# TITLE PAGE

| **Title**<br>Evaluation of the risk of atrophic acne scar formation during treatment of acne vulgaris subjects with trifarotene 50 µg/g cream versus vehicle cream over 24 weeks | | |
|---|---|---|
| **Investigational product:**<br>trifarotene 50 µg/g cream (CD5789) | **Project Number:**<br>02222 | **Clinical Study Phase:**<br>4 |

**IND Number:** CCI

**EudraCT Number:** 2020-006050-51

**Indication:** Acne vulgaris

| Protocol Amendment | Amended Protocol Sequence By Region | Version Date |
|---|---|---|
| Original | N/A | 08Dec2020 |
| Amendment No. 1 | Amended Clinical Protocol 01 – France | 24May2021 |
| Amendment No. 2 | Amended Clinical Protocol 01 – Global | 9Jul2021 |

**SPONSOR:**

| | |
|---|---|
| Name: | Galderma S.A. |
| Address: | PPD |
| Telephone: | PPD |

**For any safety questions, please contact the Clinical Safety Officer** (Advanced Clinical Pharmacovigilance) **using the contact details provided in Section 6.11.2.2.2**

For any medical questions related to the clinical study protocol, please contact the Medical Monitor using the contact details below:

| | |
|---|---|
| Name and Title: | PPD |
| Address: | PPD |
| Telephone: | PPD |
| E-mail: | PPD |

# PROTOCOL APPROVAL SIGNATURES

**Protocol Title:** Evaluation of the risk of atrophic acne scar formation during treatment of acne vulgaris subjects with trifarotene 50 µg/g cream versus vehicle cream over 24 weeks

**Protocol Number:** RD.06.SPR.202395

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation guidelines for current Good Clinical Practice and applicable regulatory requirements.

**Sponsor Signatory**

PPD

Galderma Research & Development, LLC
PPD

PPD

Signature

PPD

Date (DD-Mmm-YYYY)

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# 1 SYNOPSIS

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|---|---|
| **Title:** Evaluation of the risk of atrophic acne scar formation during treatment of acne vulgaris subjects with trifarotene 50 µg/g cream versus vehicle cream over 24 weeks | |
| **Short Title:** Study of Trifarotene cream to Assess Risk of aTrophic acne scar formation (START) | |
| **Study Phase:** | 4 |
| **Study Population:** | Subjects with moderate to severe acne vulgaris |
| **Study Objective:** | Evaluate the effect of trifarotene 50 µg/g cream versus vehicle cream on the risk of formation of atrophic acne scars in facial acne subjects. |
| **Study Design:** | This is a multicenter, randomized, double-blind, vehicle-controlled clinical study using CCI design for CCI comparison CCI<br>Eligible subjects will CCI randomised to one of the two following treatments:<br>• once-daily trifarotene 50 µg/g cream<br>• once-daily trifarotene vehicle cream<br>Refer to Section 5.1.1 – Study Schema for an illustration of the study design.<br>Subject eligibility is evaluated over a 28-day screening period. Subjects who meet eligibility criteria at the Screening visit will return to the clinic for baseline assessments and to start treatment which will continue for 24 weeks. The protocol allows subjects to be screened and qualified on the same day. Subjects will apply study medication under site staff supervision, at the Baseline visit, and reminded not to dose the first evening.<br>Following the Baseline visit, all subjects will return to the clinic for efficacy and safety evaluations at Weeks 1, 2, 4, 8, 12, 16, 20 and 24. Subjects will be provided skin care products including Cetaphil® Gentle Skin Cleanser for washing the face twice daily (morning and evening); Cetaphil® PRO Oil Absorbing Moisturizer with SPF 30 for use daily on the face (morning) and to be re-applied to face when sun exposure is expected; and Cetaphil® Moisturizing Lotion for supplemental moisturizer use, as needed. Use of an equivalent available skincare product per country is permitted as well as the subject's preferred or investigator's recommended non-comedogenic cleanser, moisturizer and sunscreen (SPF ≥30 or equivalent).<br>Subjects will receive an electronic tablet at baseline for daily recording of study medication use (electronic dosing calendar), as well as for capturing daily videos of applying study medication to each side of the face. Study medication dosing data will be uploaded for remote assessment by the clinical site. All videos will remain on the local drive of the electronic tablet and reviewed by site staff at scheduled office visits.<br>Subjects who initially fail screening may be re-screened once provided the reason for screen failure is not due to atrophic scars counts, acne severity (IGA) or lesion counts.<br>Subjects will return to the clinic for safety and efficacy assessments over the 24-week treatment period. Study procedures and assessments are performed according to the schedule of assessments (Section 5.1.2). |
| **Total number of subjects:** | An initial number of CC subjects is planned to be randomised. A blinded sample size re-estimation will be performed after C subjects complete/discontinue the |

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|---|---|
| | study (i.e. after ~33% of the initial planned subjects complete/discontinue the study) in order to evaluate the need for additional subjects to be randomized.<br><br>Site enrollment strategies should include outreach plans with a goal for approximate even distribution of male to female subjects, to the extent possible. |
| **Number of clinical centers:** | Approximately 25 sites |
| **Region(s) / country(ies) involved:** | France, Canada, United States |
| **Duration of subject participation:** | The expected duration for each subject's participation in the study is 28 weeks (including a 4-week screening period and a 24-week treatment period). |
| **Inclusion criteria** | Subjects must fulfill inclusion criteria to participate in the study.<br>1. Male or female subject aged 17 to 35 years inclusive, at Screening visit.<br>2. Subject with clinical diagnosis of acne vulgaris on the face as defined by (excluding the nose and middle zone of approximatey 2 cm):<br>a. Investigator's Global Assessment (IGA) score of 3 (Moderate) or 4 (Severe), with the same score on both sides of the face; and<br>b. A minimum of 20 inflammatory lesions (papules and pustules) in total, with at least 10 on each side; and<br>c. No more than 2 nodules (≥1cm in diameter) on the face; and<br>d. A minimum of 10 atrophic acne scars in total (≥2 mm),<br>3. Subject with a symmetrical number of the following lesions/scars on the whole face (i.e., there are no more than twice as many lesions/scars of each type on one half of the face than on the other half):<br>a. Inflammatory and non-inflammatory lesions; and<br>b. Atrophic acne scars (minimum of 4 scars per half-face)<br>4. The subject is a female of non-childbearing potential (premenarchal or postmenopausal [absence of menstrual bleeding for 1 year prior to Screening, without any other medical reason], hysterectomy or bilateral oophorectomy).<br>5. The subject is a female of childbearing potential:<br>5.1. Who is willing to undergo UPTs throughout the course of the study, as required.<br>5.2. Who has been strictly abstinent for 1 month prior to Screening and agrees to continue for the duration of the clinical study and at least 1 month after the last study drug application,<br>OR<br>Who agrees to use highly effective and approved contraceptive method(s) for the duration of the study and at least 1 month after the last study drug application. |

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|---|---|
| | Highly effective methods of contraception include:<br>a. bilateral tubal ligation;<br>b. approved combined oral contraceptives (estrogens and progesterone), implanted or injectable contraceptives, or hormonal contraceptive vaginal rings with a stable dose for at least 1 month prior to the Screening visit;<br>c. intrauterine device or intrauterine hormonal-releasing system inserted at least 1 month prior to the Screening visit;<br>d. vasectomized partner for at least 3 months prior to the Screening visit<br>Note: This criterion applies to a prepubertal female subject who begins menses during the study.<br>6. If a female of childbearing potential uses oral contraceptives that are also approved for treating acne vulgaris (such as cyproterone acetate and ethinyl estradiol; drospirenone and ethinyl estradiol; norgestimate and ethinyl estradiol; norenthindrone acetate and ethinyl estradiol; etc) the dose should be stable for at least 6 months prior to the Screening visit.<br>7. Subject having read, understood and signed the approved Informed Consent Form (ICF) prior to any participation in the clinical study. Subject under the age of 18 having signed an assent form to participate in the clinical study and their parent(s) or legal representative having read and signed the informed consent form prior to any clinical study related procedure.<br>8. Subject (and legal guardian, if applicable) agrees and is able to comply with all time commitments and procedural requirements of the protocol, including daily recording of dosing compliance by the subject using an electronic tablet provided for this study, as well as taking daily videos of study medication use. Consent to taking daily videos is mandatory for study participation at all sites.<br>9. Subject agrees to having photographs taken (mandatory for study participation, at designated imaging centers), and verified by the subject signing and dating an approved ICF (includes willingness to remove all makeup prior to study visits, remove jewelry in the areas to be photographed, keep facial hair well-groomed prior to study visits).<br>10. Subject is informed of terms pertaining to personal information protection and privacy and is willing to share personal information and data, as verified by signing a written authorization at the Screening visit. |
| **Exclusion criteria** | Subjects meeting any of the exclusion criteria are not eligible to participate in the study.<br>1. Subject with acne conglobata, acne fulminans, secondary acne [chloracne, drug-induced acne, polycystic ovary syndrome (PCOS), pyogenic arthritis-pyoderma gangrenosum-acne (PAPA), synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO), seborrhoea-acne-hirsutism-androgenetic alopecia (SAHA), Hidradenitis suppurativa (HS), congenital adrenal hyperplasia (CAH) etc.], nodulocystic acne, acne requiring systemic treatment.<br>2. Subject with any acne cyst on the face or with more than 3 excoriated acne lesions. |

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3. Subject with known active or chronic allergies or suspected allergy to trifarotene or excipients of the formulation.
4. Prior failure of trifarotene treatment including intolerance that resulted in stopping treatment; lack of clinical improvement, etc.
5. Subject with facial dermal conditions (e.g. tattoo, skin abrasion, eczema, sunburned skin, scars, nevi, etc.) that may interfere with study assessments in the opinion of the investigator.
6. Subject with excessive facial hair that would interfere with study assessments, as judged by the investigator, or unwilling to keep facial hair well-groomed prior to study visits, as judged appropriate by the investigator to perform study assessments.
7. Pregnant women (positive urine pregnancy test at the Screening or Baseline visits), breastfeeding women, or women planning a pregnancy during the study or within 1 month after the last study drug application
8. Subject with known impaired hepatic or renal functions, based on medical history.
9. Subjects taking Vitamin A supplements in excess of the recommended daily allowance (4000 – 5000 IU; no washout period is required)
10. Subjects with a washout period for **topical treatment** or procedures on the face less than:

| | |
|---|---|
| Topical treatments: Corticosteroids, antibiotics, benzoyl peroxide, azelaic acid, alpha hydroxy acids, salicylic acid, zinc containing treatments, hydroquinones, and other anti-acne treatments | 2 weeks |
| Topical retinoids | 2 weeks |
| Clascoterone cream 1% (Winlevi) | 2 weeks |
| Cosmetic/aesthetic procedures (e.g., comedo extraction, desquamating, or abrasive agents, adhesive”pore” cleansing strips) | 1 week |
| Wax epilation | 2 weeks |
| Photodynamic therapy | 4 weeks |
| Laser therapy, microdermabrasion, deep chemical peel, and other plastic surgical treatments for acne | 12 weeks |

11. Subject with a washout period for **systemic treatment** less than:

| | |
|---|---|
| Corticosteroids, (except locally acting corticosteroids such as inhaled or intrathecal), antibiotics and spironolactone | 4 weeks |

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| | |
|---|---|
| Oral retinoids/isotretinoin | 12 weeks |
| Cyproterone acetate / Chlormadinone acetate | 12 weeks |
| Immunomodulators | 12 weeks |

12. Currently receiving any prescription testosterone therapy (e.g., testosterone cypionate, testosterone enanthate, testosterone pellet, testosterone undecanoate) or on a testosterone booster or prescription testosterone (e.g., DHEA, Omnadren®, Sustanon®, testosterone cypionate, testosterone enanthate, testosterone propionate, testosterone phenylpropionate) or testosterone supplements (e.g., Tribulus).
13. The subject is unwilling to or unable to refrain from use of prohibited medication or procedures during the clinical study (see Section 5.4.12.5)
14. Subject who foresees intensive ultraviolet exposure during the study (mountain sports, sailing, sunbathing, tanning beds, etc.).
15. Subject who is at risk in terms of precautions, warnings, and contraindications for trifarotene based on approved labeling.
16. Subject with an acute / chronic disease or a history of major medical or surgical or psychiatric condition or surgical interventions that may either interfere with the interpretation of the study results and/or might put the subject at risk in the opinion of the investigator.
17. Subject under guardianship (for reason other than minor status), hospitalized subject in a public or private institution for a reason other than the research, and subject deprived of his/her freedom.
18. More than one subject sharing the same household.
19. Study site personnel, close relatives of the study site personnel (e.g., parents, children,siblings, or spouse), employees, or close relatives of employees at the Sponsor company.
20. Subject who has participated in another investigational drug or device research study within 30 days prior to Screening OR is in an exclusion period from a previous clinical study.
21. Subject who is unable to communicate or cooperate with the investigator due to history of alcohol/drug abuse, language problems, poor mental development, or impaired cognitive or verbal function.

**Investigational Products:**

| | | |
|---|---|---|
| **Drug substance:** | trifarotene (CD5789) cream | trifarotene vehicle |
| **Trade name:** | AKLIEF® | - |
| **Dose form:** | cream | cream |
| **Strength/Concentration:** | 50 µg/g | - |
| **Administration:** | topical | topical |

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**Duration:**

**Container / Size:**

Apply a thin layer to the face once daily, in the evening. The face should be washed and patted dry, before use.

One pump actuation should be enough to cover the face (i.e., forehead, cheeks, nose, and chin).

| 24 Weeks | 24 Weeks |
|---|---|
| EU: 75g pump<br>Can: 75g pump<br>US: 45g pump | EU: 75g pump<br>Can: 75g pump<br>US: 45g pump |

**Non-Investigational Study Products Provided By Sponsor:**

For use by all subjects.

| **Cetaphil® Gentle Skin Cleanser *** | **Cetaphil® PRO Oil Absorbing Moisturizer with SPF 30 *** | **Cetaphil® Moisturizing Lotion *** |
|---|---|---|
| Use twice daily in the morning and evening to wash the face and pat dry before applying topical study drug. | Use daily on the face (morning) and re-apply to face when sun exposure is expected. | For supplemental moisturizer use on the face, as needed. |
| | Moisturizer should be used as often as needed except less than 1 hour before and 1 hour after topical study drug application (in the evening). | |

* Use of an equivalent available skincare product per country is permitted, as well as the subject's preferred or investigator's recommended non-comedogenic cleanser, moisturizer and sunscreen (SPF ≥30 or equivalent).

**Study Assessments**

The following study assessments will be performed according to the frequency specified in the schedule of assessments (see Section 5.1.2):

**Efficacy:**

CCI [redacted]

**Safety:**

- Adverse events (AEs), including AEs of special interest (AESIs), treatment-emergent AEs (TEAEs) and serious AEs (SAEs)
- Local tolerability parameters (erythema, scaling, dryness and stinging/burning) on face using a 4-point numerical scale (0-3)

CCI [redacted]

| | |
|---|---|
| **Title:** Evaluation of the risk of atrophic acne scar formation during treatment of acne vulgaris subjects with trifarotene 50 µg/g cream versus vehicle cream over 24 weeks | |
| | CCI [redacted] |
| **Study Variables Analyzed**<br><br>**Efficacy:** | **Primary:**<br>• Absolute change from Baseline in total atrophic acne scar count CCI [redacted] at Week 24<br><br>**Secondary**<br>• Absolute change in total atrophic acne scar count CCI [redacted] from Baseline to Week 20<br>• Total atrophic acne scar count CCI [redacted] from Baseline to Week 24<br>• CCI [redacted] |
| **Quality of Life/Subject-Reported Outcomes:** | C [redacted] |
| **Safety:** | • Local tolerability parameters (erythema, scaling, dryness and stinging/burning) will be evaluated per half-face at each visit on a 4-point scale ranging from 0 (none) to 3 (severe).<br><br>• Incidence of all TEAEs including any dermatologic AEs per half-face, AESIs, SAEs and TEAEs leading to discontinuation |
| **Principal statistical method:** | CCI [redacted] |

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CCI [redacted]

**Efficacy Analysis**

Primary efficacy endpoint

- Absolute change from Baseline in total atrophic acne scar count at Week 24 will be summarized by treatments using descriptive statistics. The bilateral difference between products in absolute change from Baseline in total atrophic acne scar count at Week 24 will be summarized using descriptive statistics and will be analyzed on the ITT population using the Student's t-test for paired samples. The point estimate of the mean difference and the related 95% confidence interval will be presented. Assumption of normality will be checked. If normality assumption is not met, the appropriate non-parametric statistical methods will be used. PP analysis will be also performed to assess the robustness of the results obtained on the ITT population.

Secondary efficacy endpoints

- Absolute change from Baseline in total atrophic acne scar count at each intermediate post-baseline visit will be summarized by treatments using descriptive statistics. The bilateral difference between products in Absolute change from Baseline in total atrophic acne scar count at each intermediate visit will be summarized using descriptive statistics and will be analyzed on the ITT population using the Student's t-test for paired samples. The point

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estimate of the mean difference and the related 95% confidence interval will be presented. Assumption of normality will be checked. If normality assumption is not met, the appropriate non-parametric statistical methods will be used.

- Total atrophic acne scar count per half-face at each visit will be summarized by treatments on the ITT population using descriptive statistics.

[redacted]

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|---|---|
| | CCI [redacted]<br><br>**Safety**<br>• Local tolerability scores (erythema, scaling, dryness and stinging/burning) for the face will be summarized for worst post-baseline score, the final score during treatment, as well as scores for each visit.<br>• Adverse Events will be summarized using frequency tables by System Organ Class (SOC) and Preferred Term (PT) based on the Medical Dictionary for Regulatory Activities (MedDRA).<br><br>**Patient Reported Outcomes (PROs)**<br>• CCI [redacted]<br>• CCI [redacted] |

## 2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| *Abbreviation* | *Term* |
|---|---|
| °C | Degrees Celsius |
| °F | Degrees Fahrenheit |
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| BPO | Benzoyl Peroxide |
| CDMS | Clinical Data Management System |
| CRA | Clinical Research Associate |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| CSR | Clinical Study Report |
| DMP | Data Management Plan |
| EDC | Electronic Data Capture |
| e.g. | For Example (Latin: exempli gratia) |
| ET | Early Termination |
| etc. | *Et cetera* |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HIPAA | Health Insurance Portability and Accountability Act of 1996 |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| i.e. | That is (Latin: id est) |
| IEC | Independent Ethics Committee |
| CCI | CCI [redacted] |
| IL | Inflammatory Lesions |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| ITT | Intention-to-treat |
| IUD | Intrauterine Device |
| J2R | Jump-to-Reference |
| LOAEL | Lowest-observed-adverse-effect level |
| LOCF | Last Observation Carried Forward |
| LSI | Last Subject In (Last subject enrolled/randomized) |

| *Abbreviation* | *Term* |
|---|---|
| CCI [redacted] | [redacted] |
| MD | Medical Doctor |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mL | milliliter |
| MNAR | Missing Not At Random |
| NIL | Non-Inflammatory Lesions |
| NOAEL | No Observed Adverse Effect Level |
| OTC | Over-the-Counter |
| PK | Pharmacokinetics |
| PP | Per-Protocol |
| PT | Preferred term |
| CCI [redacted] | [redacted] |
| RAR | Retinoic Acid Receptor |
| RXR | Retinoid X Receptor |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAF | Safety |
| SCARS | Self-assessment of Clinical Acne-Related Scars |
| SGA | Scar Global Assessment |
| SIN | Subject Identification Number |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| SPF | Sun Protection Factor |
| TEAE | Treatment-Emergent Adverse Event |
| TL | Total lesions |
| UPT | Urine Pregnancy Test |
| USA | United States of America |
| UV | Ultraviolet |
| WOCBP | Women of child-bearing potential |

# 3 BACKGROUND AND RATIONALE

## 3.1 Medical Background and Rationale

Acne vulgaris (AV) is a common, chronic, inflammatory disorder estimated to affect 9.4% of the global population that usually starts in early adolescence (ultimately affecting approximately 85% of adolescents); however, AV can occur at any age and persist well into adulthood (Heidel B, 2016; Tan J, 2015). Acne is a multifactorial inflammatory disease affecting pilosebaceous follicles (Dreno 2005, Gollnick 2003, Tsatsou, 2014). In European populations over 70–80 % of all males will experience acne in some point of their lifetime. In the USA, acne has been reported to affect an estimated number of over 25 (17–45) million Americans (Tsatsou, 2014). As acne is a chronic and relapsing disease, normalizing follicular desquamation is then the key to achieve and maintain control of acne. This is a polymorphic disease in which several types of lesions are usually present at the same time: primary lesions, found in active acne defined by the non-inflammatory and the inflammatory lesions; secondary lesions which came from the first ones and which are defined by scarring and postinflammatory hyperpigmentation (PIH). It can persist for years and result in disfigurement and permanent scarring (Koo et al., 1991). The consequences of AV and its sequelae may include physical (e.g., skin discomfort/pain, erythema, hyperpigmentation, scarring), psychological (e.g., anxiety, poor self-esteem, depression, suicidal ideation), and social repercussions (e.g., avoidance of interpersonal interactions). Teenagers with even mild acne feel stigmatized and frustrated (Osterweil N, 1993). The incidence of AV typically increases throughout adolescence, and the severity of both physical and psychosocial sequelae tend to increase as AV severity worsens (Silverberg JI, 2014; Tan J 2017).

Secondary acne lesions, including atrophic scars, are an unfortunate clinical outcome of acne (Layton, et al., 1994). Acne scars are not uniform and there are several subtypes. Some are more hypertrophic and keloidal in appearance, while others could be more atrophic (Goodman, et al., 2000; Goodman, et al., 2006(a); Goodman, et al., 2006(b)). The severity of the acne scars is correlated with the acne grade and with the delay between the start of the disease and the start of an adapted treatment. In her clinical evaluation of acne scarring, Layton indicated that facial scarring occurs to some degree in most acne sufferers (95% of the population) even in the mild to moderate population. Although not universal, acne scars generally occur more with inflammatory acne lesions that were not properly treated (Layton, et al., 1994).

Loss of dermal matrix is a contributing factor in atrophic acne scars (Kang, et al., 2005). This loss of dermal matrix consists in degradation of collagen produced by intracellular pathway activated by inflammation during the acne lesion formation (Kang, et al., 2005) (Trivedi, 2006). This leads to the transcription factor activation coding for matrix-degrading metalloproteinases (MMPs). MMPs degrade extracellular matrix molecules during physiological and pathological tissue remodeling. Three MMPs (MMP-1 [collagenase], MMP-3 [stromelysin] that can initiate collagen degradation and MMP-9 [gelatinase] that can further degrade collagen fragments) have been shown to be increased in inflammatory acne lesion *in vivo* (Kang, et al., 2005) (Trivedi, 2006) (Fisher, et al., 2000) (Papakonstantinou, et al., 2005). The same enzymes are involved in the remodeling of the dermal matrix in the photoaging process (Kang, et al., 1997) (Kang, et al., 1998) (Fisher, et al., 2000).

Over the past decades, significant evidence has demonstrated that topical retinoids can stimulate dermal fibroblasts to produce more procollagen in photoaged skin (Kang, et al., 1997) (Kang, et al., 1998) (Fisher, et al., 2000). Type I and type III procollagen are reduced in photodamaged skin but it has been demonstrated that isotretinoin, either oral or topical, protects against UV-induced loss of procollagen, leading to MMP-1, 3 and MMP-9 decrease in relation to the duration of the treatment (Kang, et al., 1997) (Kang, et al., 1998) (Fisher, et al., 2000). This increase in collagen production is clinically appreciated as effacement of wrinkles. After 24 weeks of treatment with topical retinoid, an increase of the epidermal thickness has been observed (Kang, et al., 2001) (Philips, et al., 2002).

As photodamage lesions and atrophic acne scars are partially linked to a dermal matrix loss, a potential effect of trifarotene to prevent secondary acne lesions (scars) of occurring and/or to improve the pre-existing ones might exist.

Today it is established including in the guidelines that retinoids acts in the pathology of acne vulgaris: a potent modulator of cellular differentiation and keratinisation. Topical retinoids have been the first-line treatment for most forms of acne vulgaris (Bayramgurler D et al, 2017). Trifarotene, a new generation topical retinoid with its unique mechanism of action, binds to specific retinoic acid nuclear receptor (RAR-ɤ) (Thoreau E, 2018). Current evidence suggests that topical trifarotene normalizes the differentiation of follicular epithelial cells resulting in decreased microcomedo formation. It may be an ideal topical agent with high selectivity towards gamma receptors, skin metabolism and with very low systemic absorption for management of acne treatment (Del Rosso 2011, Gollnick H, 2003, Eichenfield LF, 2013, Strauss JS, 2007).

Proper skin care is considered an important component of the total management for patients with AV. There are several ways to mitigate adverse effect and prevent further worsening of skin tolerability. These include initiating patients on lower concentrations of topical retinoids, choosing cream or lotion (than gel) and trifarotene being a highly selective RAR-ɤ with low concentration and in cream formulation with adequate recommendations for its use would be appropriate in acne subjects. Skin irritation can lead to poor compliance and subsequently lack of efficacy. Hence, the addition of a topical gentle moisturizer for these subjects (Del Rosso, 2013; Davis and Callender, 2010) and recommendation for avoiding sun exposure is a part of the skin care regimen for these acne subjects. Minimizing skin irritation and photoprotection can be achieved by the use of non-comedogenic moisturizers with appropriate SPF that hydrate and protect the skin from UV irradiation (Schorr E.S., 2012; Whitney P., 2014; Del Rosso, 2013). Also, using an appropriate cleanser should reduce oil on the face and therefore should not affect skin hydration or the skin barrier function.

Currently, trifarotene 50 µg/g cream is commercially approved in countries including France, Canada and the United States for the treatment of acne vulgaris. Registration studies included two 12-week pivotal trials to confirm safety and efficacy (Tan J, et al, 2019). A long-term safety study was also conducted involving once daily treatment for 1 year that showed trifarotene 50 µg/g cream was well-tolerated, without undue safety risks (Blume-Peytavi U, et al, 2019).

A small, single-arm, open-label, Phase 3b study (Galderma protocol RD.06.SPR.118295) showed that over a 24 week treatment period, trifarotene reduced inflammatory and non-

inflammatory acne lesions. This study also included atrophic scar counts as an exploratory endpoint and showed a mean absolute change from baseline in total atrophic scars of 3.4 scars, for the full-face at Week 24, in the subset of subjects with atrophic scars at baseline. Although these data are limited, they provide supportive evidence that trifarotene may have benefit in the treatment of acne lesions to decrease the risk of atrophic scar formation.

This controlled clinical study using trifarotene cream for the treatment of facial acne will assess its effect on the risk of formation of atrophic scars, during treatment of acne vulgaris.

### 3.2 Risk/Benefit Assessment

This study is evaluating trifarotene (CD5789) cream which is a commercially available drug in France, Canada and the United States for the treatment of acne vulgaris. Evaluation of a commercially-approved product, when used for the approved indication of acne vulgaris and according to approved labeling instructions for use, poses a low risk to subjects to participate for 24 weeks. Supporting registration studies included a multicenter, long-term safety study with once daily treatment for 1-year and showed trifarotene cream to be well-tolerated, without undue safety risks (Blume-Peytavi U, et al, 2019).

The CCI study design limits the direct benefit to subjects as CCI will be treated with trifarotene vehicle, as a basis for intra-subject comparisons. All subjects will be informed of the CCI study design and must provide written consent to participate. Subjects will be reminded throughout the study that they are free, at any time, to withdraw from the study, regardless of reason. Furthermore, the protocol includes a provision that allows the investigator to withdraw a subject for any dramatic, clinically significant differences in appearance between CCI face treatment may be indicated, based on the investigator's clinical judgement.

A small, single-arm, open-label, Phase 3b study showed that over a 24-week treatment period, trifarotene reduced the inflammatory and non-inflammatory acne lesions CCI

The most serious risk associated with retinoids is related to teratogenicity and embryotoxicity. Systemic exposure to trifarotene, like with all retinoids, may cause fetal harm following systemic exposure in pregnant women. The safety margin calculation for trifarotene (CD5789) cream was performed using $AUC_{0\text{-}24hr}$ corresponding to the LOAEL obtained during toxicological studies in dogs, NOAEL obtained during teratogenicity studies in the most sensitive species (i.e. rabbit) and data obtained from human PK studies (acne patients and healthy volunteers).

Trifarotene (CD5789) cream has low systemic exposure resulting in a high safety margin of 98 for teratogenicity and the ratio to systemic effect is <1170 for general toxicity. Women of

childbearing potential will be required to be strictly abstinent or to use an effective contraceptive method during the study and for at least one month after the last study drug application.

Topical retinoids may be associated with skin irritation, particularly in the two first weeks of therapy (Leyden JJ, 1998). [redacted]

Overall, the risk/benefit assessment is reasonable to evaluate safety and efficacy of trifarotene (CD5789) cream when used for the treatment of acne vulgaris over 24-weeks, to assess effect on the risk of atrophic scar formation.

### 3.3 Drug profile

Topical retinoids play a central part in the treatment of acne due to their keratolytic activity modulation of proliferation and differentiation of keratinocytes leading to the elimination of the lesion (Pawin H, 2004), and anti-inflammatory activity.

Retinoids exert their effects on a molecular level through nuclear receptors: Retinoic Acid Receptor (RAR) and Retinoid X Receptor (RXR), which each have three sub-types α, β and γ.

[redacted]

### 3.4 Dose selection rationale

Trifarotene cream 50µg/g when applied once daily has been shown to be safe and effective in the treatment of acne vulgaris. The commercially-approved trifarotene cream and dosing instructions for the treatment of acne vulgaris will be used as part of this study.

# 4 STUDY OBJECTIVE and ENDPOINTS

## 4.1 Study objective

The main objective of this clinical study is to evaluate the effect of trifarotene compared to its vehicle on the risk of formation of atrophic acne scars after 24 weeks of treatment in facial acne subjects assessed by atrophic acne scars count.

Safety will also be evaluated.

## 4.2 Study endpoints

Study endpoints that will support safety and efficacy results are summarized below.

### 4.2.1 Primary Endpoint

- Absolute change from Baseline in total atrophic acne scar count CCI at Week 24

### 4.2.2 Secondary Endpoints

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

CCI [redacted]

[redacted]

### 4.2.4 Safety

- Local tolerability parameters (erythema, scaling, dryness and stinging/burning) will be evaluated per half-face at each visit on a 4-point scale ranging from 0 (none) to 3 (severe).
- Incidence of all TEAEs including any dermatologic AEs per half-face, AESIs, SAEs and TEAEs leading to discontinuation

## 5 INVESTIGATIONAL PLAN

### 5.1 Overall Study Design

This is a multi-center, randomized, double-blind, vehicle-controlled study using CCI [redacted] comparison CCI [redacted] to evaluate the safety and efficacy of trifarotene (CD5789) cream for preventing the risk of atrophic scar formation (Section 5.1.1 - Study Schema). CCI [redacted]

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

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

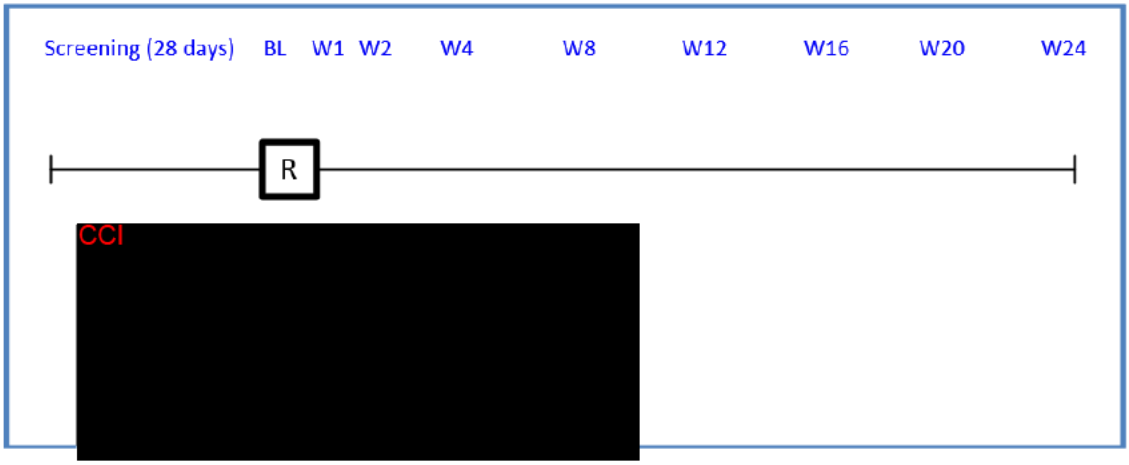
application frequency for the topical study drug, up to a maximum of 2 weeks, within the first four (4) weeks of the treatment period (Section 5.4.8 – Dose Modification).

Subjects will receive an electronic tablet at baseline for daily recording of study medication use (electronic dosing calendar), as well as for capturing daily videos of applying study medication to each side of the face. Study medication dosing data will be uploaded for remote assessment by the clinical site, and will serve as the primary means for recording dosing compliance (Section 5.4.6.4 – Treatment Compliance – Primary Source Data). All videos will remain on the local drive of the study electronic tablet, and reviewed by site staff at scheduled office visits for supportive evidence of treatment compliance (Section 5.4.6.5 – Treatment Compliance – Supportive Video Evidence).

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 atrophic scar counts, acne severity (IGA) or lesion counts.

Subjects will return to the clinic for safety and efficacy assessment at Weeks 1, 2, 4, 8, 12, 16, 20 and 24. Study procedures and assessments are performed according to the schedule of assessments (Section 5.1.2).

### 5.1.1 Study Schema




T: trifarotene (CD5789) cream
TV: trifarotene vehicle

R Randomization (split-face design)

BL: Baseline visit
W: Scheduled visit week

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

### 5.1.2 Schedule of Assessments

#### *5.1.2.1 Study Assessment 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 scar and acne assessments, local tolerability assessment and imaging (for designated imaging centers).

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

- Remote Visits (phone, etc) in lieu of scheduled office visits
    - for safety and wellness assessment (concomitant medications, AEs, etc)
- Subject questionnaire completion
    - sent to subject by email or mail
    - subject signs, dates and returns, by email of mail.
- Collection of previously dispensed study drugs, from an adult family member, along with the study electronic tablet
    - Weighing of returned topical study drug is required
    - A follow-up phone call with the subject is required to review the dosing compliance and returned study drug, for appropriate clarification in study medication use.
- Dispensing of new study drug, non-investigational supplies (non-IP supplies, electronic tablet after video reviews, 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 supply use, and to use the newly dispensed study drug 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 judgment 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 of the subject to perform:

- CCI [redacted]

### *5.1.2.2 Study Assessment Schedule*

| Procedures | Screening[g] | Baseline | Week 1 | Week 2 | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 | Week 24/ ET[i] |
|---|---|---|---|---|---|---|---|---|---|---|
| | ≤28 days | -- | ±2 days | ±2 days | ±3 days | ±3 days) | ±7 days | ±7 days | ±7 days | ±7 days |
| Informed Consent / Assent [including daily videos (all subjects); static images (designated imaging centers only)] | X | X[h] | | | | | | | | |
| Demographics / Medical History | X | X | | | | | | | | |
| Previous Therapies and Medications[a] | X | X | | | | | | | | |
| Concomitant Medications / Therapies / Procedures | X | X | X | X | X | X | X | X | X | X |
| Inclusion / Exclusion Criteria | X | X | | | | | | | | |
| Urine Pregnancy Test[k] | X | X | X | X | X | X | X | X | X | X |
| CCI | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| | | | | | | | | | | |
| Adverse Events[e] | X | X | X | X | X | X | X | X | X | X |
| Subject Satisfaction CCI | | | | | | | | | | |
| | | | | | | | | | | |
| CCI | | | | | | | | | | |
| Randomization (assign kit in increasing sequential order) | | X | | | | | | | | |
| Study Drug[l] | | | | | CCI | | | | | |
| Non-Investigational Products | | D | | | D | D | D | D | D | |

| Procedures | Screening[g] | Baseline | Week 1 | Week 2 | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 | Week 24/ ET[i] |
|---|---|---|---|---|---|---|---|---|---|---|
| | ≤28 days | -- | ±2 days | ±2 days | ±3 days | ±3 days) | ±7 days | ±7 days | ±7 days | ±7 days |
| CCI [redacted] | | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| CCI [redacted] | | | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Exit Form | | | | | | | | | | X |

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

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

## 5.2 Discussion of Study Design

This is a Phase 4 clinical study to assess the effect of commercially marketed trifarotene cream (AKLIEF), when used according to its labeling information (indication, selected population, dose regimen) for the treatment of acne lesions to evaluate the risk of atrophic scar formation.

A CCI [redacted] is utilized to minimize CCI [redacted] variability to reduce the relative number of subjects to be enrolled to achieve the desired study power. A vehicle control provides a reliable comparative treatment to judge effects of trifarotene (CD5789) cream. All subjects will

receive skincare products for daily use, with frequent clinic visits for ongoing subject evaluation and to ensure safety. Topical treatment with a vehicle-control along with a skincare regimen has shown some degree of clinical benefit in acne studies.

Subject safety will be appropriately monitored throughout the 24-week treatment period with 8 scheduled post-baseline visits which occur every 4 weeks, along with two early visits for added safety checks and subject counseling (Week 1 and Week 2). A multicenter, long-term safety study with once daily treatment for 1-year showed trifarotene 50 µg/g cream to be well-tolerated, without undue safety risks (Blume-Peytavi U, et al, 2019).

CCI [redacted]

The CCI [redacted] design limits the direct benefit to subjects as half of the face will be treated with trifarotene vehicle. All subjects will be informed of the split-face study design and must provide written consent to participate. Subjects will be reminded throughout the study that they are free, at any time, to withdraw from the study, regardless of reason. Furthermore, the protocol includes a provision that allows the investigator to withdraw a subject for any dramatic, clinically significant differences in appearance between the right and left sides of the face where full face treatment may be indicated, based on the investigator's clinical judgement.

An escalating study stipend is planned as part of the consent document, which includes subject compensation for time and nominal expenses associated with study visits, but is also intended to provide an incentive for subject participation in a split-face design, where direct subject benefit is limited, and offer a means to appropriately encourage participation over the full 24-week treatment period. The proposed compensation levels will be reviewed by an ethics committee to ensure they are reasonable and appropriate.

A 24-week treatment period is utilized knowing acne is a chronic skin condition, which should be sufficient to assess clinical effect on the basis of the following points:

- Scarring appears secondarily to acne lesions and may correspond to a resolution of these lesions
- It is generally agreed in acne clinical studies that a 12-week treatment period is sufficient to evaluate the efficacy on the acne lesions. An additional 12 weeks is included to further evalute the clinical outcomes associated with treatment of acne lesions
- 24 weeks is considered adequate to allow for potential underlying tissue remodeling by dermal fibroblasts and collagen production associated with trifarotene 50 µg/g cream treatment, and any effects thereof that may translate to clinical improvement of scars

Overall, the study design is considered to be scientifically robust and clinically relevant for evaluating trifarotene (CD5789) cream for the treatment of acne lesions to assess the risk of atrophic scar formation.

## 5.3 Selection of Study Population

### 5.3.1 Number of Planned Subjects

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

Site enrollment strategies should include outreach plans with a goal for approximate even distribution of male to female subjects, to the extent possible. Refer to Section 7.2 for the statistical considerations on which the sample size is based.

### 5.3.2 Inclusion Criteria

Subjects must fulfill inclusion criteria to participate in the study:

1. Male or female subject aged 17 to 35 years inclusive, at Screening visit.
2. Subject with clinical diagnosis of acne vulgaris on the face as defined by (excluding the nose and middle zone of approximatey 2 cm):

CCI

[redacted]

CCI [redacted]

3. Subject with a symmetrical number of the following lesions/scars on the whole face (i.e., there are no more than twice as many lesions/scars of each type on one half of the face than on the other half):
   a. Inflammatory and non-inflammatory lesions; and
   b. Atrophic acne scars (minimum of 4 scars per half-face)
4. The subject is a female of non-childbearing potential (premenarchal or postmenopausal [absence of menstrual bleeding for 1 year prior to Screening, without any other medical reason], hysterectomy or bilateral oophorectomy).
5. The subject is a female of childbearing potential:

   5.1 Who is willing to undergo UPTs throughout the course of the study, as required.

   5.2 Who has been strictly abstinent for 1 month prior to Screening and agrees to continue for the duration of the clinical study and at least 1 month after the last study drug application, OR

   Who agrees to use highly effective and approved contraceptive method(s) for the duration of the study and at least 1 month after the last study drug application.

   Highly effective methods of contraception include:

   a. bilateral tubal ligation;
   b. approved combined oral contraceptives (estrogens and progesterone), implanted or injectable contraceptives, or hormonal contraceptive vaginal rings with a stable dose for at least 1 month prior to the Screening visit;
   c. intrauterine device or intrauterine hormonal-releasing system inserted at least 1 month prior to the Screening visit;
   d. vasectomized partner for at least 3 months prior to the Screening visit

   Note: This criterion applies to a prepubertal female subject who begins menses during the study.
6. If a female of childbearing potential uses oral contraceptives that are also approved for treating acne vulgaris (such as cyproterone acetate and ethinyl estradiol; drospirenone and ethinyl estradiol; norgestimate and ethinyl estradiol; norenthindrone acetate and ethinyl estradiol; etc) the dose should be stable for at least 6 months prior to the Screening visit.
7. Subject having read, understood and signed the approved Informed Consent Form (ICF) prior to any participation in the clinical study. Subject under the age of 18 having signed an assent form to participate in the clinical study and their parent(s) or legal representative having read and signed the informed consent form prior to any clinical study related procedure.
8. Subject (and legal guardian, if applicable) agrees and is able to comply with all time commitments and procedural requirements of the protocol, including daily recording of dosing compliance by the subject using an electronic tablet provided for this study, as well as

taking daily videos of study medication use. Consent to taking daily videos is mandatory for study participation at all sites.

9. Subject agrees to having photographs taken (mandatory for study participation, at designated imaging centers), and verified by the subject signing and dating an approved ICF (includes willingness to remove all makeup prior to study visits, remove jewelry in the areas to be photographed, keep facial hair well-groomed prior to study visits).
10. Subject is informed of terms pertaining to personal information protection and privacy and is willing to share personal information and data, as verified by signing a written authorization at the Screening visit.

### 5.3.3 Exclusion Criteria

Subjects meeting any of the exclusion criteria are not eligible to participate in the study:

1. Subject with acne conglobata, acne fulminans, secondary acne [chloracne, drug-induced acne, polycystic ovary syndrome (PCOS), pyogenic arthritis-pyoderma gangrenosum-acne (PAPA), synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO), seborrhoea-acne-hirsutism-androgenetic alopecia (SAHA), Hidradenitis suppurativa (HS), congenital adrenal hyperplasia (CAH) etc.], nodulocystic acne, acne requiring systemic treatment.
2. Subject with any acne cyst on the face or with more than 3 excoriated acne lesions.
3. Subject with known active or chronic allergies or suspected allergy to trifarotene or excipients of the formulation.
4. Prior failure of trifarotene treatment including intolerance that resulted in stopping treatment; lack of clinical improvement, etc.
5. Subject with facial dermal conditions (e.g. tattoo, skin abrasion, eczema, sunburned skin, scars, nevi, etc.) that may interfere with study assessments in the opinion of the investigator.
6. Subject with excessive facial hair that would interfere with study assessments, as judged by the investigator, or unwilling to keep facial hair well-groomed prior to study visits, as judged appropriate by the investigator to perform study assessments.
7. Pregnant women (positive urine pregnancy test at the Screening or Baseline visits), breastfeeding women, or women planning a pregnancy during the study or within 1 month after the last study drug application
8. Subject with known impaired hepatic or renal functions, based on medical history.
9. Subjects taking Vitamin A supplements in excess of the recommended daily allowance (4000 – 5000 IU; no washout period is required)
10. Subjects with a washout period for **topical treatment** or procedures on the face less than:

| | |
|---|---|
| Topical treatments: Corticosteroids, antibiotics, benzoyl peroxide, azelaic acid, alpha hydroxy acids, salicylic acid, zinc containing treatments, hydroquinones, and other anti-acne treatments | 2 weeks |
| Topical retinoids | 2 weeks |
| Clascoterone cream 1% (Winlevi) | 2 weeks |
| Cosmetic/aesthetic procedures (e.g., comedo extraction, desquamating, or abrasive agents, adhesive"pore" cleansing strips) | 1 week |
| Wax epilation | 2 weeks |
| Photodynamic therapy | 4 weeks |
| Laser therapy, microdermabrasion, deep chemical peel, and other plastic surgical treatments for acne | 12 weeks |

11. Subject with a washout period for **systemic treatment** less than:

| | |
|---|---|
| Corticosteroids, (except locally acting corticosteroids such as inhaled or intrathecal), antibiotics and spironolactone | 4 weeks |
| Oral retinoids/isotretinoin | 12 weeks |
| Cyproterone acetate / Chlormadinone acetate | 12 weeks |
| Immunomodulators | 12 weeks |

12. Currently receiving any prescription testosterone therapy (e.g., testosterone cypionate, testosterone enanthate, testosterone pellet, testosterone undecanoate) or on a testosterone booster or prescription testosterone (e.g., DHEA, Omnadren®, Sustanon®, testosterone cypionate, testosterone enanthate, testosterone propionate, testosterone phenylpropionate) or testosterone supplements (e.g., Tribulus).
13. The subject is unwilling to or unable to refrain from use of prohibited medication or procedures during the clinical study (see Section 5.4.12.5)
14. Subject who foresees intensive ultraviolet exposure during the study (mountain sports, sailing, sunbathing, tanning beds, etc.).
15. Subject who is at risk in terms of precautions, warnings, and contraindications for trifarotene based on approved labeling.
16. Subject with an acute / chronic disease or a history of major medical or surgical or psychiatric condition or surgical interventions that may either interfere with the interpretation of the study results and/or might put the subject at risk in the opinion of the investigator.

17. Subject under guardianship (for reason other than minor status), hospitalized subject in a public or private institution for a reason other than the research, and subject deprived of his/her freedom.
18. More than one subject sharing the same household.
19. Study site personnel, close relatives of the study site personnel (e.g., parents, children,siblings, or spouse), employees, or close relatives of employees at the Sponsor company.
20. Subject who has participated in another investigational drug or device research study within 30 days prior to Screening OR is in an exclusion period from a previous clinical study.
21. Subject who is unable to communicate or cooperate with the investigator due to history of alcohol/drug abuse, language problems, poor mental development, or impaired cognitive or verbal function.

### 5.3.4 Removal of Subjects from Therapy or Assessments

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

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

Possible reasons for discontinuing the study are summarized in Table 1:

**Table 1: Possible Reasons for Study Discontinuation**

| | |
|---|---|
| **Pregnancy:** | Withdraw the Subject from the clinical study and follow the procedure described in Section 6.11.2.2.5 |
| **Lack of Efficacy:** | Investigator judgment only: based on therapeutic/disease-state expectations. If subject opinion only, mark "subject request" and document it in the comment section of the Exit Form. |
| **Adverse Event:** | Complete an Adverse Event Form. |
| **Death:** | Death of the subject. |
| **Withdrawal by Subject [a]:** | Includes consent withdrawal, subject relocation, schedule conflicts. Explain the reason for withdrawal in the comment section of the Exit Form. |
| **Withdrawal by Parent / Guardian [a]** | An indication that a study participant has been removed from the study by the parent or legal guardian. Explain the reason for withdrawal in the comment section of the Exit Form. |

| | |
|---|---|
| **Protocol Violation:** | Explain the violation in the comment section of the Exit Form. |
| **Lost to Follow-up:** | Confirmed with two documented phone calls and a certified letter (delivery receipt requested) without answer. Explain in the comment section of the Exit Form. |
| **Non-Compliance with Study Drug:** | An indication that a subject has not agreed with or followed the instructions related to the study medication. |
| **Physician Decision [a, b]:** | A position, opinion or judgment reached after consideration by a physician with reference to subject. Explain the reason in the comment section of the Exit Form. |
| **Site Terminated by Sponsor:** | An indication that the clinical study was stopped at a particular site by its sponsor. |
| **Study Terminated by Sponsor:** | An indication that the clinical study was stopped by its sponsor. |
| **Sponsor Request:** | An indication that the study subject was removed from the study at the sponsor's request. |
| **Other [a]:** | This category is to be used for a subject who discontinues due to a reason other than as specified in the predefined categories above. Explain the reason for discontinuation in the comment section of the Exit Form. |

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

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

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

When a subject discontinues the study, he/she will be fully assessed whenever possible, and followed according to guidelines presented in Section 5.5.1 - Early Termination Visit.

Reasonable efforts will be made to contact subjects who are lost to follow-up (e.g., non-response/contact after 2 phone calls and a certified letter with return receipt). These efforts must be documented in the subject's file.

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

#### *5.3.4.1 Pregnancy*

Subjects will be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the investigator. **If a subject becomes pregnant, the investigator must withdraw the subject from the study without delay. The subject must not continue further use of the study drug.**

The investigator must:

- Follow the procedures for reporting/follow-up of a pregnancy within 24 hours (see Section 6.11.2.2.2) of receipt of the information.
- Complete as fully as possible the applicable Pregnancy Surveillance Form(s) (see Section 6.11.2.2.5).
- Monitor and record the progress of the pregnancy until its outcome. Contact the subject's regular physician (general practitioner or gynecologist) or hospital staff to obtain further details and ask for regular follow-up information.
- Provide trimonthly updates until the final outcome of the pregnancy. If the subject can no longer be reached (lost to follow-up), documentation of the non-response/contact with 2 phone calls and a letter (certified with return receipt) is required.
- If the pregnancy leads to an abortion (i.e., voluntary abortion, spontaneous abortion, or therapeutic abortion), in utero death, or congenital anomaly, follow the procedure for declaration of/reporting an SAE (Section 6.11.2.2.2).

In the event that a subject is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the Sponsor after delivery.

Full details will be recorded on the withdrawal page (exit form), or an SAE report will be completed if the subject has completed the study. Pregnancy is not to be considered as an AE; however, it must be monitored and reported as described in Section 6.11.2.2.5.

## 5.4 Investigational Products

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

### 5.4.1 Study Drug Description

Table 2 summarizes the investigational medication.

**Table 2: Description of the Study Drugs**

| | Topical trifarotene (CD5789) cream | Topical trifarotene vehicle cream |
|---|---|---|
| Trade Name | AKLIEF® | - |
| Name of Drug Substance | trifarotene | - |
| Pharmaceutical Form | cream | |
| Strength/ Concentration | 50 µg/g | - |
| Route | topical | |
| Packaging (type and size) | **France**: 75 g bottle with pump and overcap<br>**Canada**: 75 g bottle with pump and overcap<br>**US**: 45 g bottle with pump and overcap | |
| Storage conditions | **France, US:** Store at 20-25°C (68-77°F)<br>Excursions permitted to 15°C - 30°C (59°F to 86° F)<br><br>**Canada:** Store at room temperature (15°C to 30°C).<br>Keep from freezing. Keep out of reach and sight of children. | |
| Duration of administration | 24 Weeks | |
| Manufacturer<br>*(Name and address)* | **Canada, US**<br>GALDERMA PRODUCTION INC<br>19400 Route Transcanadienne, Baie-d'Urfé<br>H9X 3S4, Québec, Canada<br><br>**France**<br>Laboratoires GALDERMA<br>ZI Montdésir<br>74540 Alby-sur-Chéran<br>France | |

### 5.4.2 Instructions for Use – Study Drug and Non-Investigational Products

Guidelines for using the study drug and non-investigational products are summarized in Table 3.

**Table 3: Guidelines for Using Study Drug and Non-Investigational Products**

| | **Trifarotene (CD5789) cream OR Trifarotene vehicle cream** | |
|---|---|---|
| Study Drug Usage | General instructions (more detailed instructions will accompany study drug to apply which product on which side of the face)<br>• Apply a thin layer of the assigned study drug to the proper side of the face, once daily, in the evening. The face should be washed and patted dry, before use.<br>• One pump actuation should be enough to cover the side of the face (i.e., forehead, cheek, nose, and chin).<br><br>The first application of study drug will occur at the clinic under site staff supervision, during the Baseline visit. The subject should be reminded not to dose that evening.<br><br>The Investigator may instruct dose reduction of study drug (detailed subject instruction will be provided) and re-evaluate at each visit to modify accordingly following the baseline visit. **Dose reduction should occur for both sides of the face even if only one side is affected.** Refer to Section 5.4.8 – Dose Modification. | |
| Non-Investigational Product Use Guidelines * | | |
| Cetaphil® Gentle Skin Cleanser ** | Guideline is to use twice daily, on the face, morning and evening.<br><br>After washing the face in the evening, pat dry before applying the topical study drug. | |
| Cetaphil® PRO Oil Absorbing Moisturizer with SPF 30 ** | Use daily on the face (morning), and re-apply to face when sun exposure is expected. | Moisturizer should be used as often as needed except less than 1 hour before and 1 hour after study drug application (in the evening). |
| Cetaphil® Moisturizing Lotion ** | For supplemental moisturizer use on the face, as needed. | |
| Duration of administration | 24 Weeks | |

* These are guidelines for non-investigational product use and will not be recorded as protocol deviations. Subjects will be counselled on the importance of using non-investigational products per the study guidelines, throughout the study. Compliance and protocol deviation reporting will apply only to study drug.

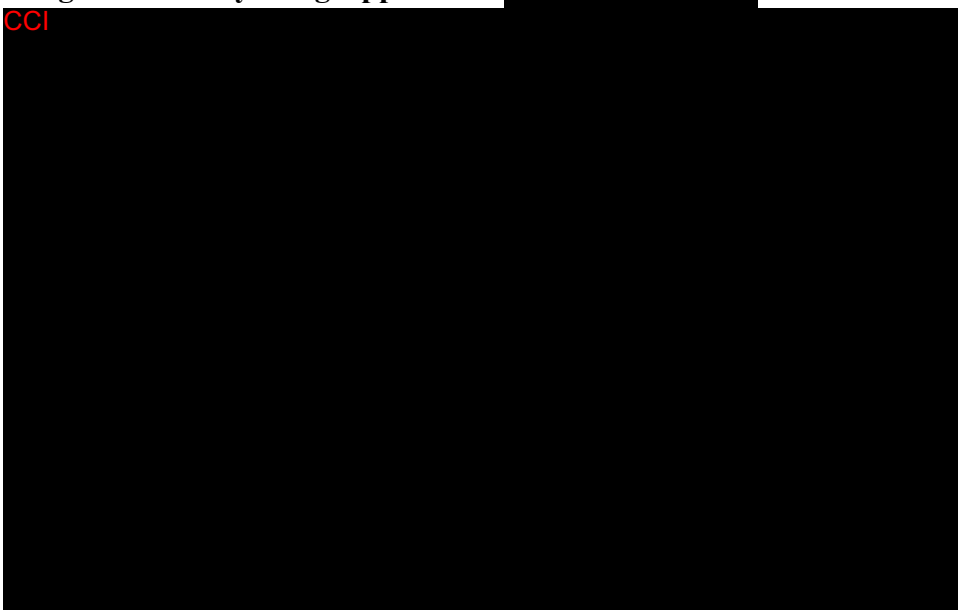
** Commercially available product provided by the Sponsor for use in this study. Use of an equivalent available skincare product per country is permitted as well as the subject's preferred or investigator's recommended non-comedogenic cleanser, moisturizer and sunscreen (SPF ≥30 or equivalent).

### 5.4.3 Study Drug Application with Video Collection

**NOTE: At the Baseline visit, the subject will apply study drug to each side of the face under site staff supervision, to ensure proper use. The subject will be instructed not to apply study drug on the first evening.**

The subject will apply the proper study drug on each half-face once a day (evenings): chin, cheek, nose and forehead (**avoiding application in/close to eyes, angles of the mouth, lips and mucous membranes**). Refer to Figure 1 for study drug application.

**Figure 1: Study Drug Application** CCI




The objective is to cover each CCI with a thin layer of the proper study drug, even on areas on the face with no clinically evident acne (no spot or localized treatment). One pump actuation should be enough to cover the forehead, cheek, nose, and chin. Avoid application in/close to eyes, or angles of the mouth, lips and mucous membrane.

The study drug should not be applied to cuts, abrasions, eczematous, or sunburned skin.

Each evening, subjects will collect a video of applying the study drug, as follows:

1. Have the study drug available and the electronic tablet ready for use
2. Wash hands
3. Wash the entire face with Cetaphil Gentle Skin Cleanser or approved cleanser
4. Pat dry the face
5. Begin recording with the study electronic tablet
6. Follow instructions for applying the proper study drug to the RIGHT side of the face
    a. Briefly video the study drug container and label, to document which product was applied
    b. Apply a thin layer of study drug to the entire RIGHT face (forehead, nose, cheek, chin). DO NOT SPOT APPLY
    c. One pump actuation should be adequate
    d. Avoid eyes, lips and mucous membranes
7. Wash hands
8. Follow instructions for applying the proper study drug to the LEFT side of the face.

a. Briefly video the study drug container and label, to document which product was applied.
b. Apply a thin layer of study drug to the entire LEFT face (forehead, nose, cheek, chin). DO NOT SPOT APPLY
c. One pump actuation should be adequate
d. Avoid eyes, lips and mucous membranes

9. Stop video recording (and follow further instructions associated with the electronic tablet)

The video capture of study drug use will be used as supportive evidence of treatment compliance (Section 5.4.6.5 - Treatment Compliance – Supportive Video Evidence).

### 5.4.4 Other Subject Instructions

The subject should maintain a consistent lifestyle throughout the study regarding exposure to external factors that may produce an exacerbation of their acne. These factors include, but are not limited to, excessive exposure to UV radiation (occupational exposure to the sun, sunbathing, tanning salon use, phototherapy, etc.). Subjects should avoid excessive sun exposure, wind and cold, as much as possible during the study. The subject will be instructed to apply the Cetaphil PRO Moisturizer with SPF30 (or permitted alternative sunscreen with SPF equivalent) on the face every morning, and re-apply to the face when sun exposure is expected. Subject should use protective apparel (e.g, hat) when sun exposure cannot be avoided. Avoid sunless tanning products for the duration of the study. Extra care should be taken to wear protective clothing and sunglasses and avoid sun exposure from 10 AM to 3 PM.

Cosmetics may generally be used during the study, but not on study visit days (or must be removed at least 30 minutes prior to study visit). Non-comedogenic cosmetics (cosmetics that do not cause acne) may be used as well as eye and lip makeup. Cosmetics can be applied after the study drug has dried. Foundation make-up is allowed on the days of study visits as long as subjects wash their face at least 30 minutes prior to the study visit. Use of moisturizing foundation will be acceptable during the study if subject has a history of safe usage of the foundation.

Study drug application should not occur on the first evening if first dose occurred at the clinic. Study drug should be applied approximately 1 hour before or 1 hour after application of any other permitted skin care products (e.g. non-comedogenic moisturizers, cosmetic products, etc). Subjects will video the application of study drug to both sides of the face each evening using the study assigned electronic tablet.

Products containing alcohol, alpha hydroxy or glycolic acids and astringents should not be used during the study.

Face shaving is allowed during the study. Male subjects with excessive facial hair that would interfere with acne assessments, as judged by the investigator, are not eligible to participate in the study. Male subjects with facial hair will be expected to keep areas well-groomed prior to study visits, as judged appropriate by the investigator, to perform the acne assessments.

Subjects should wash their face and remove all makeup at least 30 minutes prior to each scheduled clinic visit and should not apply any other topical products to the face or eye area until the study visit has been completed. If a subject arrives having not removed all makeup, subject will be required to remove the residual makeup at the clinic and wait at least 30 minutes prior to procedures.

Subjects who are wearing a face mask should continue to do so until seated in an exam room, in accordance with your local guidelines. Mask removal is required for the investigator to perform the study assessments.

Subjects enrolled at designated imaging centers will also be asked to remove all jewelry, eyewear and pull hair back from their face, prior to study imaging.

### 5.4.5 Packaging and Labelling

Study medication will be individually labeled and assembled into kits, for subject assignment. Product appearance, packaging and labeling will ensure subject and clinical site blinding. Study drug labeling (e.g., instructions and/or label color, etc) will make it clear which product is applied to each half of the face.

Each subject kit will include a total of 7 dispensers: 6 dispensers for each scheduled dispensing visit (Baseline and Weeks 4, 8, 12, 16, 20), with 1 extra dispenser, if needed (eg, lost pump, etc). Each dispenser will contain the following quantities of study drug:

- Two (2) pumps (1 trifarotene cream; 1 trifarotene cream vehicle)

Each kit will include a total of 14 pumps (7 trifarotene cream; 7 trifarotene cream vehicle). Individual pumps will be uniquely labeled (e.g., pump 1, 2, 3, etc), within each kit, to assess product usage over a specific visit interval and overall.

### 5.4.6 Study Drug Management

#### *5.4.6.1 Storage of Study Drug*

Study drug must be stored in a safe and secure area with restricted access, upon receipt and throughout the study. Refer to storage conditions as specified in Section 5.4.1 – Study Drug Description.

Storage should be temperature monitored daily, and if a temperature excursion occurs, the designated personnel should promptly inform the study monitor, as specified in the current version of the pharmacy manual.

#### *5.4.6.2 Study Drug Shipment and Accountability*

The drug depot will ship appropriate quantities of study drug kits to each site, based upon individual site needs and within whole block sizes, as specified per the randomization list.

Upon receipt, the site must conduct a complete inventory of all study drug kits. If a damaged shipment is received and/or a temperature excursion has been experienced, the site will notify the Sponsor/CRO and follow the guidelines according to the current version of the pharmacy manual.

All study drug sent to the Investigator/Institution will be accounted for and no unauthorized use is permitted. Subjects will be instructed to return all study drug and the study electronic tablet per the Schedule of Assessments (Section 5.1.2).

The investigator or designee will maintain accurate records of supplies received, inventoried at the clinical study site and used per subject. Used and unused study drug will be appropriately reconciled by the monitor and returned to the Sponsor or designee for destruction as instructed by the Sponsor (Section 5.4.6.3 – Dispensing and Return of Study Drug).

#### *5.4.6.3 Dispensing and Return of Study Drug*

Designated study personnel at each investigational site will be responsible for dispensing the study drug at the appropriate visits and will record the dispensing information for each subject (see Section 5.1.2 – Schedule of Assessments).

Each subject will receive a study drug dispenser at each designated dispensing visit. The visit designation will be captured on the study drug dispenser. Study drugs within each kit will be uniquely identified with the corresponding kit number and a pump identifier to assess usage for each CCI [redacted], per dosing interval. Upon dispensing, the affixed portion of the label will remain on the dispensing box. The tear-off portion of the label is to be removed from the dispenser and attached to the appropriate drug accounting record.

Each subject will be instructed on the importance of returning study drug (used and/or unused) as specified in the schedule of assessments (Section 5.1.2). Drug accountability and dosing compliance will be assessed by the designated clinical study center personnel. Subjects will be instructed to return the electronic tablet and all study medication at each study visit, for review by study personnel in the presence of the subject. At study visits Week 1 and Week 2, study drug dispensed at Baseline will be re-dispensed after compliance checks are completed (see Section 5.4.6.4 – Treatment Compliance – Primary Source Data).

In the event of early termination/suspension of the clinical study, a rapid recall of study drug will be initiated. The Investigator or designee must immediately instruct the subjects to stop the study drug and return all study drug to the clinical study center.

For subjects who do not complete the entire clinical study, all used and unused study drug should be returned by the subjects to the clinical study center.

At the conclusion of the study, the used and unused study drug will be returned to the Sponsor or designee in charge of the study drug management.

#### *5.4.6.4 Treatment Compliance – Primary Source Data*

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

CCI [redacted]

(Section 5.1.2 – Schedule of Assessments). The subject-reported data in the dosing calendar will be used as the primary source data for calculating treatment compliance, per each CCI [redacted]. Results are uploaded to a secure portal for remote monitoring, with subject counseling, as needed, throughout the study.

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

Any missed dose will be considered a protocol deviation, based on recordings in the dosing calendar. Subjects should be appropriately counseled on the importance of following study drug dosing instructions and daily recordings in the dosing calendar.

Subjects should be reminded and encouraged to follow guidelines for non-study product use, throughout the study (Section 5.4.2 – Instructions for Use).

#### *5.4.6.5 Treatment Compliance – Supportive Video Evidence*

The assigned electronic tablet will also be used by subjects to capture videos of study drug application, for each CCI [redacted], on a daily basis (Section 5.4.3 – Study Drug Application with Video Collection). The study drug label will be apparent in the video to confirm which product was applied to each side of the face (e.g., red label = right side of face, etc). All videos are collected and stored locally and securely on the electronic tablet. There are no video uploads or transfer from the local device. Only designated site staff will have access to view these videos on the electronic tablet.

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

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

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

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

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

### 5.4.7 Method of Subject ID and Treatment Assignment

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

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

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

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

Refer to Section 5.1.1 for an illustration of the study design and split-face treatment allocation.

### 5.4.8 Dose Modification

If a subject experiences persistent skin dryness or irritation, the Investigator may consider a reduced application frequency for the study drug in the first 4 weeks of the study, for a maximum duration of 2 weeks. In such cases, the treatment on each CCI should be reduced in a similar fashion, even if the irritation is only on one CCI

Subjects should be instructed to capture all missed applications in the dosing calendar. Sites will record the timing and details of a prescribed dose reduction for topical medication in source records.

Signs and symptoms of local cutaneous irritation will be considered as Adverse Events if they are severe enough to lead to permanent discontinuation of study drug or if they require the use of concomitant treatment including OTC products (other than moisturizers). Refer to Section 6.11.1 for further details on local tolerability assessment.

### 5.4.9 Allocation Concealment and Blinding

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

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

- Members of the study team or site staff will not have access to the randomized treatment assignment.
- Study drug will have similar appearance, packaging and use instructions as the corresponding vehicle.

### 5.4.10 Unblinding During the Clinical Study

At the initiation of the study, site staff will be instructed on the method to follow for emergency breaking of the blind. The randomization information for any particular subject may be made available to the investigator in the event of a medical emergency or an AE that necessitates identification of the study drugs for the welfare of that participant. Whenever possible, the investigator should consult with the medical monitor and the Sponsor before breaking the blind, to discuss the decision. Emergency un-blinding during the clinical study may be required for regulatory reasons (for expedited safety reporting).

When the blinding code is broken, the reason must be fully documented. If the code is broken by the investigator, the subject must be withdrawn from the study after completing early termination procedures.

Advanced Clinical Pharmacovigilance should be contacted to report any unblinding (refer to Section 6.11.2.2.2 for Advanced Clinical Pharmacovigilance contact information). To avoid bias and to ensure the integrity of the blind, personnel directly involved with the ongoing conduct of the study from the Sponsor, CRO, or other investigational study centers will not have access to any information that may lead to unblinding.

The randomization code will remain blinded to all study sites and study team members until completion of the study, and after the study database has been locked.

### 5.4.11 Non-Investigational Study Supplies

The Sponsor or designee will supply the following non-investigational supplies or equivalent available skincare product per country including:

- Cetaphil® Gentle Skin Cleanser
- Cetaphil® PRO Oil Absorbing Moisturizer with SPF 30
- Cetaphil® Moisturizing Lotion

Refer to guidelines for using the cleanser and moisturizer (Section 5.4.2 – Instructions for Use).

Upon receipt of non-investigational supplies, the site must conduct an inventory of all non-investigational supplies. If a damaged shipment is received and/or a temperature excursion has been experienced, the site will notify the Sponsor/CRO and follow the guidelines according to the current version of the pharmacy manual.

The investigator or designee will maintain accurate records of non-investigational supplies received and dispensed. The monitor will confirm global accountability of non-investigational supplies (total received = total dispensed + total unused non-dispensed). All unused non-investigational supplies will be returned to the Sponsor or designee.

### 5.4.12 Prior and Concomitant Therapy

#### *5.4.12.1 Definition*

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

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

Concomitant therapies are defined as:

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

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

#### *5.4.12.2 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.

#### *5.4.12.3 Recording*

Previous and concomitant therapies are to be recorded on the Drugs/Therapies form (for drugs/therapies) and/or on the Medical and Surgical Procedures form (for medical/surgical procedures) in the case report form (CRF).

Concomitant therapies are to be recorded, reviewed, and updated at each visit. Every attempt should be made to keep concomitant therapy dosing and regimen constant during the study.

#### *5.4.12.4 Authorized Medication/Therapy*

Unless specified as prohibited medication/therapy (see Section 5.4.12.5), all therapies are authorized, including the following as long as they are not indicated for the treatment of acne vulgaris.

Topical products:

The following topical products are authorized on the treated areas:

- mild or soapless cleanser
- A non-comedogenic sunscreen (SPF ≥30 or equivalent), non-comedogenic moisturizer (as needed but respecting an interval of approximately 1 hour before or 1 hour after the topical study drug application)

Systemic treatments:

The following systemic medications are permitted if they are not indicated for the treatment of acne vulgaris:

- The use of non-steroidal anti-inflammatory drugs (NSAIDs) is acceptable for up to 21 days (cumulative) of treatment; however, it should be avoided during the 1-week period prior to the final study assessment (Week 24).
- Topical antibiotics prescribed for localized dermal infections
- Penicillin G or V

#### *5.4.12.5 Prohibited Medication/Therapy*

Medications/therapies listed in Table 4 are prohibited during the study as they may interfere with efficacy and/or safety assessments.

**Table 4: List of Prohibited Medications/Therapies During Study**

| |
|---|
| **Topical treatments on the face**: |
| Corticosteroids, antibiotics , benzoyl peroxide, azelaic acid, alpha hydroxyl acids, salicylic acid, zinc containing treatments, other anti-acne treatments or other acne treatments (e.g., salicylic acid treatments) |
| Retinoids |
| Cosmetic/aesthetic procedures on the face (e.g., comedone extraction, desquamating or abrasive agents, adhesive pore cleansing strips) |
| Wax epilation |
| Photodynamic therapy |
| Laser therapy, microdermabrasion, deep chemical peel, and other plastic surgical treatments for acne |
| Agents with potential drying effects on the skin: i.e. antibacterial soaps, astringents, other alcohol-containing topical preparations |
| Use of tanning booths or lamps, as well as sunless tanning products |
| Intensive ultraviolet (UV) radiation exposure (mountain sports, sailing, sunbathing, etc.) |

**Table 4: List of Prohibited Medications/Therapies During Study**

| |
|---|
| **Systemic treatments**: |
| Initiate use of combined oral contraceptives (estrogens and progesterone), implantable/injectable contraceptives, hormonal contraceptive vaginal rings or change of dose (of existing medication) |
| Initiate use of combined oral contraceptives approved as acne treatments (e.g., Ortho Tri-Cyclen®, Yaz®, Diane-35®), or change of dose (of existing medication) |
| Corticosteroids (except locally acting corticosteroids such as inhaled or intrathecal), antibiotics (except penicillin G and V) |
| Oral retinoids / isotretinoin |
| Cyproterone acetate / chlormadinone acetate |
| Spironolactone |
| Immunomodulators |
| Vitamin A supplements exceeding the recommended daily allowance (4000 – 5000 IU) |
| Prescription testosterone therapy (e.g., testosterone cypionate, testosterone enanthate, testosterone pellet, testosterone undecanoate) or on a testosterone booster or prescription testosterone (e.g., DHEA, Omnadren®, Sustanon®, testosterone cypionate, testosterone enanthate, testosterone propionate, testosterone phenylpropionate) or testosterone supplements (e.g., Tribulus) |
| **Other:** |
| Any drug (topical or systemic) or procedures that are used off label for the treatment of acne vulgaris |

If a prohibited therapy becomes necessary for the safety of the subject, the investigator should notify the medical monitor and discuss possible alternatives. If a subject receives a prohibited therapy during the clinical study (e.g., inadvertent short-term use), the investigator should also notify the medical monitor and discuss whether or not it is appropriate for the subject to continue receiving study drugs.

## 5.5 Duration of Subject Participation

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

### 5.5.1 Early Termination Visit

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

Refer to Section 5.3.4 for reasons for early study discontinuation.

### 5.5.2 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 5.1.2 – Schedule of Assessments may be conducted, as appropriate.

## 6 STUDY ASSESSMENTS

The protocol specifies the planned efficacy and safety assessments.

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 scar and acne assessments local tolerability assessment and imaging (for designated imaging centers).

Any facial observations clearly judged by the investigator to be related to the mask (e.g. erythema or dermatitic effects) will be noted in source records and included in the CRF comments, attributable to the mask (e.g., increased erythema along mask edge, etc). An AE form can be submitted at the discretion of the investigator. If mask effects remain detectable at the time of the acne assessments and local tolerability assessments, they should be considered and reported as part of these assessments.

Refer to Section 5.1.2 – Schedule of Assessments for guidelines to ensure safety of enrolled subjects and continuity of scheduled follow-up visits.

### 6.1 Efficacy Assessments

Efficacy measurements should be conducted by the investigators (or designees) or by subjects (for subject-reported assessments) according to Section 5.1.2 - Schedule of Assessments.

Evaluators must complete standardized training prior to performing the following assessments: atrophic scar severity (SGA), atrophic scar counts, acne severity (IGA), inflammatory lesion counts (papules and pustules), non-inflammatory lesion counts (open and closed comedones), and other lesion counts (nodules and cysts). Refer to Section 8.1 – Personnel Training for further details on site personnel training.

**Notes:**

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[redacted]

[redacted]

CCI [redacted]

CCI [redacted]

[redacted]

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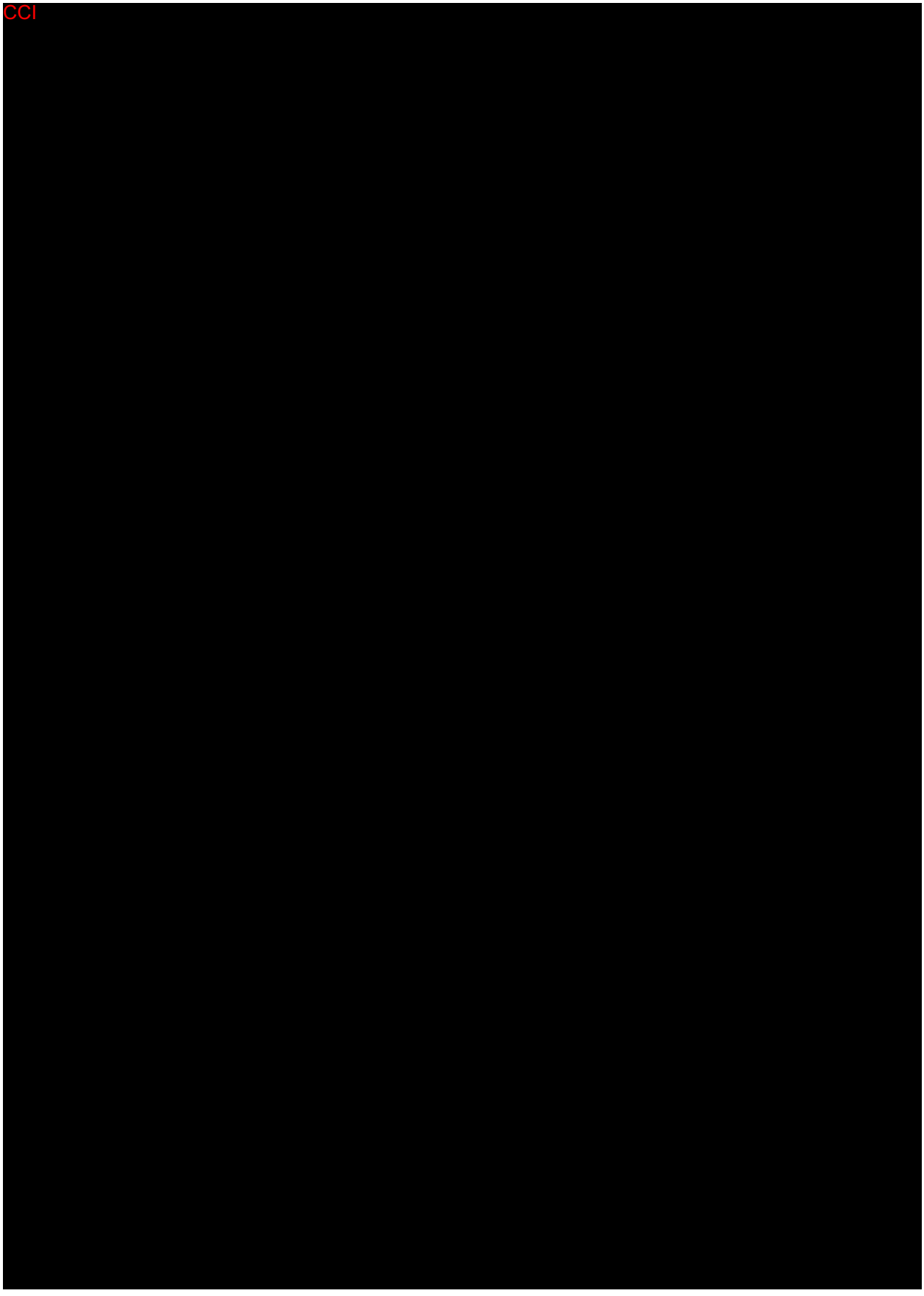

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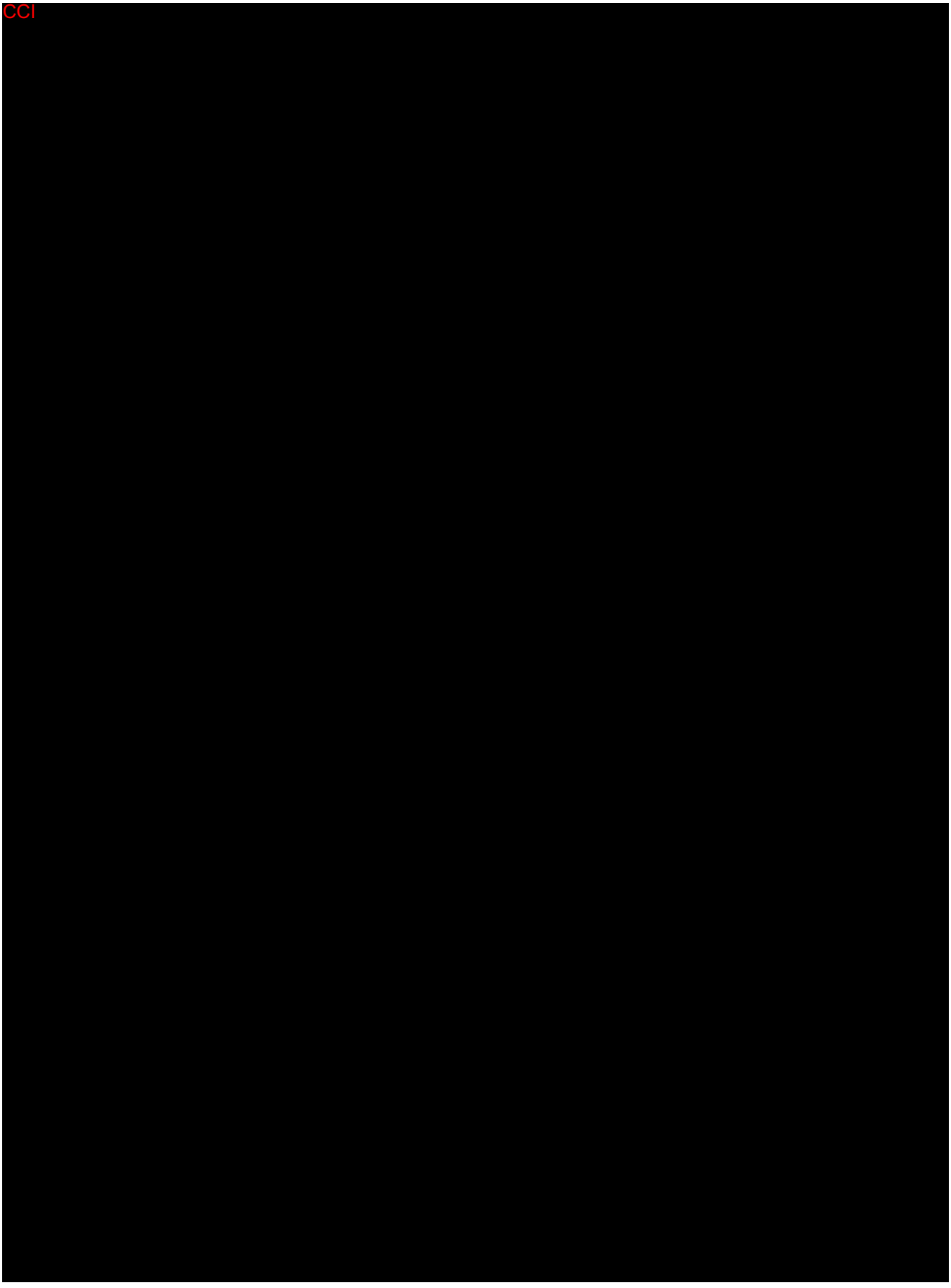

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### 6.11 Safety Assessments

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

#### 6.11.1 Local Tolerability Assessment

Local tolerability assessment(s) on each CCI will include erythema, scaling, dryness and burning/stinging at visits specified in the schedule of assessments (Section 5.1.2). Table 7 summarizes the local tolerability assessment. Burning/stinging will be recorded by the investigator after discussion with the subject.

Local tolerability assessments for each CCI are reported as a global rating for each tolerability parameter, based on clinical judgment of the investigator.

**Table 7 Local Tolerability Assessment**

| | | |
|---|---|---|
| **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 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.

### 6.11.2 Adverse Events

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

#### *6.11.2.1 Definitions*

##### *6.11.2.1.1 Adverse Events*

According to ICH E2A, an AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory value), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Thus, any new sign, symptom or disease, or any clinically significant worsening of an existing sign, symptom or disease compared to the condition at the first visit (including disease treated), should be considered as an AE. Lack of efficacy is not considered as an AE.

Each new episode of a chronic disease (e.g., hay fever, allergy, etc.) should be reported as a new AE.

Notes:

- Any new sign or symptom reported by the subject that appears after accidental or intentional overdose or misuse should also be reported as an AE.
- Whenever possible, a diagnosis should be reported on the AE form rather than the signs, symptoms or abnormal laboratory values associated with the report of an AE. However, a diagnosis should be reported only if, in the Investigator's judgment, it is relatively certain. Otherwise, symptoms, signs, or laboratory values should be used to describe the AE.
- Pregnancy is not to be considered as an AE; however, is an important medical event that must be monitored as described in Section 6.11.2.2.5.

#### *6.11.2.1.2 Serious Adverse Events*

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the safety of the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasia, or convulsions that do not result in hospitalization.

Note:

The term “life-threatening” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe.

Inpatient hospitalization is considered to have occurred if the subject has had to stay for a night at the hospital. The criterion for prolongation of hospitalization is also defined as an extra night at the hospital. Hospitalization may not constitute sufficient grounds to be considered as an SAE if it is solely for the purpose of a diagnostic tests (even if related to an AE), elective hospitalization for an intervention that was already planned before subject enrollment in the clinical study, admission to a day-care facility, social admission (e.g., if the subject has no place to sleep), or administrative admission (e.g., for a yearly examination).

#### *6.11.2.1.3 Adverse Events of Special Interest*

An AESI is a noteworthy event for the particular study drug that can be appropriate for the Sponsor to monitor closely. It could be serious or non-serious and AESIs could include events that might be potential precursors or prodromal symptoms for more serious medical conditions in susceptible individuals.

The AEs of Special Interest for this protocol are pre-defined as follows:

- Related cutaneous AEs which lead to permanent treatment discontinuation
- Suspicion of allergic contact reaction related to the study drug (see Section 6.11.2.2.4)

For AESIs, the Investigator is required to complete the AESI Form and follow the AESI reporting procedures in Section 6.11.2.2.3 even if the event is considered non-serious according to the usual regulatory criteria. For suspected sensitizations associated with study medication use, follow the re-challenge with the study drug patch test procedures in Section 6.11.2.2.4 (and subsequent ingredient patch testing, if the re-challenge with the study drug is positive or equivocal).

#### *6.11.2.1.4 Unexpected Adverse Drug Reaction*

According to ICH E6, an unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable study drug information (e.g., reference safety information in Investigator Brochure, package insert/summary of product characteristics, etc).

#### *6.11.2.1.5 Adverse Event Reporting Period*

The clinical study period during which AEs must be reported is the period from when the subject signed the ICF to the end of the subject's participation.

The Sponsor should be informed if the Investigator becomes aware of any unusual safety information or any safety information that appears to be drug-related involving a subject who has participated in a clinical study, even after a subject has completed the clinical study.
The Investigator should be diligent in looking for possible latent safety effects that may not appear until a medication has been discontinued.

#### *6.11.2.1.6 Adverse Event Severity*

Severity is a clinical determination of the intensity of an AE and not of a disease.

The Investigator is to classify the intensity of AEs using the following definitions as a guideline for all AEs. For this classification, the Investigator will take into account the possible range of the intensity of the event and report the grade of intensity which is the most appropriate according his medical judgment.

| | |
|---|---|
| Mild | Awareness of signs or symptom, but easily tolerated. |
| Moderate | Discomfort, enough to cause interference with usual activity |
| Severe | Incapacitating with inability to work or perform usual activity |

*6.11.2.1.7 Relationship to the Study Drug*

The investigator is to determine whether there is a reasonable causal relationship between the study drug and the AE. Medical judgment should be used to determine the relationship, considering all relevant factors including the pattern of reaction, temporal relationships, positive challenge or rechallenge, relevant medical history, and confounding factors such as co-medication or concurrent diseases.

The expression "reasonable causal relationship" is meant to convey in general that there are facts or arguments to suggest a causal relationship (ICH E2A, Section IIIA 1).

The relationship assessment for an AE is to be completed using the following definitions as a guideline for all AEs occurring during clinical studies conducted or sponsored by GALDERMA R&D:

**Reasonable possibility:**

- According to the Investigator, there is a reasonable possibility (i.e., suggestive evidence or arguments) that there is a causal relationship irrespective of the dose administered between:
  - The study drug and the AE, or
  - The study procedure and the AE (e.g, procedure include use of cleanser, moisturizer, etc.)

**No reasonable possibility:**

- No suggestive evidence or arguments can be identified regarding a causal relationship between the study drug or study procedure and the AE.

### *6.11.2.2 Reporting Procedures*

*6.11.2.2.1 Procedures for Reporting Adverse Events*

The collection of AEs is from the time that a subject signs the ICF to their final visit.

At each post-enrollment visit, the Investigator (or sub-Investigator) will question the subject about AEs using an open non-persuasive question to elicit reporting of AEs, for example: "Have you noticed any change in your health since the last visit?" Directed questioning and examination will then be performed, as appropriate.

Any AE occurring during the AE reporting period, whether it is related to the study drug or not, will be recorded immediately in the source document, and described on the Adverse Event Form along with the date of onset, severity, relationship to the study drug, and outcome, without omitting any requested and known information. Additional information may be requested under certain circumstances. Adverse Events assessed as related to the treatment will be monitored

until they are completely or satisfactorily resolved. Other AEs will be monitored until the last visit if they are not resolved or satisfactorily resolved.

The Investigator will obtain and maintain in the subject's files all pertinent medical records, information and medical judgment from colleagues who assisted in the treatment and follow-up of the subject. If necessary, the Investigator will contact the subject's personal physician or hospital staff to obtain further details.

For SAEs (see Section 6.11.2.2.2), AESIs (see Section 6.11.2.2.3), and pregnancies (see Section 6.11.2.2.5), Advanced Clinical Pharmacovigilance is to be informed immediately by fax or email (preferred method). The event must be reported by fax or sent by e-mail within 24 hours of receipt of the information (contact details provided in Section 6.11.2.2.2).

#### *6.11.2.2.2 Procedure for Reporting a Serious Adverse Event*

For an SAE occurring during the period of the clinical study, regardless of whether it is related to the treatment or not, and of whether it is expected or not, the Investigator must do the following:

1. Take prompt and appropriate medical action, if necessary. The safety of the subject is the first priority.
2. Ensure that the event is classified as an SAE. Immediately inform Advanced Clinical Pharmacovigilance of the event (within 24 hours of knowledge of the event) by fax or email and discuss further actions to be taken. Email is the preferred method.

   Advanced Clinical Pharmacovigilance:

   DrugSafetyPV@advancedclinical.com (preferred method)
   or
   E-Fax: 1-847-589-5211

3. Complete the Adverse Event Form provided in the CRF as fully as possible.
4. Ensure that the event is classified as an SAE in the CRF.
5. Print and complete the Serious Adverse Event Form available in the electronic data capture (EDC) system as PDF document. Fax or scan and send by e mail the completed form, accompanied by any other relevant information or medical records (e.g., laboratory test results) within 24 hours to Advanced Clinical Pharmacovigilance. The demographics, medical history, previous and concomitant therapies, and adverse event pages of the CRF must be completed and available for review in the EDC system at the time of the report.
6. Monitor and record the progress of the event until it resolves or reaches a clinically stable outcome, with or without sequelae. For follow-up evaluations, notify Advanced Clinical Pharmacovigilance of updates within 24 hours. Serious Adverse Events will be monitored until the Investigator and Sponsor agree that the event is satisfactorily resolved.

7. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject. If necessary, contact the subject's personal physician or hospital staff to obtain further details.
8. Inform Advanced Clinical Pharmacovigilance of the final outcome of the event. Send a revised or updated Serious Adverse Event Form and Adverse Event Form, if appropriate.
9. Comply with the applicable regulatory requirement(s) related to the reporting of SAEs to the Institutional Review Board (IRB) / Independent Ethics Committee (IEC).

If there are serious, unexpected adverse drug reactions associated with the use of the study drug, the Sponsor or designee will notify the appropriate regulatory agency(ies), Ethics Committees (EC), and all participating Investigators on an expedited basis.

#### *6.11.2.2.3 Procedure for Reporting an Adverse Event of Special Interest*

For any AESI (see Section 6.11.2.1.3) occurring during the period of the clinical study, whether related to the treatment or not, and whether expected or not, the Investigator is to do the following:

1. Take prompt and appropriate medical action, if necessary. The safety of subjects is the first priority.
2. Immediately inform Advanced Clinical Pharmacovigilance of the event by fax or email and discuss further actions to be taken (Section 6.11.2.2.2).
3. Complete the Adverse Event Form provided in the CRF as fully as possible.
4. Ensure that the event is classified as an AESI in the CRF.
5. Print the Adverse Event form. Fax or scan and send by e mail the completed form, accompanied by any other relevant information or medical records (e.g. laboratory test results) within 24 hours to Advanced Clinical Pharmacovigilance. The demographics, medical history, previous and concomitant therapies, and adverse event pages of the CRF must be completed and available for review in the EDC system at the time of the report.
6. Monitor and record the progress of the event until it resolves or reaches a clinically stable outcome, with or without sequelae. For follow-up evaluations, notify Advanced Clinical Pharmacovigilance within 24 hours. AESIs will be monitored until the Investigator and Sponsor agree that the event is satisfactorily resolved.
7. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject. If necessary, contact the subject's personal physician or hospital staff to obtain further details.
8. Inform Advanced Clinical Pharmacovigilance of the final outcome of the event. Send a revised or updated Adverse Event Form, if appropriate.

#### *6.11.2.2.4 Procedures for Suspected Allergic Contact Reaction to Topical Study Medication (Re-Challenge Patch Test and Ingredient Patch Testing)*

If a subject experience a suspected allergic contact reaction associated with study medication use, the following actions should be taken to characterize the event:

- Stop all study medication.
- Take a picture of the affected area and the non-affected surrounding skin
- Document the event as an Adverse Event of Special Interest, contact immediately Advanced Clinical Pharmacovigilance and report the event within 24hrs (see Section 6.11.2.2.2).
- The subject continues to be followed for scheduled study visits while awaiting the re-challenge test results.

**a) Re-Challenge with Assigned Topical Study Medication**

1) After all signs and symptoms of AESI have resolved and after a minimum of two weeks from last dose application, perform a re-challenge test with the study drug. Scheduling on a Monday or Tuesday is ideal, as it ensures the 48-hour and 72-96 hour follow-up assessments occur on weekdays (Table 8).
2) Ensure the subject has not been under any treatment with corticosteroids or antihistamines of any route of administration the week before testing.
3) Ensure that the skin on the back has not been exposed to the sun or artificial UV sources the week before testing.
4) Apply an appropriate quantity of the topical study drug to fill in the cupule of the test chamber to a naïve zone on the back either the right or left side of the center line (or the inner forearm if the back cannot be tested). If no test chamber is available on site, patch test units will be provided by the Sponsor or designee. Apply an empty test chamber as a control for the re-challenge test with topical study drug (note: an empty test chamber will not be needed for ingredient testing, if such test is warranted, as the Sponsor/designee will provide one or more controls for testing). The use of semi-occlusive conditions depends on the irritant potential of the study product and the intensity of the reaction that was observed. The method to be used should be discussed with the Medical Monitor.

   Choose a skin site that was not previously involved in the inflammatory skin reaction. Cover the test chamber for 48 hours with a hypoallergenic tape.
5) Subject should be informed about avoiding exercise, showers, application of toiletries products, etc. to keep the test system dry
6) After 48 hours, remove the test chamber and evaluate the site and take photos after each reading (Table 9):
   - at approximately 30 minutes after patch test removal (1st reading) and,
   - 24 to 48 hours later (i.e., 72 or 96 hours after application) (2nd reading).

- If the result of the second reading is equivocal, the Investigator or at the Sponsors request, may perform an optional 3rd reading at 96 to 120 hours later (i.e., 6 to 7 days after application of the patch).
- Pictures of each reading and the reading results should be sent to Advanced Clinical Pharmacovigilance and medical monitor.

**Table 8 Patch Testing Readout Schedule**

| Day Patch Test Starts | 1st reading + Photographs<br><br>48 hours after study product application (30 minutes after patch test removal) | 2nd reading + Photographs<br><br>72 to 96 hours after study product application (24 to 48 hours after patch test removal) | 3rd reading (optional) + Photographs<br><br>6 or 7 days after study product application (96 to 120 hours after patch removal) |
|---|---|---|---|
| If test starts on **Monday**: | Wednesday | Thursday or Friday | Monday |
| If test starts on **Tuesday**: | Thursday | Friday | Monday or Tuesday |

Refer to Table 9 for the scoring system at each readout used by the International Contact Dermatitis Research Group (ICDRG) (Spiewak, 2008).

**Table 9 Grading System for Suspected Allergic Contact Reaction**

| Score | Morphology | Interpretation |
|---|---|---|
| - | No skin changes in the tested area | Negative |
| ? | Faint, non-palpable erythema | Doubtful reaction |
| + | Palpable erythema (moderate edema or infiltrate), papules not present or scarce, vesicles not present | Weak positive reaction |
| ++ | Strong infiltrate, numerous papules, vesicles present | Strong positive reaction |
| +++ | Erythema, infiltration, confluent vesicles, bullae or ulceration | Extreme positive reaction |
| ir | Inflammation sharply limited to the exposed area, lack of infiltrate, small petechiae, pustules, and efflorescences other than papules and vesicles | Irritant reaction |
| Nt | | Not tested |

7) At the last reading, the investigator will refer to Table 10 and provide an overall interpretation regarding a possible sensitization reaction, which is based on results using the ICDRG scale.

**Table 10 Investigator Overall Conclusion of Suspected Sensitization**

| Sensitization Reaction | |
|---|---|
| 0 | Negative (absence of reaction or might be irritant reaction) |
| 1 | Equivocal |
| 2 | Positive |

8) In case of negative reaction, the subject may resume study treatment if appropriate. Otherwise, the subject should complete end of study procedures.

9) If the re-challenge with assigned topical study medication is positive or equivocal, notify Advanced Clinical Pharmacovigilance and medical monitor immediately. Except in specific situations, ingredient patch testing of the topical study medication will be initiated as directed by the Sponsor (with individual ingredients at different concentrations if applicable, and possibly negative and positive controls) after a minimum of an additional two weeks (but not later than 6 months) and after all signs and symptoms have resolved.

   - The Sponsor will provide a letter to the investigator with blinded results for ingredient testing, and further instructions how the subject and his/her primary care provider can determine test results, while maintaining blinding of the investigator and site staff (Appendix 14.6).

   **Note**: Ingredient testing will follow the above process beginning with step number 4, with testing of the individual ingredients (and controls, as applicable). The Sponsor or designee will provide the necessary supplies for ingredient testing. Given the delay when ingredient testing supplies may arrive, subjects may receive treatment for their acne other than the study drug, and should stop all acne therapy a minimum of 1 week before ingredient testing.

**b) In case of suspicion of immediate contact skin reaction (such as urticaria)**

A case-by-case approach will be applied and the procedure to follow will be discussed with the Sponsor.

*6.11.2.2.5 Procedures for Reporting Pregnancies*

Any pregnancy occurring during clinical studies, where the fetus could have been exposed to the study drug, must be monitored until its outcome in order to ensure the complete collection of safety data.

If a subject becomes pregnant, the Investigator is to do the following:

1. Immediately inform Advanced Clinical Pharmacovigilance of the event by fax or email (Section 6.11.2.2.2).
2. **Withdraw the subject from the clinical study**.
3. Complete the Pregnancy Surveillance Form – Part I: History and Start of Pregnancy, provided by the Clinical Research Associate (CRA) at the beginning of the clinical study, as fully as possible. Inform Advanced Clinical Pharmacovigilance of the pregnancy by sending this pregnancy form along with the Exit Form within 24 hours to Advanced Clinical Pharmacovigilance (see Section 6.11.2.2.2).
4. Monitor and record the progress of the pregnancy until its outcome. Contact the subject's regular physician (general practitioner or gynecologist) or hospital staff to obtain further details and ask for regular follow-up information.
5. Inform Advanced Clinical Pharmacovigilance of the progress by tri-monthly updates until the final outcome of the pregnancy, within 24 hours of receiving updates. If the subject can no longer be reached (lost to follow-up), documentation of the non-response/contact with two telephone calls and a letter (certified with return receipt) is required.
6. At the outcome of the pregnancy, complete the Pregnancy Surveillance Form – Part II: Course and Outcome of Pregnancy, as fully as possible. Send this pregnancy form to Advanced Clinical Pharmacovigilance within 24 hours (see Section 6.11.2.2.2).
7. If the pregnancy leads to an abortion (voluntary, spontaneous or therapeutic), in-utero death, or congenital anomaly, follow the procedure for reporting an SAE (see Section 6.11.2.2.2).

# 7 PLANNED STATISTICAL ANALYSES

## 7.1 Statistical Analysis Plan

A statistical analysis plan (SAP) will be developed and issued as a separate document. The SAP will contain a more detailed and technical description of specific data conventions, calculations and of statistical procedures for executing the analysis strategies. The SAP will be finalized prior to the database lock.

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.

Post hoc exploratory analyses will also be clearly identified in the Clinical Study Report (CSR).

## 7.2 Sample Size Determination

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

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

| Study | $\mu_{Trifarotene}$ | $\sigma_{Trifarotene}$ |
|---|---|---|
| RD.06.SPR.CCI | -3.4 | 9.48 |

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

CCI t there are no data for estimating the variability of the difference between trifarotene 50 µg/g cream and vehicle cream.

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

| Study | $\mu_{ABPO\ Forte}$ | $\sigma_{ABPO\ Forte}$ | $\mu_{Vehicle}$ | $\sigma_{Vehicle}$ | $\mu_{Diff}$ | $\sigma_{Diff}$ |
|---|---|---|---|---|---|---|
| RD.03.SPR.CCI | | | | | | |

Under the following hypotheses:

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

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

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

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

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

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

### 7.3 Populations Analyzed, Evaluability and Limitation / Evaluation of Bias

The Intention-to-Treat (ITT) population will be used for the analyses of efficacy endpoints on the face. The Per Protocol (PP) population will be used for a sensitivity analysis of the primary endpoint. The Safety population (SAF) will be used for all safety analyses.

#### 7.3.1 Intent-to-treat (ITT) population

The ITT population is defined as all randomized subjects and will be used for the analyses of efficacy endpoints on the face.

#### 7.3.2 Per Protocol (PP) population

The Per Protocol (PP) population is defined as comprising the ITT population subjects who are compliant to the treatment application (i.e. with an overall compliance between 80% - 120% inclusive), whose Baseline and Week 24 total atrophic acne scar counts are performed and who

have no major deviations from the protocol that could have a significant effect on the efficacy of the study treatment (e.g. errors in treatment assignment, use of prohibited medications).

### 7.3.3 Safety (SAF) Population

The SAF population is defined as comprising the ITT population subjects who applied/took the study drug at least once and will be used for all safety analyses.

## 7.4 Statistical Analysis

The main objective of this study is to evaluate the efficacy and safety outcomes of of trifarotene treatment versus vehicle with 24 weeks of treatment.

### 7.4.1 General Methods

All data collected will be summarized by descriptive statistics and frequency tables as appropriate.

### 7.4.2 Demographics and Subject Disposition

Subject demographics and baseline characteristics will be summarized with descriptive statistics and frequency tables as appropriate. Subject disposition will be summarized with the number of subjects in each population, the number and percentage of subjects who complete the study, along with the number and percentage of subjects who do not complete the study for each discontinuation reason as specified on the eCRFs.

### 7.4.3 Efficacy Analysis

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

The hypothesis tests for the secondary efficacy endpoints are conditional on the success of the primary endpoint.

CCI [redacted]

CCI [redacted]

CCI [redacted]

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

#### *7.4.3.1 Primary Efficacy Endpoint*

Absolute change from Baseline in total atrophic acne scar count at Week 24 will be summarized by treatments using descriptive statistics. The bilateral difference between products in absolute change from Baseline in total atrophic acne scar count at Week 24 will be summarized using descriptive statistics and will be analyzed on the ITT population using the Student's t-test for paired samples. The point estimate of the mean difference and the related 95% confidence interval will be presented. Assumption of normality will be checked. If normality assumption is not met, the appropriate non-parametric statistical methods will be used. PP analysis will be also performed to assess the robustness of the results obtained on the ITT population.

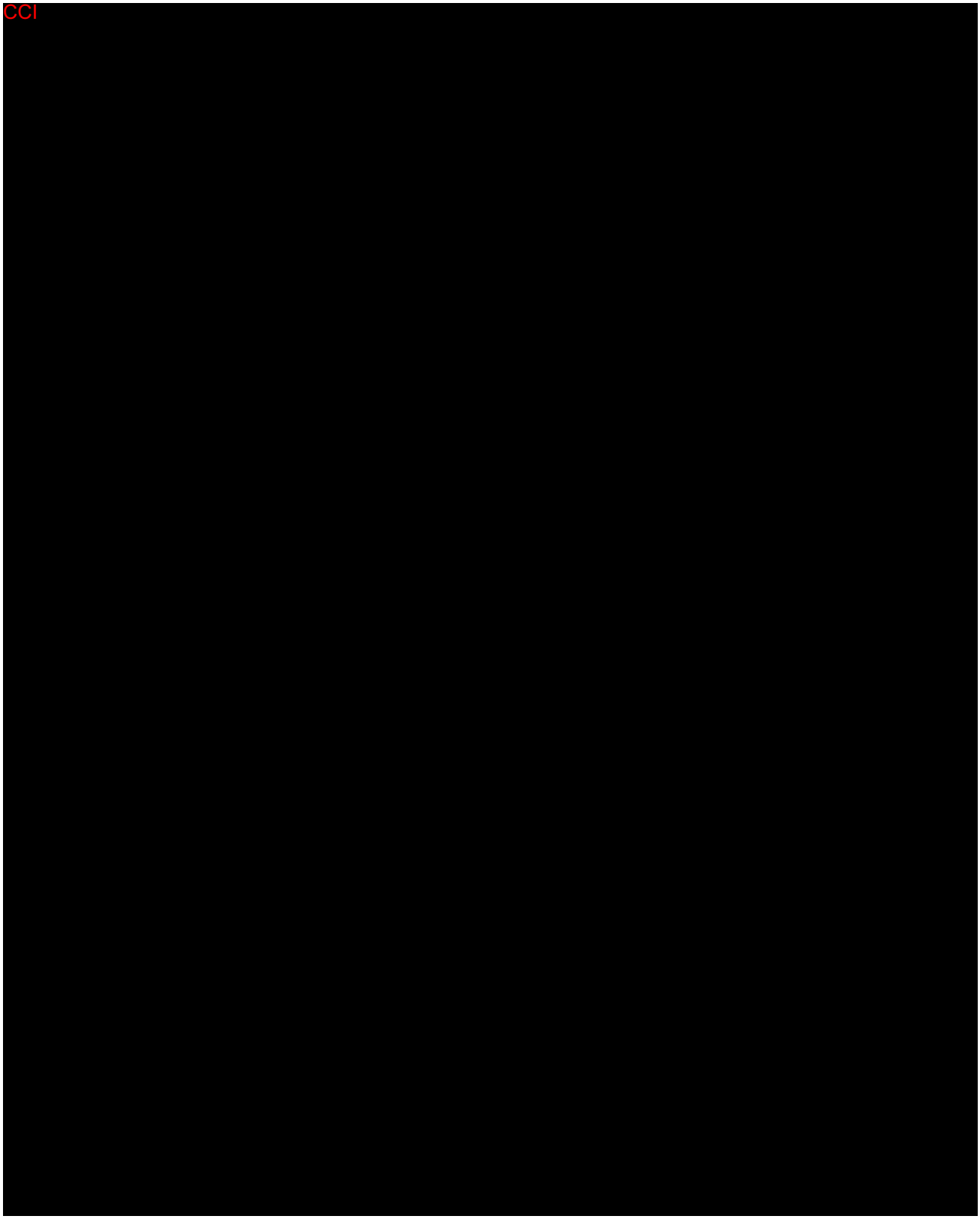
#### *7.4.3.2 Secondary Efficacy Endpoints*

Secondary efficacy endpoints include:

- Absolute change from Baseline in total atrophic acne scar count at each intermediate post-baseline visit will be summarized by treatments using descriptive statistics. The bilateral difference between products in Absolute change from Baseline in total atrophic acne scar count at each intermediate visit will be summarized using descriptive statistics and will be analyzed on the ITT population using the Student's t-test for paired samples. The point estimate of the mean difference and the related 95% confidence interval will be presented. Assumption of normality will be checked. If normality assumption is not met, the appropriate non-parametric statistical methods will be used.
- Total atrophic acne scar count per CCI [redacted] at each visit will be summarized by treatments on the ITT population using descriptive statistics.

CCI [redacted]

CCI



#### *7.4.3.3 Missing Data*

Missing values of atrophic acne scar counts will be imputed using MI (Multiple Imputation) 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 MI procedure.

Missing values of acne lesion counts, SGA scores and IGA scores will be imputed using Last Observation Carried Forward (LOCF). Moreover, for binary endpoints Missing as Failure (MAF) method will be used as additional analysis.

For the sensitivity analyses of the primary endpoint, missing data will be imputed using a Jump-to-Reference (J2R) approach under the Missing Not At Random (MNAR) assumption and Last Observation Carried Forward (LOCF).

#### *7.4.3.4 Sensitivity Analyses*

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

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

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[redacted]

### 7.4.5 Safety Analysis

Analysis of safety results include:

- Local tolerability scores (erythema, scaling, dryness and stinging/burning) for face will be summarized using frequency tables for worst post-baseline score, the final score during treatment, as well as scores for each visit.

- Adverse Events will be summarized using frequency tables by System Organ Class (SOC) and Preferred Term (PT) based on the Medical Dictionary for Regulatory Activities (MedDRA).

# 8 TRAINING / MONITORING / DATA MANAGEMENT / QUALITY ASSURANCE

## 8.1 Personnel Training

Study monitors and all relevant personnel will be trained before study initiation on the condition to be treated, the standard operating procedures to be used in this clinical study, the protocol, and all study-specific procedures. Team organization, communication, and operational issues will also be discussed and agreed upon.

Investigators, study coordinators and other applicable personnel will be trained before study initiation at an investigator meeting and/or onsite training visit. Training will include, but not limited to, the protocol, ICH/GCP, study-specific procedures (including efficacy assessment scales and instruction for use of the study drug) and CRF completion.

All personnel involved in the study conduct will receive training before participating in any procedure and/or evaluation. Each study center will have a training record as part of the site file and TMF.

Completion of standardized rater training is required before performing acne assessments, including:


Certificates will be issued to document successful rater training completion. Recommended rater credentials are provided in Section 6.2 – Rater Credentials for Efficacy Assessments.

Relevant staff at sites designated to perform study imaging must complete photography training and submit required test photos.

## 8.2 Monitoring

Data for each subject will be documented in source records and recorded on CRFs. Data collection must be completed for each subject who signs an ICF and is administered study drug.

In accordance with current GCP and ICH guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the CRF are accurate and reliable.

The investigator must permit the monitor, the IEC/IRB, the Sponsor's internal auditors, and representatives from regulatory authorities direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the CRFs.

## 8.3 Data Management

The Sponsor or designee will be responsible for activities associated with the data management of this study. This will include, but not limited to, setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. All data management activities will be detailed in a Data Management Plan (DMP).

Study sites will enter data into an electronic data capture (EDC) system by completing the CRF via a secure internet connection. Data entered into the CRF must be verifiable against source documents at the study center. Data to be recorded directly on the CRF will be considered the source document. Any changes to the data entered into the EDC system will be recorded in the audit trail.

## 8.4 Clinical Study Conduct

With the exception of avoiding an immediate risk to a subject, the investigator should not deviate from the clinical study protocol or implement any changes without written approval from the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment.

Changes that involve only logistical or administrative changes to the clinical study protocol are authorized. The investigator should document and explain any deviation from the clinical study protocol.

## 8.5 Protocol Amendments

The Sponsor may modify the clinical study protocol at any time for ethical, medical, or scientific reasons. Any amendments will be handled according to applicable local regulations.

Non-substantial protocol amendments (such as those pertaining to typographical errors, changes in study personnel, etc.) will not be submitted to the regulatory authorities but will be submitted to IRB/IEC for information only. The Sponsor will ensure an acknowledgement is received and filed. All non-substantial amendments will be included in subsequent submissions to regulatory authorities in cases of a substantial amendment.

### 8.6 Quality Management and Risk Evaluation

The quality of the study will be monitored for potential risks, with mitigating strategies identified, as defined in a separate risk management plan. The Sponsor will document a plan to ensure appropriate oversight and quality of the study.

### 8.7 Quality Assurance / Audit / Inspection

At the completion of the study, digital images will be forwarded to the Sponsor according to agreed upon format.

Audits of clinical study centers may be conducted by the Sponsor/designee or regulatory authorities before, during, or after the clinical study.

The Investigator will allow and assist the Sponsor/designee and any regulatory agency to have direct access to all requested clinical study-related records.

For the audits performed by, or on behalf of the Sponsor, audit certificate(s) will be provided by Quality Assurance.

## 9 ETHICS AND GENERAL CLINICAL STUDY CONSIDERATIONS

### 9.1 Institutional Review Board or Independent Ethics Committee

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the subjects, and any other relevant study documentation will be submitted to the appropriate IEC/IRB. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the study drug is released to the investigator. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study such as amendments to the protocol, the ICF or other study documentation. The written approval of the IEC/IRB together with the approved ICF must be filed in the study files.

The investigator will report promptly to the IEC/IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The investigator will submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

## 9.2 Regulatory Authorities

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

## 9.3 Ethical Conduct of the Clinical Study

This clinical study will be conducted in accordance with the protocol, the Declaration of Helsinki, and the ICH GCP, and in compliance with other applicable regulatory requirements.

## 9.4 Subject Information and Consent

All subjects who participate in this clinical study are required to be fully informed about the clinical study in accordance with GCPs guidelines, country regulations and guidelines (e.g., HIPAA, in the US), in accordance with local requirements.

All minor subjects who participate in this clinical study must be accompanied by a parent/guardian. Subjects and parent/guardians are required to be fully informed about the clinical study in accordance with GCP guidelines and relevant country regulations (e.g., for the US, HIPAA), in accordance with local requirements.

The investigator or designated personnel will inform the subject of the objectives, methods, anticipated benefits and potential risks and inconveniences of the study. The subject should be given every opportunity to ask for clarification of any points she/he does not understand and, if necessary, ask for more information. At the end of the interview, the subject will be given ample time to consider the study. Subjects will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the investigator in the investigator's study file. A signed and dated copy of the subject ICF will be provided to the subject or his/her authorized representative.

It should be emphasized that the subject may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the study, a new ICF will be approved by the IEC(s)/IRB(s) (and regulatory authorities, if required). The study subjects will be informed about this new information and reconsent will be obtained.

## 9.5 Subject Confidentiality

Monitors, auditors, and other authorized agents of the sponsor and/or its designee, the IEC(s)/IRB(s) approving this research, and the US Food and Drug Administration, as well as that of any other applicable agency(ies), will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identities will remain confidential.

All personal data collected and processed for the purposes of this study should be managed by the investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the applicable national and/or local laws and regulations (HIPAA for the US) on personal data protection.

## 9.6 Contractual Requirements

A contractual agreement will be signed between the Sponsor or CRO designee and each Investigator/Institution. This document will contain supplementary information, including financial terms, confidentiality, the clinical study schedule, third party responsibility, and publication rights.

## 9.7 Data Collection and Source Documentation

The Investigator must maintain all required records for all subjects. Data for this clinical study will be recorded in the subject's source documents, subject photographs and on the CRFs provided by the Sponsor. All data should be recorded on the CRFs completely and promptly.

The Investigator must keep accurate study records, other than the CRFs, of all subject visits, being sure to include all pertinent clinical study-related information (unless the CRF will serve as the source, such as subjects recording data directly to the electronic CRF). A statement should be made indicating that the subjects have been included in this clinical study and have provided signed written Informed Consent and Assent as applicable. All AEs must be thoroughly documented.

Results of any diagnostic tests conducted during the clinical study should also be included in the source documentation.

### 9.8 Insurance

The Sponsor will ensure appropriate insurance exists for the conduct of this study.

## 10 PUBLIC DISCLOSURE OF CLINICAL STUDY

This clinical study will be recorded to a freely accessible public registry.

# 11 REPORT AND PUBLICATION, INCLUDING ARCHIVING

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study (end of study defined as the date of the last visit of the last subject), all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file. This file will be available for inspection by the Sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the investigational product. It is the responsibility of the Sponsor to inform the study center when these documents no longer need to be retained. The investigator must contact the Sponsor before destroying any study-related documentation. In addition, all subject medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

If the investigator retires, relocates, or withdraws from the responsibility of keeping the clinical study records for any other reasons, custody must be transferred to a person who will accept the responsibility. The Sponsor/CRO must be notified in writing of the name and address of the new custodian.

The Sponsor must review and approve any results of the study or abstracts for professional meetings prepared by the investigator(s). Published data must not compromise the objectives of the study. Data from individual study centers in multicenter studies must not be published separately.

# 12 SUSPENSION OR PREMATURE TERMINATION

The Sponsor will suspend or terminate the study if so instructed by the IRB/IEC or regulatory authority, or if it is judged that the subjects are subjected to unreasonable risks, or for valid scientific or administrative reasons.

The Sponsor may also decide to close a single study site due to unsatisfactory subject enrollment or non-compliance with the protocol, GCP, or applicable regulatory requirements.

In the event of premature termination, the Sponsor will provide information on the handling of currently enrolled subjects who have not completed the study.

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# 14 APPENDICES

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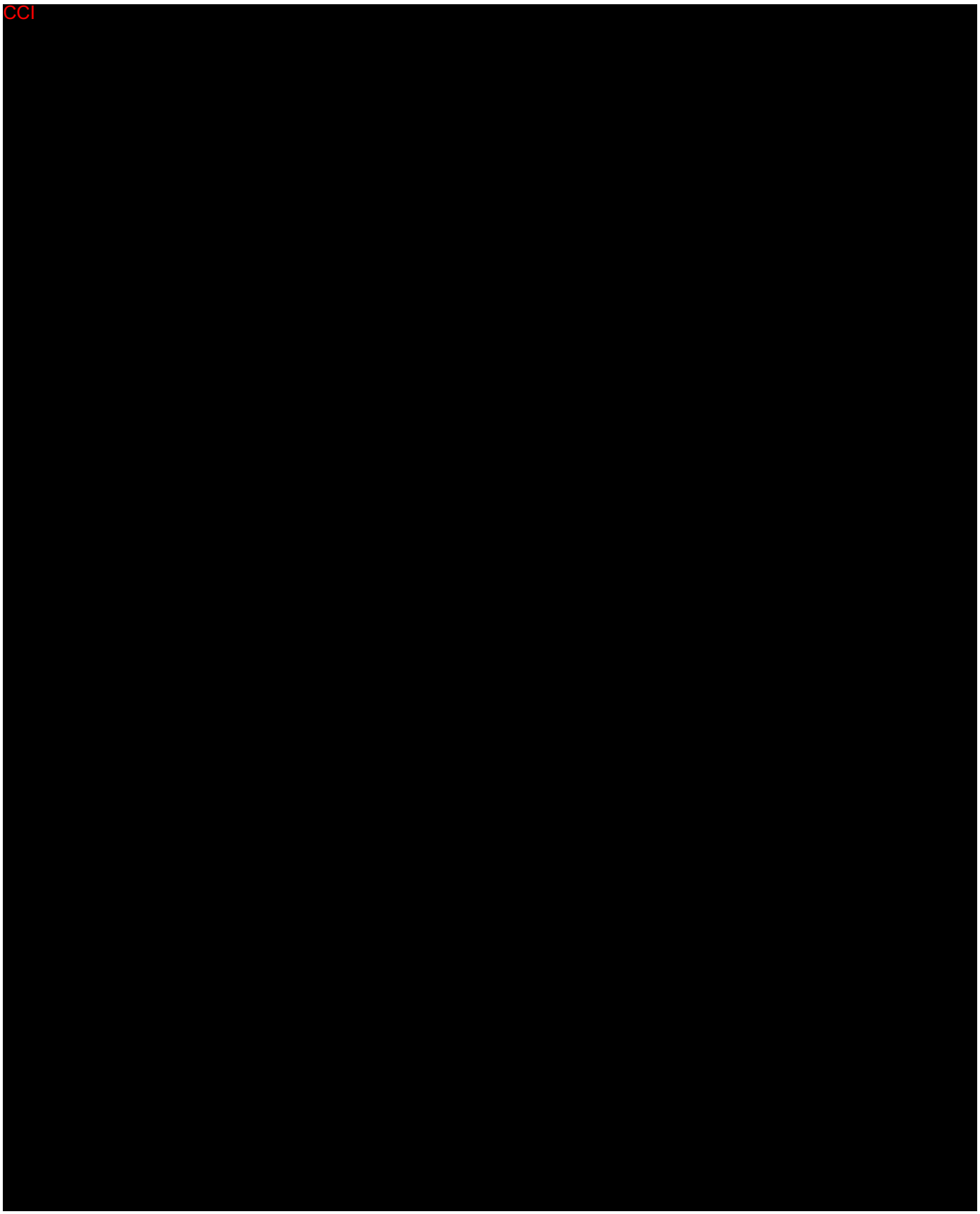

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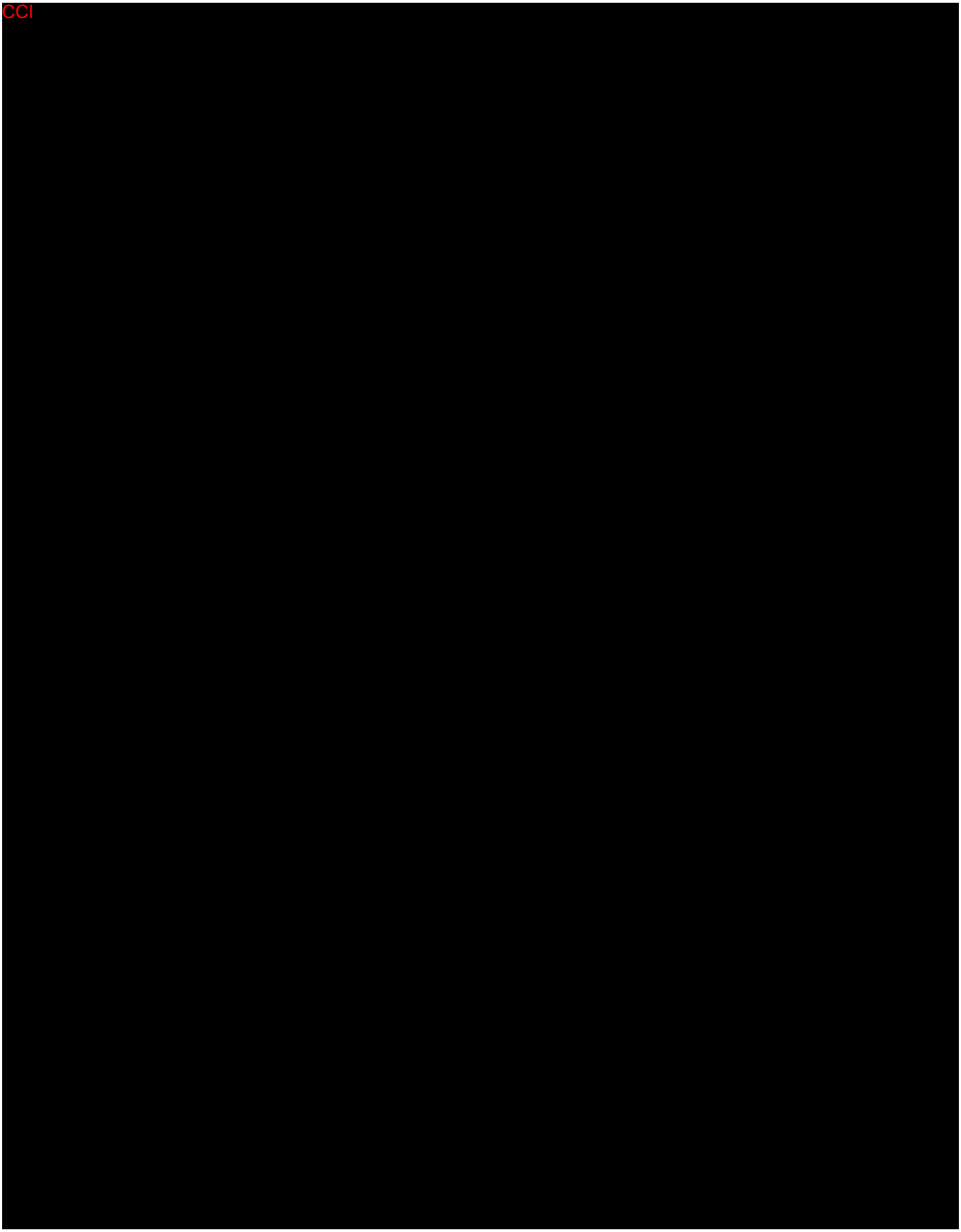

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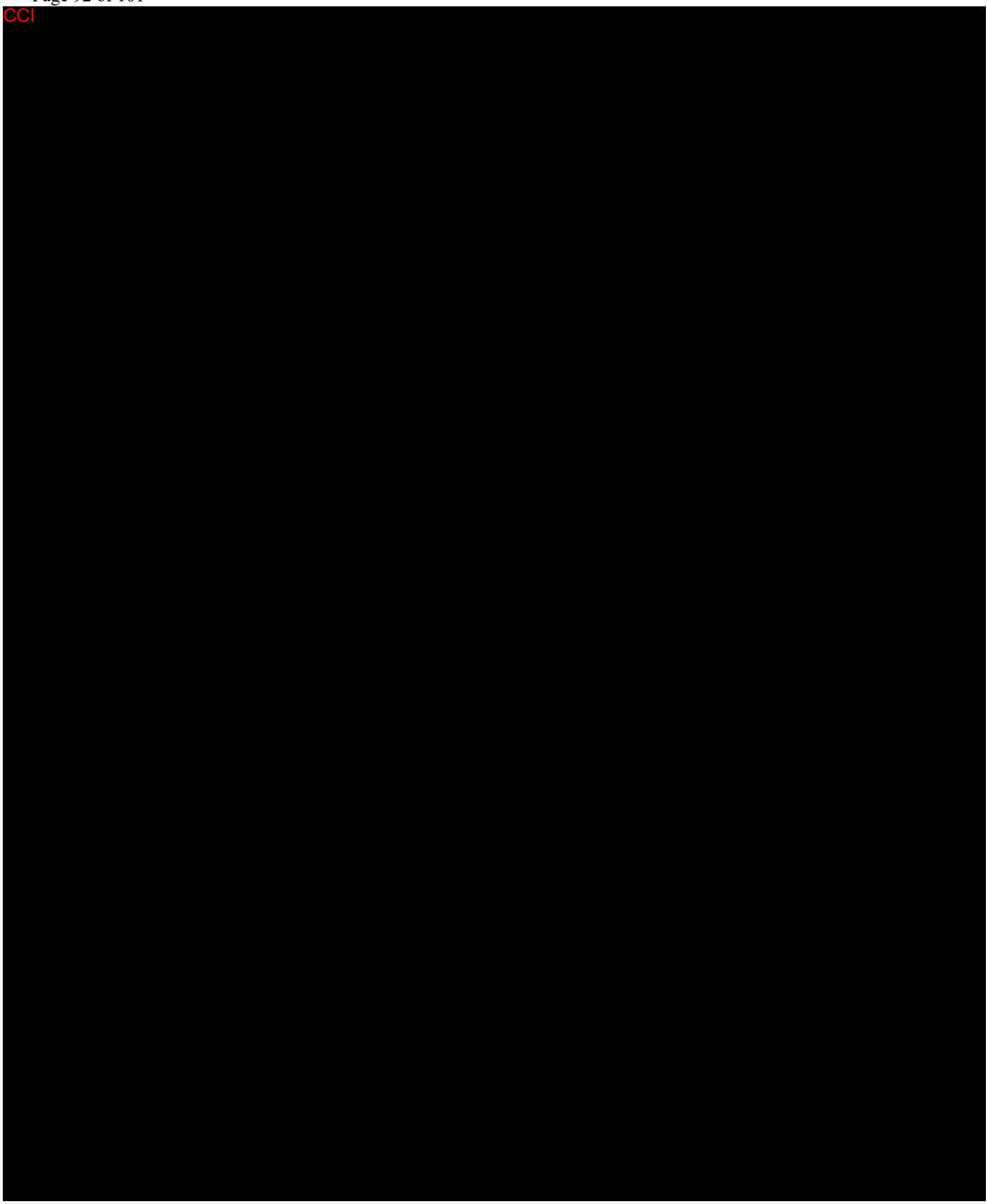

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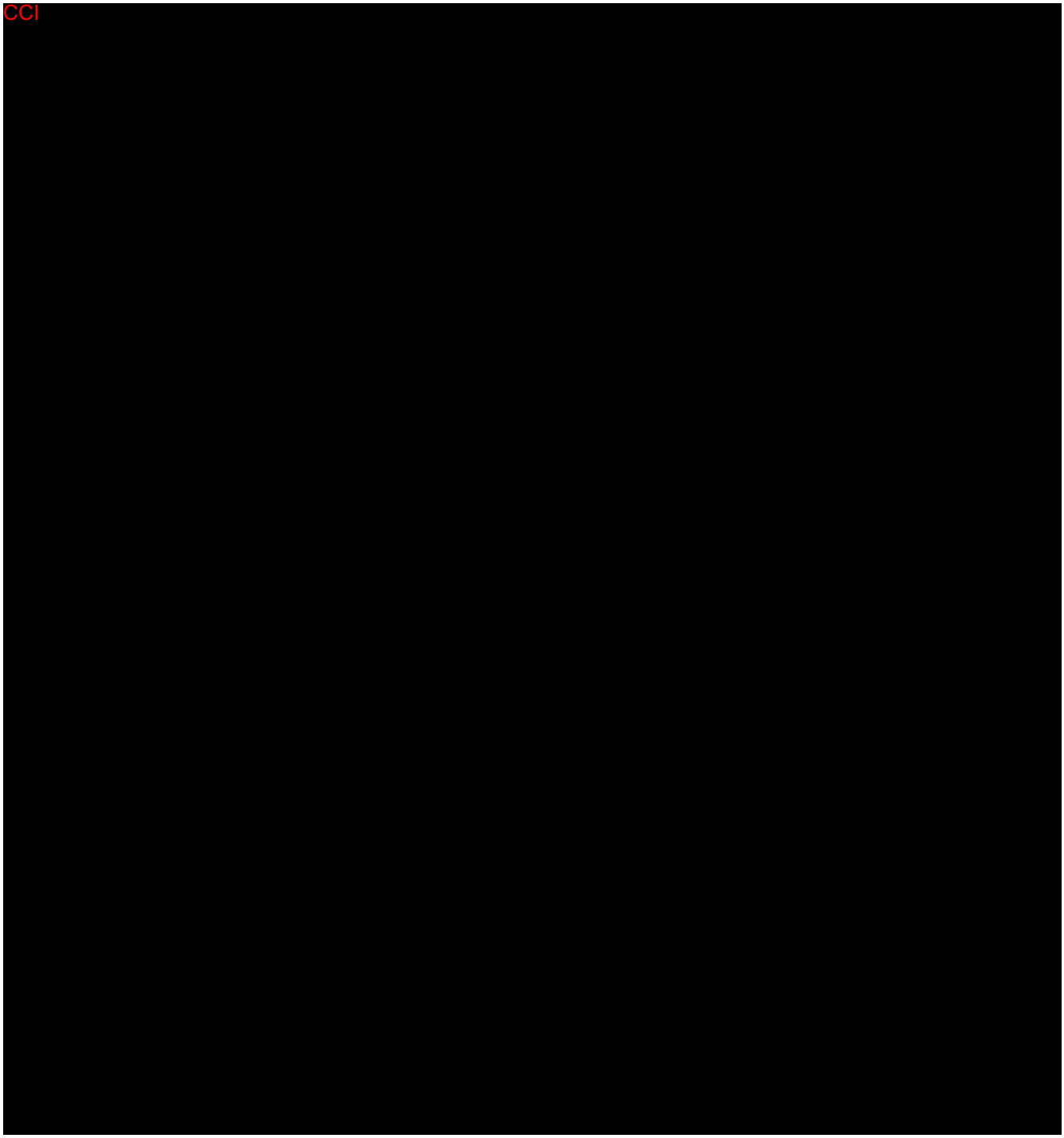

## 14.5 Acne Lesion Count

Lesions within the middle zone (2 cm) including the nose, under the jawline or along the hairline (including eyebrows) will **not** be included in the counts.

**Right Forehead**:
Open comedones: _____
Closed comedones: _____
Papules: _____
Pustules: _____
Nodules: _____
Cysts: _____

**Left Forehead**:
Open comedones: _____
Closed comedones: _____
Papules: _____
Pustules: _____
Nodules: _____
Cysts: _____

**Right Cheek**:
Open comedones: _____
Closed comedones: _____
Papules: _____
Pustules: _____
Nodules: _____
Cysts: _____

**Left Cheek**:
Open comedones: _____
Closed comedones: _____
Papules: _____
Pustules: _____
Nodules: _____
Cysts: _____

**Right Chin**:
Open comedones: _____
Closed comedones: _____
Papules: _____
Pustules: _____
Nodules: _____
Cysts: _____

**Left Chin**:
Open comedones: _____
Closed comedones: _____
Papules: _____
Pustules: _____
Nodules: _____
Cysts: _____

## 14.6 Investigator Notification of Ingredient Patch Test Results

**Dear <u>Investigator,</u>**

The accompanying form provides results of the ingredient patch testing for the topical study drug in Galderma clinical protocol: 202395.

If results for any of tested ingredients are positive or equivocal, please advise the subject to contact his/her primary care physician for further information (**this should be a physician different than the study investigator(s), to maintain the study blind**).

This contact should be made no later than 5 business days after the date of receiving the ingredient test results.

The subject should provide the primary care physician with the form appended to this letter containing blinded test results, and discuss whether it is relevant to unblind the results. If the decision is to unblind, the physician should contact the Clinical Safety Officer (contact details provided on the form).

Sincerely,

Study No.: **202395** Subject No.: _____

Dear < subject's primary care provider – **not affiliated with the clinical study** >

Please be informed that _____ (subject's name) took part in protocol 202395, "***Evaluation of the risk of atrophic acne scar formation during treatment of acne vulgaris subjects with trifarotene 50 µg/g cream versus vehicle cream over 24 weeks***"

During the performance of the rechallenge patch test, it appeared that the subject presented a hypersensitivity reaction to the topical study drug. Subsequent patch testing was performed including each of the individual chemical compounds (excipients) and active substance that comprise the topical study drug formulation. The purpose is to identify the chemical compound(s) that may be causing this reaction.

Because this study is blinded, we are not able to reveal which chemical compound(s) is causing this reaction. If you consider that knowing the agent that is causing this reaction is relevant to the subject's health status and that may be decisive in care management, please, send this form to the study Sponsor or representative by using the contact details below:

Advanced Clinical Pharmacovigilance: DrugSafetyPV@advancedclinical.com

**Please mention the study ID (RD.06.SPR.202395) and "ingredient test results" in your message subject.**

Within 5 business days you should receive the unblinded test results.

| **Blinded Ingredient Codes** | **Test Result** |
|---|---|
| | |
| | |
| | |
| | |
| | |
| | |

Principal investigator: _____ Date: _____

***Name / Signature***

## INVESTIGATOR SIGNATURE PAGE

**Protocol Title**: Evaluation of the risk of atrophic acne scar formation during treatment of acne vulgaris subjects with trifarotene 50 µg/g cream versus vehicle cream over 24 weeks

**Protocol Number:** RD.06.SPR.202395

**Confidentiality and Current Good Clinical Practice (GCP)/E6(R2) Compliance Statement**

- I, the undersigned, have reviewed this protocol, including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), GCP, and relevant International Council for Harmonisation guidelines.
- I am thoroughly familiar with the appropriate use of the study drug as described in this protocol and any other available information (e.g., approved product labeling, investigator's brochure, etc)
- Once the protocol has been approved by the independent ethics committee (IEC)/institutional review board (IRB), I will not modify this protocol without obtaining prior approval of Galderma R&D and of the IEC/IRB. I will submit the protocol amendments and/or any informed consent form modifications to Galderma R&D and the IEC/IRB, and approval will be obtained before any amendments are implemented.
- I ensure that all persons or party assisting me with the study are adequately qualified and informed about the Galderma R&D study drug and of their delegated study-related duties and functions as described in the protocol.
- I ensure that source documents and study records that include all pertinent observations on each of the site's study subjects will be attributable, legible, contemporaneous, original, accurate, and complete.
- I understand that all information obtained during the conduct of the study with regard to the subject's state of health will be regarded as confidential. No subject's name will be disclosed. All subjects will be identified by assigned numbers on all case report forms, laboratory samples, or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.
- Information developed in this clinical study may be disclosed by Galderma R&D to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

_____

Investigator Name (print) Investigator Signature

_____

Investigator Title Date (DD-Mmm-YYYY)

_____

Institution