Name	Reason for Signature	Date
PPD	Approver	PPD

CLINICAL TRIAL PROTOCOL

PROTOCOL NUMBER: RD.06.SPR.204245

CONFIDENTIAL

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TITLE PAGE

Title Evaluation of acne-induced hyperpigmentation during treatment of acne vulgaris subjects with trifarotene 50 µg/g cream versus vehicle cream over 24 weeks.		
Project Name or CD number: CD5789	**Project Number:** 1294	**Clinical Trial Phase:** IV

CCI [redacted]

EudraCT Number 2021-003608-41

SPONSOR:

Name:	**GALDERMA RESEARCH & DEVELOPMENT, LLC**
Address:	PPD
Telephone:	PPD
Name:	**GALDERMA S.A.**
Address:	PPD
Telephone:	PPD

For any safety questions, please contact the Clinical Safety Officer (Drug Safety physician/Medical Monitor**) using the contact details provided in Section 6.3.6.2.2**

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

Name and Title:	PPD – Medical Monitor
Address:	PPD
Telephone:	PPD
E-mail:	PPD

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

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1 SYNOPSIS

Clinical Trial Title: Evaluation of acne-induced hyperpigmentation during treatment of acne vulgaris subjects with trifarotene 50 µg/g cream versus vehicle cream over 24 weeks.	
Short Title: Ak**L**ief **E**valuation in **A**cne-induced **P**ost-Inflammatory Hyperpigmentation **(LEAP)**	
Clinical Trial Phase:	IV
Clinical Trial Population:	Subjects with moderate facial acne vulgaris
Clinical Trial Objectives:	The purpose of this study is to evaluate the efficacy and safety of Trifarotene 50 µg/g cream compared to its vehicle cream in the treatment of moderate acne vulgaris with acne-induced post-inflammatory hyperpigmentation (PIH) in subjects with Fitzpatrick Skin Types I-VI.
Clinical Trial Design:	Multi-center, randomized, controlled, double-blinded, vehicle-controlled, parallel-group study vs vehicle in subjects with Fitzpatrick Skin Types I-VI with moderate acne vulgaris on the face treated with trifarotene 50 µg/g cream once daily for 24 weeks.
Total number of subjects:	Approximately 120 subjects are planned to be randomized in a CCI ratio (i.e., approximately 60 in each group). Target enrollment should include an approximate distribution of 30% Fitzpatrick Skin Types I-III (light skin) and 70% IV-VI (dark skin).
Number of clinical trial centers:	Approximately 20 sites
Region(s) / country(ies) involved:	Germany, Spain, and United States
Enrollment Period	Approximately 6 months after the Investigator Meeting
Duration of subject participation:	The expected duration for each subject's participation in the study is 7 months. 10 visits (Screening, Baseline, Week 1, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24).
Inclusion criteria	Subjects must fulfill inclusion criteria to participate in the study. 1. Male or female subject of any ethnic background of at least 13-35 years old, 2. Subject with clinical diagnosis of acne vulgaris and PIH, defined by: a) moderate acne on the face (acne IGA=3); b) with minimum of 20 inflammatory lesions and 25 non inflammatory lesions on the face (excluding the nose); c) moderate to marked PIH on the face (ODS hyperpigmentation scale 4-6); d) No more than one acne nodule or cyst (≥ 1 cm) on face (excluding the nose), 3. Subject with any Fitzpatrick Skin Type I to VI (target patient enrollment according to FST), 4. Female subjects of childbearing potential must have a negative urine pregnancy test (UPT) at Baseline visit (Visit 2),

Clinical Trial Title: Evaluation of acne-induced hyperpigmentation during treatment of acne vulgaris subjects with trifarotene 50 µg/g cream versus vehicle cream over 24 weeks.	
	5. Female subjects of childbearing potential (ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile) must agree either to commit to true abstinence throughout the study, when this is in line with the preferred and usual lifestyle of the subject, or to use an adequate and approved method of contraception throughout the study. This criterion also applies to a prepubertal female subject who begins menses during the study. * In Germany only, if a subject has reached Tanner stage 3 breast development, even if not having menarche, the subject will be considered a female of childbearing potential. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception Adequate and approved methods of contraception applicable for the subject and/or her partner are defined below: • Progestogen-only oral hormonal contraception • Combination of male condom with cap, diaphragm, or sponge with spermicide (double barrier methods) (*In Germany only, double barrier methods are not considered an adequate and approved method of contraception). Note: "double barrier methods" refers to simultaneous use of a physical barrier by each partner. Use of a single barrier method (e.g. condom) together with a spermicide is not acceptable. • Combined (estrogen- and progestogen-containing) oral, intravaginal, or transdermal hormonal contraception • Injectable or implanted hormonal contraception • Intrauterine devices or intrauterine hormone-releasing system • Bilateral tubal ligation or tube insert (such as the Essure system) at least 3 months before the study • Bilateral vasectomy of partner at least 3 months before the study 6. Female subjects of non-childbearing potential, e.g.: premenses, post-menopausal (absence of menstrual bleeding for 1 year prior to Baseline, without any other medical reason), hysterectomy, bilateral salpingectomy, or bilateral oophorectomy, 7. Subject having read, understood and signed the approved Informed Consent Form (ICF) prior to any participation in the clinical trial. Subject under the age of 18 having signed an assent form to participate in the clinical trial and their parent(s) or legal representative having read and signed the informed consent form prior to any clinical trial related procedures, samples and photos are collected, 8. Apprised of the Health Insurance Portability and Accountability Act (HIPAA), if in the US and is willing to share personal information and data, as verified by signing a written authorization at the screening visit. 9. Subject willing and able to comply with the requirements of the trial protocol. Subject must adhere to the visit schedule, concomitant therapy prohibitions, and must be compliant to the treatment. (for subjects who are minors, the

<table>
<tr><td colspan="2">Clinical Trial Title: Evaluation of acne-induced hyperpigmentation during treatment of acne vulgaris subjects with trifarotene 50 µg/g cream versus vehicle cream over 24 weeks.</td></tr>
<tr><td></td><td>parent(s)/legal representative must be also willing and able to help the subject comply with study requirements).</td></tr>
<tr><td>Exclusion criteria</td><td>Subjects meeting any of the exclusion criteria are not eligible to participate in the study.
1. Subject with severe acne (IGA > 3),
2. Subject with more than 1 nodule/cyst on the face (excluding the nose),
3. Subject with acne conglobata, acne fulminans, secondary acne (chloracne, drug-induced acne, etc.), nodulocystic acne, acne requiring systemic treatment,
4. Subject with damaged facial skin (e.g., tattoo, skin abrasion, eczema or sunburned skin) that may interfere with study assessments,
5. Female subject who is pregnant, lactating or planning a pregnancy during the study,
6. Female subject of childbearing potential using combined oral contraceptives approved as acne treatments (e.g., Ortho Tri-Cyclen®, Yaz®, Diane-35®), in whom the dose has not been stable for at least 6 months prior to the Baseline visit,
7. Subject with known impaired hepatic or renal functions,
8. Subject with a wash-out period for topical treatment or procedures on the face less than:
<table>
<tr><td>Topical treatments: Corticosteroids, antibiotics, benzoyl peroxide, azelaic acid, hydroxyacids, Zinc containing treatments, other anti-inflammatory drugs or other acne treatments (for example salicylic acid treatments/ transdermal contraceptives are forbidden if used to treat acne)</td><td>2 Weeks</td></tr>
<tr><td>Retinoids (including fixed drug combinations)</td><td>4 Weeks</td></tr>
<tr><td>Cosmetic/aesthetic procedures on the face (e.g., comedone extraction, desquamating, or abrasive agents, adhesive cleansing strips)</td><td>1 Week</td></tr>
<tr><td>Wax epilation</td><td>2 Weeks</td></tr>
<tr><td>Photodynamic therapy</td><td>6 Weeks</td></tr>
<tr><td>Laser therapy, microdermabrasion, deep chemical peel, plastic surgery for acne</td><td>3 months</td></tr>
</table>
9. Subject with a wash-out period for systemic treatment less than:
<table>
<tr><td>Corticosteroids, (except locally acting corticosteroids such as inhaled or intrathecal or dermal application at distance from the face), tetracyclines, other antibiotics (except penicillin)</td><td>1 month</td></tr>
<tr><td>Oral retinoids/isotretinoin</td><td>6 months</td></tr>
</table></td></tr>
</table>

Clinical Trial Title: Evaluation of acne-induced hyperpigmentation during treatment of acne vulgaris subjects with trifarotene 50 µg/g cream versus vehicle cream over 24 weeks.

	Cyproterone acetate / Chlormadinone acetate: 6 months Spironolactone/ Drospirenone: 3 months Immunomodulators: 3 months Oral contraceptives for acne: 1 month Note: No time frame period is specified for medicated shaving creams, after-shaves, colognes, astringents, or preparations with alcohol, but their application is prohibited during the study. 10. Subject with active or chronic skin allergies, 11. Subject with known or suspected allergy to the investigational product, 12. Subject who has used tanning booths or lamps or had excessive ultraviolet (UV) radiation exposure within 1 month prior to clinical trial entry or foresees intensive UV exposure during the study (mountain sports, sailing, sunbathing, etc.), 13. Subject who is at risk in terms of precautions, warnings, and contraindications, 14. Subject with a beard or other facial hair that might interfere with study assessments, 15. Subject with an acute / chronic disease or a history of major medical or psychiatric condition or surgical interventions that, in the opinion of the investigator, might put the subject at risk, 16. Subject under guardianship, hospitalized subject in a public or private institution for a reason other than the research, and subject deprived of his/her freedom, 17. Subject who has participated in another investigational drug or device research study within 30 days prior to enrollment OR is in an exclusion period from a previous clinical trial, 18. Subject who is unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function.
Investigational Products:	**Trifarotene –** refer to Study Schema
Drug substance:	Trifarotene (CD5789) Cream
Trade name:	AKLIEF®
Dose form:	Cream
Strength/Concentration	50 µg/g
Administration:	Topical Apply a thin layer to the face once daily, in the evening. The face should be washed with provided cleanser and patted dry, before use. One pump actuation should be enough to cover the face (i.e., forehead, cheeks, nose, and chin).
Duration:	24 weeks
Investigational Products:	**Trifarotene vehicle –** refer to Study Schema

<table>
<tr><td colspan="2">Clinical Trial Title: Evaluation of acne-induced hyperpigmentation during treatment of acne vulgaris subjects with trifarotene 50 µg/g cream versus vehicle cream over 24 weeks.</td></tr>
<tr><td>Name:
Trade Name:
Dose form:
Strength/Concentration
Administration:

Duration:</td><td>Trifarotene vehicle
-
Cream
-
Topical
Apply a thin layer to the face once daily, in the evening. The face should be washed with provided cleanser and patted dry, before use.

One pump actuation should be enough to cover the face (i.e., forehead, cheeks, nose, and chin).
24 weeks</td></tr>
<tr><td>Non-Investigational Study Products Provided By Sponsor:</td><td>For use by all subjects on the face for 24 weeks.<table><tr><th>Cetaphil® Gentle Skin Cleanser* (Code 1747)</th><th>Cetaphil® Dermacontrol Moisturizer SPF 30* (Code 494)</th><th>Cetaphil® Moisturizing Lotion* (Code 1745)</th></tr><tr><td>Topical, for face washing twice daily in the morning and in the evening.</td><td>Topical, for use daily on the face (morning) and to be re-applied to face before sun exposure.</td><td>Topical, extra moisturizer to be used as needed.</td></tr></table>* Commercial name may differ across countries.</td></tr>
<tr><td>Study Assessments</td><td>The following study assessments will be performed according to the frequency specified in the schedule of assessments (see Section 5.1.1):

Efficacy:

PIH
Investigator performed activities:
• Overall Disease Severity hyperpigmentation scores (9-point scale) from 0 (Clear) to 8 (Severe) at Screening, Baseline, Week 12, 16, 20 and 24 or early termination visits
CCI
  </td></tr>
</table>

Clinical Trial Title: Evaluation of acne-induced hyperpigmentation during treatment of acne vulgaris subjects with trifarotene 50 µg/g cream versus vehicle cream over 24 weeks.	
	CCI [redacted]
	Safety: • Recording of adverse event(s) at each study visit • Local tolerability on the face assessed for each individual sign (erythema, scaling, dryness, and stinging/burning) at each study visit
	CCI [redacted]

Clinical Trial Title: Evaluation of acne-induced hyperpigmentation during treatment of acne vulgaris subjects with trifarotene 50 µg/g cream versus vehicle cream over 24 weeks.	
Study Variables Analyzed **Efficacy:**	**Primary efficacy variables:** • Absolute change from Baseline in PIH Overall Disease Severity scores at Week 24 **Secondary efficacy variables** **PIH** • Percent change from Baseline in PIH Overall Disease Severity scores at Week 24 • Absolute and percent change from Baseline in PIH Overall Disease Severity scores at Week 12, 16 and 20
Quality of Life/Subject-Reported Outcomes:	CCI [redacted]
Safety:	• Incidence of Adverse Events • Local tolerability (erythema, scaling, dryness and stinging/burning)
Other variables:	CCI [redacted]
Principal statistical method:	CCI [redacted]

Clinical Trial Title: Evaluation of acne-induced hyperpigmentation during treatment of acne vulgaris subjects with trifarotene 50 µg/g cream versus vehicle cream over 24 weeks.	
	CCI [redacted]
	Efficay Analysis **Primary** • Absolute change from Baseline in PIH Overall Disease Severity scores of the face will be analyzed at Week 24 using an ANCOVA with treatment, analysis center and Baseline score as fixed effects; the p-values for the treatment comparison, estimates of the treatment difference and the 95% confidence interval of the difference will be generated from the ANCOVA model.

Clinical Trial Title: Evaluation of acne-induced hyperpigmentation during treatment of acne vulgaris subjects with trifarotene 50 µg/g cream versus vehicle cream over 24 weeks.	
	Secondary • Percent change from Baseline in PIH Overall Disease Severity scores will be analyzed at Week 24 using an ANCOVA with treatment, analysis center and Baseline score as fixed effects; the p-values for the treatment comparison, estimates of the treatment difference and the 95% confidence interval of the difference will be generated from the ANCOVA model. • Absolute and percent change from Baseline in PIH Overall Disease Severity scores will be analyzed at Week 12, 16 and 20 using an ANCOVA with treatment, analysis center and Baseline score as fixed effects; the p-values for the treatment comparison, estimates of the treatment difference and the 95% confidence interval of the difference will be generated from the ANCOVA model. CCI [redacted]

Clinical Trial Title: Evaluation of acne-induced hyperpigmentation during treatment of acne vulgaris subjects with trifarotene 50 µg/g cream versus vehicle cream over 24 weeks.	
	CCI **Safety** • Local tolerability scores (erythema, scaling, dryness and stinging/burning) of the 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 version 23.0 or later).

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
CDMS	Clinical Data Management System
CR	Copy Reference
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization – Parexel
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
FSI	First Subject In (first subject screened, i.e., who signs the Informed Consent Form)
FST	Fitzpatrick Skin Type
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
IL	Inflammatory Lesions
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intention-to-treat
IUD	Intrauterine Device
LOAEL	Lowest-observed-adverse-effect level
LOCF	Last Observation Carried Forward
LSI	Last Subject In (Last subject enrolled/randomized)
LSO	Last Subject Out (Last subject who completed his/her last clinical trial visit)

Abbreviation	*Term*
CCI	CCI
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
PIE	Post-Inflammatory Erythema
PIH	Post-Inflammatory Hyperpigmentation
PK	Pharmacokinetics
PP	Per-Protocol
PT	Preferred term
CCI	CCI
RAR	Retinoic Acid Receptor
RXR	Retinoic X Receptor
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAF	Safety
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 is one of the most common skin disorders treated by dermatologists. While acne is highly prevalent in youth with around 85% of teenagers affected at some point in time. As shown in an epidemiological study (Alexis, 2007 and Canavan 2016) and by Halder and his group (Halder 1983) that the diagnosis of acne was the most common diagnosis in both light and white patients across all Fitzpatrick skin phototypes (1-VI) (Halder 1983, Kligman 1958, Taylor 2002, Pochi 1988, and Callender 2004). Post-inflammatory dyspigmentation in darker skin phototypes (IV-VI), often referred as hyperpigmentation (PIH). However, in patients with lighter Fitzpatrick Skin Types (I-III), the post-inflammatory dyspigmentation may be hyperpigmentation (PIH) and maybe discrete erythematous macules, post-inflammatory erythema (PIE), as any resolving cutaneous inflammatory process may have residual erythema or pigmentation. (Yoon-Soo 2013)

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

As acne is a chronic and relapsing disease normalizing follicular desquamation is then the key to achieve and maintain control of acne. Today it is established that retinoids such as trifarotene acts in the pathology of Acne vulgaris: they are a potent modulator of inflammation, cellular differentiation and keratinisation. Mechanistically, trifarotene binds to specific retinoic acid nuclear receptors (RAR-γ). Trifarotene is active and stable in keratinocytes but rapidly metabolized by human hepatic microsomes compared to other topical retinoids, leading to improved safety.

Current evidence suggests that topical trifarotene normalizes the differentiation of follicular epithelial cells resulting in decreased microcomedone formation. Topical depigmenting and anti-pigmenting activity of trifarotene was shown in in vivo studies lasting 6 weeks in the SKH2 mouse. Unlike other retinoids, and potentially due to a weaker penetration in hyperkeratotic tail skin, adapalene 0.1% showed no significant depigmenting activity after 6 weeks of topical application on the SKH2 mouse tail. In contrast, trifarotene showed significant depigmenting activity at 0.01% on the pigmentation score at day 43. After UVR induction, in the same mouse model, the anti-pigmenting activity of trifarotene was again highly statistically significant. (Aubert 2018).

Post-inflammatory hyperpigmentation occurs at the site of acne inflammatory lesions and its severity correlates with the severity of the inflammatory process. It is, at least partially, reversible, however, it may take several months before it resolves spontaneously, causing considerable disfigurement and distress (Grimes 2006). Post-inflammatory hyperpigmentation is frequently resistant to single modality treatments and only topical retinoids have been proven

slightly efficacious in well-designed controlled studies with long term treatments of 18 to 40 weeks (Bulengo-Ransby 1993). In acne, this post inflammatory process might be prevented by reducing inflammation using timely and judicious treatments with concomitant sun protection (Kubba 2009). The management of post-inflammatory hyperpigmentation should therefore begin with the treatment of the underlying inflammatory dermatosis.

Topical retinoids are used for the management of acne (Taylor 2009) and are therefore of interest in the treatment of post acne post-inflammatory hyperpigmentation. For example, topical tretinoin, a first-line treatment for mild-to-moderate acne has been shown to reduce the appearance of PIH, but it has also been shown to lighten normal skin. The ideal treatment for acne-induced hyperpigmentation in patients with acne would be a single agent that is effective against both acne-induced hyperpigmentation and acne lesions. Although most treatments are effective against only one of these conditions, topical retinoids are an important exception because they offer efficacy against both. Additionally, topical retinoids are beneficial for skin of color as they treat not only the active acne lesions, but also help ameliorate PIH (Davis 2010).

Their mechanism of action includes inhibition of toll-like receptor (TLR)-2, reduction of the formation of hyper-proliferative keratins, and inhibition of the AP-1 pathway, thereby reducing inflammation (Taylor 2009). An additional property of topical retinoids that makes these agents appealing for use in skin of color patients is their ability to improve PIH by inhibition of melanosome transfer and facilitating melanin dispersion and removal (Davis 2010 and Yin 2014). In this regard, an open label trial, without placebo control, suggested adapalene monotherapy in patients with mild to moderate acne vulgaris could both prevent and reduce acne-associated hyperpigmentation in persons of color (Jacyk 2001). However, older generation retinoids are also known to induce irritation which may in turn generate post inflammatory pigmentation (Davis 2010). Skin hyperpigmentation: 1/1220 (0.1%) for active and 0/1200 for vehicle. Application site discoloration: 2/1220 (0.2%) for active and 0/1200 for vehicle. Trifarotene, a new generation topical retinoid with its uniquely selective mechanism of action on RAR-ɤ, induces less irritation and may therefore be an ideal topical agent for both the management of acne and the treatment of acne-induced hyperpigmentation associated with it.

A major concern with the use of topical retinoids in skin of color includes the potential for inducing a retinoid dermatitis, which is characterized by xerosis, peeling, and erythema of the skin (Taylor 2009). There are several ways to mitigate this adverse effect and prevent further worsening of acne-induced pigmentation. These include initiating patients on lower concentrations of topical retinoids, or choosing cream or lotion (over gel). Trifarotene, being a selective RAR-ɤ agonist with low concentration and in cream formulation would be appropriate for use in PIH acne. Also, the addition of a topical gentle moisturizer (Davis 2010, Yin 2014, and Taylor 2009) and avoiding sun exposure is recommended as part of the skin care regimen in acne patients. 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 2012, Del Rosso 2013, and Zeichner, 2011). As exposure to UV radiation is known to contribute to pigment disorders including PIH, solar protection is a key element in its management (Khemis 2007).

To ensure reliability of the efficacy assessments, patients will be instructed to avoid sun exposure during the course of the study and to use at least twice-daily a broad-spectrum sunscreen (SPF 30+). Moisturizing cream will also be provided for daily use to limit irritation. Also, using an appropriate cleanser will reduce oil on the face and will not affect skin hydration or the skin barrier function.

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

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

3.2 Risk/Benefit Assessment

The most serious risk associated with retinoids is related to teratogenicity and embryotoxicity. CD5789, like all retinoids, may cause fetal harm following systemic exposure in pregnant women. Therefore, 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. Postmenopausal status, where relevant, will be assessed and confirmed prior to subject participation in the study.

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

Long-term safety data for the trifarotene product have shown that the safety profile remains stable with a long-term use. Therefore, given the documented effectiveness of trifarotene cream 50 µg/g in the treatment of acne, the benefit/risk of 6 months' exposure to treatment with trifarotene or vehicle is considered to be positive.

Any subject is free to discontinue his/her participation in this clinical trial at any time and for whatever reason, specified or unspecified, 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.

No invasive methods will be used during this trial.

Subjects will be followed regularly during the trial, especially for adverse events, approximately once a month for 6 months.

Consequently, based on available safety data and the proposed trial design, no safety issues others than those reported are expected following topical administration of trifarotene cream.

3.3 Drug Profile

Retinoids play a central part in the treatment of acne due to their keratolytic activity and modulation of proliferation and differentiation of keratinocytes leading to the elimination of comedones (Pawin 2004).

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

CCI

3.4 Dose Selection Rationale

Trifarotene cream 50µg/g when applied once daily for 12 weeks has been shown to be safe and effective in the treatment of acne vulgaris, with FDA-approval for US commercial use granted in October 2019 (Appendix 14.8 – AKLIEF Prescribing Information).

The commercially-approved trifarotene dosing regimen will be used to evaluate efficacy and safety of trifarotene 50 µg/g cream versus vehicle cream on the risk of formation of acne-induced post-inflammatory hyperpigmentation.

4 STUDY OBJECTIVE AND ENDPOINTS

4.1 Study Objective

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

4.2 Study Endpoints

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

4.2.1 Primary Efficacy Endpoint

- Absolute change from Baseline in PIH Overall Disease Severity scores at Week 24

4.2.2 Secondary Efficacy Endpoints

Post-inflammatory Hyperpigmentation:

- Percent change from Baseline in PIH Overall Disease Severity scores at Week 24
- Absolute and percent change from Baseline in PIH Overall Disease Severity scores at Week 12, 16 and 20.

CCI

[redacted]

4.2.4 Safety

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

CCI [redacted]

5 INVESTIGATIONAL PLAN

5.1 Overall Study Design

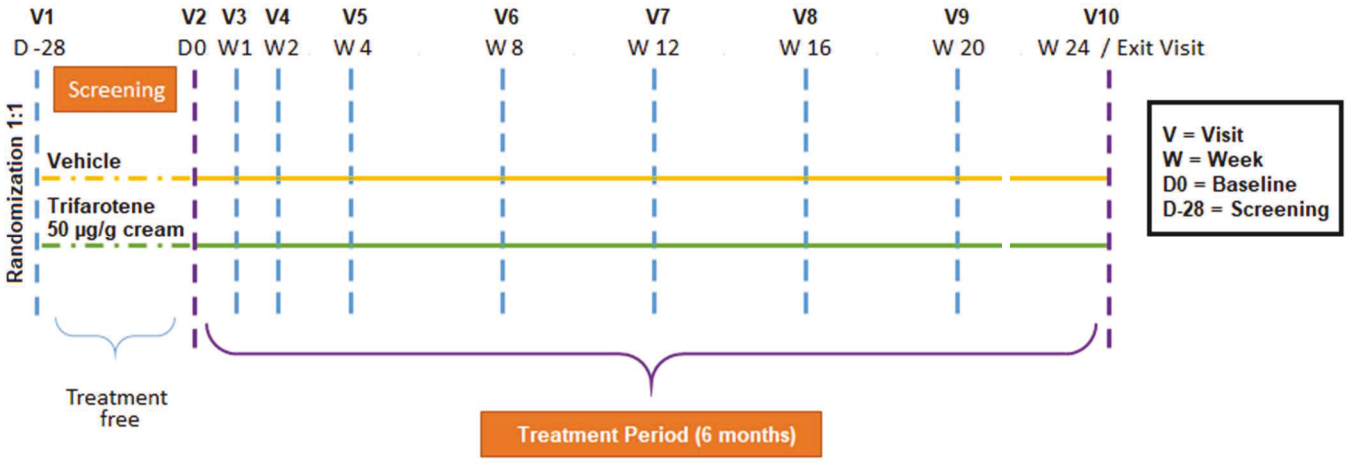
This is a multi-center, randomized (1:1), double-blind, vehicle-controlled, parallel-group study evaluating trifarotene cream in treating acne-induced hyperpigmentation in patients with acne. Approximately 120 randomized subjects aged 13-35 are planned, at approximately 20 study centers in the United States and Europe. Target enrollment should include an approximate distribution of Fitzpatrick Skin Types, 30% light skin (I-III) and 70% dark skin (IV-VI).

Subject eligibility will be evaluated over a 28-day screening period. Qualifying subjects will complete Baseline assessments and be randomized (1:1) to Trifarotene or Vehicle for a 24-week treatment period. Subjects will be provided skin care products including Cetaphil® Gentle Skin Cleanser for washing the face twice daily (morning and evening); Cetaphil® Dermacontrol Moisturizer with SPF 30 for use daily on the face (morning) and to be re-applied to face before sun exposure, and Cetaphil® Moisturizing Lotion for extra moisturizer as needed. If a subject experiences persistent dryness or irritation, the investigator may consider a reduced application frequency for the topical study drug, over a maximum of 2 weeks, within the first four (4) weeks of the treatment period (Section 5.4.8 – Dose Modification of Topical Study Drug).

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

Subjects will return to the clinic for safety and efficacy assessment at Weeks 1, 2, 4, 8, 12, 16, 20 and 24. Study procedures and assessments are performed according to the schedule of assessments (Section 5.1.1).

Study Schema



5.1.1 Schedule of Assessments

5.1.1.1 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 acne assessments (IGA, lesion counts), local tolerability assessment and imaging.

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

- Remote Visits (phone, etc) in lieu of scheduled office visits
  - for safety and wellness assessment (concomitant medications, AEs, etc)
- Questionnaire completion
  - sent to subject by email or mail
  - subject signs, dates and returns, by email of mail.
- Collection of previously dispensed study drugs and dosing calendar, from an adult family member
  - Weighing of returned topical study drug is required
  - A follow-up phone call with the subject is required to review the dosing calendar and returned study drugs, for appropriate clarification in study medication use.

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

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

Subjects must be present in the office for the following assessments:

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

5.1.1.2 Study Assessment Schedule

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

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

PROCEDURES	CLINICAL TRIAL VISITS									
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**
	Screening (Up to 28 days prior to Baseline)	**Baseline**	**Week 1** (±1 d)	**Week 2** (±1 d)	**Week 4** (±3 d)	**Week 8** (±3 d)	**Week 12** (±3 d)	**Week 16** (±3 d)	**Week 20** (±3 d)	**Week 24** (±5 d) or ET
Return of investigational products and accountability					X	X	X	X	X	X
Subject Diary/Compliance[d]			X	X	X	X	X	X	X	X
Exit form										X

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

5.2 Discussion of Study Design

This study will evaluate acne-induced hyperpigmentation during treatment of acne vulgaris subject with trifarotene 50 µg/g cream versus vehicle cream over 24 weeks.

This is a Phase 4 clinical study to assess the effect of commercially-marketed AKLIEF® (trifarotene) 50 µg/g cream, when used according to its labeling information (indication, selected population, dose regimen) for the treatment of acne lesions to evaluate the risk of post-inflammatory pigment formation.

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, which include two early visits for additional safety checks and subject counselling (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 2019).

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:

- Post-inflammatory hyperpigmentation appears secondarily to acne lesions and may correspond to 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 evaluate the clinical outcomes associated with treatment of acne lesions.
- PIH reflects an acquired increase in cutaneous pigmentation induced by inflammation. This acquired excess pigment may be present in the epidermis, dermis, or both. Cutaneous inflammatory response results in release and subsequent oxidation of arachidonic acid to prostaglandins, leukotrienes, and other mediators. These products of inflammation alter the activity of both immune cells and melanocytes. In the epidermis, the effect is stimulation of melanocytes, with consequent increase in the synthesis of melanin and its transfer to the keratinocytes. In the dermis, the excess melanin is derived from pigmentary incontinence resulting from incidental damage to the melanocytes residing in the basal layer. Dermal melanin is phagocytosed by macrophages (melanophages). PIH occurs in areas of acne papules, pustules, and nodules, and its severity correlates with the severity of the inflammatory process and the underlying propensity based on the skin type. However, it may take several months to resolve spontaneously.
- Retinoids are useful in the treatment of hyperpigmentation because they reduce epidermal melanin by blocking the transcription of tyrosinase, inducing desquamation, dispersing

keratinocyte pigment granules and enhance epidermal cell turnover via epidermopoiesis. (Geria 2011).

- 24 weeks of trifarotene 50 µg/g cream treatment is considered adequate to allow for potential improvement of underlying acne-induced hyperpigmentation, and to observe any effects thereof that may translate to clinical improvement of post-inflammatory hyperpigmentation (PIH).

Overall, the study design is considered to be scientifically robust and clinically relevant for evaluating trifarotene cream for the treatment of acne lesions to assess the effect of such such treatment on post-inflammatory pigment formation.

5.3 Selection of Study Population

5.3.1 Number of Planned Subjects

Approximately 120 subjects are planned to be randomized in a [redacted] ratio (i.e. approximately 60 per group), active to vehicle. Target enrollment should include an approximate distribution of Fitzpatrick skin phototypes, 30% light skin (I-III) and 70% dark skin (IV-VI).

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 of any ethnic background of at least 13-35 years old,
2. Subject with clinical diagnosis of acne vulgaris, defined by:
    a) moderate acne on the face (IGA=3);
    b) with minimum of 20 inflammatory lesions and 25 non inflammatory lesions on the face (excluding the nose);
    c) moderate to marked PIH on the face (ODS hyperpigmentation scale 4-6);
    d) No more than one acne nodule or cyst (≥ 1 cm) on the face (excluding the nose),
3. Subject with any Fitzpatrick Skin Type I to VI (target patient enrollment according to FST),
4. Female subjects of childbearing potential must have a negative urine pregnancy test (UPT) at Baseline visit (Visit 2),
5. Female subjects of childbearing potential (ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile) must agree either to commit to true abstinence throughout the study, when this is in line with the preferred and usual lifestyle of the subject, or to use an adequate and approved method of contraception throughout the study. This criterion also applies to a prepubertal female subject who begins menses during the study.

*In Germany only, if a subject has reached Tanner stage 3 breast development, even if not having menarche, the subject will be considered a female of childbearing potential. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Adequate and approved methods of contraception applicable for the subject and/or her partner are defined below:

- Progestogen-only oral hormonal contraception
- Combination of male condom with cap, diaphragm, or sponge with spermicide (double barrier methods) (*In Germany only, double barrier methods are not considered an adequate and approved method of contraception).

  Note: "double barrier methods" refers to simultaneous use of a physical barrier by each partner. Use of a single barrier method (e.g. condom) together with a spermicide is not acceptable.
- Combined (estrogen- and progestogen-containing) oral, intravaginal, or transdermal hormonal contraception
- Injectable or implanted hormonal contraception
- Intrauterine devices or intrauterine hormone-releasing system
- Bilateral tubal ligation or tube insert (such as the Essure system) at least 3 months before the study
- Bilateral vasectomy of partner at least 3 months before the study

6. Female of non-childbearing potential, e.g.: premenses, post-menopausal (absence of menstrual bleeding for 1 year prior to Baseline, without any other medical reason), hysterectomy, bilateral salpingectomy, bilateral oophorectomy,
7. Subject having read, understood and signed the approved Informed Consent Form (ICF) prior to any participation in the clinical trial. Subject under the age of 18 having signed an assent form to participate in the clinical trial and their parent(s) or legal representative having read and signed the informed consent form prior to any clinical trial related procedure, samples and photos are collected,
8. Apprised of the Health Insurance Portability and Accountability Act (HIPAA), if in the US and is willing to share personal information and data, as verified by signing a written authorization at the screening visit.
9. Subject willing and able to comply with the requirements of the trial protocol. Subjects must adhere to the visit schedule, concomitant therapy prohibitions, and must be compliant to the treatment. (for subjects who are minors, the parent(s)/legal representative must be also willing and able to help the subject comply with study requirements).

5.3.3 Exclusion Criteria

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

1. Subject with severe acne (IGA > 3),
2. Subject with more than 1 nodule/cyst on the face (excluding the nose),
3. Subject with acne conglobata, acne fulminans, secondary acne (chloracne, drug-induced acne, etc.), nodulocystic acne, acne requiring systemic treatment,
4. Subject with damaged facial skin (e.g. tattoo, skin abrasion, eczema or sunburned skin) that may interfere with study assessments,
5. Female subject who is pregnant, lactating or planning a pregnancy during the study,
6. Female subject of childbearing potential using combined oral contraceptives approved as acne treatments (e.g., Ortho Tri-Cyclen®, Yaz®, Diane-35®), in whom the dose has not been stable for at least 6 months prior to the Baseline visit,
7. Subject with known impaired hepatic or renal functions,
8. Subjects with a washout period for topical treatment or procedures on the face less than:

Topical treatments: Corticosteroids, antibiotics, benzoyl peroxide, azelaic acid, hydroxyacids, Zinc containing treatments, other anti-inflammatory drugs or other acne treatments (for example salicylic acid treatments/ transdermal contraceptives are forbidden if used to treat acne)	2 Weeks
Retinoids (including fixed drug combinations)	4 Weeks
Cosmetic/aesthetic procedures on the face (e.g., comedone extraction, desquamating, or abrasive agents, adhesive cleansing strips)	1 Week
Wax epilation	2 Weeks
Photodynamic therapy	6 Weeks
Laser therapy, microdermabrasion, deep chemical peel, plastic surgery for acne	3 months

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

Corticosteroids, (except locally acting corticosteroids such as inhaled or intrathecal or dermal application at distance from the face), tetracyclines, other antibiotics (except penicillin)	1 month
Oral retinoids/isotretinoin	6 months

Cyproterone acetate / Chlormadinone acetate	6 months
Spironolactone/ Drospirenone	3 months
Immunomodulators	3 months
Oral contraceptives for acne	1 month

Note: No time frame period is specified for medicated shaving creams, after-shaves, colognes, astringents, or preparations with alcohol, but their application is prohibited during the study.

10. Subject with active or chronic skin allergies,
11. Subject with known or suspected allergy to the investigational product,
12. Subject who has used tanning booths or lamps or had excessive ultraviolet (UV) radiation exposure within 1 month prior to clinical trial entry or foresees intensive UV exposure during the study (mountain sports, sailing, sunbathing, etc.),
13. Subject who is at risk in terms of precautions, warnings, and contraindications,
14. Subject with a beard or other facial hair that might interfere with study assessments,
15. Subject with an acute / chronic disease or a history of major medical or psychiatric condition or surgical interventions that, in the opinion of the investigator, might put the subject at risk,
16. Subject under guardianship, hospitalized subject in a public or private institution for a reason other than the research, and subject deprived of his/her freedom,
17. Subject who has participated in another investigational drug or device research study within 30 days prior to enrollment OR is in an exclusion period from a previous clinical trial,
18. Subject who is unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral 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.

Table 1: Reasons for Study Discontinuation

Pregnancy:	Withdraw the Subject from the clinical trial and follow the procedure described in Section 6.3.6.2.5
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]:	A position, opinion or judgment reached after consideration by a physician with reference to subject. Explain the reason in the comment section of the Exit Form.
Site Terminated by Sponsor:	An indication that the clinical study was stopped at a particular site by its sponsor.
Study Terminated by Sponsor:	An indication that the clinical study was stopped by its sponsor.
Sponsor Request:	An indication that the study subject was removed from the study at the sponsor's request.
Other[a]:	This category is to be used for a subject who discontinues due to a reason other than as specified in the predefined categories above. Explain the reason for discontinuation in the comment section of the Exit Form.

[a] If reason for discontinuation is "withdrawal by subject" , "withdrawal by parent/guardian", "physician decision" or "other", the subject will be questioned to rule out the possibility of an AE (this should be documented in the comment section of the Exit Form).

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

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

When a subject discontinues the study, he/she will be fully assessed whenever possible, and followed according to guidelines presented in Section 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 drugs.**

The investigator must:

- Follow the procedures for reporting/follow-up of a pregnancy within 24 hours (see Section 6.3.6.2.5) of receipt of the information.
- Complete as fully as possible the applicable Pregnancy Surveillance Form(s).
- 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 6.3.6.2.2).

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 6.3.6.2.5.

5.4 Investigational Products

The products used in this clinical trial are which is under the name Aklief® (trifarotene) Cream 0.005% and trifarotene vehicle for purposes of this double-blind study. See Study Schema.

5.4.1 Study Drug Description

Table 2 summarizes the investigational medications.

Table 2: Description of the Study Drugs

Investigational Products: *	**Topical Trifarotene (CD5789) Cream**
Trade Name	AKLIEF®
Name of Drug Substance	trifarotene
Pharmaceutical Form	Cream
Strength/ Concentration	50 µg/g
Route	Topical
Packaging (type and size)	45 g bottle with pump and overcap (US) 75 g bottle with pump and overcap (EU)
Storage conditions	Store at 20-25°C (68-77°F) Excursions permitted to 15°C - 30°C (59°F to 86° F). (US) Store below 25°C (77°F), do not freeze or refrigerate (EU)
Duration of administration	24 weeks
Manufacturer *(Name and address)*	GALDERMA PRODUCTION INC (for US product) 19400 Route Transcanadienne Baie-d'Urfé, Québec, Canada H9X 3S4 Laboratoires GALDERMA (EU) ZI Montdésir 74540 Alby-sur-Chéran France

Investigational Products: *	**Topical Trifarotene Vehicle**
Trade Name or Equivalent	**N/A**
Name of Drug Substance	Vehicle
Pharmaceutical Form	Cream
Strength/ Concentration	**N/A**
Route	Topical
Packaging (type and size)	45 g bottle with pump and overcap (US) 75 g bottle with pump and overcap (EU)
Storage conditions	Store at 20-25° C (68-77° F) Excursions permitted to 15° C - 30° C (59° F to 86° F). (US) Store below 25°C (77°F), do not freeze or refrigerate (EU)

Investigational Products: *	Topical Trifarotene (CD5789) Cream
Duration of administration	24 weeks
Manufacturer *(Name and address)*	GALDERMA PRODUCTION INC (for US product) 19400 Route Transcanadienne Baie-d'Urfé, Québec, Canada H9X 3S4 Laboratoires GALDERMA (EU) ZI Montdésir 74540 Alby-sur-Chéran France

* Study design includes an active arm and a comparator arm. See Study Schema

5.4.2 Instructions for Use – Study Drugs and Non-Investigational Products

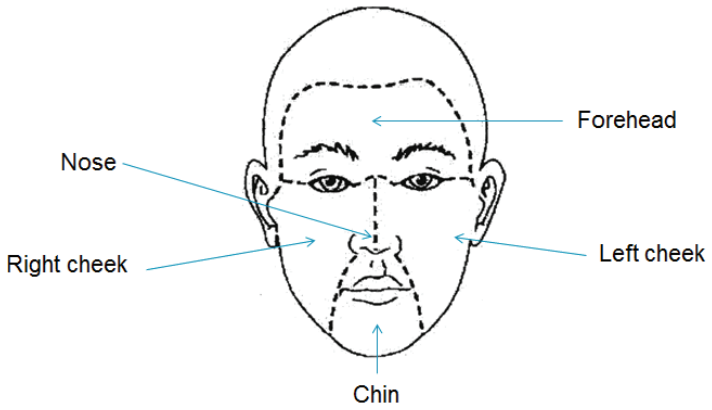
Table 3: Guidelines for Using Study Drugs and Non-Investigational Products

	Trifarotene Cream OR Trifarotene Vehicle Cream
Study Drug Usage	• 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). The Investigator may instruct alternate day regimen application of the topical study drug (detailed subject instruction will be provided) and re-evaluate at each visit to modify accordingly following the Baseline visit. Refer to Section 5.4.8 – Dose Modification of Topical Study Drug.
Non-Investigational Product Use Guidelines *	
Cetaphil® Gentle Skin Cleanser: Topical, wash face, twice daily, in the morning and evening.	
Cetaphil® Dermacontrol Moisturizer SPF 30: Topical, apply after morning cleansing. If sun exposure during the day, reapply every two hours.	
Cetaphil® Moisturizing Lotion: Topical, if extra moisture is needed, apply as needed.	
Duration of administration for the above products: 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 products. Alternative cleanser and moisturizers are not permitted, only the supplied non-investigational products to be used.

5.4.3 Topical Study Medication Application

The subject will apply the topical study drug on the face once a day (evenings): chin, left cheek, right cheek, nose and forehead (avoiding application in/close to eyes, angles of the mouth, lips and mucous membranes).



Avoid application in/close to eyes, or angles of the mouth, lips and mucous membrane.

The objective is to cover the face with a thin layer of the 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, right cheek, left 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.

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® Dermacontrol Moisturizer with SPF30 on the face every morning, and re-apply to the face and other exposed skin 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.

Topical study drug should be applied approximately 1 hour before or 1 hour after application of any other permitted skin care products (e.g. cosmetic products).

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.

Photographed subjects 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 (bottle pumps for trifarotene/vehicle) and assembled into kits, for subject assignment. Product appearance, packaging and labeling will ensure subject and clinical site blinding.

Each subject will have approximately 7 dispensing packs per kit, each pack containing 2 pumps to dispense according to the schedule of assessments (Baseline, Week 4, Week 8, Week 12, Week 16, Week 20 and Extra). However only 1 bottle will be dispensed at each dispensing interval. The extra bottle is in case the subject loses or runs out of IP. Subjects should be instructed to apply the IP daily to their face for 24 weeks.

5.4.6 Study Drug Management

5.4.6.1 Storage of Study Drugs

Study drugs 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 Accountability

Upon receipt of the study drugs, the site must conduct a complete inventory of all study drugs. 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 drugs sent to the Investigator/Institution will be accounted for and no unauthorized use is permitted. Subjects will be instructed to return all study drugs and dosing calendar per the Schedule of Assessments (Section 5.1.1.2) to review usage and dosing compliance. Subjects will be counseled on the importance of following study drugs dosing instructions.

The investigator or designee will maintain accurate records of supplies received, inventoried at the clinical trial site and used per subject. Used and unused study drugs 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 Drugs

Designated study personnel at each investigational site will be responsible for dispensing and retrieving the study drugs at the appropriate visits. They will also record the dispensing and returning information for each subject (see Section 5.1.1.2).

Each subject will receive study drug at Baseline, Week 4, Week 8, Week 12, Week 16, and Week 20 visits. Study drugs within each kit will be uniquely identified with a corresponding kit number and a bottle identifier to aid compliance assessment, 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 their study drugs (used and/or unused) as specified in the schedule of assessments (Section 5.1.1.2). Drug accountability and dosing compliance will be assessed by the designated site personnel. Subjects will be instructed to return the dosing calendar and all study medication at each study visit, for review by study personnel in the presence of the subject. At study visits Week 1 and Week 2, study drugs dispensed at Baseline will be re-dispensed after compliance checks are completed (see Section 5.4.6.4 – Treatment Compliance).

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

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

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

5.4.6.4 Treatment Compliance

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

A dosing calendar will be provided to the subject with clear directions for completion at each dispensing visit (Section 5.1.1.2). Subjects will record daily use of topical study drug. Subjects will be instructed to return the dosing calendar and all study medication at each study visit, for review by study personnel in the presence of the subject.

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

- **Topical study drug (study cream)**: Treatment compliance will be assessed using the subject dosing calendar, and derived from the total expected doses and number of actual doses recorded in the dosing calendar (based on CRF data entries), over a given visit interval.

Inadvertent missed doses of topical study drug will be considered protocol deviations, as confirmed by discussions with the subject after reviewing the dosing calendar, and subjects should be appropriately counseled on the importance of following study drug dosing instructions.

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

5.4.7 Method of Assigning Subjects to Treatment Groups

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 PIH severity (ODS), acne severity (IGA) or acne lesion counts.

Randomization will be stratified by study centers using the IRT system. Upon confirmation of subject eligibility, the IRT will be used to assign the blinded study drug. The randomization code will ensure the treatment assignment is random and is allocated in an overall CCI ratio,

active to vehicle. Refer to Section 5.1.1 for an illustration of the study design and 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 topical study drug in the first 4 weeks of the study, for a maximum duration of 2 weeks. Subjects should be instructed to capture all missed topical 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 topical study drug or if they require the use of concomitant treatment including OTC products (other than moisturizers). Refer to Section 6.3.4 for further details on local tolerability assessment.

5.4.9 Allocation Concealment and Blinding

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

All attempts will be made to keep the study site staff and subjects blinded to study treatment throughout the study. Members of the site staff will not have access to the randomized treatment assignment. Active study medications 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 trial may be required for regulatory reasons (for expedited safety reporting).

When the blinding code is broken, the date and reason must be fully documented. The source note must also include a record of the discussion with the Medical Monitor. If the code is broken by the investigator, the subject must be withdrawn from the study after completing early termination procedures.

The Investigator has the sole responsibility for determining if unblinding of a subject's study treatment assignment is warranted. Subject safety must always be the first consideration in making such a decision. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Medical Monitor prior to unblinding a subject's study treatment assignment unless this could delay emergency treatment of the subject. If this is not possible and the situation is an emergency the Principal Investigator or his delegated deputy may break the blind and contact the medical monitor as soon as possible thereafter. The applicable Sponsor standard operating procedure (SOP) will be followed for blind breaking

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 including:

- Cetaphil® Gentle Skin Cleanser
- Cetaphil® Dermacontrol Moisturizer SPF 30
- Cetaphil® Moisturizing Lotion

Alternative cleanser and moisturizers are not permitted, only the supplied non-investigational products above to be used. Refer to guidelines for using the cleanser and moisturizer (Section 5.4.2 – Instructions for Use). Topical retinoids are known to induce skin irritation and use of a moisturizer should minimize irritation and enhance compliance with using the topical study drug.

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 should maintain records of non-investigational supplies received and dispensed. The monitor will confirm global accountability of non-investigational supplies (total received and dispensed).

Sites will be provided a stipend to locally source their own urine pregnancy test kits for use in the study.

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 trial.

Alternative cleanser and moisturizers are not permitted, only the supplied non-investigational products to be used.

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:

- Cetaphil® Gentle Skin Cleanser
- Cetaphil® Dermacontrol Moisturizer SPF 30 (once the topical study drug has dried)
- Cetaphil® Moisturizing Lotion (once the topical study drug has dried)

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., comedo extraction, desquamating or abrasive agents, adhesive pore cleansing strips) • Wax epilation • Photodynamic therapy • Laser therapy, microdermabrasion, deep chemical peel, plastic surgery 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 for the duration
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) • Anticoagulants and Methoxyflurate
Other: • Any drugs (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 7 months (24 weeks (6 months) of treatment and up to 28-day period between screening and baseline).

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 5.1.1.2 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 acne assessments (IGA, lesion counts), 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 5.1.1.2– 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 trained designees) or by subjects (for subject-reported assessments) according to Section 5.1.1.2 - Schedule of Assessments.

Evaluators must complete standardized training prior to performing the following assessments: Overall Disease Severity Hyperpigmentation, CCI [redacted] Refer to Section 8.1 – Personnel Training for further details on site personnel training. Acne severity grading (IGA) and lesion counts will be performed separately. The acne severity assessments will be performed before the lesion counting.

CCI [redacted]

PIH

Investigator performed activities:

- Overall Disease Severity hyperpigmentation scores (9-point scale) from 0 (Clear) to 8 (Severe) at Screening, Baseline, Week 12, 16, 20 and 24 or early termination visits

CCI [redacted]

CCI

[redacted]

6.1.1 Overall Disease Severity Scale

Table 5: Overall Disease Severity Hyperpigmentation

Grading Scale of Outcome Measures	
Grade	Overall Disease Severity
0	Normal
1	Present, but < mild
2	Mild (slightly noticeable)
3	Between mild and moderate
4	Moderate (noticeable)
5	Between moderate and marked
6	Marked (distinctive)
7	Between marked and severe
8	Severe (very distinctive)

(Grimes, 2006)

CCI

[redacted]

CCI

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

6.3.4 Safety Assessments

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

6.3.5 Local Tolerability Assessment

Local tolerability assessment(s) on the face will include erythema, scaling, dryness and burning/stinging. at visits specified in the schedule of assessments (Section 5.1.1.2). Table 9 summarizes the local tolerability assessment. Burning/stinging will be recorded by the investigator after discussion with the subject.

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

Table 9: 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 topical study drug application before each visit. The Investigator will ask open-ended questions, taking care not to influence the subject's answer, such as "Have you experienced any sensations such as stinging/burning after the last dose of study medication?"

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

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

OR

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

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

6.3.6 Adverse Events

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

6.3.6.1 Definitions

6.3.6.1.1 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 (new or exacerbated) 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 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, it is an important medical event that must be monitored as described in Section 6.3.6.2.5.

Events NOT Meeting the AE Definition

Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

6.3.6.1.2 Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met. A serious adverse event (SAE) is any untoward medical occurrence that:

- 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 were 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 diagnostic tests (even if related to an AE), elective hospitalization for an intervention that was already planned before subject enrollment in the clinical trial, 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).

6.3.6.1.3 Adverse Events of Special Interest

An AESI is a noteworthy treatment-emergent 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:

- Erythema, scaling, dryness, stinging/burning, and other related cutaneous AEs which lead to permanent treatment discontinuation
- Suspicion of allergic contact reaction related to the study drug (see Section 6.3.6.2.4)

For AESIs, the Investigator is required to complete the AESI Form, within 72 hours of the event, and follow the AESI reporting procedures in Section 6.3.6.1.3 even if the event is considered non-serious according to the usual regulatory criteria.

For suspected sensitizations associated with topical study medication use, follow the rechallenge with assigned topical study drug patch test procedures in Section 6.3.6.2.4 (and subsequent ingredient patch testing, if the rechallenge with assigned topical study drug is positive or equivocal).

6.3.6.1.4 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).

Expectedness of SAEs related to trifarotene will be assessed against the trifarotene package insert.

6.3.6.1.5 Adverse Event Reporting Period

The clinical trial 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 trial, even after a subject has completed the clinical trial.
The Investigator should be diligent in looking for possible latent safety effects that may not appear until a medication has been discontinued.

6.3.6.1.6 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

6.3.6.1.7 Relationship to the Study Drugs and/or Clinical Trial Procedures

The investigator is to determine whether there is a reasonable causal relationship between the occurrence of the AE and exposure to the study drug and/or clinical trial procedures (eg. use of moisturizer). 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 trials 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 (investigational product or vehicle) and the AE,
  - The clinical trial protocol procedure and the AE.

No reasonable possibility:

- No suggestive evidence or arguments can be identified regarding a causal relationship between the study drugs.

For AEs graded to be a reasonable possibility of being related to study drugs, the Investigator will determine whether they are related to topical or oral study drug, or both.

6.3.6.2 Reporting Procedures

6.3.6.2.1 Procedures for Reporting Adverse Events

The collection of AEs is from the time that a subject sign 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 6.3.6.2.2), AESIs (see Section 6.3.6.2.3), and pregnancies (see Section 6.3.6.2.5), refer to the sections listed for further reporting requirements.

6.3.6.2.2 Procedure for Reporting a Serious Adverse Event

For an SAE occurring during the period of the clinical trial, 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. Immediately inform Parexel 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.

   Parexel Pharmacovigilance:
   email: NorthAmerica_Medical@parexel.com (preferred method)
   or
   Safety fax number: +1 781 434 5957

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 Parexel 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 Parexel

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 Parexel 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).

6.3.6.2.3 Procedure for Reporting an Adverse Event of Special Interest

For any treatment-emergent AESI occurring during the period of the clinical trial, 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 Parexel Pharmacovigilance of the event by fax or email and discuss further actions to be taken (Section 6.3.6.2.2).
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 and that all relevant CRF pages have been updated (e.g. medical history, concomitant medications, procedures, AE, etc.)
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 72 hours to Parexel 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 Parexel Pharmacovigilance. 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 Parexel Pharmacovigilance of the final outcome of the event. Send a revised or updated Adverse Event Form, if appropriate.

6.3.6.2.4 Procedures for Suspected Allergic Contact Reaction to Topical Study Medication (Rechallenge Patch Test and Ingredient Patch Testing)

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

- Stop study medication.
- Take a picture of the affected area and the non-affected surrounding skin with the supplied photo equipment and upload to the vendor's portal.
- Document the event as an Adverse Event of Special Interest, report the event within 72 hrs to Parexel Pharmacovigilance (see Section 6.3.6.2.3).
- The subject continues to be followed for scheduled study visits while awaiting the rechallenge test results.

a) Rechallenge with Assigned Topical Study Medication

1. After all signs and symptoms of AESI have resolved and after a minimum of two weeks from last topical dose application, perform a rechallenge test with the assigned topical 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 10).
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 ultraviolet sources the Week before testing.
4. Apply an appropriate quantity of the assigned 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 rechallenge test with assigned 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 10):

- 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 Parexel Pharmacovigilance and medical monitor.

Table 10: Patch Testing Readout Schedule

Day Patch Test Starts	**1st reading + Photographs** 48 hours after study product application (30 minutes after patch test removal)	**2nd reading + Photographs** 72 to 96 hours after study product application (24 to 48 hours after patch test removal)	**3rd reading (optional) + Photographs** 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 11 for the scoring system at each readout used by the International Contact Dermatitis Research Group (ICDRG) (Spiewak, 2008).

Table 11: 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 12 and provide an overall interpretation regarding a possible sensitization reaction, which is based on results using the ICDRG scale.

Table 12: 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 absence of negative reaction, the subject may resume study treatment if appropriate. Otherwise, the subject should complete end of study procedures.

9. If the rechallenge with assigned topical study medication is positive or equivocal, notify Parexel 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.

6.3.6.2.5 Procedures for Reporting Pregnancies

Any pregnancy occurring during clinical trials, 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 Parexel Pharmacovigilance of the event by fax or email (Section 6.3.6.2.2).
2. **Withdraw the subject from the clinical trial**.

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 trial, as fully as possible. Inform Parexel Pharmacovigilance of the pregnancy by sending this pregnancy form along with the Exit Form within 24 hours to Parexel Pharmacovigilance (see Section 6.3.6.2.2).
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 Parexel Pharmacovigilance of the progress by trimonthly 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 nonresponse/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 Parexel Pharmacovigilance within 24 hours (see Section 6.3.6.2.2).
7. Any pregnancy with serious complications, spontaneous or therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defect must be recorded and reported within 24 hours in accordance with the procedure for reporting SAEs. (see 6.3.6.2.2) Section.

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 Calculation

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

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

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

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

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 PP population is defined as any subjects in the ITT population who had compliance to the study treatment between 80% and 120% and assessments of the primary endpoint at Baseline and Week 24, without any major deviations that could have a significant effect on the efficacy of the study treatment (e.g. errors in treatment assignment, use of prohibited medications). The PP population will be used for a sensitivity analysis of the primary endpoint.

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 acne-induced hyperpigmentation during the treatment of acne vulgaris subjects treated with trifarotene 50 µg/g cream versus vehicle over 24 weeks.

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 $\alpha = 0.05$.

7.4.3.1 Primary Efficacy Endpoint

- Absolute change from Baseline in PIH Overall Disease Severity scores of the face will be analyzed at Week 24 using an ANCOVA with treatment, analysis center and Baseline score as fixed effects; the p-values for the treatment comparison, estimates of the treatment difference and the 95% confidence interval of the difference will be generated from the ANCOVA model.

7.4.3.2 Secondary Endpoints

- Percent change from Baseline in PIH Overall Disease Severity scores will be analyzed at Week 24 using an ANCOVA with treatment, analysis center and Baseline score as fixed effects; the p-values for the treatment comparison, estimates of the treatment difference and the 95% confidence interval of the difference will be generated from the ANCOVA model.
- Absolute and percent change from Baseline in PIH Overall Disease Severity scores will be analyzed at Week 12, 16 and 20 using an ANCOVA with treatment, analysis center and Baseline score as fixed effects; the p-values for the treatment comparison, estimates of the treatment difference and the 95% confidence interval of the difference will be generated from the ANCOVA model.

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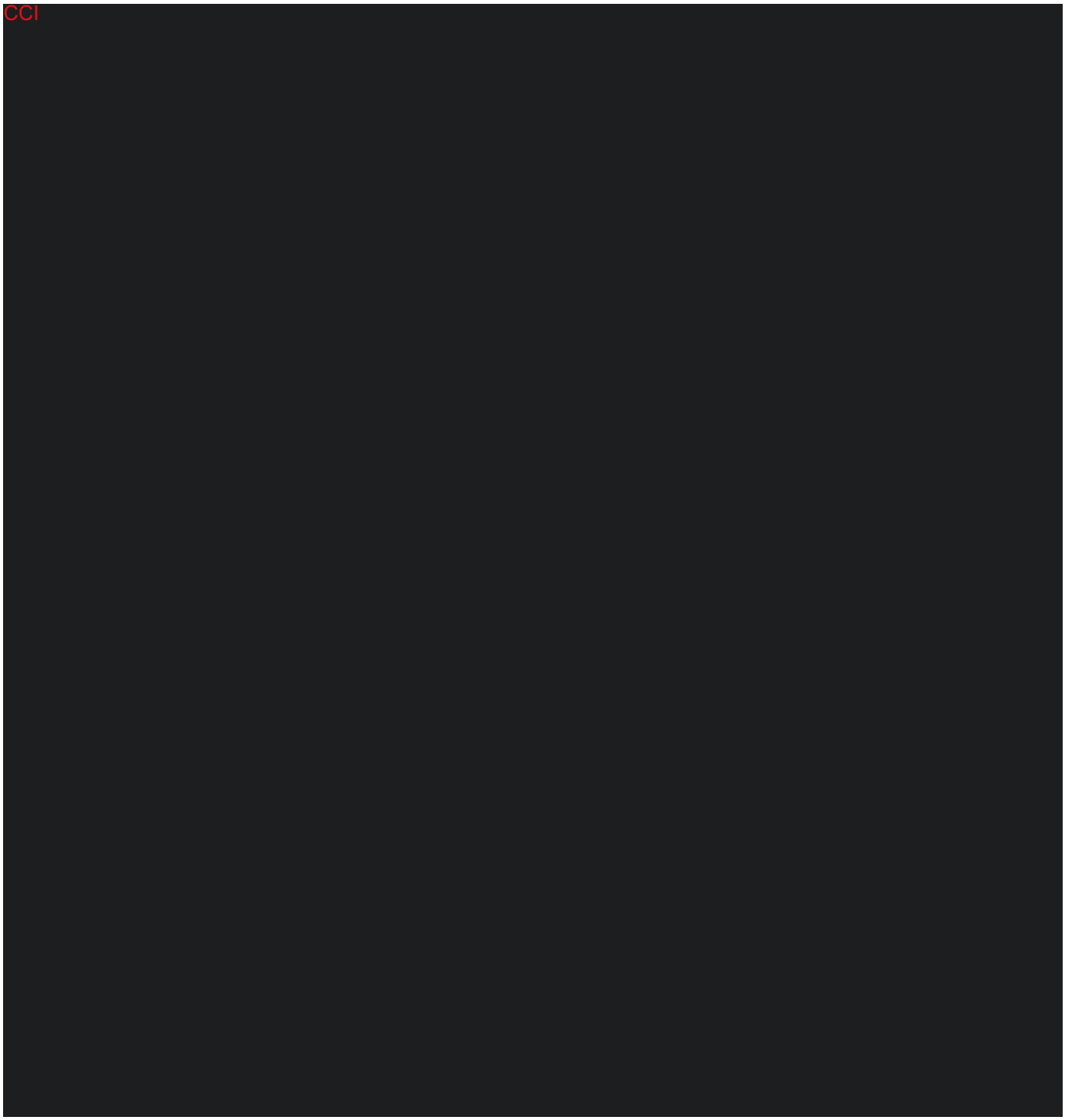

7.4.3.3 Missing Data

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

For the primary MAR based multiple imputation, the MI procedure of the SAS system will be used to generate sets of data with missing values imputed from observed data. It is expected that the pattern of missing data will be monotonic, with slight deviations being corrected by the Markov Chain Monte Carlo (MCMC) method of the MI procedure.

Linear regression will be employed to model the missing lesion count data and a logistic regression model will be used for the ordinal scores, with the following covariates included in the imputation model: treatment and non-missing data from earlier time points. IGA success will be calculated from the imputed IGA scores.

For the sensitivity analyses of the primary endpoint, missing data will be imputed using a Pattern-Mixture Model (PMM) for implementing a Copy Reference (CR) 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. Missing data of primary endpoint will be imputed using a Pattern-Mixture Model (PMM) for implementing a Copy Reference (CR) under the Missing Not At Random (MNAR) assumption, by using the profiles from Vehicle subjects with observed data to impute missing data.
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.

7.4.3.5 Analysis Centers

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

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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), IRT, 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 eTMF.

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

- Overall Disease Severity hyperpigmentation scoring
- PIH improvement assessment (Likert scale)
- Investigator Global Assessment

- IL and NIL lesion counting

Certificates will be issued to document successful training completion.

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. All monitoring activities will be detailed in a Monitoring Plan.

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.

The Sponsor does not have to notify non-substantial amendments to the regulatory authorities or IRB/IEC. However, non-substantial amendments will be recorded and detailed in subsequent submissions (e.g., in the subsequent notification 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 the agreed upon format.

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

The Investigator will allow and assist the Sponsor/designee and any regulatory agency to have direct access to all requested clinical trial-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 trial will be conducted in accordance with the protocol, the HELSINKI declaration (1964) and subsequent amendments, and the ICH GCP, and in compliance with applicable regulatory requirements.

9.4 Subject Information and Consent

All subjects who participate in this clinical trial are required to be fully informed about the clinical trial 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., HIPAA in the US), in accordance with local requirements.

The investigator or designated personnel will inform the subject of the objectives, methods, anticipated benefits, photography, 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 trial 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 trial 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 trial-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 trial 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 trial 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 trial 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 trial 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.

13 REFERENCES

Alexis AF, Sergay AB, and Taylor SC. Common dermatologic disorders in skin of color: a comparative practice survey. Cutis.2007;80(5):387-394.

Aubert J, et al. Nonclinical and human pharmacology of the potent and selective topical retinoic acid receptor gamma agonist trifarotene. Br J Dermatol 2018; 179:231–232.

Blume-Peytavi U, Fowler J, Kemény L, et al. Long-term safety and efficacy of trifarotene 50 µg/g cream, a first-in-class RAR-γ selective topical retinoid, in patients with moderate facial and truncal acne. J Eur Acad Dermatol Venereol. 2020 Jan;34(1):166-173.

Bowe WP and Kircik LH. The Importance of Photoprotection and Moisturization in Treating Acne Vulgaris. JDD August 2014; Vol 13 (8); s89.Yin and McMichael, 2014.

Bulengo-Ransby SM, Griffiths CE, Kimbrough-Green CK, et al. Topical tretinoin (retinoic acid) therapy for hyperpigmented lesions caused by inflammation of the skin in black patients. N Engl J Med. 1993;328(20):1438-1443.

Callender VD. Acne in ethnic skin: Special considerations for therapy. Dermatol Ther.2004;17(2):184-195.

Canavan TN, Chen E, Elewski BE. Dermatol Ther (Heidelb); 19 Aug 2016.

Davis EC and Callender VD. A Review of Acne in Ethnic Skin. Pathogenesis, Clinical Manifestations, and Management Strategies. Journal of Clinical and Aesthetic Dermatology, 2010, 3, 4.

Del Rosso JQ. The role of skin care as an integral component in the management of acne vulgaris: Part 1: The importance of cleanser and moisturizer ingredients, design, and product selection. J Clin Aesthet Dermatol.2013;6(12):19-27.

Del Rosso JQ and Brandt S. The role of skin care as an integral component in the management of acne vulgaris. Part 2: Tolerability and performance of a designated skin care regimen using a foam wash and moisturizer SPF 30 in patients with acne vulgaris undergoing active treatment. J Clin Aesthet Dermatol. 2013;6(12):28-36.

Fisher, et al. Immunological identification and functional quantitation of retinoic acid and retinoid X receptor proteins in human skin J. Biol. Chem., 269 (1994), pp. 20629-20635.

Geria AN, Lawson CN, Halder RM. Topical retinoids for pigmented skin. J Drugs Dermatol. 2011 May;10(5):483-9.

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

Halder RM, Grimes PE, McLaurin CI, et al. Incidence of common dermatoses in a predominantly black dermatologic practice. Cutis. 1983;32(4):388-390.

Heidel B; Canavan TN, Chen E, et al. Optimizing Non-Antibiotic Treatments for Patients with Acne: A Review. Dermatol Ther. Aug 2016: 1-24.

Jacyk WK and Mpofu P. Adapalene gel 0.1% for topical treatment of acne vulgaris in African patients. Cutis 2001 Oct;68(4 Suppl):48-54.

Khemis A, Kaiafa A, Queille-Roussel C, et al. Evaluation of efficacy and safety of rucinol serum in patients with melasma: a randomized controlled trial. Br J Dermatol. 2007 May;156(5):997-1004.

Kligman AM and Shelley WB. An investigation of the biology of the human sebaceous gland. J Invest Dermatol. 1958;30(3):99-125.

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

Kubba R, Bajaj AK, Thappa DM, Sharma R, et al. Acne in India: Guidelines for Management - IAA consensus document. Post-inflammatory hyperpigmentation in acne. Year: 2009, Vol: 75, Issue : 7, Page: 54.

Leyden JJ. Topical treatment of acne vulgaris: retinoids and cutaneous irritation. J Am Acad Dermatol. 1998;38:S1-S4.

Pawin H, Beylot C, Chivot M, et al. Physiopathology of acne vulgaris: recent data, new understanding of the treatments. Eur J Dermatol. 2004;14:4–12.

Pochi PE and Strauss JS. Sebaceous gland activity in black skin. Dermatol Clin. 1988;6(3): 349-351.

Savory SA, Agim NG, Mao R, et al. Reliability assessment and validation of the postacne hyperpigmentation index (PAHPI), a new instrument to measure postinflammatory hyperpigmentation from acne vulgaris. J Am Acad Dermatol. 2014 Jan;70(1):108-14. doi: 10.1016/j.jaad.2013.09.017. Epub 2013 Oct 28. PMID: 24176524.

Schorr ES, Sidou F, and Kerrouche N. Adjunctive use of a facial moisturizer SPF 30 containing ceramide precursor improves tolerability of topical tretinoin 0.05%: a randomized, investigator-blinded, split-face study. J Drugs Dermatol. 2012;11(9):1104-1107.

Taylor SC, Grimes PE, Lim J, et al. Postinflammatory hyperpigmentation Cutan Med Surg Jul-Aug 2009;13(4):183-91.

Taylor SC, Cook-Bolden F, Rahman Z, et al. Acne vulgaris in skin of color. J Am Acad Dermatol. 2002;46(suppl 2):98S-106S.

Taylor S, Summers P, Kelly AP, et al. Dermatology for skin of color, McGraw-Hill Companies, New York, NY (2009), pp. 269-274.

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

Yin NC and McMichael AJ. Acne in patients with skin of color: practical management. Am J Clin Dermatol. 2014 Feb;15(1):7-16.

Yoon-Soo C, Bae-Harboe, and Graber EM. Easy as PIE (Post-inflammatory erythema) J Clin Aesthet Dermatol. 2013 Sep; 6(9): 46–47.

Zeichner J. Strategies to minimize irritation and potential iatrogenic post-inflammatory pigmentation when treating acne patients with skin of color. J Drugs Dermatol Dec 2011;10(12 Suppl): s25-6.

14 APPENDICES

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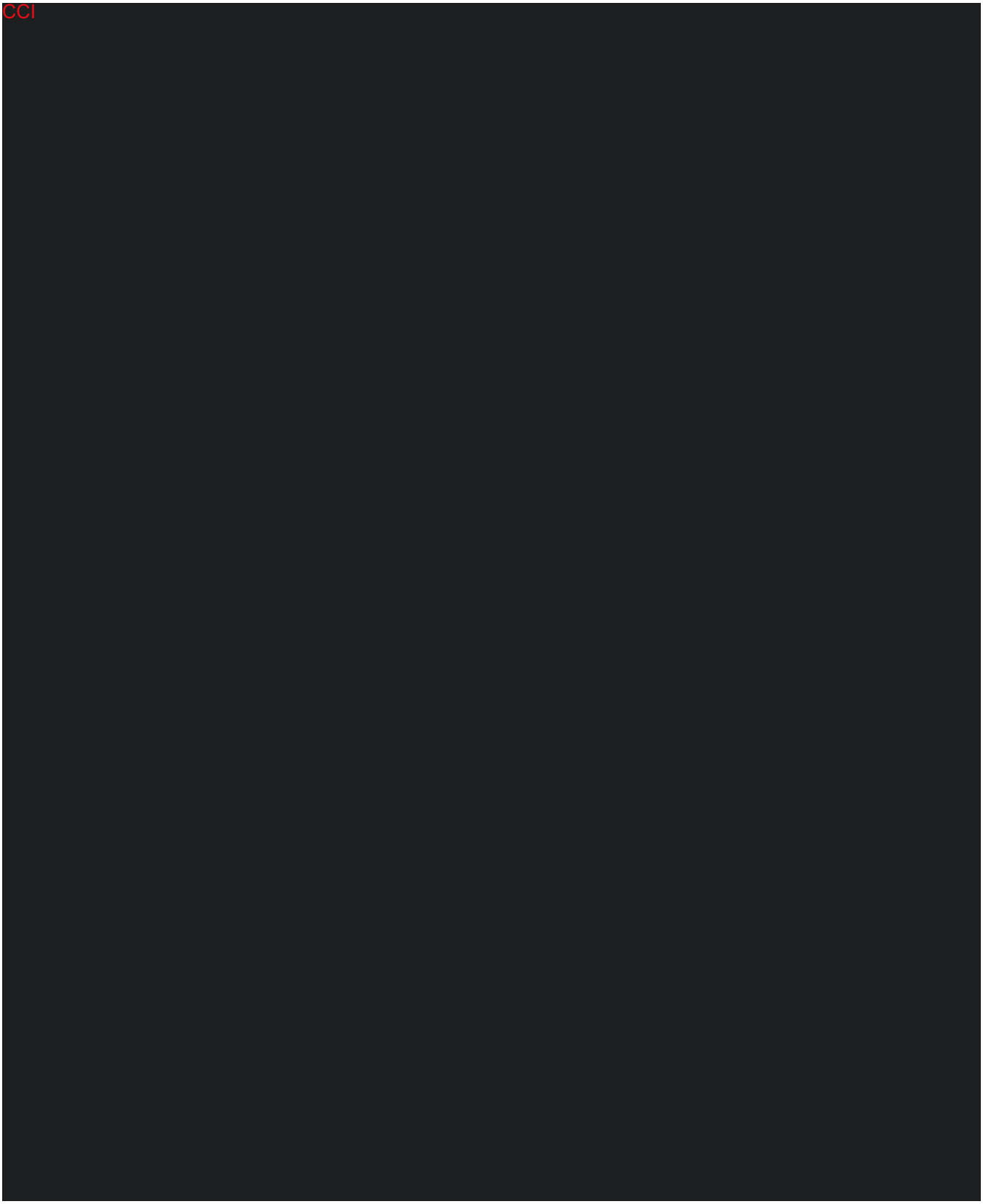

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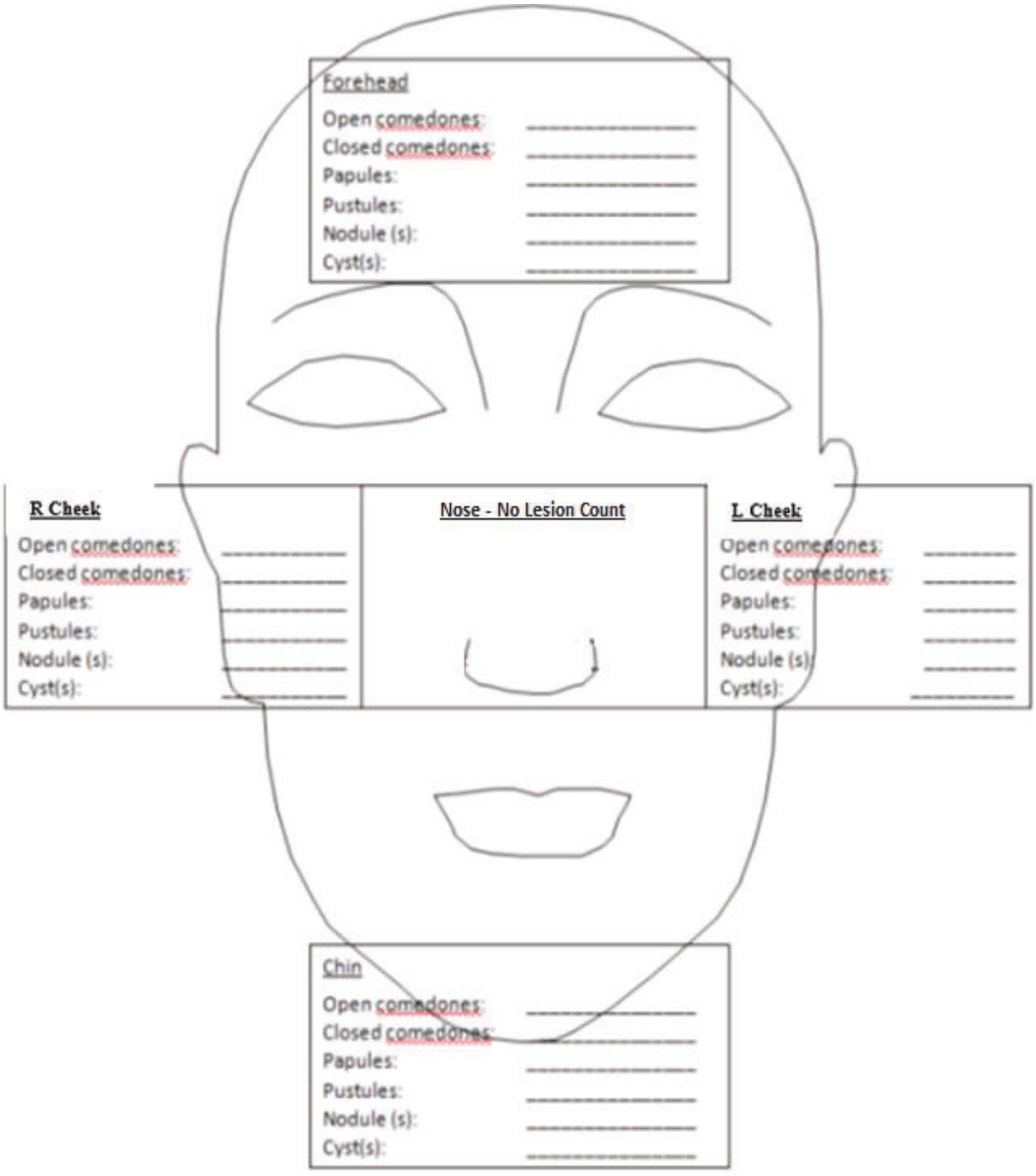
14.6 Fitzpatrick Skin Classification

The Fitzpatrick skin classification is based on the skin's unprotected response to the first 30 to 45 minutes of sun exposure after a winter season without sun exposure. The categories of skin types are as follows:

I	White; very fair; red or blonde hair; blue eyes; freckles	Always burns easily; never tans
II	White; fair; red or blonde hair; blue, hazel, or green eyes	Always burns easily; tans minimally
III	Cream white; fair with any eye or hair color; very common	Burns moderately; tans gradually
IV	Brown; typical Mediterranean white skin	Burns minimally; always tans well
V	Dark brown; mid-eastern skin types, black hair, olive skin	Rarely burns; tans profusely
VI	Black; black hair, black eyes, black skin	Never burns; deeply pigmented

14.7 Acne Harmonization Lesion Count

Notes: Lesions on the nose and under the jawline or along the hairline (including eyebrows) will not be included in the counts.



TOTAL for the Face

Open comedones: _____	Papules: _____	Nodule (s): _____
Closed comedones: _____	Pustules: _____	Cyst(s): _____

14.8 Investigator Notification of Ingredient Patch Test Results

Dear Investigator,

The accompanying form provides results of the ingredient patch testing for the topical study drug in Galderma clinical protocol: 204245.

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.: **204245** 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 204245, "***Evaluation of acne-induced hyperpigmentation 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 double-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:

Parexel Pharmacovigilance: SAEReports@parexel.com

Please mention the study ID (RD.06.SPR.204245) 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

14.9 AKLIEF (trifarotene) Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AKLIEF Cream safely and effectively. See full prescribing information for AKLIEF Cream.

AKLIEF® (trifarotene) cream, for topical use
Initial U.S. Approval: 2019

INDICATIONS AND USAGE
AKLIEF Cream is a retinoid indicated for the topical treatment of acne vulgaris in patients 9 years of age and older. (1)

DOSAGE AND ADMINISTRATION
- For topical use only. Not for oral, ophthalmic or intravaginal use.
- Apply a thin layer of AKLIEF Cream to the affected areas of the face and/or trunk once a day, in the evening, on clean and dry skin. Avoid contact with the eyes, lips, paranasal creases, and mucous membranes. (2)

DOSAGE FORMS AND STRENGTHS
Cream: 0.005% trifarotene. (3)

CONTRAINDICATIONS
None (4)

WARNINGS AND PRECAUTIONS
- Skin irritation: Erythema, scaling, dryness, and stinging/burning may be experienced with use of AKLIEF Cream. Use a moisturizer from the initiation of treatment, and, if appropriate, reduce the frequency of application of AKLIEF Cream, suspend or discontinue use. (5.1)
- Ultraviolet Light and Environmental Exposure: Minimize exposure to sunlight and sunlamps. Use sunscreen and protective clothing over treated areas when exposure cannot be avoided. (5.2)

ADVERSE REACTIONS
Most common adverse reactions (incidence ≥ 1%) in patients treated with AKLIEF Cream were application site irritation, application site pruritus, and sunburn (6).

To report SUSPECTED ADVERSE REACTIONS, contact Galderma Laboratories, L.P. at 1-866-735-4137 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
AKLIEF Cream is a retinoid indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.

2 DOSAGE AND ADMINISTRATION
Apply a thin layer of AKLIEF Cream to the affected areas once daily, in the evening, on clean and dry skin.

- One pump actuation should be enough to cover the face (i.e., forehead, cheeks, nose, and chin).
- Two actuations of the pump should be enough to cover the upper trunk (i.e., reachable upper back, shoulders and chest). One additional pump actuation may be used for middle and lower back if acne is present.

The use of a moisturizer is recommended as frequently as needed from the initiation of treatment.
Avoid contact with the eyes, lips, paranasal creases, mucous membranes.
AKLIEF Cream is for topical use only. Not for oral, ophthalmic, or intravaginal use.

3 DOSAGE FORMS AND STRENGTHS
Cream: 0.005%. Each gram of AKLIEF Cream contains 50 mcg of trifarotene in a white cream.

4 CONTRAINDICATIONS
None

5 WARNINGS AND PRECAUTIONS

5.1 Skin Irritation
Patients using AKLIEF Cream may experience erythema, scaling, dryness, and stinging/burning. Maximum severity of these reactions typically occurred within the first 4 weeks of treatment, and severity decreased with continued use of the medication. Depending upon the severity of these adverse reactions, instruct patients to use a moisturizer, reduce the frequency of application of AKLIEF Cream, or suspend use temporarily. If severe reactions persist the treatment may be discontinued.

Avoid application of AKLIEF to cuts, abrasions, or eczematous or sunburned skin. Use of "waxing" as a depilatory method should be avoided on skin treated with AKLIEF Cream.

5.2 Ultraviolet Light and Environmental Exposure
Minimize unprotected exposure to ultraviolet rays (including sunlight and sunlamps) during treatment with AKLIEF. Warn patients who normally experience high levels of sun exposure and those with inherent sensitivity to sun to exercise caution. Use of sunscreen products and protective clothing over treated areas is recommended when exposure cannot be avoided.

6 ADVERSE REACTIONS

6.1 Clinical trials experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect rates observed in practice. In the three Phase 3 clinical trials, a total of 1673 subjects with acne vulgaris on the face and trunk, 9 years and older were exposed to AKLIEF Cream. Of these, 1220 subjects were treated once daily for up to 12 weeks and 453 were treated once daily for up to 1 year.

Adverse reactions reported in the 2 randomized, double-blind, vehicle-controlled 12-week clinical trials in ≥1.0% of subjects treated with AKLIEF Cream (and for which the rate exceeded the rate for vehicle), as well as the corresponding rates reported in subjects treated with the vehicle cream are presented in Table 1.

Table 1. Adverse Reactions Occurring in ≥ 1.0% of Subjects with Acne Vulgaris of the Face and Trunk in the Two 12-week Phase 3 Clinical Trials

Preferred Term	AKLIEF Cream (N= 1220)	Vehicle Cream (N=1200)
Application site irritation	91 (7.5)	4 (0.3)
Application site pruritus	29 (2.4)	10 (0.8)
Sunburn	32 (2.6)	6 (0.5)

Additional adverse reactions that were reported in more than one subject treated with AKLIEF Cream (and at a frequency <1%) included application site pain, application site dryness, application site discoloration, application site rash, application site swelling, application site erosion, acne, dermatitis allergic, and erythema.

In the one-year, open-label safety trial that included 453 subjects 9 years and older, with acne vulgaris of the face and trunk, the pattern of adverse reactions for AKLIEF Cream was similar to that experienced in the 12-week controlled trials. A total of 12.6% of subjects had at least one adverse reaction during the trial, and 2.9% of subjects had an adverse reaction leading to treatment discontinuation. The most common adverse reactions (≥ 1% of subjects) for the entire trial were application site pruritus (4.6%), application site irritation (4.2%), and sunburn (5.5%). The frequency of adverse reactions decreased over time.

Skin irritation was evaluated by active assessment of erythema, scaling, dryness, and stinging/burning and collected separately. In the two 12-week Phase 3 clinical trials, these signs/symptoms were assessed at baseline and at least one post-baseline visit, in 1214 subjects (for face) and 1202 subjects (for trunk) treated with AKLIEF Cream. The percentage of subjects who were assessed to have these signs and symptoms at any post baseline visit and at a severity worse than baseline are summarized in Table 2.

Table 2. Application Site Tolerability Reactions at Any Post Baseline Visit

Face	AKLIEF N=1214 Maximum Severity during Treatment			Vehicle Cream N= 1194 Maximum Severity during Treatment		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Erythema	30.6%	28.4%	6.2%	21%	6.8%	0.8%
Scaling	37.5%	27.1%	4.9%	23.7%	5.9%	0.3%
Dryness	39%	29.7%	4.8%	29.9%	6.8%	0.8%
Stinging/Burning	35.6%	20.6%	5.9%	15.9%	3.8%	0.5%
Trunk	**N=1202**			**N=1185**		
Erythema	26.5%	18.9%	5.2%	12.7%	4.4%	0.4%
Scaling	29.7%	13.7%	1.7%	13.2%	2.6%	0.1%
Dryness	32.9%	16.1%	1.8%	17.8%	3.9%	0.1%
Stinging/Burning	26.1%	10.9%	4.3%	9.2%	2.2%	0.5%

Local tolerability on the face in subjects treated with AKLIEF Cream worsened for any of the signs/symptoms compared with baseline to a score of moderate for up to 30% of subjects, or severe for up to 6% of subjects. On the trunk, the corresponding percentages were up to 19% (moderate) and up to 5% (severe). The scores reached maximum severity at Week 1 for the face, and at Week 2 to 4 of treatment for the trunk, and decreased thereafter.

In the open-label, 1-year Phase 3 trial, the local tolerability profile was comparable to that observed in the two pivotal Phase 3 trials.

7 DRUG INTERACTIONS

Topical application of AKLIEF Cream is not expected to affect the circulating concentrations of oral hormonal contraceptives containing ethinyl estradiol and levonorgestrel.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from clinical trials with AKLIEF Cream use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There are case reports of major birth defects similar to those seen in fetuses exposed to oral retinoids in pregnant women exposed to other topical retinoids, but these case reports do not establish a pattern or association with retinoid-related embryopathy.

In animal reproduction studies, oral doses of trifarotene administered to pregnant rats and rabbits during organogenesis that resulted in systemic exposures more than 800 times the systemic exposure at the maximum recommended human dose (MRHD) of AKLIEF Cream resulted in adverse fetal effects, including fetal deaths and external, visceral, and skeletal malformations *(see Data)*.
The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Oral administration of trifarotene to pregnant rats during the period of organogenesis at doses that resulted in systemic exposures greater than 1600 times those in humans at the MRHD of AKLIEF Cream resulted in adverse fetal effects, including fetal deaths, reduced mean fetal weight, and external, visceral, and skeletal malformations.

Oral administration of trifarotene to pregnant rabbits during the period of organogenesis at doses that resulted in systemic exposures at least 800 times those in humans at the MRHD of AKLIEF Cream resulted in adverse fetal effects, including defects of the tail, limbs, urogenital organs, and vertebral column.

Trifarotene administered orally to female rats from gestation Day 6 to lactation Day 20, at doses that resulted in systemic exposures up to 594 times those in humans at the MRHD of AKLIEF Cream, had no effect on maternal function or behavior, including gestation, delivery, pup-rearing, lactation and nursing, or survival or development of pups. There were no effects of maternal treatment on behavior, learning, memory, or reproductive function of pups.

8.2 Lactation

Risk Summary

There are no data on the presence of trifarotene in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies, trifarotene was present in rat milk with oral administration of the drug. When a drug is present in animal milk, it is likely that the drug will be present in human milk. It is possible that topical administration of large amounts of trifarotene could result in sufficient systemic absorption to produce detectable quantities in human milk *(see Clinical Considerations)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AKLIEF Cream and any potential adverse effects on the breastfed infant from AKLIEF Cream or from the underlying maternal condition.

Clinical Considerations

To minimize potential exposure to the breastfed infant via breastmilk, use AKLIEF Cream on the smallest area of skin and for the shortest duration possible while breastfeeding. Advise breastfeeding women not to apply AKLIEF Cream directly to the nipple and areola to avoid direct infant exposure.

8.4 Pediatric Use

Safety and effectiveness of AKLIEF Cream for the topical treatment of acne vulgaris have been established in pediatric patients age 9 years to 17 years based on evidence from well-controlled clinical trials, a long-term safety trial, and a pharmacokinetic trial. A total of 897 pediatric subjects aged 9 to 17 years received AKLIEF Cream in the clinical trials *[see Clinical Pharmacology (12.3) and Clinical Studies (14)]*.

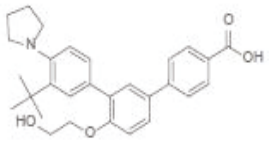
Safety and effectiveness of AKLIEF Cream have not been established in pediatric subjects under the age of 9 years.

8.5 Geriatric use

Clinical trials of AKLIEF Cream did not include any subjects aged 65 years and over to determine whether they respond differently than younger subjects.

11 DESCRIPTION

AKLIEF Cream for topical administration contains 0.005% (50 mcg/g) trifarotene. Trifarotene is a terphenyl acid derivative and is a retinoid. The chemical name of trifarotene is 3"-tert-Butyl-4'-(2-hydroxy-ethoxy)-4"-pyrrolidin-1-yl-[1,1',3',1"]terphenyl-4-carboxylic acid. Trifarotene has the molecular formula of $C_{29}H_{33}NO_4$, the molecular weight of 459.58, and the following structural formula:



Trifarotene is a white to off-white to slightly yellow powder with the melting point of 245°C. It is practically insoluble in water with pKa1 of 5.69 and pKa2 of 4.55.

AKLIEF (trifarotene) Cream 0.005% contains the following inactive ingredients: allantoin, copolymer of acrylamide and sodium acryloyldimethyltaurate, dispersion 40% in isohexadecane, cyclomethicone, 5% ethanol, medium-chain triglycerides, phenoxyethanol, propylene glycol, purified water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Trifarotene is an agonist of retinoic acid receptors (RAR), with particular activity at the gamma subtype of RAR. Stimulation of RAR results in modulation of target genes which are associated with various processes, including cell differentiation and mediation of inflammation. The exact process by which trifarotene ameliorates acne is unknown.

12.2 Pharmacodynamics

At the approved recommended dosage, AKLIEF Cream does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Pharmacokinetics of trifarotene was evaluated in a study involving 19 adult subjects with acne vulgaris following once daily application of AKLIEF Cream for 29 days (daily dose range 1.5 g/day to 2 g/day) to the face, shoulders, chest and upper back.

Absorption

Systemic concentrations were at steady state following 2 weeks of treatment and were quantifiable in 7 subjects. Steady state C_{max} ranged from below the limit of quantification (less than 5 pg/mL) to 10 pg/mL and AUC_{0-24h} ranged from 75 to 104 pg.h/mL in adults. No drug accumulation is expected with long-term use.

Distribution

Plasma protein binding is approximately 99.9%.

Elimination

The terminal half-life ranged from 2 to 9 hours.

Metabolism

Trifarotene is primarily metabolized by CYP2C9, CYP3A4, CYP2C8, and to a lesser extent by CYP2B6 *in vitro*.

Excretion

Trifarotene is primarily excreted by the feces.

Specific Populations

Pediatric Patients

Steady state C_{max} ranged from less than 5 pg/mL to 9 pg/mL and AUC_{0-24h} ranged from 89 to 106 pg.h/mL in pediatrics (10 to 17-years-old). Steady state conditions were achieved in patients following 2 weeks of topical administration. No drug accumulation is expected with long-term use.

Drug Interactions Studies

Clinical Studies and Model-Based Approaches

No clinically significant differences in the pharmacokinetics of trifarotene were predicted when used concomitantly with fluconazole (a moderate CYP2C9 and CYP3A inhibitor).

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: AKLIEF Cream is not expected to inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4, or induce CYP1A2, 2B6, and 3A4.

Transporter Systems: AKLIEF Cream is not expected to inhibit MATE, OATP, OAT, OCT, BCRP, P-gp, BSEP, or MRP.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Trifarotene was not carcinogenic when topically applied to mice daily for up to 24 months in the vehicle of the product (AKLIEF Cream) at concentrations of 0.0005% or 0.001% w/w. The systemic exposures at the highest doses evaluated in mice were approximately 82 (males) and 99 (females) times higher than the human exposure at the MRHD of AKLIEF Cream.

Trifarotene was not carcinogenic when administered orally to rats daily for up to 24 months at doses up to 0.75 mg/kg/day in males and 0.2 mg/kg/day in females. The systemic exposures at the highest doses evaluated in rats were approximately 645 (males) and 1642 (females) times higher than the human exposure at the MRHD of AKLIEF Cream.

Trifarotene was negative in an in vitro bacterial reverse mutation (Ames) assay, an in vitro micronucleus assay in primary human lymphocytes, an in vitro mouse lymphoma assay with L5178Y/$TK^{+/-}$ cells, and an in vivo micronucleus assay in rats.

Trifarotene was assessed for effects on fertility or general reproductive function in rats. Males received trifarotene via oral gavage for 4 weeks prior to mating, during mating, and up to scheduled termination (approximately 6 weeks in total), and females were treated via oral gavage for 2 weeks prior to mating through Day 7 of gestation. No adverse effects on fertility or reproductive parameters, including sperm motility and concentration, were observed at the highest doses evaluated, which resulted in systemic exposures approximately 1755 (males) and 1726 (females) times higher than the human exposure at the MRHD of AKLIEF Cream.

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16 HOW SUPPLIED/STORAGE AND HANDLING

AKLIEF Cream, 0.005% is provided as a white cream supplied in the following packaging configurations with corresponding NDC numbers:

- 30-gram pump NDC 0299-5935-30
- 45-gram pump NDC 0299-5935-45
- 75-gram pump NDC 0299-5935-75

Storage and Handling

- Store at 20 to 25°C (68 to 77°F) with excursions permitted to 15°to 30°C (59° to 86°F).
- Keep away from heat.
- Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

Advise the patient to:

- Cleanse the area to be treated; pat dry. Apply AKLIEF Cream as a thin layer once daily in the evening to the face, avoiding the eyes, lips, nasolabial folds, and mucous membranes. A thin layer of AKLIEF Cream may also be applied to the chest, shoulders, and back.
- Avoid applying AKLIEF Cream to damaged skin (such as cuts, abrasions), eczematous areas, and sunburned skin.
- Reduce the risk of such irritation, use a moisturizer from the start of treatment, and, if appropriate, reduce the frequency of application of AKLIEF Cream or suspend use temporarily. AKLIEF Cream may cause irritation such as erythema, scaling, dryness, and stinging or burning.
- Minimize exposure to sunlight, including sunlamps and phototherapy devices.
- Use sunscreen products and protective apparel (e.g., hat) over treated areas when exposure to sunlight cannot be avoided.
- Avoid concomitant use of other potentially irritating topical products (medicated or not).
- Use AKLIEF Cream on the smallest area of skin and for the shortest duration possible while breastfeeding. Advise breastfeeding women not to apply AKLIEF Cream directly to the nipple and areola to avoid direct infant exposure.

Marketed by:
GALDERMA LABORATORIES, L.P.
Fort Worth, Texas 76177 USA

Made in Canada

14.10 Investigator Signature Page

Protocol Title: Evaluation of acne-induced hyperpigmentation during treatment of acne vulgaris subjects with trifarotene 50 µg/g cream versus vehicle cream over 24 weeks. (Version 00)

Protocol Number: RD.06.SPR.204245

Confidentiality and Current GCP Compliance Statement

I, the undersigned, have reviewed this protocol (and amendments), including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), GCP, and relevant ICH guidelines.

Once the protocol has been approved by the IEC/IRB, I will not modify this protocol without obtaining prior approval of the Sponsor and of the IEC/IRB. I will submit the protocol amendments and/or any ICF modifications to the Sponsor/designee and the IEC/IRB, and approval will be obtained before any amendments are implemented.

I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all CRFs, 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 the Sponsor to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

_____ _____

Investigator Signature Date

_____

Printed Name