the schedule of assessments (see section 3.1.2). Burning/stinging will be recorded by the investigator after discussion with the subject. Local tolerability assessments for the face are reported as a global rating for each tolerability parameter, based on clinical judgment of the investigator.

Table 4 Local Tolerability Assessments

Erythema - abnormal redness of the skin		
None	**0**	No erythema
Mild	**1**	Slight pinkness present
Moderate	**2**	Definite redness, easily recognized
Severe	**3**	Intense redness
Scaling - abnormal shedding of the stratum corneum		
None	**0**	No scaling
Mild	**1**	Barely perceptible shedding, noticeable only on light scratching or rubbing
Moderate	**2**	Obvious but not profuse shedding
Severe	**3**	Heavy scale production
Dryness - brittle and/or tight sensation		
None	**0**	No dryness
Mild	**1**	Slight but definite roughness
Moderate	**2**	Moderate roughness
Severe	**3**	Marked roughness
Stinging/Burning - pricking pain sensation immediately after dosing		
None	**0**	No stinging/burning
Mild	**1**	Slight warm, tingling/stinging sensation; not really bothersome
Moderate	**2**	Definite warm, tingling/stinging sensation that is somewhat bothersome
Severe	**3**	Hot, tingling/stinging sensation that has caused definite discomfort

The severity of each sign and symptom should be based after the last topical study drug application before each visit. The Investigator will ask open-ended questions, taking care not to influence the subject's answer, such as "Have you experienced any sensations such as stinging/burning after the last dose of study medication?".

An Adverse Event page must be completed for local tolerability signs and symptoms if the severity of the signs and symptoms assessed with the local tolerability scale is such that:

- The subject permanently discontinues the treatment at his/her request or at the Investigator's request

  OR
- The subject requires concomitant treatment, including OTC products or any other medications (other than moisturizer).

Any new sign or symptom, which is not included in the scheduled evaluation of tolerability, should be recorded as an Adverse Event, including those of mild intensity.

3.6 Other Assessments

Standardized photography at designated sites (for visual evidence of treatment effect from Baseline to Week 12).

4 SAMPLE SIZE CONSIDERATION

The sample size calculation is based on the results of the study RD.06.SPR.18251 "A Multi-Center, Randomized, Double-Blind, Parallel-Group Vehicle Controlled Study To Compare The Efficacy And Safety Of CD5789 50µg/g Cream Versus Vehicle Cream In Subjects With Acne Vulgaris" and RD.06.SPR.18252 "A Multi-Center, Randomized, Double-Blind, Parallel-Group Vehicle Controlled Study To Compare The Efficacy And Safety Of CD5789 50µg/g Cream Versus Vehicle Cream In Subjects With Acne Vulgaris".

Table 5 Results for Total Lesion Counts of studies RD.06.SPR.18251 and RD.06.SPR.18252

Study	Variable	$\mu_{Trifarotene} - \mu_{Vehicle}$	σ_{Diff}
18251	Facial TLC (ITT, OC)	-11.3	31.1
18251	Facial TLC (ITT, LOCF)	-10.6	32.4
18252	Facial TLC (ITT, OC)	-13.2	31.9
18252	Facial TLC (ITT, LOCF)	-12.7	32.5

Under the hypothesis that the use of Trifarotene and Doxycycline will improve the reduction of facial total lesion counts up to a mean difference of -15 with respect to the use of Vehicle and Placebo and considering a standard deviation of 32.5, the sample size can be calculated according to the following formula [1]:

$$N_{T+D} = k \cdot N_{TVeh+DPbo}$$

$$N_{TVeh+DPbo} = \left(1 + \frac{1}{k}\right) \cdot \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \cdot {\sigma_{Diff}}^2}{\left(\mu_{T+D} - \mu_{TVeh+DPbo}\right)^2}$$

Table 6 Sample Size Calculation

α (2-sided)	β	μ_{Diff}	σ_{Diff}	k	N_{T+D}	$N_{TVeh+DPbo}$	$N_{T+D} + N_{TVeh+DPbo}$
0.05	0.2	-15.0	32.5	2	112	56	168

Considering a two-sided α=0.05, β=0.2 (i.e. 80% power), a 2:1 allocation ratio between T+D and TVeh+DPbo (preferable in order to collect more safety data on the combination and for ethical reasons) and a proportion of drop-outs and non-evaluable subjects around 15%, **at least 198 subjects (132+66) are planned to be randomized**.

5 POPULATIONS ANALYZED

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 any subjects in the ITT population who had compliance to the study treatment (both topical and oral) between 80% and 120% and assessments of the primary endpoint at Baseline and Week 12, without any major deviations that could have a significant effect on the efficacy of the study treatment (e.g. errors in treatment assignment, use of prohibited medications). The PP population will be used for a sensitivity analysis of the primary endpoint. Subjects of the PP population will be summarized and analyzed according to the treatment they were randomized to.

Potential major protocol deviations may include but are not limited to:

1. Eligibility deviations (inclusion/exclusion criteria);
2. Improper administration of study medications;
3. Noncompliance with study medications;
4. Noncompliance with study procedures if the consequence of noncompliance would compromise either the subject's safety and/or the study integrity, primary endpoint, and/or is not in line with Good Clinical Practice (GCP)/ICH guidelines;
5. Use of prohibited concomitant therapies;
6. Accidental unblinding;
7. Medication dispensing errors;
8. Acne lesion counts performed by a non-approved evaluator.

The final list of major protocol deviation criteria, subjects who have any major protocol deviations and subjects excluded from the per protocol (PP) population will be documented in the blind review memo before database lock. Decisions made regarding the exclusion of subjects and/or subject data from analyses will be made prior to database lock and unblinding and will be documented in blind review memo.

5.3 Safety Population

The Safety (SAF) population is defined as comprising the ITT population subjects who applied/took the study drug (i.e. either topical or oral treatment or both) 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 (i.e. the earliest one between topical and oral treatments) 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 (defined as the earliest date of either Topical or Oral treatment) 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 by treatment group (randomized subjects only) and overall (screened subjects) for the following categories:

- Subjects screened
- Subjects eligible
- 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 topical treatment
- Subjects randomized who completed the topical treatment
- Subjects randomized who discontinued the topical treatment
  - Reasons for topical treatment discontinuation
- Subjects randomized who discontinued the topical treatment due to COVID-19
  - Reasons for topical treatment discontinuation due to COVID-19
- Subjects randomized who underwent the oral treatment
- Subjects randomized who completed the oral treatment
- Subjects randomized who discontinued the oral treatment
  - Reasons for oral treatment discontinuation
- Subjects randomized who discontinued the oral treatment due to COVID-19
  - Reasons for oral treatment discontinuation due to COVID-19
- Subjects randomized who underwent both topical and oral treatment
- Subjects randomized who completed both topical and oral treatment
- Subjects randomized who discontinued the topical or the oral treatment
  - Reasons for topical or oral treatment discontinuation
- Subjects randomized who discontinued the topical or the oral treatment due to COVID-19
  - Reasons for topical or oral 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 topical treatments, discontinued oral treatments 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 by treatment group and overall 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 and major protocol deviations due to COVID-19 will be summarized using frequencies and proportions (n, %) of subjects in the ITT population for each deviation coded term by treatment group and overall.

A listing of all protocol deviations will be provided.

6.2.4 Data Sets Analysed

Frequencies and proportions (n, %) of subjects will be summarized by treatment group (randomized subjects only) and overall (screened subjects) for each inclusion/exclusion criterion not met.

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

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 by treatment group and overall using the ITT population for the following demographic data and baseline characteristics:

- Age (years)
- Age Groups
  - 12-17 years old
  - >= 18 years old
  - 13-35 years old
- Sex
  - Male
  - Female

- Ethnicity
  - Hispanic or Latino
  - Not Hispanic or Latino
- 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 Global Assessment of Facial Acne
  - 0 - Clear
  - 1 - Almost Clear
  - 2 - Mild
  - 3 - Moderate
  - 4 - Severe
- Baseline Face Inflammatory Lesion Counts
- Baseline Face Non-Inflammatory Lesion Counts

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 by treatment group and overall 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 (defined as the earliest day between the day of first topical treatment and the day of first oral treatment); 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 1, 2020, B3/C3 format). Medical history diseases and prior and concomitant medical/surgical procedures will be coded using MedDRA dictionary (version 23.0).

Summaries will be presented by treatment group and 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 topical and/or oral treatment, study duration will be calculated as date of end of participation minus date of first treatment (defined as the earliest date between the date of first topical treatment and the date of first oral treatment) plus one (1).

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

Topical treatment duration will be calculated as date of last topical treatment minus date of first topical 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 group in the ITT population.

Oral treatment duration will be calculated as date of last oral treatment minus date of first oral 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 group in the ITT population.

Treatment duration will be calculated as date of last treatment (i.e. the latest date between the date of last topical treatment and the date of last oral treatment) minus date of first treatment (i.e. the earliest date between the date of first topical treatment and the date of first oral 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 group in the ITT population.

Listings inclusive of study duration, topical treatment duration, oral treatment duration and treatment duration will be provided.

6.2.7.2 Compliance and Drug Accountability

Topical and oral compliances are calculated as follows:

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

$$\text{Compliance}_{\text{Oral}} = 100\frac{\text{Actual Tablets}}{\text{Planned Tablets} - \text{Missed Tablets due to Prescribed Dose Reductions}}$$

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

Planned tablets are calculated as the number of days between start date and stop date of each compliance evaluation period. For the Baseline-Week 1 period, an additional tablet has to be added due to BID oral drug administration on day 2.

Topical and Oral Drugs Combined Compliance is derived as the farthest from 100% in absolute value between Topical Compliance and Oral Compliance.

Topical, oral and combined compliances 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 group in the ITT population.

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

Listings for topical and oral compliances will be provided.

Listings for topical and oral drug accountability will be provided.

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 topical and oral drugs by treatment group 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/Tablets 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 topical and oral 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 group 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 12.

Subjects will be summarized and analyzed according to the treatment they were randomized to.

All efficacy data (including efficacy data of incomplete treatments) will be listed.

6.3.1 Missing Data Pattern

Distinct missing data patterns of total lesion counts, inflammatory lesion counts, non-inflammatory lesion counts and Investigator Global Assessment (IGA) scores of facial acne with their corresponding frequencies and proportions (n, %) of subjects will be presented in order to establish whether they are monotone or non-monotone.

6.3.2 Efficacy Data Summary

6.3.2.1 Acne Lesion Counts

Facial total lesion counts, inflammatory lesion counts, non-inflammatory lesion counts and their absolute and percent changes from baseline will be summarized at each analysis visit using descriptive statistics (n, mean, standard deviation, median, first and third quartile, min and max) by treatment group in the ITT population.

Summaries will be presented overall and by analysis centers.

Line plots will be produced over time for each treatment group to summarize the mean absolute change from baseline in facial total lesion counts, inflammatory lesion counts, non-inflammatory lesion counts.

6.3.2.2 Investigator Global Assessment of Facial Acne

IGA scores and their absolute changes from baseline will be summarized at each analysis visit using descriptive statistics (n, mean, standard deviation, median, first and third quartile, min and max) by treatment group in the ITT population.

Frequencies and proportions (n, %) of subjects for each score of Investigator Global Assessment (IGA) of facial acne will be summarized at each analysis visit by treatment group in the ITT population.

Summaries will be presented overall and by analysis centers.

Bar charts will be produced over time for each treatment group to summarize the proportions of subjects for each score of Investigator Global Assessment (IGA) of facial acne.

Line plots will be produced over time for each treatment group to summarize the mean absolute changes from baseline of IGA scores.

Frequencies and proportions (n, %) of subjects achieving and not achieving Investigator Global Assessment (IGA) Success (defined as an IGA score of 1 - Almost Clear or 0 - Clear and at least a 2-grade improvement from Baseline) will be summarized at each analysis visit by treatment group in the ITT population.

Summaries will be presented overall and by analysis centers.

Bar charts and line plots will be produced over time for each treatment group to summarize the proportions of subjects achieving Investigator Global Assessment (IGA) Success.

6.3.2.3 Acne-Specific Quality of Life Questionnaire (Acne-QoL)

Frequencies and proportions (n, %) of subjects for each answer of each question of the Acne-Specific Quality of Life Questionnaire will be summarized at baseline, week 12 and week12/early termination by treatment group in the ITT population.

Domain scores and total score of the Acne-Specific Quality of Life Questionnaire and their absolute changes from baseline will be summarized using descriptive statistics (n, mean, standard deviation, median, first and third quartile, min and max) at baseline, week 12 and week12/early termination by treatment group in the ITT population.

Summaries at week 12/early termination will include the available week 12 assessments and the early termination assessments for all subjects who do not have week 12 assessments.

6.3.2.4 Subject Satisfaction Questionnaire on Using the Assigned Study Treatment (Topical and Oral)

Frequencies and proportions (n, %) of subjects for each answer of each question of the Subject Satisfaction Questionnaire on Using the Assigned Study Treatment (Topical and Oral) will be summarized at week 12 and week12/early termination by treatment group in the ITT population.

Summaries at week 12/early termination will include the available week 12 assessments and the early termination assessments for all subjects who do not have week 12 assessments.

6.3.2.5 Topical Study Drug (Study Cream) Acceptability Questionnaire

Frequencies and proportions (n, %) of subjects for each answer of each question of the Topical Study Drug (Study Cream) Acceptability Questionnaire will be summarized at week 12 and week12/early termination by treatment group in the ITT population.

Summaries at week 12/early termination will include the available week 12 assessments and the early termination assessments for all subjects who do not have week 12 assessments.

6.3.3 Analysis of Primary Endpoint

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

$$\begin{cases} H_0: \mu_{T+D} = \mu_{TVeh+DPbo} \\ H_a: \mu_{T+D} \neq \mu_{TVeh+DPbo} \end{cases}$$

where μ_{T+D} is the mean absolute change in facial total lesion counts from baseline at week 12 of T+D treatment group and $\mu_{TVeh+DPbo}$ is the mean absolute change in facial total lesion counts from baseline at week 12 of TVeh+DPbo treatment group.

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.

Absolute change in facial total lesion counts from baseline to week 12 will be analyzed using an ANCOVA with treatment, analysis center (see definition in section 6.3.7.4) and baseline total lesion count as fixed effects; the p-values for the treatment comparison, estimates of the treatment difference and the 95% confidence interval of the difference will be generated from the ANCOVA model.

For analysis of absolute change in facial total lesion counts from baseline to week 12, missing lesion 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. Linear regression will be employed to model the missing lesion counts, with the following covariates included in the imputation model: treatment and non-missing total lesion counts from earlier time points (see section 6.3.7.2 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. Analysis of absolute change in facial total lesion counts from baseline to week 12 will be repeated on the ITT population by imputing missing data using Multiple Imputation (MI) based on a Pattern-Mixture Model under the Missing Not At Random (MNAR) assumption,

using the profiles from TVeh+DPbo subjects with observed data to impute missing data (see section 6.3.7.2 for further details);

2. Analysis of absolute change in facial total lesion counts from baseline to week 12 will be repeated on the ITT population by imputing missing data using Last Observation Carried Forward (LOCF);
3. Observed Case (OC) analysis of absolute change in facial total lesion counts from baseline to week 12 on the ITT population;
4. Analysis of absolute change in facial total lesion counts from baseline to week 12 will be repeated on the PP population.

6.3.5 Analysis of Secondary Endpoints

The hypothesis test for the secondary endpoints can be formally defined as follows:

$$\begin{cases} H_0: \mu_{T+D} = \mu_{TVeh+DPbo} \\ H_a: \mu_{T+D} \neq \mu_{TVeh+DPbo} \end{cases}$$

where μ_{T+D} is the mean absolute change in facial inflammatory and non-inflammatory lesion counts from baseline at week 12 of T+D treatment group and $\mu_{TVeh+DPbo}$ is the mean absolute change in facial inflammatory and non-inflammatory lesion counts from baseline at week 12 of TVeh+DPbo treatment group and

$$\begin{cases} H_0: \pi_{T+D} = \pi_{TVeh+DPbo} \\ H_a: \pi_{T+D} \neq \pi_{TVeh+DPbo} \end{cases}$$

where π_{T+D} is the proportion of subjects achieving IGA Facial Success at week 12 of T+D treatment group and $\pi_{TVeh+DPbo}$ is the proportion of subjects achieving IGA Facial Success at week 12 of TVeh+DPbo treatment group.

The hypothesis tests for the secondary endpoints will be evaluated on the ITT population at the two-sided significance level $\alpha = 0.05$. The adjustment for multiple comparisons is described in section 6.3.7.5.

Absolute change in facial inflammatory/non-inflammatory lesion counts from baseline to week 12 will be analyzed using an ANCOVA with treatment, analysis center (see definition in section 6.3.7.4) and baseline inflammatory/non-inflammatory lesion count as fixed effects; the p-values for the treatment comparison, estimates of the treatment difference and the 95% confidence interval of the difference will be generated from the ANCOVA model.

For analysis of absolute change in facial inflammatory/non-inflammatory lesion counts from baseline to week 12, missing lesion 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. Linear regression will be employed to model the missing lesion

counts, with the following covariates included in the imputation model: treatment and non-missing inflammatory/non-inflammatory lesion counts from earlier time points (see section 6.3.7.2 for further details).

The proportion of subjects achieving IGA Facial Success at week 12 will be analyzed using a Cochran-Mantel-Haenszel (CMH) test stratified by analysis center (see definition in section 6.3.7.4); strata-adjusted success proportions, strata-adjusted difference in success proportions between treatment groups and the 95% confidence interval of the difference will be based on the large sample approximation method for binary data using Mantel-Haenszel stratum weights [2] and the Sato variance estimator [3].

For analysis of proportion of subjects achieving IGA Facial Success at week 12, missing ordinal IGA scores 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. Logistic regression will be employed to model the missing ordinal IGA scores, with the following covariates included in the imputation model: treatment and non-missing ordinal IGA scores from earlier time points (see section 6.3.7.2 for further details). IGA Facial Success will be calculated from the imputed ordinal IGA scores.

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6.3.7 Statistical/Analytical Issues

6.3.7.1 Adjustments for Covariates

The analysis of absolute and percent change in facial total, inflammatory and non-inflammatory lesion counts from baseline to week 4, week 8 and week 12 will use an adjustment for the number of baseline total, inflammatory and non-inflammatory lesion counts as described in sections 6.3.3, 6.3.5 and 6.3.6.

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

6.3.7.2 Handling of Dropouts or Missing Data

For primary, secondary and exploratory analyses, missing data for acne lesion counts and IGA ordinal scores will be imputed using Multiple Imputation (MI) under the Missing At Random (MAR) assumption.

Independent imputations will be performed for total, inflammatory and non-inflammatory lesion counts and IGA ordinal scores.

Absolute and percent change from baseline in total, inflammatory and non-inflammatory lesion counts will be derived from the corresponding imputed lesion counts.

IGA Facial Success will be calculated from the imputed ordinal IGA scores.

The following steps will be followed:

1. For total, inflammatory, non-inflammatory lesion counts and IGA scores, the missingness pattern in the data will be evaluated. 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. 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 IGA scores only, the maximum value for imputed variables will be set to 4, in order to force PROC MI to redraw another value for imputation when an intended imputed value is greater than the 4. Imputed values will be rounded to the nearest integer. The seed number will be set to 202394 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 202394. These imputations will use the following models:
   2.1. For total, inflammatory and non-inflammatory lesion counts, a linear regression model will be used with covariates for treatment and non-missing total, inflammatory and non-inflammatory lesion count from earlier scheduled time points including baseline. 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 IGA scores, a logistic regression model will be used with covariates for treatment and non-missing ordinal IGA scores from earlier scheduled time points including baseline. IGA Facial Success will be calculated from the imputed ordinal IGA scores.
3. The imputed datasets will be analyzed as specified in sections 6.3.3, 6.3.5 and 6.3.6.
4. The resulting analysis on the imputed datasets will then be combined to produce a single set of statistics as follows:
   4.1. For total, inflammatory and non-inflammatory lesion counts, results from the ANCOVA analysis will be combined using the SAS PROC MIANALYZE.
   4.2. For binary outcome, the results from the CMH analysis will be combined using the procedure by Rubin [4] and Li et al. [5] 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. Both these methods will be used as

described in the Bohdana Ratitch, et al. "Combining Analysis Results from Multiply Imputed Categorical Data", 2013, PharmaSUG Proceedings, Paper SP-03 [6].

The number of fifty (50) imputations was selected in order to prevent a power falloff due to choosing a number of imputations too small [7].

As sensitivity analysis of the primary endpoint, the primary analysis will be repeated on the ITT population by imputing total lesion counts on the basis of a Pattern-Mixture Model under the Missing Not At Random (MNAR) assumption, using the profiles from TVeh+DPbo 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.

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.

6.3.7.3 Interim Analyses and Data Monitoring

No interim analysis is planned for this study.

6.3.7.4 Multicenter 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 a small number of randomized subjects, then these centers will be pooled in order for analyses to be carried out. The process of combining centers will be based on the ITT population, and same pooling will be repeated for PP population.

A small center is defined as a center which randomizes less than 12 subjects. First, centers 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 with the smallest center within the same latitude zone. If there is a further need to combine data (the size of the pooled centers includes less than 12 subjects), the next smallest center will be combined with the next largest of the small centers, until the criterion of a minimum of 12 subjects is met. The process will continue until all pooled centers have a minimum of 12 subjects within the same latitude zone. Any remaining small centers of a latitude zone will be pooled with the last pooled center within the same latitude zone. 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 has less than 12 subjects in the ITT population in total, then centers will be added to the list of small centers in another latitude and then combined as above. This decision will be documented in clinical report.

6.3.7.5 Multiple Comparison/Multiplicity

In order to maintain the overall type I error rate at 0.05, a predefined hierarchal testing procedure will be implemented to test the T+D treatment against TVeh+DPbo treatment.

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 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. Absolute change in facial inflammatory lesion counts from Baseline to Week 12
2. Absolute change in facial non-inflammatory lesion counts from Baseline to Week 12
3. IGA Facial Success Rate 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 exploratory efficacy endpoints. p-values and 95% confidence intervals will presented for descriptive purposes only.

6.3.7.6 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.

6.3.7.7 Active-Control Studies Intended to Show Equivalence

Not applicable.

6.3.7.8 Examination of Subgroups

No subgroup analysis is planned for this study.

6.3.7.9 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

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 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 - 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 using descriptive statistics (n, mean, standard deviation, median, first and third quartile, min and max) by treatment group and overall in the Safety population.

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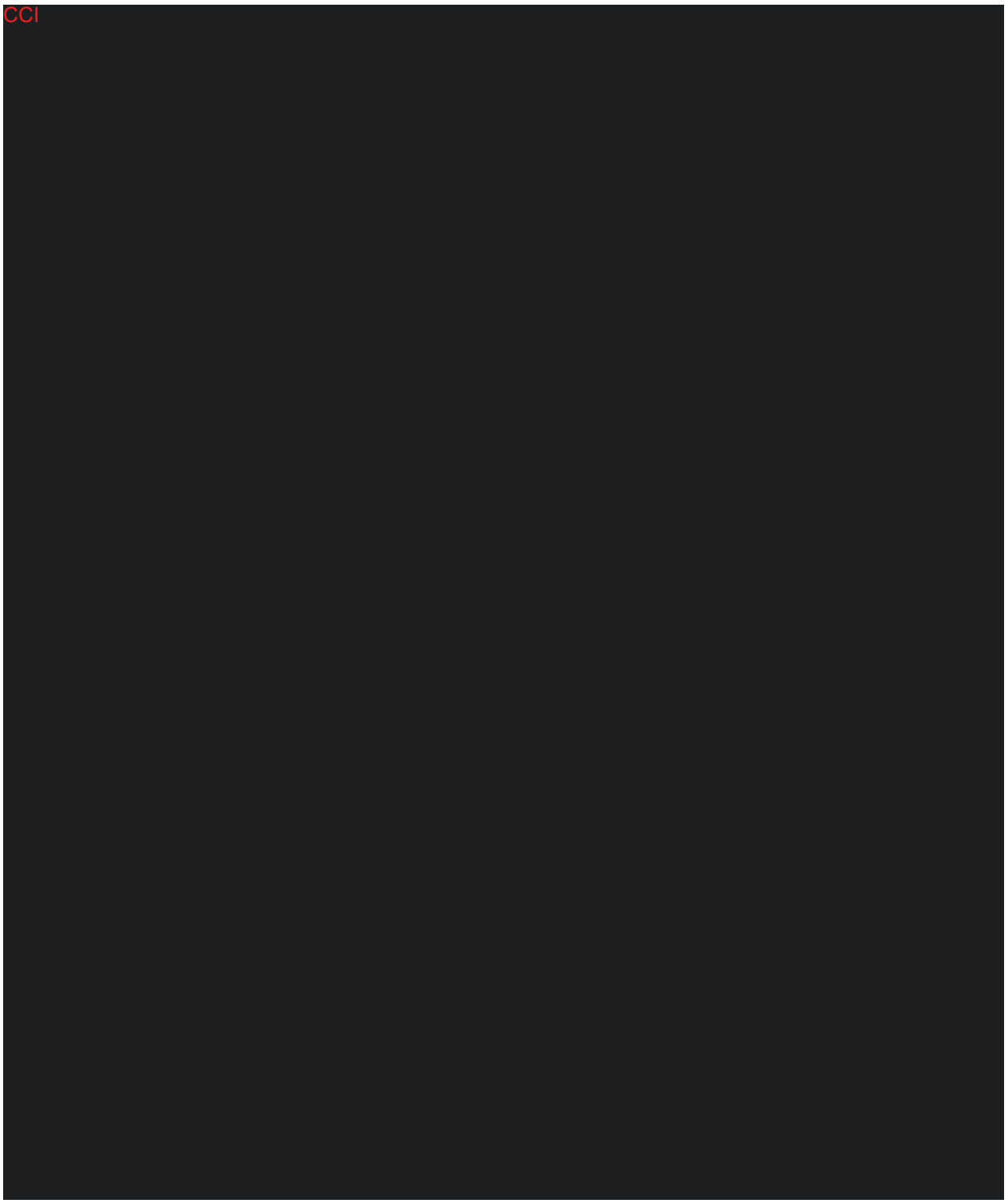

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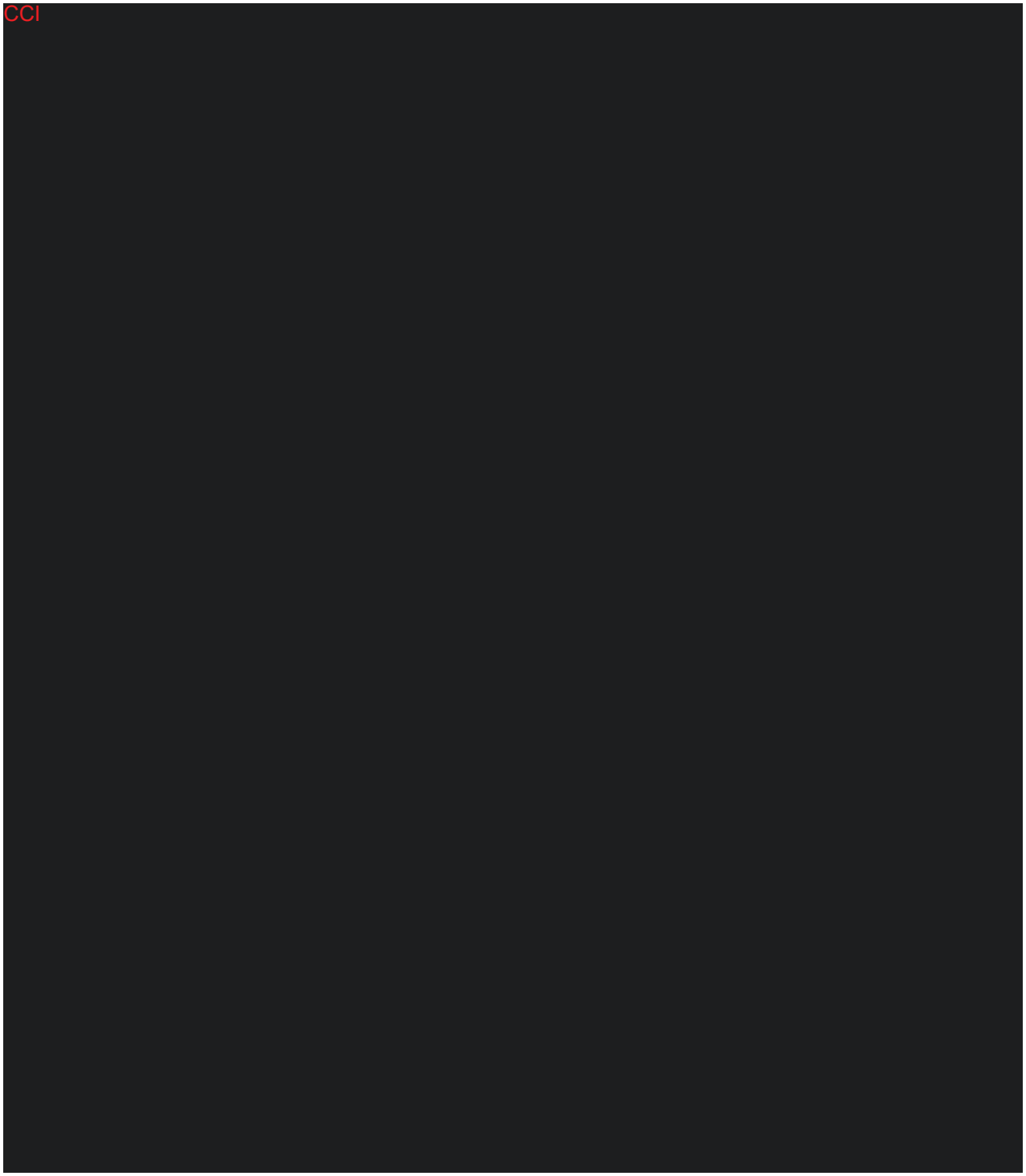

6.4.4 Clinical Laboratory Evaluation

A listing of pregnancy test results will be provided.

6.4.5 Vital Signs

Not applicable.

6.4.6 Physical Findings

Not applicable.

6.4.7 Local Tolerability

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 using descriptive statistics (n, mean, standard deviation, median, first and third quartile, min and max) by treatment group and overall in the Safety population.

Frequencies and proportions (n, %) 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 at each analysis visit 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).

Line plots will be produced over time for each treatment group to summarize the mean score of each local tolerability parameter.

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

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