CLINICAL TRIAL PROTOCOL
PROTOCOL NUMBER: RD.06.SPR.202394

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TITLE PAGE

Title A Multi-Center, Randomized, Double-Blind, Placebo Controlled Study To Compare Efficacy and Safety of Trifarotene (CD5789) Cream When Used with an Oral Antibiotic for the Treatment of Severe Acne Vulgaris		
Project Name or CD number: CD5789	**Project Number:** 02222	**Clinical Trial Phase:** IV

IND Number 111091

SPONSOR:

Name:	GALDERMA RESEARCH & DEVELOPMENT, LLC
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For any safety questions, please contact the Clinical Safety Officer (Advanced Clinical Pharmacovigilance**) using the contact details provided in** Section 6.6.2.2.2

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

Name and Title:	PPD MD PPD, Medical and Safety Monitoring
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: A Multi-Center, Randomized, Double-Blind, Placebo Controlled Study To Compare Efficacy and Safety of Trifarotene (CD5789) Cream When Used with an Oral Antibiotic for the Treatment of Severe Acne Vulgaris	
Short Title: Doxycycline **U**se in **A**ssociation with Ak**L**ief **(DUAL)**	
Clinical Trial Phase:	IV
Clinical Trial Population:	Subjects with severe facial acne vulgaris
Clinical Trial Objectives:	Demonstrate that daily use of topical trifarotene (CD5789) cream associated with oral antibiotic therapy is safe and effective in subjects with severe facial acne vulgaris.
Clinical Trial Design:	This is a multicenter, randomized, double blind, placebo-controlled clinical study in subjects with severe facial inflammatory acne vulgaris. The study will evaluate once daily topical trifarotene 50µg/g (CD5789) cream associated with oral doxycycline 120mg (T+D) compared to trifarotene vehicle and doxycycline placebo (TVeh+DPbo), as illustrated in Section 5.1.1 – Study Schema. Subject eligibility is evaluated over a 28-day screening period. Qualified subjects will complete baseline assessments and be randomized (2:1) to T+D or TVeh+DPbo for a 12 week treatment period. Subjects will be provided skin care products including Cetaphil® Gentle Skin Cleanser for washing the face twice daily (morning and evening); Cetaphil® PRO Oil Absorbing Moisturizer with SPF 30 for use daily on the face (morning) and to be re-applied to face and other exposed skin when sun exposure is expected; and Cetaphil® Moisturizing Lotion for supplemental moisturizer use, as needed. Use of the subject's preferred or investigator's recommended non-comedogenic cleanser, moisturizer and sunscreen (SPF ≥30) is permitted. 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 the acne severity (IGA) or lesion counts. Subjects will return to the clinic for safety and efficacy assessment at Weeks 1, 2, 4, 8 and 12. Study procedures and assessments are performed according to the schedule of assessments (Section 5.1.2).
Total number of subjects:	At least 198 subjects are planned to be randomized. Target enrollment should include an approximate even distribution of male to female subjects, and adult (≥18 years) and adolescent subjects (12-17 years).
Number of clinical trial centers:	Approximately 30 sites
Region(s) / country(ies) involved:	United States, Puerto Rico
Duration of subject participation:	The expected duration for each subject's participation in the study is 16 weeks (including a 4-week screening period and a 12-week treatment period).

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Inclusion criteria	Subjects must fulfill inclusion criteria to participate in the study. 1. The subject is male or female, 12 years of age and older, at Screening visit. 2. Subject with clinical diagnosis of acne vulgaris, defined by Investigator's Global Assessment (IGA) score of 4 (Severe) 3. Subject with at least 20 inflammatory lesions (papules and pustules) and 30 to 120 non-inflammatory lesions (open comedones and closed comedones) on the face, excluding the nose. 4. The subject is a female of non-childbearing potential (premenarchal or postmenopausal [absence of menstrual bleeding for 1 year prior to Screening, without any other medical reason], hysterectomy or bilateral oophorectomy). 5. The subject is a female of childbearing potential: 5.1. Who is willing to undergo UPTs throughout the course of the study, as required. 5.2. Who has been strictly abstinent for 1 month prior to Screening and agrees to continue for the duration of the clinical trial and at least 1 month after the last study drug ingestion / application, OR Who agrees to use highly effective and approved contraceptive method(s) for the duration of the study and at least 1 month after the last study drug ingestion / application. Highly effective methods of contraception include: 5.2.a. bilateral tubal ligation; 5.2.b. approved combined oral contraceptives (estrogens and progesterone), implanted or injectable contraceptives, or hormonal contraceptive vaginal rings with a stable dose for at least 1 month prior to the Screening visit, with an appropriate barrier form of contraception (with a spermicide) including diaphragm, condom, cervical cap or sponge; 5.2.c. intrauterine device or intrauterine hormonal-releasing system inserted at least 1 month prior to the Screening visit; 5.2.d. vasectomized partner for at least 3 months prior to the Screening visit Note: This criterion applies to a prepubertal female subject who begins menses during the study 6. If a female of childbearing potential uses oral contraceptives that are also approved for treating acne vulgaris (such as cyproterone acetate and ethinyl estradiol; drospirenone and ethinyl estradiol; norgestimate and ethinyl estradiol; norenthindrone acetate and ethinyl estradiol; etc) the dose should be stable for at least 6 months prior to the Screening visit, and agree to use an

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	appropriate barrier form of contraception, with a spermicide, including diaphragm, condom, cervical cap or sponge. 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. 8. Subject (and legal guardian, if applicable) is willing and able to comply with all time commitments and procedural requirements of the protocol, including daily recordings in the study drug dosing calendar, etc. 9. Subject agrees to participate in the photograph sub-study (mandatory to main study participation, at designated centers), verified by signing and dating an approved ICF (includes willingness to remove all makeup prior to study visits, remove jewelry in the areas to be photographed, keep facial hair well-groomed prior to study visits). 10. Subject is apprised of HIPAA (Health Insurance Portability and Accountability Act) and is willing to share personal information and data, as verified by signing a written authorization at the Screening visit.
Exclusion criteria	Subjects meeting any of the exclusion criteria are not eligible to participate in the study. 1. Body weight <45 kg at Screening visit. 2. Subject with more than 4 nodules or cysts or combination thereof, on the face. 3. Subject with known active or chronic allergies or suspected allergy to trifarotene or tetracycline class antibiotics (including pseudomembranous colitis or antibiotic-associated colitis). 4. Subjects with nodulocystic or conglobate acne, acne fulminans, or secondary acne (chloracne, drug-induced acne, etc). 5. Prior failure of trifarotene treatment including intolerance that resulted in stopping treatment; lack of clinical improvement, etc. 6. Subject with facial dermal conditions (e.g. tattoo, skin abrasion, eczema, sunburned skin, scars, nevi, etc.) that may interfere with study assessments in the opinion of the investigator. 7. Subject with excessive facial hair that would interfere with study assessments, as judged by the investigator, or unwilling to keep facial hair well-groomed prior to study visits, as judged appropriate by the investigator to perform study assessments. 8. Pregnant women (positive urine pregnancy test at the Screening or Baseline visits), breastfeeding women, or women planning a pregnancy during the study or within 1 month after the last study drug ingestion / application

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9. Subject with known impaired hepatic or renal functions, based on medical history.
10. Subjects taking Vitamin A supplements in excess of the recommended daily allowance (4000 – 5000 IU; no washout period is required)
11. Subjects with a washout period for **topical treatment** or procedures on the face less than:

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

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

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

13. Currently receiving any prescription testosterone therapy (e.g., testosterone cypionate, testosterone enanthate, testosterone pellet, testosterone undecanoate) or on a testosterone booster or prescription testosterone (e.g., DHEA, Omnadren®, Sustanon®, testosterone cypionate, testosterone enanthate, testosterone propionate, testosterone phenylpropionate) or testosterone supplements (e.g., Tribulus).
14. The subject is unwilling to or unable to refrain from use of prohibited medication or procedures during the clinical trial (see Section 5.4.13.5)

<table>
<tr><td colspan="3">Clinical Trial Title: A Multi-Center, Randomized, Double-Blind, Placebo Controlled Study To Compare Efficacy and Safety of Trifarotene (CD5789) Cream When Used with an Oral Antibiotic for the Treatment of Severe Acne Vulgaris</td></tr>
<tr><td></td><td colspan="2">15. Subject who foresees intensive UV exposure during the study (mountain sports, sailing, sunbathing, tanning beds, etc.).
16. Subject who is at risk in terms of precautions, warnings, and contraindications for trifarotene or doxycycline hyclate.
17. Subject with an acute / chronic disease or a history of major medical or surgical or psychiatric condition or surgical interventions that may either interfere with the interpretation of the trial results and/or might put the subject at risk in the opinion of the investigator.
18. Subject under guardianship (for reason other than minor status), hospitalized subject in a public or private institution for a reason other than the research, and subject deprived of his/her freedom.
19. More than one subject sharing the same household.
20. Subject who has participated in another investigational drug or device research study within 30 days prior to Screening OR is in an exclusion period from a previous clinical trial.
21. Subject who is unable to communicate or cooperate with the investigator due to history of alcohol/drug abuse, language problems, poor mental development, or impaired cognitive or verbal function</td></tr>
<tr><td>Investigational Products:

Drug substance:
Trade name:
Dose form:
Strength/Concentration:
Administration:</td><td colspan="2">Trifarotene + Doxycycline (T+D) – refer to Section 5.1.1 – Study Schema

<table>
<tr><td>Trifarotene (CD5789) Cream</td><td>Doxycycline hyclate delayed-release</td></tr>
<tr><td>AKLIEF®</td><td>DORYX® MPC (modified polymer coat)</td></tr>
<tr><td>Cream</td><td>Tablet</td></tr>
<tr><td>50 µg/g</td><td>120 mg</td></tr>
<tr><td>Topical

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).</td><td>Oral

Day 1
• Take one tablet by mouth in the evening.
Day 2
• Take one tablet by mouth, morning and evening.
Day 3 and beyond
• Take one tablet by mouth in the evening.

<u>General</u>
• Tablet should be swallowed whole, not chewed or crushed, with adequate amounts of fluid.
• Remain upright (sitting or standing) for at least 2 hours after intake.</td></tr>
</table></td></tr>
</table>

Clinical Trial Title: A Multi-Center, Randomized, Double-Blind, Placebo Controlled Study To Compare Efficacy and Safety of Trifarotene (CD5789) Cream When Used with an Oral Antibiotic for the Treatment of Severe Acne Vulgaris

Investigational Products: **Trifarotene vehicle + Doxycycline placebo (TVeh+DPbo) -** refer to Section 5.1.1 – Study Schema

		• May be taken with food or milk if gastric irritation occurs. ***Note: Use all tablets in one bottle before opening a new bottle.***
Duration:	12 Weeks	12 Weeks

Name:	Trifarotene vehicle	Doxycycline placebo
Trade Name:	-	-
Dose form:	Cream	Tablet
Strength/Concentration:	-	-
Administration:	Topical	Oral
	Apply a thin layer to the face once daily, in the evening. The face should be washed with cleanser and patted dry, before use. One pump actuation should be enough to cover the face (i.e., forehead, cheeks, nose, and chin).	**Day 1** • Take one tablet by mouth in the evening. **Day 2** • Take one tablet by mouth, morning and evening. **Day 3 and beyond** • Take one tablet by mouth in the evening. **General:** • Tablet should be swallowed whole, not chewed or crushed, with adequate amounts of fluid. • Remain upright (sitting or standing) for at least 2 hours after intake. • May be taken with food or milk if gastric irritation occurs. ***Note: Use all tablets in one bottle before opening a new bottle.***
Duration:	12 Weeks	12 Weeks

<table>
<tr><td colspan="2">Clinical Trial Title: A Multi-Center, Randomized, Double-Blind, Placebo Controlled Study To Compare Efficacy and Safety of Trifarotene (CD5789) Cream When Used with an Oral Antibiotic for the Treatment of Severe Acne Vulgaris</td></tr>
<tr><td>Non-Investigational Study Products Provided By Sponsor:</td><td>For use by all subjects.
<table>
<tr><th>Cetaphil® Gentle Skin Cleanser</th><th>Cetaphil® PRO Oil Absorbing Moisturizer with SPF 30</th><th>Cetaphil® Moisturizing Lotion</th></tr>
<tr><td rowspan="2">Use twice daily in the morning and evening to wash the face and pat dry before applying topical study drug.</td><td>Use daily on the face (morning) and re-apply to face and other exposed skin when sun exposure is expected.</td><td>For supplemental moisturizer use on the face, as needed.</td></tr>
<tr><td colspan="2">Moisturizer should be used as often as needed except less than 1 hour before and 1 hour after topical study drug application (in the evening).</td></tr>
</table></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 5.1.2):

Efficacy:
• Acne total (TL), inflammatory (IL) and non-inflammatory (NIL) lesion counts
• Investigator Global Assessment (IGA) of facial acne using a 5-point numerical scale (0-4)

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

Subject Reported Outcomes:
• Quality Of Life questionnaire
o Acne-Specific Quality of Life questionnaire (Acne-QoL) for subjects 13-35 years, at time of Screening
• Subject satisfaction questionnaire
• Topical study drug acceptability questionnaire

Other:
• Standardized photography at designated sites (for visual evidence of treatment effect from Baseline to Week 12)</td></tr>
</table>

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Study Variables Analyzed **Efficacy:**	**Primary:** • Absolute change in facial total lesion (TL) counts from Baseline to Week 12 **Secondary** • Absolute change in facial IL/NIL counts from Baseline to Week 12 • Facial Success Rate at Week 12, defined as the proportion of subjects who achieve an IGA score of 1 (Almost Clear) or 0 (Clear) and at least a 2-grade improvement from Baseline to Week 12 CCI [redacted]
Quality of Life/Subject-Reported Outcomes:	• Acne QoL at Baseline and Week 12/Early termination for subjects 13-35 years, at time of Screening • Subject satisfaction questionnaire at Week 12/Early termination • Topical study drug acceptability questionnaire at Week 12/Early termination
Safety:	• Local tolerability parameters (erythema, scaling, dryness and stinging/burning) will be evaluated at each visit on a 4-point scale ranging from 0 (none) to 3 (severe). • Incidence of TEAEs including AESIs, SAEs and TEAEs leading to discontinuation
Principal statistical method:	The Intent-to-treat (ITT) population is defined as all randomized subjects and will be used for the analyses of efficacy endpoints. The Per Protocol (PP) population is defined as any subjects in the ITT population who have compliance to the study treatment (both topical and oral) between 80% and 120% and assessments of the primary endpoint at Baseline and Week 12, without any major deviations that could have a significant effect on the efficacy of the study treatment (e.g. errors in treatment assignment, use of prohibited medications). The PP population will be used for a sensitivity analysis of the primary endpoint. The Safety (SAF) population is defined as comprising the ITT population subjects who applied/took the study drugs at least once and will be used for all safety analyses. The main objective of this study is to evaluate the efficacy and safety outcomes of treatment of trifarotene in association with doxycycline versus trifarotene vehicle and doxycycline placebo with 12 weeks of treatment. All data collected will be summarized by descriptive statistics and frequency tables as appropriate.

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	The hypothesis test for the primary efficacy endpoint will be evaluated on the ITT population at the significance level $\alpha = 0.05$. The hypothesis tests for the secondary efficacy endpoints are conditional on the success of the primary endpoint. The hypothesis tests for the secondary efficacy endpoints will be evaluated on the ITT population according to the following predefined order, all at the same significance level $\alpha = 0.05$, moving to the next hypothesis test only after a success on the previous hypothesis test. 1) Absolute Change in facial IL counts from Baseline to Week 12 2) Absolute Change in facial NIL counts from Baseline to Week 12 3) Facial Success Rate at Week 12 This approach does not inflate the Type I error rate as long as the hypothesis tests for the secondary efficacy endpoints are conditional on the success of the primary endpoint, there is a prospective specification of the testing sequence and no further testing is performed once the sequence breaks, that is, further testing stops as soon as there is a failure of a hypothesis test in the sequence to show significance at the predefined alpha level. No hypothesis test will be evaluated for the exploratory efficacy endpoints. p-values and 95% confidence intervals will presented for descriptive purposes only. **Efficay Analysis** **Primary** • Absolute change in facial total lesion counts from Baseline to Week 12 will be analyzed using an ANCOVA with treatment, analysis center and baseline count as fixed effects; the p-values for the treatment comparison, estimates of the treatment difference and the 95% confidence interval of the difference will be generated from the ANCOVA model **Secondary** • Absolute change in facial IL/NIL lesion counts from Baseline to Week 12 will be analyzed using an ANCOVA with treatment, analysis center and baseline count as fixed effects; the p-values for the treatment comparison, estimates of the treatment difference and the 95% confidence interval of the difference will be generated from the ANCOVA model • Facial Success Rate at Week 12 will be analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by analysis center; strata-adjusted difference in success proportions between treatment groups and the 95% confidence interval of the difference will be based on the large sample approximation method for binary data

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	CCI **Subject-Reported Outcomes (PROs)** • Acne-QoL scores will be summarized by visit using descriptive statistics/frequency tables as applicable • Subject satisfaction questionnaire scores will be summarized by visit using frequency tables • Topical study drug acceptability questionnaire will be summarized by visit using frequency tables **Safety** • Local tolerability scores (erythema, scaling, dryness and stinging/burning) 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 22.1 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
BPO	Benzoyl Peroxide
CDMS	Clinical Data Management System
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
DMP	Data Management Plan
EDC	Electronic Data Capture
e.g.	For Example (Latin: exempli gratia)
ET	Early Termination
etc.	*Et cetera*
FDA	Food and Drug Administration
FSI	First Subject In (first subject screened, i.e. who signs the Informed Consent Form)
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
IGA	Investigator's Global Assessment
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

Abbreviation	***Term***
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)
MI	Multiple Imputation
MD	Medical Doctor
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
NIL	Non-Inflammatory Lesions
NOAEL	no observed adverse effect level
OTC	Over-the-Counter
PK	Pharmacokinetics
PP	Per-Protocol
PT	Preferred term
QOL	Quality of Life
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
T+D	Topical trifarotene and oral doxycycline treatment group
TEAE	Treatment-Emergent Adverse Event
TL	Total lesions
TVeh+DPbo	Topical trifarotene vehicle and oral doxycycline placebo treatment group
UPT	Urine Pregnancy Test
USA	United States of America
UV	Ultraviolet
WOCBP	Women of child-bearing potential

3 BACKGROUND AND RATIONALE

3.1 Medical Background and Rationale

Acne vulgaris (AV) is a common, chronic, inflammatory disorder that usually starts in early adolescence (ultimately affecting approximately 85% of adolescents); however, AV can occur at any age and persist well into adulthood (Heidel B, 2016). In the USA, acne has been reported to affect over 25 (17–45) million Americans (Tsatsou, 2014). As acne is a chronic and relapsing disease, normalizing follicular desquamation is then the key to achieve and maintain control of acne. It can persist for years and result in disfigurement and permanent scarring (Koo et al., 1991). Acne is a multifactorial inflammatory disease affecting pilosebaceous follicles (Dreno 2005, Gollnick 2003, Tsatsou, 2014). The consequences of AV may include physical (e.g., skin discomfort/pain, erythema, hyperpigmentation, scarring), psychological (e.g., anxiety, poor self-esteem, depression, suicidal ideation), and social repercussions (e.g., avoidance of interpersonal interactions). Teenagers with even mild acne feel stigmatized and frustrated (Osterweil N, 1993). The incidence of severe AV typically increases throughout adolescence, and the severity of both physical and psychosocial sequelae tend to increase as AV severity worsens.(Silverberg JI, 2014; Tan J 2017). Thus, a need exists for efficacious, well-tolerated, and safe therapies for severe AV.

Current guidelines for severe AV recommend a rational combination therapy regimen (e.g., topical agents [retinoid and or benzoyl peroxide] and an oral antibiotic). Today it is established that retinoids act in the pathology of acne vulgaris: they are potent modulators of cellular differentiation and keratinisation. Topical retinoids have been the first-line treatment for most forms of acne vulgaris (Bayramgurler D et al, 2017). Trifarotene (AKLIEF®) cream is a new generation topical retinoid with *in-vitro* data showing high selectively in targeting retinoic acid receptor gamma (RAR-ɤ), the most common RAR found in the skin. (Thoreau E, 2018). Current evidence suggests that topical trifarotene normalizes the differentiation of follicular epithelial cells resulting in decreased microcomedo formation. It may be an ideal topical agent with high selectivity towards gamma receptors, skin metabolism and with very low systemic absorption. Safety and efficacy of using trifarotene to treat acne was confirmed in two pivotal studies that has resulted in FDA approval in October 2019.

Oral antibiotic therapy continues to be an integral part of the therapeutic armamentarium for AV, including in published AV treatment guidelines, primarily for patients with moderate-to-severe disease, used in combination with topical therapy. (Del Rosso 2011, Gollnick H, 2003, Eichenfield LF, 2013, Strauss JS, 2007). The rationale for the use of doxycycline vs. tetracycline for treatment of AV include the apparent need for less frequent daily dosing, lower prevalence of less sensitive P. acnes bacterial strains, and greater lipophilicity than tetracycline. (Leyden JJ, 2011, Smith K, 2005) in addition, enteric coated doxycycline exhibits favorable overall efficacy and safety. (Del Rosso JQ, 2009, 2011; Kim S, 2013, Gollnick H, 2003, Kircik L. 2010). Doxycycline and minocycline are the most widely recommended oral antibiotics used for AV treatment (Zaenglein AL, 2016, Thiboutot D, 2009). The American Academy of Dermatology (AAD) guidelines do not favor the use of one over the other, although minocycline

is associated with greater potential to cause rare but severe AEs, such as drug hypersensitivity syndrome, autoimmune reactions (hepatitis, lupus-like syndrome), and secondary pseudotumor cerebri (benign intracranial hypertension). (Zaenglein AL, 2016, Thiboutot D. 2009, Descamps V. 2017, Roman CJ, 2016, Shapiro L. 1997, Kim S, 2013). Common doxycycline side effects include gastrointestinal events, which are reduced with enteric–coated tablet (Kircik L, 2010), and dose-related photosensitivity (Doryx PI, Zaenglein AL, 2016, Kim S, 2013). Tetracyclines have been shown to exhibit both antibacterial and anti-inflammatory properties; furthermore, extensive basic science and clinical data supports the anti-inflammatory effects of doxycycline for the treatment of inflammatory facial dermatoses (e.g., papulopustular rosacea, AV).(Mays RM, 2012, Sapadin AN, 2006; Del Rosso JQ, 2004). To avoid bacterial resistance, it is recommended that the administration of systemic antibiotics be limited to the shortest possible duration, and that a topical therapy (such as retinoids) be given concomitantly and as maintenance therapy (Zaenglein AL, et al. 2016, Del Rosso JQ, 2016).

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

This clinical trial is designed to demonstrate that a daily treatment regimen of trifarotene (CD5789) cream in association with oral doxycycline is safe and effective for the treatment of severe facial AV.

3.2 Risk/Benefit Assessment

Oral antibiotic therapy is an integral part of the therapeutic options for AV, including in published AV treatment guidelines, primarily for patients with severe disease, used in association with topical therapy (Del Rosso 2011, Gollnick H, 2003, Eichenfield LF, 2013, Strauss JS, 2007).

This study is evaluating use of a topical retinoid, trifarotene (AKLIEF®) cream, in association with oral doxycycline hyclate delayed release tablets (DORYX® MPC, 120mg), which are both FDA-approved for the treatment of AV.

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

Trifarotene (CD5789) cream has low systemic exposure resulting in a high safety margin of 98 for teratogenicity and the ratio to systemic effect is <1170 for general toxicity. Women of childbearing potential will be required to be strictly abstinent or to use an effective contraceptive method during the study and for at least one month after the last study drug application. Due to doxycycline's potential for reducing effectiveness of oral contraceptives, subjects using oral contraceptives must also agree to use an appropriate barrier form of contraception (with a spermicide) including diaphragm, condom, cervical cap or sponge, or agree to use other permitted forms of birth control.

Topical retinoids may be associated with skin irritation, particularly in the two first weeks of therapy (Leyden JJ, 1998). Similar findings were observed in the trifarotene pivotal clinical studies, where skin irritation was managed by use of moisturizers and/or with temporary reductions in dose frequency (Tan, J et al J Am Acad Dermatol 2019).

Overall, the risk/benefit assessment is reasonable to evaluate safety and efficacy of trifarotene (CD5789) cream when used in association with oral doxycycline for the treatment of acne, over 12 weeks.

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 the comedo (Pawin H, 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.

Trifarotene (CD5789) cream, developed by GALDERMA R&D for topical administration, shows selective binding to RAR and not to RXR. *In vitro* gene transactivation studies show a very high selectivity for RARγ over RARα and RARβ. RARγ receptors are known to be present in relatively larger numbers in the target organ (i.e. the skin) (Fisher GJ, 1994).

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). DORYX® MPC (doxycycline hyclate delayed-release) in 120mg tablets is commercially approved in the US for the treatment of AV (Appendix 14.7 – DORYX MPC Prescribing Information).

The commercially-approved trifarotene dosing regimen will be used in association with oral doxycycline to evaluate safety and efficacy in the treatment of severe AV. Topical therapy associated with an oral antibiotic is a clinically-accepted strategy for the treatment of severe AV (Del Rosso 2011, Gollnick H, 2003, Eichenfield LF, 2013, Strauss JS, 2007).

4 STUDY OBJECTIVE AND ENDPOINTS

4.1 Study Objective

The purpose of this study is to demonstrate that a daily treatment regimen of topical trifarotene 50µg/g (CD5789) cream when used in association with oral doxycycline hyclate delayed-release tablets (DORYX MPC, 120mg) is safe and effective for the treatment of severe facial AV.

4.2 Study Endpoints

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

4.2.1 Primary Endpoint

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

4.2.2 Secondary Endpoints

- Absolute change in facial IL/NIL counts from Baseline to Week 12
- Facial Success Rate at Week 12, defined as the proportion of subjects who achieve an IGA score of 1 (Almost Clear) or 0 (Clear) and at least a 2-grade improvement from Baseline to Week 12

CCI [redacted]

4.2.4 Quality of Life / Subject Reported Outcomes

- Acne-QoL at Baseline and Week 12/Early termination for subjects 13-35 years, at time of Screening
- Subject satisfaction questionnaire at Week 12/Early termination
- Topical study drug acceptability questionnaire at Week 12/Early termination

4.2.5 Safety

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

5 INVESTIGATIONAL PLAN

5.1 Overall Study Design

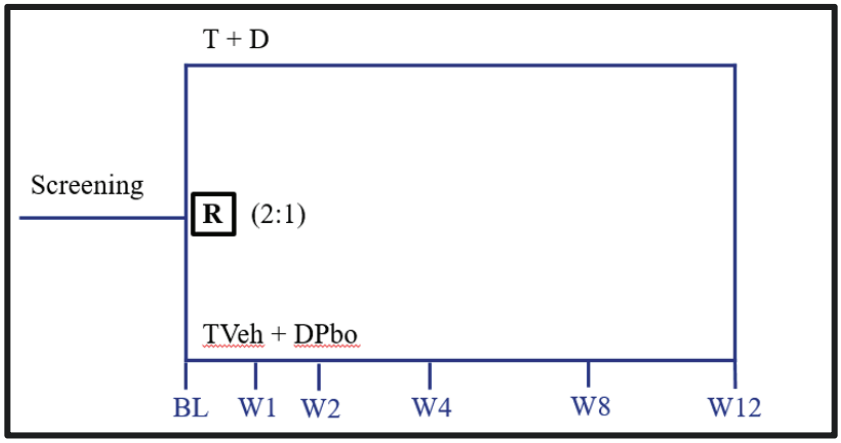
This is a multi-center, randomized (2:1), double-blind, placebo-controlled study evaluating the safety and efficacy of T+D compared to TVeh+DPbo for the treatment of severe facial AV (Section 5.1.1 - Study Schema). At least 198 randomized subjects aged 12 and older are planned, at approximately 30 study centers in the United States and Puerto Rico. Target enrollment should include an approximate even distribution of male to female subjects, and adult (≥18 years) and adolescent subjects (12-17 years).

Subject eligibility is evaluated over a 28-day screening period. Qualified subjects will complete baseline assessments and be randomized (2:1) to T+D or TVeh+DPbo for a 12 week treatment period. Subjects will be provided skin care products including Cetaphil® Gentle Skin Cleanser for washing the face twice daily (morning and evening); Cetaphil® PRO Oil Abosorbing Moisturizer with SPF 30 for use daily on the face (morning) and to be re-applied to face and other exposed skin when sun exposure is expected; and Cetaphil® Moisturizing Lotion for supplemental moisturizer use, as needed. Use of the subject's preferred or investigator's recommended non-comedogenic cleanser, moisturizer and sunscreen (SPF ≥30) is permitted. If a subject experiences persistent dryness or irritation, the investigator may consider a reduced application frequency for the topical study drug, over a maximum of 2 weeks, within the first four (4) weeks of the treatment period (Section 5.4.8 – Dose Modification of Topical Study Drug). Dose modification for oral study drug is allowed for safety reasons only, and should be based on individual investigator clinical judgment (Section 5.4.9).

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

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

5.1.1 Study Schema



T+D: Topical trifarotene (CD5789) cream + oral doxycycline (DORYX MPC, 120mg) ◊

TVeh+DPbo: Topical trifarotene vehicle + oral doxycycline placebo ◊

R 2:1 randomization (active/active to vehicle/placebo)

BL: Baseline visit
W: Scheduled visit week
◊: Doxycycline and placebo dosing:

- Day 1 – 1 tablet in the evening
- Day 2 – 1 tablet in the morning and evening
- Day 3 and beyond – 1 tablet in the evening

5.1.2 Schedule of Assessments

5.1.2.1 Study Assessment Considerations Pertaining to the COVID-19 Pandemic

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

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

- Remote Visits (phone, etc) in lieu of scheduled office visits
  - for safety and wellness assessment (concomitant medications, AEs, etc)
- Questionnaire completion
  - sent to subject by email or mail
  - subject signs, dates and returns, by email of mail.
- Collection of previously dispensed study drugs and dosing calendar, from an adult family member
  - Weighing of returned topical study drug is required
  - A follow-up phone call with the subject is required to review the dosing calendar and returned study drugs, for appropriate clarification in study medication use.
- Dispensing of new study drugs and non-investigational supplies (a new dosing calendar, non-IP supplies, etc) to an adult family member
  - Weighing of topical study drug is required, before dispensing
  - A follow-up phone call with the subject is required to convey reminders on proper instructions for study medication and other supplies use, and to use the newly dispensed study drugs beginning that evening (and to stop using previously dispensed medication, if not returned).
- FDA COVID-19 guidance allows for secure delivery for self-administered study medication. In cases where a family member is not available for dispensing study medication and other supplies, delivery using an express courier with appropriate temperature control capability is permitted. A follow-up phone call is required in these circumstances to confirm receipt and provide the subject with appropriate reminders and proper instuctions for study medication and other supply use.

  Note: The decision to dispense additional study drug should be based on the investigator's clinical judgement that ongoing dosing does not pose undue safety risks to the subject, and that the subject is willing to continue using the study

drug. In all cases for maintaining study drug availability to subjects, existing requirements for maintaining study supply accountability remain.

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

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

5.1.2.2 Study Assessment Schedule

Procedures	Screening [g]	Baseline	Week 1	Week 2	Week 4	Week 8	Week 12 / ET [i]
	≤28 days	--	(±2 days)	(±2 days)	(±3 days)	(±3	(±3 days)
Informed Consent / Assent	X	X [h]					
Demographics / Medical History	X	X					
Previous Therapies and Medications [a]	X	X					
Concomitant Medications / Therapies / Procedures	X	X	X	X	X	X	X
Inclusion / Exclusion Criteria	X	X					
Urine Pregnancy Test [k]	X	X	X	X	X	X	X
Acne Severity Assessment (IGA) [b,j]	X	X	X	X	X	X	X
Lesion Counts [c,j]	X	X	X	X	X	X	X
Local Tolerability [d]		X	X	X	X	X	X
Adverse Events [e]		X	X	X	X	X	X
Subject Satisfaction Questionnaire with Assigned Study Treatment (study cream and study tablet)							X
Topical Study Drug Acceptability Questionnaire							X
Acne Specific QOL [f]		X					X
Photographs (face; at designated centers) [m]		X					X
Randomization		X					
Study Drug [l]		W/D	I/W	I/W	C/I/W/D	C/I/W/D	C/I/W
Subject Dosing Calendar		D	C/R/D	C/R/D	C/R/D	C/R/D	C/R
Exit Form							X

For study drugs and/or dosing calendar: W=Weigh; D=Dispense; R=Review; C=Collect and I=Inspect (includes returning all study drugs, for weighing bottle pumps and tablet counting; the study drugs dispensed at Baseline are re-dispensed at Week 1 and Week 2)

a Acne treatment for the previous 6 months and all other therapies for the previous 4 weeks. Therapy that continues after baseline should be recorded on the concomitant medication CRF.

b Global assessment of acne severity is conducted on the face (IGA), **and should be performed before lesion counts**

c Inflammatory lesions (papules, pustules), non-inflammatory lesions (open and closed comedones) and other lesions (nodules, cysts) will be counted, on the face.

d The Investigator must record and grade the severity of the signs and record the assessment of symptoms of local tolerability (erythema, dryness, scaling, and stinging/burning) at each visit. Severity grading is based on signs/symptoms occurring after the last dose of topical study drug before the visit. A sign/symptom which requires concomitant medication/therapy or results in permanent discontinuation of topical study drug should be recorded as an AE.

e AE onset after subject signature of the ICF should be recorded on the AE CRF.

f Subjects aged 13-35 years at time of Screening will complete the Acne Specific QOL.

g Screening may be completed over several visits, over a 28-day period. Screening and Baseline may be completed on the same day, provided the subject meets eligibility requirements and does not require a washout period. Subjects may be re-screened one time, provided the reason for re-screening is not due to acne severity or lesion counts.

h If Screening and Baseline occur as separate visits, the ICF does not have to be signed again at Baseline.

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

j These assessments are to be performed by the same evaluator throughout the study, for a given subject. If it is not possible to use the same evaluator to follow a given subject, it is recommended that evaluations between the primary and subsequent evaluator overlap (both evaluators should examine the subject together and discuss findings) for at least one visit.

k For WOCBP only. Mandatory at Screening, Baseline, Week 12 and ET visits. UPT is required at other visits if no menstrual period has occurred in the preceding four weeks. For prepubertal subjects, reconfirm pre-menses status at every visit and, in case of status change, collect information on contraceptive measures and perform a UPT according to the schedule for WOCBP. Sites will provide UPT supplies (hCG sensitivity ≤25 mIU/mL).

l Study drug refers to both topical and oral medications. Only topical study drug will be weighed (W). Oral study medication (tablets) will be inspected (I)/counted, upon return, for ongoing compliance counseling. For compliance calculations, tablets dispensed will be based on fill count.

m Consent to facial photography for visual evidence of treatment effect is mandatory to study participation, but only applies to designated imaging centers. Consent to photographs of patch testing results (suspected contact allergic reaction) is mandatory for all subjects to participate in the study.

5.2 Discussion of Study Design

This study will evaluate the safety and efficacy of topical trifarotene (CD5789) cream when used in association with oral doxycycline for the treatment of severe AV (refer to Section 5.1.1 – Study Schema). Topical therapy when used in association with an oral antibiotic allows clinicians to target multiple pathophysiologic pathways, with clinical studies having reported the benefits of using topical and oral antibiotic therapy for treating severe acne vulgaris (Gollnick H, 2003; Thiboutot D. 2005; 2006). Although guidelines exist that specify benzoyl peroxide (BPO) be used with other therapies for severe acne, clinicians vary in how they treat severe acne in real-world practice and there are patients where using BPO is not possible (irritation) or not preferred (fear of causing wrinkles; stains clothes, sheets, towels; etc).

The study is utilizing trifarotene 50 µg/g (AKLIEF®) cream and doxycycline hyclate delayed-release tablets (DORYX® MPC, 120mg) which are both approved in the US for the treatment of AV. Subjects will be instructed to use trifarotene (CD5789) cream once daily on the face following the commercially approved labeling. Oral doxycycline (DORYX MPC, 120mg) use is consistent with the commercially approved labeling for DORYX MPC (See Appendix 14.7 – DORYX MPC Prescribing Information).

Study treatment include T+D and TVeh+DPbo and will be blinded and randomly assigned to minimize bias (Section 5.1.1 – Study Schema). Use of a vehicle/placebo control arm is consistent with FDA's standard for generating valid scientific evidence to definitively support safety and efficacy. The vehicle/placebo arm accounts for the effects of treatment that do not depend on the test articles (trifarotene + oral doxycycline). The study is designed to mitigate safety risks by using a 2:1 randomization (active/active to vehicle/placebo), along with frequent clinic visits over the 12-week treatment period (Weeks 1, 2, 4, 8 and 12). Subjects in both study arms will follow a skincare regimen of cleanser and moisturizer use, where studies have shown some subjects will benefit.

The study involves a 12-week treatment period which is considered appropriate to evaluate clinical improvement in facial AV. The treatment period is consistent with clinical standards to avoid prolonged use of antibiotic therapy and risk of bacterial resistance.

Five visits to the clinical site are planned during the treatment period for investigators to evaluate any potential tolerability signs/symptoms and to counsel the subject on the importance of following dosing instructions. Prior trifarotene studies have shown tolerability symptoms peak early in the treatment period, and can be appropriately managed with ongoing subject counseling and moisturizer use (Tan, J et al. J Am Acad Dermatol. 2019). The protocol allows investigators to prescribe a dose reduction for the topical study drug to manage tolerability signs/symptoms within the first four weeks, if needed (Section 5.4.8). Dose modification for the oral study drug is allowed for safety reasons only, and should be based on individual investigator clinical judgment (Section 5.4.9).

Overall, the study design is considered to be scientifically robust and clinically relevant for evaluating topical trifarotene (CD5789) cream in association with oral antibiotic therapy for the safe and effective treatment of severe AV.

5.3 Selection of Study Population

5.3.1 Number of Planned Subjects

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

Refer to Section 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. The subject is male or female, 12 years of age and older, at Screening visit.

2. Subject with clinical diagnosis of acne vulgaris, defined by Investigator's Global Assessment (IGA) score of 4 (Severe)
3. Subject with at least 20 inflammatory lesions (papules and pustules) and 30 to 120 non-inflammatory lesions (open comedones and closed comedones) on the face, excluding the nose.
4. The subject is a female of non-childbearing potential (premenarchal or postmenopausal [absence of menstrual bleeding for 1 year prior to Screening, without any other medical reason], hysterectomy or bilateral oophorectomy).
5. The subject is a female of childbearing potential:

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

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

   OR

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

   Highly effective methods of contraception include:

   5.2.a. bilateral tubal ligation;

   5.2.b. approved combined oral contraceptives (estrogens and progesterone), implanted or injectable contraceptives, or hormonal contraceptive vaginal rings with a stable dose for at least 1 month prior to the Screening visit, with an appropriate barrier form of contraception (with a spermicide) including diaphragm, condom, cervical cap or sponge;

   5.2.c. intrauterine device or intrauterine hormonal-releasing system inserted at least 1 month prior to the Screening visit;

   5.2.d. vasectomized partner for at least 3 months prior to the Screening visit

   Note: This criterion applies to a prepubertal female subject who begins menses during the study
6. If a female of childbearing potential uses oral contraceptives that are also approved for treating acne vulgaris (such as cyproterone acetate and ethinyl estradiol; drospirenone and ethinyl estradiol; norgestimate and ethinyl estradiol; norenthindrone acetate and ethinyl estradiol; etc) the dose should be stable for at least 6 months prior to the Screening visit, and agree to use an appropriate barrier form of contraception, with a spermicide, including diaphragm, condom, cervical cap or sponge.
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.

8. Subject (and legal guardian, if applicable) is willing and able to comply with all time commitments and procedural requirements of the protocol, including daily recordings in the study drug dosing calendar, etc.
9. Subject agrees to participate in the photograph sub-study (mandatory to main study participation, at designated centers), verified by signing and dating an approved ICF (includes willingness to remove all makeup prior to study visits, remove jewelry in the areas to be photographed, keep facial hair well-groomed prior to study visits).
10. Subject is apprised of HIPAA (Health Insurance Portability and Accountability Act) and is willing to share personal information and data, as verified by signing a written authorization at the Screening visit.

5.3.3 Exclusion Criteria

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

1. Body weight <45 kg at Screening visit.
2. Subject with more than 4 nodules or cysts or combination thereof, on the face.
3. Subject with known active or chronic allergies or suspected allergy to trifarotene or tetracycline class antibiotics (including pseudomembranous colitis or antibiotic-associated colitis).
4. Subjects with nodulocystic or conglobate acne, acne fulminans, or secondary acne (chloracne, drug-induced acne, etc.).
5. Prior failure of trifarotene treatment including intolerance that resulted in stopping treatment; lack of clinical improvement, etc.
6. Subject with facial dermal conditions (e.g. tattoo, skin abrasion, eczema, sunburned skin, scars, nevi, etc.) that may interfere with study assessments in the opinion of the investigator.
7. Subject with excessive facial hair that would interfere with study assessments, as judged by the investigator, or unwilling to keep facial hair well-groomed prior to study visits, as judged appropriate by the investigator to perform study assessments.
8. Pregnant women (positive urine pregnancy test at the Screening or Baseline visits), breastfeeding women, or women planning a pregnancy during the study or within 1 month after the last study drug ingestion / application
9. Subject with known impaired hepatic or renal functions, based on medical history.
10. Subjects taking Vitamin A supplements in excess of the recommended daily allowance (4000 – 5000 IU; no washout period is required)
11. Subjects with a washout period for **topical treatment** or procedures on the face less than:

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

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

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

13. Currently receiving any prescription testosterone therapy (e.g., testosterone cypionate, testosterone enanthate, testosterone pellet, testosterone undecanoate) or on a testosterone booster or prescription testosterone (e.g., DHEA, Omnadren®, Sustanon®, testosterone cypionate, testosterone enanthate, testosterone propionate, testosterone phenylpropionate) or testosterone supplements (e.g., Tribulus).
14. The subject is unwilling to or unable to refrain from use of prohibited medication or procedures during the clinical trial (see Section 5.4.13.5)
15. Subject who foresees intensive UV exposure during the study (mountain sports, sailing, sunbathing, tanning beds, etc.).
16. Subject who is at risk in terms of precautions, warnings, and contraindications for trifarotene or doxycycline hyclate.
17. Subject with an acute / chronic disease or a history of major medical or surgical or psychiatric condition or surgical interventions that may either interfere with the interpretation of the trial results and/or might put the subject at risk in the opinion of the investigator.

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

5.3.4 Removal of Subjects From Therapy or Assessments

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

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

Reasons for discontinuing the study are summarized in Table 1:

Table 1: Reasons for Study Discontinuation

Pregnancy:	Withdraw the Subject from the clinical trial and follow the procedure described in Section 6.6.2.2.2
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 6.6.2.2.2) of receipt of the information.
- Complete as fully as possible the applicable Pregnancy Surveillance Form(s) (see Section 6.6.2.2.5).
- Monitor and record the progress of the pregnancy until its outcome. Contact the subject's regular physician (general practitioner or gynecologist) or hospital staff to obtain further details and ask for regular follow-up information.
- Provide trimonthly updates until the final outcome of the pregnancy. If the subject can no longer be reached (lost to follow-up), documentation of the non-response/contact with 2 phone calls and a letter (certified with return receipt) is required.
- If the pregnancy leads to an abortion (i.e., voluntary abortion, spontaneous abortion, or therapeutic abortion), in utero death, or congenital anomaly, follow the procedure for declaration of/reporting an SAE (Section 6.6.2.2.2).

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

Full details will be recorded on the withdrawal page (exit form), or an SAE report will be completed if the subject has completed the study. Pregnancy is not to be considered as an AE; however, it must be monitored and reported as described in Section 6.6.2.2.5.

5.4 Investigational Products

Investigational products include trifarotene (CD5789) cream, trifarotene vehicle, doxycycline hyclate delayed-release tablets (DORYX MPC, 120mg) and doxycycline placebo for purposes of this double-blind study. The study design includes an active arm (T+D) and a comparator arm (TVeh+DPbo). See Section 5.1.1 – Study Schema.

5.4.1 Study Drug Description

Table 2 summarizes the investigational medications.

Table 2: Description of the Study Drugs

Investigational Products: * **T + D**	**Topical Trifarotene (CD5789) Cream**	**Oral Doxycycline 120mg Tablet**
Trade Name	AKLIEF®	DORYX® MPC (modified polymer coat)
Name of Drug Substance	trifarotene	doxycycline hyclate delayed-release
Pharmaceutical Form	Cream	Tablet
Strength/ Concentration	50 µg/g	120mg
Route	Topical	Oral
Packaging (type and size)	45 g bottle with pump and overcap	Bottles of 30 tablets
Storage conditions	Store at 20-25°C (68-77°F) Excursions permitted to 15°C - 30°C (59°F to 86° F).	Store at 25° C (77° F) Excursions permitted to 15° C to 30° C (59° F to 86° F)
Duration of administration	12 Weeks	12 Weeks
Manufacturer *(Name and address)*	GALDERMA PRODUCTION INC 19400 Route Transcanadienne, Baie-d'Urfé H9X 3S4, Québec, Canada	Mayne Pharma International Pty Ltd 1538 Main North Road Salisbury South, SA 5106 Australia

Investigational Products: * **TVeh + DPbo**	**Topical Trifarotene Vehicle**	**Oral Doxycycline Placebo**
Trade Name or Equivalent	-	-
Name of Drug Substance	-	-
Pharmaceutical Form	Cream	Tablet
Strength/ Concentration	-	-
Route	Topical	Oral
Packaging (type and size)	45 g bottle with pump and overcap	Bottles of 30 tablets
Storage conditions	Store at 20-25° C (68-77° F) Excursions permitted to 15° C - 30° C (59° F to 86° F).	Store at 25° C (77° F) Excursions permitted to 15°C to 30° C (59° F to 86° F)
Duration of administration	12 Weeks	12 Weeks
Manufacturer *(Name and address)*	GALDERMA PRODUCTION INC 19400 Route Transcanadienne, Baie-d'Urfé H9X 3S4, Québec, Canada	Mayne Pharma International Pty Ltd 1538 Main North Road Salisbury South, SA 5106 Australia

* Study design includes an active arm (T+D) and a comparator arm (TVeh+DPbo). See Section 5.1.1 – Study Schema

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

Guidelines for using study drugs and non-investigational products is summarized in Table 3.

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

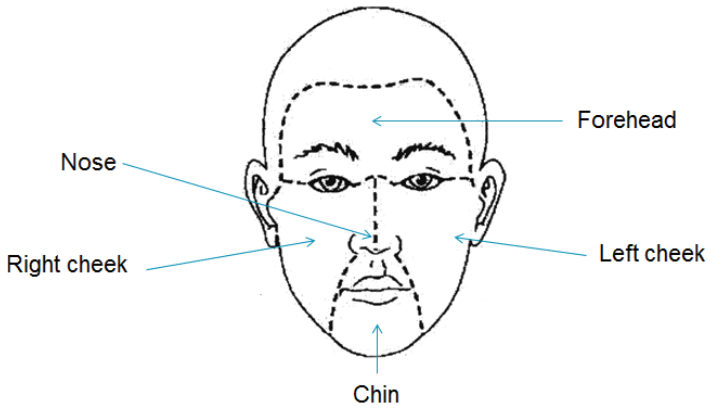
	Trifarotene (CD5789) Cream OR Trifarotene Vehicle Cream	**Doxycycline 120mg Tablet OR Doxycycline Placebo Tablet**
Study Drug Usage	• Apply a thin layer to the face once daily, in the evening. The face should be washed and patted dry, before use. • One pump actuation should be enough to cover the face (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. Dose modification for oral study drug is allowed for safety reasons only, and should be based on individual investigator clinical judgment (Section 5.4.9).	• **Day 1** Take one tablet by mouth in the evening. • **Day 2** Take one tablet by mouth, morning and evening. • **Day 3 and beyond** Take one tablet by mouth in the evening. **General:** • Tablet should be swallowed whole, not chewed or crushed, with adequate amounts of fluid. • Remain upright (sitting or standing) for at least 2 hours after intake • May be taken with food or milk if gastric irritation occurs ***Note: Use all tablets in one bottle before opening a new bottle.***
Non-Investigational Product Use Guidelines *	**For use by all subjects**	
Cetaphil® Gentle Skin Cleanser **	Guideline is to use twice daily, on the face, morning and evening. After washing the face in the evening, pat dry before applying the topical study drug.	
Cetaphil® PRO Oil Absorbing Moisturizer with SPF 30 **	Use daily on the face (morning), and re-apply to face and other exposed skin when sun exposure is expected.	Moisturizer should be used as often as needed except less than 1 hour before and 1 hour after topical study drug application (in the evening).
Cetaphil® Moisturizing Lotion **	For supplemental moisturizer use on the face, as needed.	
Duration of administration	12 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.

** Subject's preferred /investigator recommended non-comedogenic cleanser, moisturizer and sunscreen (SPF ≥30) may 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 PRO Moisturizer with SPF30 (or permitted alternative sunscreen) 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. non-comedogenic moisturizers, cosmetic products, etc).

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

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

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

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

Subjects participating in the photography sub-study (at designated centers) will also be asked to remove all jewelry, eyewear and pull hair back from their face, prior to study imaging.

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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 5.1.2) 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).

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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 5.1.2 – Schedule of Assessments). Subjects will record daily use of topical study drug and oral study medication. Subjects will be instructed to return the dosing calendar and all study medication at each study visit, for review by study personnel in the presence of the subject.

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

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

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

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

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

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5.4.8 Dose Modification - Topical Study Drug

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 6.6.1 for further details on local tolerability assessment.

5.4.9 Dose Modification – Oral Study Drug

Dose modification for oral study drug is allowed for safety reasons only, and should be based on individual investigator clinical judgment.

Investigators should follow the Warnings and Precautions for DORYX MPC (Appendix 14.7) which includes the discontinuation of oral study drug use if certain medical conditions develop. The decision to discontinue oral study medication due to photosensitivity / exaggerated sunburn reaction require investigator clinical judgment, considering the severity of the condition and location of the erythema (generalized or restricted to areas where topical study drug is applied).

5.4.10 Allocation Concealment and Blinding

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

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

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

Advanced Clinical Pharmacovigilance should be contacted to report any unblinding (refer to Section 6.6.2.2.2 for Advanced Clinical Pharmacovigilance contact information). To avoid bias and to ensure the integrity of the blind, personnel directly involved with the ongoing conduct of the study from the Sponsor, CRO, or other investigational study centers will not have access to any information that may lead to unblinding

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

5.4.12 Non-Investigational Study Supplies

The Sponsor or designee will supply the following non-investigational supplies including:

- Cetaphil® Gentle Skin Cleanser (16oz)
- Cetaphil® PRO Oil Absorbing Moisturizer with SPF 30
- Cetaphil® Moisturizing Lotion

Refer to guidelines for using the cleanser and moisturizer (Section 5.4.2 – Instructions for Use). 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 will maintain accurate records of non-investigational supplies received and dispensed. The monitor will confirm global accountability of non-investigational supplies (total received and dispensed). All unused non-investigational supplies will be returned to the Sponsor or designee.

5.4.13 Prior and Concomitant Therapy

5.4.13.1 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.

5.4.13.2 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.

5.4.13.3 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.

5.4.13.4 Authorized Medication/Therapy

Unless specified as prohibited medication/therapy (see Section 5.4.13.5), all therapies are authorized, including the following as long as they are not indicated for the treatment of acne vulgaris.

Topical products:

The following topical products are authorized on the treated areas:

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

Systemic treatments:

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

- The use of non-steroidal anti-inflammatory drugs (NSAIDs) is acceptable for up to 21 days (cumulative) of treatment; however, it should be avoided during the 1-week period prior to the final study assessment (Week 12).
- Topical antibiotics prescribed for localized dermal infections
- Penicillin G or V

5.4.13.5 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
Intensive ultraviolet (UV) radiation exposure (mountain sports, sailing, sunbathing, etc.)
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)
Antacids containing aluminum, calcium or magnesium, bismuth subsalicylate and iron-containing preparations

Table 4: List of Prohibited Medications/Therapies During Study

Prescription testosterone therapy (e.g., testosterone cypionate, testosterone enanthate, testosterone pellet, testosterone undecanoate) or on a testosterone booster or prescription testosterone (e.g., DHEA, Omnadren®, Sustanon®, testosterone cypionate, testosterone enanthate, testosterone propionate, testosterone phenylpropionate) or testosterone supplements (e.g., Tribulus)
Other:
Any drug (topical or systemic) or procedures that are used off label for the treatment of acne vulgaris

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

5.5 Duration of Subject Participation

The expected duration for each subject's participation in the study is approximately 16 weeks (including a 4-week screening period and a 12-week treatment period).

5.5.1 Early Termination Visit

When a subject does not complete the clinical study, he/she will be fully assessed, if such assessment is possible. The procedures designated for the Week 12/Early Termination visit should be completed for all subjects discontinuing the study and the appropriate CRF page should be completed.

Refer to Section 5.3.4 for reasons for early study discontinuation.

5.5.2 Unscheduled Visit

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

Assessments to be conducted at the unscheduled visit will depend on the reason for the visit: Any of the procedures/assessments listed in Section 5.1.2 – Schedule of Assessments may be conducted, as appropriate.

6 STUDY ASSESSMENTS

The protocol specifies the planned efficacy and safety assessments.

Subjects who are wearing a face mask should continue to do so until seated in an exam room, in accordance with your local guidelines. The general sequence of examinations should begin with a wellness assessment, review of dosing calendar/compliance and completion of subject questionnaires prior to performing 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 5.1.2 – 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 5.1.2 - Schedule of Assessments.

Evaluators must complete standardized training prior to performing the following assessments: acne severity (IGA), inflammatory lesion counts (papules and pustules), non-inflammatory lesion counts (open and closed comedones), and other lesion counts (nodules and cysts). Refer to Section 8.1 – 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.

Throughout the study when possible, the same evaluator should perform the IGA and lesion counts, for each individual subject. In the event there is a change in the assigned evaluator for a given subject, the reason for change should be documented. If it is not possible to use the same evaluator to follow a given subject, it is recommended that evaluations between the primary and subsequent evaluator overlap (both evaluators should examine the subject together and discuss findings) for at least one visit.

6.1.1 IGA - Investigator Global Assessment of Facial Acne

The IGA will be performed by trained evaluators.

The areas defined for IGA assessment are forehead, each cheek, chin, and nose. The IGA is reported as a global assessment, considering all areas as a whole.

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

The IGA will be assessed according to the schedule of assessments (Section 5.1.2) using the scale shown in Table 5

Table 5: Investigator Global Assessment Scale

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

6.1.2 Lesion Counts on the Face

Lesions Counts will be performed by trained evaluators.

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

The lesion counts will be performed separately on the face (forehead, left cheek, chin and right cheek). Lesions on the nose and under the jawline or along the hairline (including eyebrows) will not be included in the counts. Refer to sample worksheet for performing facial lesion counts (Appendix 14.5).

Inflammatory lesions

- Papule: A small, solid elevation less than 5 mm in diameter. Most of the lesion is above the surface of the skin.

- Pustule: A small, circumscribed elevation of the skin which contains yellow-white exudate.

Non-inflammatory lesions

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

Other lesions

- Nodule: A circumscribed, elevated, solid lesion at least 0.5 cm in diameter with palpable depth.
- Cyst: A smooth, dome-shaped, elevated, freely moveable, skin-colored, round-to-ovoid lesion greater than 0.7 cm in diameter.

Total lesions

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

6.2 Subject Reported Outcomes / Assessments

Subject-reported assessments should be completed prior to performing any acne assessments to minimize any impact on the subject responses. The questionnaires completed will be considered as source data and the answers will be entered into the CRF by the site. **The designated study personnel should check the questionnaire for completeness prior to the subject leaving the office**.

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

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

The questionnaire will measure the impact of facial acne on health-related quality of life. There are 19 questions, with multiple-choice responses on a 0-6 scale. Questions are separated into 4 domains: Self-perception (5 questions - total score range from 0 to 30), Role-emotional (5 questions - total score range from 0 to 30), Role-social (4 questions - total score range from 0 to 24), and Acne symptoms (5 questions - total score range from 0 to 30).

The Acne-QoL questionnaire is found in Appendix14.1.

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

Prior to any acne assessment, subjects will complete a satisfaction questionnaire at Week 12/Early Termination visit regarding use of the assigned study treatment (topical study drug and oral study drug) (see Appendix14.2). **The designated study personnel should check the questionnaires for completeness prior to the subject leaving the office**.

6.2.3 Topical Study Drug (Study Cream) Acceptability Questionnaire

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

6.3 Other Assessments

6.3.1 Fitzpatrick Skin Type

At the Screening/Baseline visit, the investigator will record the subject's skin type using the Fitzpatrick Skin Classification (Appendix 14.4).

6.4 Central Imaging

At designated study centers (approximately 15), facial photographs will be taken at visits specified in Section 5.1.2 - Schedule of Assessments. Subjects screened at designated imaging centers must consent to the imaging sub-study to participate in the main study, to ensure an adequate number of images are collected. A listing of the designated imaging sites will be maintained by the central imaging vendor.

Subjects will remove any jewelry from the areas to be photographed. It is recommended that subjects be acclimated for at least 15 minutes to ambient conditions within the clinic (and mask removal, if subject is wearing a mask), before any photographs are taken. Subjects will be provided with a standardized headband to keep hair away from the face.

6.4.1 CR-VISIA Imaging (Face)

Facial imaging will be performed at visits specified in Section 5.1.2 - Schedule of Assessments. Subjects will be carefully positioned for each photograph. General imaging guidelines include:

- A standardized matte cloth will be draped over the subjects' clothing.
- A neutral, non-smiling expression with eyes and mouth gently closed.
- Remove eyeglasses and all facial makeup and jewelry.

- Keep facial hair well-groomed prior to study visits, as judged appropriate by the investigator.

The Sponsor or designee may request image re-shoots due to poor image quality or other reasons. Attempts should be made to complete image re-shoots within 1 week. Full imaging details will be documented in the imaging manual.

6.5 Imaging of Safety Observations

The study requires re-challenge patch testing (with the assigned topical study drug) and topical study drug ingredient patch testing, if the re-challenge is equivocal or positive. These patch tests will include taking photographs of tested areas for visual confirmation of the results (Section 6.6.2.2.4). These images will be taken by site staff using non-central imaging equipment.

These photos will focus on the patch tested area(s) on the body and not including the subject's face and will serve only as confirmation of diagnosis. Images should be referenced by the subject's study number only and avoid other subject identifiers.

6.6 Safety Assessments

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

6.6.1 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 5.1.2). Table 6 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 6: 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.

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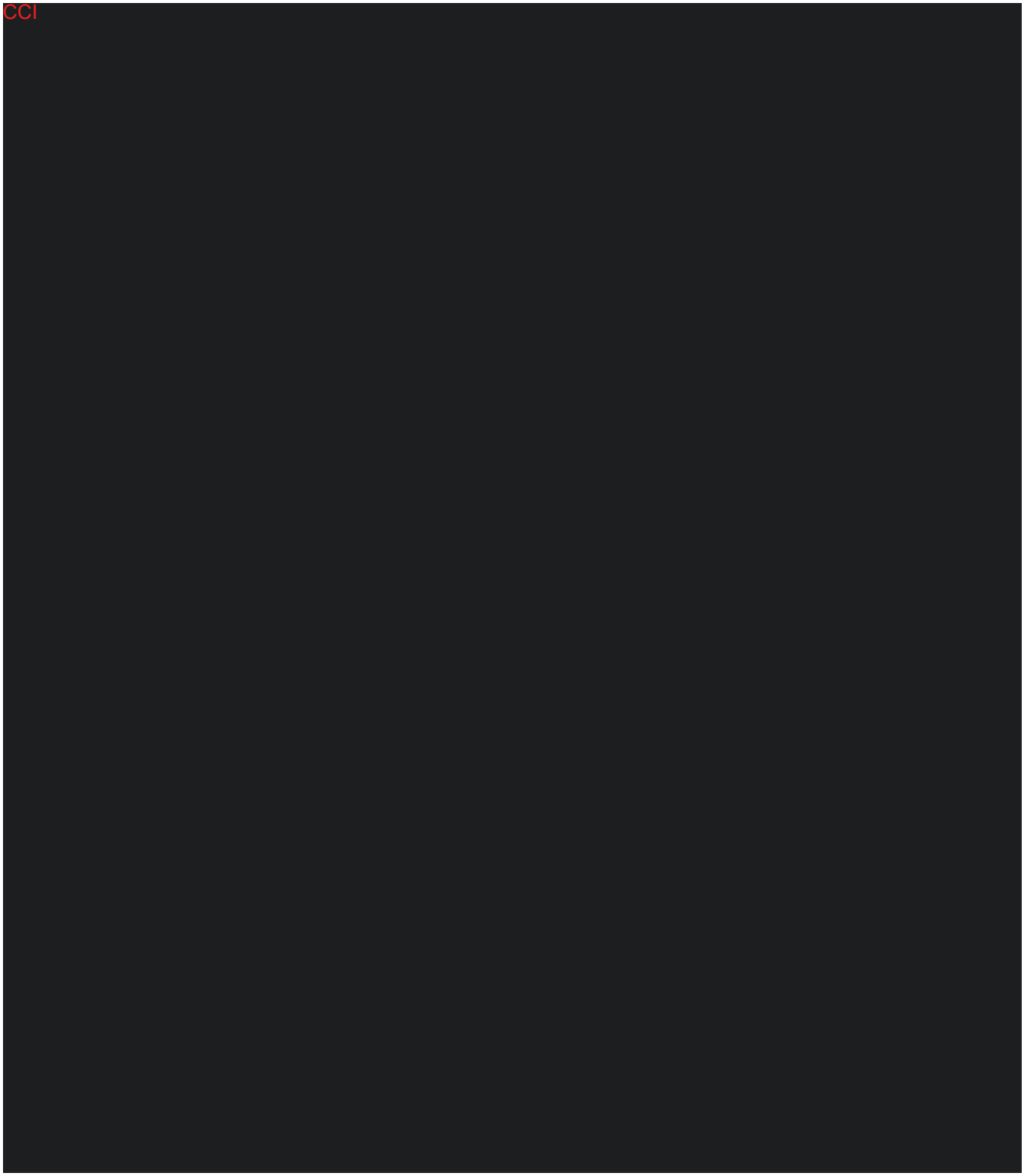

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7 PLANNED STATISTICAL ANALYSES

7.1 Statistical Analysis Plan

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

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

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

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

7.2 Sample Size Determination

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

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

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

$N_{Trifa+Doxy} = k \cdot N_{Vehicle+Placebo}$

$$N_{Vehicle+Placebo} = \left(1 + \frac{1}{k}\right) \cdot \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \cdot {\sigma_{Diff}}^2}{\left(\mu_{Trifa+Doxy} - \mu_{Vehicle+Placebo}\right)^2}$$

α (2-sided)	β	μ_{Diff}	σ_{Diff}	k	N_1	N_2	N_1+N_2
0.05	0.2	-15.0	32.5	2	112	56	168

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

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 (both topical and oral) between 80% and 120% and assessments of the primary endpoint at Baseline and Week 12, without any major deviations that could have a significant effect on the efficacy of the study treatment (e.g. errors in treatment assignment, use of

prohibited medications). The PP population will be used for a sensitivity analysis of the primary endpoint.

7.3.3 Safety (SAF) Population

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

7.4 Statistical Analysis

The main objective of this study is to evaluate the efficacy and safety outcomes of of trifarotene treatment in associaton with oral doxycycline versus placebo and vehicle with 12 weeks of treatment.

7.4.1 General Methods

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

7.4.2 Demographics and Subject Disposition

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

7.4.3 Efficacy Analysis

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

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

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

1) Absolute Change in facial IL lesion counts from Baseline to Week 12
2) Absolute Change in facial NIL lesion counts from Baseline to Week 12
3) Facial Success Rate at Week 12

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

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

7.4.3.1 Primary Efficacy Endpoint

Absolute Change in facial total lesion counts from Baseline to Week 12 will be analyzed using an ANCOVA with treatment, analysis center and baseline count as fixed effects; the p-values for the treatment comparison, estimates of the treatment difference and the 95% confidence interval of the difference will be generated from the ANCOVA model.

7.4.3.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- Absolute Change in facial IL/NIL counts from Baseline to Week 12 will be analyzed using an ANCOVA with treatment, analysis center and baseline count as fixed effects; the p-values for the treatment comparison, estimates of the treatment difference and the 95% confidence interval of the difference will be generated from the ANCOVA model.

- Facial Success Rate at Week 12 will be analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by analysis center; strata-adjusted difference in success proportions between treatment groups and the 95% confidence interval of the difference will be based on the large sample approximation method for binary data.

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7.4.3.4 Missing Data

The primary method of imputation for missing data of primary, secondary and exploratory 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 IGA 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) under the Missing Not At Random (MNAR) assumption and Last Observation Carried Forward (LOCF).

7.4.3.5 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) under the Missing Not At Random (MNAR) assumption, by using the profiles from Vehicle+Placebo 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.

7.4.4 Subject-Reported Outcomes

- Acne-Specific Quality of Life questionnaire (Acne-QoL) scores will be summarized by visit using descriptive statistics/frequency tables as applicable.
- Subject satisfaction questionnaire scores will be summarized by visit using frequency tables.
- Topical study drug acceptability questionnaire will be summarized by visit using frequency tables.

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).

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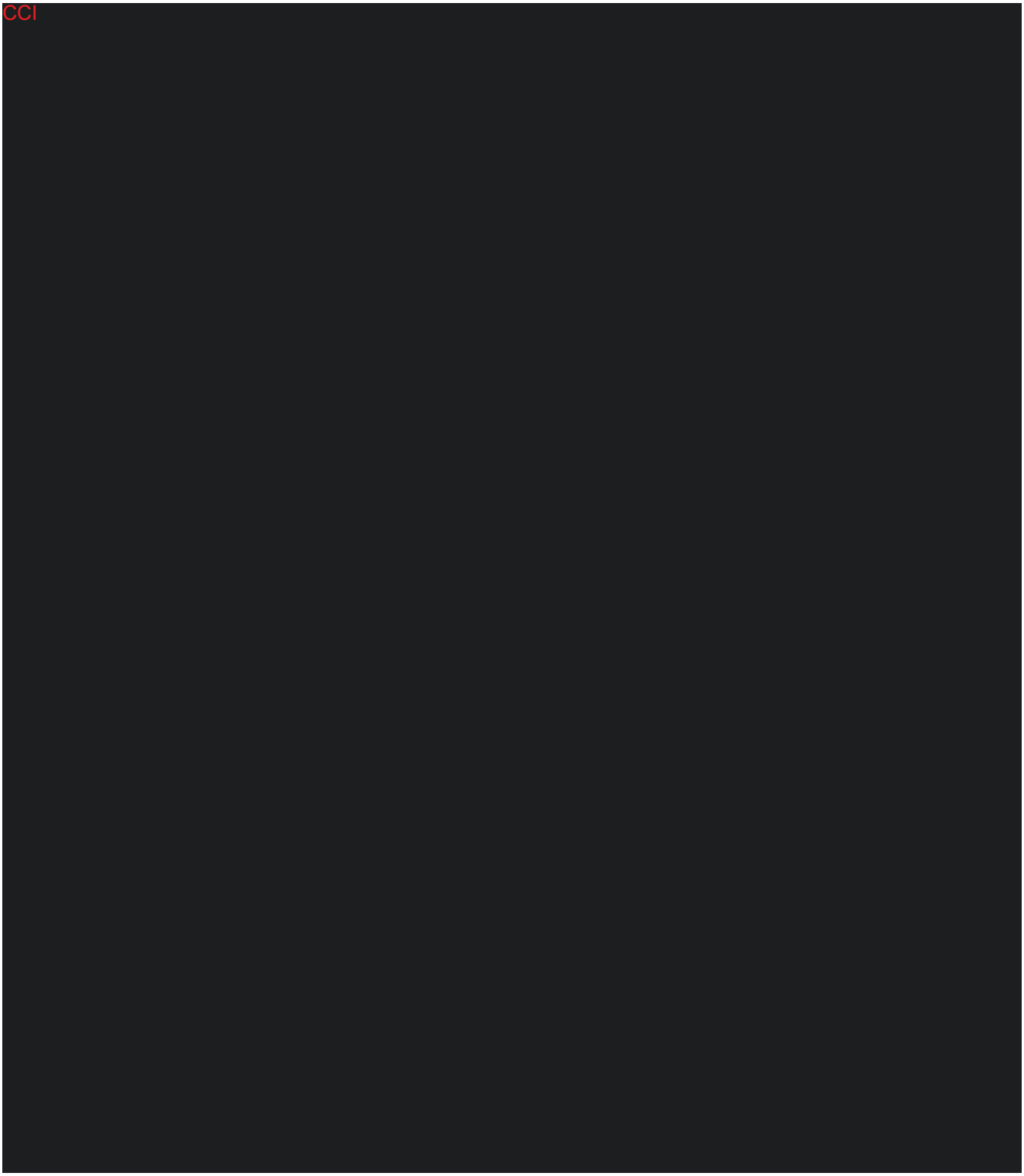

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10 PUBLIC DISCLOSURE OF CLINICAL STUDY

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.

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14 APPENDICES

14.1 Acne Specific Quality of Life Questionnaire

The investigator or designee will ensure proper completion of the questionnaire by reviewing in full upon completion by the subject and prior to the subject leaving the site.

1.	In the past WEEK, how unattractive did you feel because of your facial acne?						
	extremely ☐	very much ☐	quite a bit ☐	a good bit ☐	somewhat ☐	a little bit ☐	not at all ☐
2.	In the past WEEK, how embarrassed did you feel because of your facial acne?						
	extremely ☐	very much ☐	quite a bit ☐	a good bit ☐	somewhat ☐	a little bit ☐	not at all ☐
3.	In the past WEEK, how self-conscious (uneasy about oneself) did you feel about your facial acne?						
	extremely ☐	very much ☐	quite a bit ☐	a good bit ☐	somewhat ☐	a little bit ☐	not at all ☐
4.	In the past WEEK, how upset were you about having facial acne?						
	extremely ☐	very much ☐	quite a bit ☐	a good bit ☐	somewhat ☐	a little bit ☐	not at all ☐
5.	In the past WEEK, how annoyed did you feel at having to spend time every day cleaning and treating your face because of facial acne?						
	extremely ☐	very much ☐	quite a bit ☐	a good bit ☐	somewhat ☐	a little bit ☐	not at all ☐

6.	In the past WEEK, how dissatisfied with your self-appearance did you feel because of your facial acne?						
	extremely ☐	very much ☐	quite a bit ☐	a good bit ☐	somewhat ☐	a little bit ☐	not at all ☐
7.	In the past WEEK, how concerned or worried were you about not looking your best because of your facial acne?						
	extremely ☐	very much ☐	quite a bit ☐	a good bit ☐	somewhat ☐	a little bit ☐	not at all ☐
8.	In the past WEEK, how concerned or worried were you that your acne medication/products were working fast enough in clearing up the acne on your face?						
	extremely ☐	very much ☐	quite a bit ☐	a good bit ☐	somewhat ☐	a little bit ☐	not at all ☐
9.	In the past WEEK, how bothered did you feel about the need to always have medication or cover-up available for the acne on your face?						
	extremely ☐	very much ☐	quite a bit ☐	a good bit ☐	somewhat ☐	a little bit ☐	not at all ☐
10.	In the past WEEK, how much was your self-confidence (sure of yourself) negatively affected because of your facial acne?						
	extremely ☐	very much ☐	quite a bit ☐	a good bit ☐	somewhat ☐	a little bit ☐	not at all ☐
11.	In the past WEEK, how concerned or worried were you about meeting new people because of your facial acne?						
	extremely ☐	very much ☐	quite a bit ☐	a good bit ☐	somewhat ☐	a little bit ☐	not at all ☐
12.	In the past WEEK, how concerned or worried were you about going out in public because of your facial acne?						
	extremely ☐	very much ☐	quite a bit ☐	a good bit ☐	somewhat ☐	a little bit ☐	not at all ☐
13.	In the past WEEK, how much was socializing with people a problem for you because of your facial acne?						
	extremely ☐	very much ☐	quite a bit ☐	a good bit ☐	somewhat ☐	a little bit ☐	not at all ☐
14.	In the past WEEK, how much was interacting with the opposite sex (or same sex if gay or lesbian) a problem because of your facial acne?						
	extremely ☐	very much ☐	quite a bit ☐	a good bit ☐	somewhat ☐	a little bit ☐	not at all ☐
15.	In the past WEEK, how many bumps did you have on your face?						
	extensive ☐	a whole lot ☐	a lot ☐	a moderate amount ☐	some ☐	very few ☐	none ☐

16.	In the past WEEK, how many bumps full of pus did you have on your face?						
	extensive	a whole lot	a lot	a moderate amount	some	very few	none
	☐	☐	☐	☐	☐	☐	☐
17.	In the past WEEK, how much scabbing from your facial acne did you have?						
	extensive	a whole lot	a lot	a moderate amount	some	very few	none
	☐	☐	☐	☐	☐	☐	☐
18.	In the past WEEK, how concerned or worried were you about scarring from your facial acne?						
	extremely	very much	quite a bit	a good bit	somewhat	a little bit	not at all
	☐	☐	☐	☐	☐	☐	☐
19.	In the past WEEK, how oily was your facial skin?						
	extremely	very much	quite a bit	a good bit	somewhat	a little bit	not at all
	☐	☐	☐	☐	☐	☐	☐

14.2 Subject Satisfaction Questionnaire on Using the Assigned Study Treatment

Instructions: Complete the following questionnaire based on using the assigned study treatment: the study cream and the study tablet.

1. How bothered were you by the treatment side effects?

[ ]1 Not bothered at all
[ ]2 Bothered somewhat
[ ]3 Bothered
[ ]4 Bothered a great deal

2. How satisfied were you with the time it took for treatment to work?

[ ]1 Very satisfied
[ ]2 Satisfied
[ ]3 Somewhat satisfied
[ ]4 Not satisfied

3. How satisfied were you with the effectiveness of the treatment?

[ ]1 Very satisfied
[ ]2 Satisfied
[ ]3 Somewhat satisfied
[ ]4 Not satisfied

4. How do you feel about yourself, since starting your treatment?

[ ]1 Very much better
[ ]2 A lot better
[ ]3 A little better
[ ]4 Worse

5. Overall, are you satisfied with the treatment?

[ ]1 Very satisfied
[ ]2 Satisfied
[ ]3 Somewhat satisfied
[ ]4 Not satisfied

6. Would you consider using this treatment again?

[ ]1 Yes
[ ]2 No

7. Did you use the provided moisturizing lotion?

[ ]1 Yes
[ ]2 No

   a. If yes, would you say (check as many answers as you wish)

      [ ]1 The moisturizer helps to reduce irritation
      [ ]2 The moisturizer helps me use the study treatments every day
      [ ]3 The moisturizer was pleasant to use
      [ ]4 None of the above

14.3 Topical Study Drug Acceptability Questionnaire

1. For each of the characteristics below, please tell us whether you agree or disagree:

The topical study drug ("study cream"):	1 - Strongly disagree	2 - Disagree	3 - Agree	4 - Strongly agree
Spreads easily				
Is pleasant to apply				
Is absorbed quickly into the skin				
Is non-sticky				
Does not make my skin feel oily				

2. Overall, how satisfied are you with how easy to use the topical study drug ("study cream") is ?
   4 - Very satisfied
   3 - Satisfied
   2 - Unsatisfied
   1 - Very unsatisfied

3. Would you say the cosmetic properties of the topical study drug ("study cream") encouraged you to continue with the treatment?
   ☐ Yes ☐ No

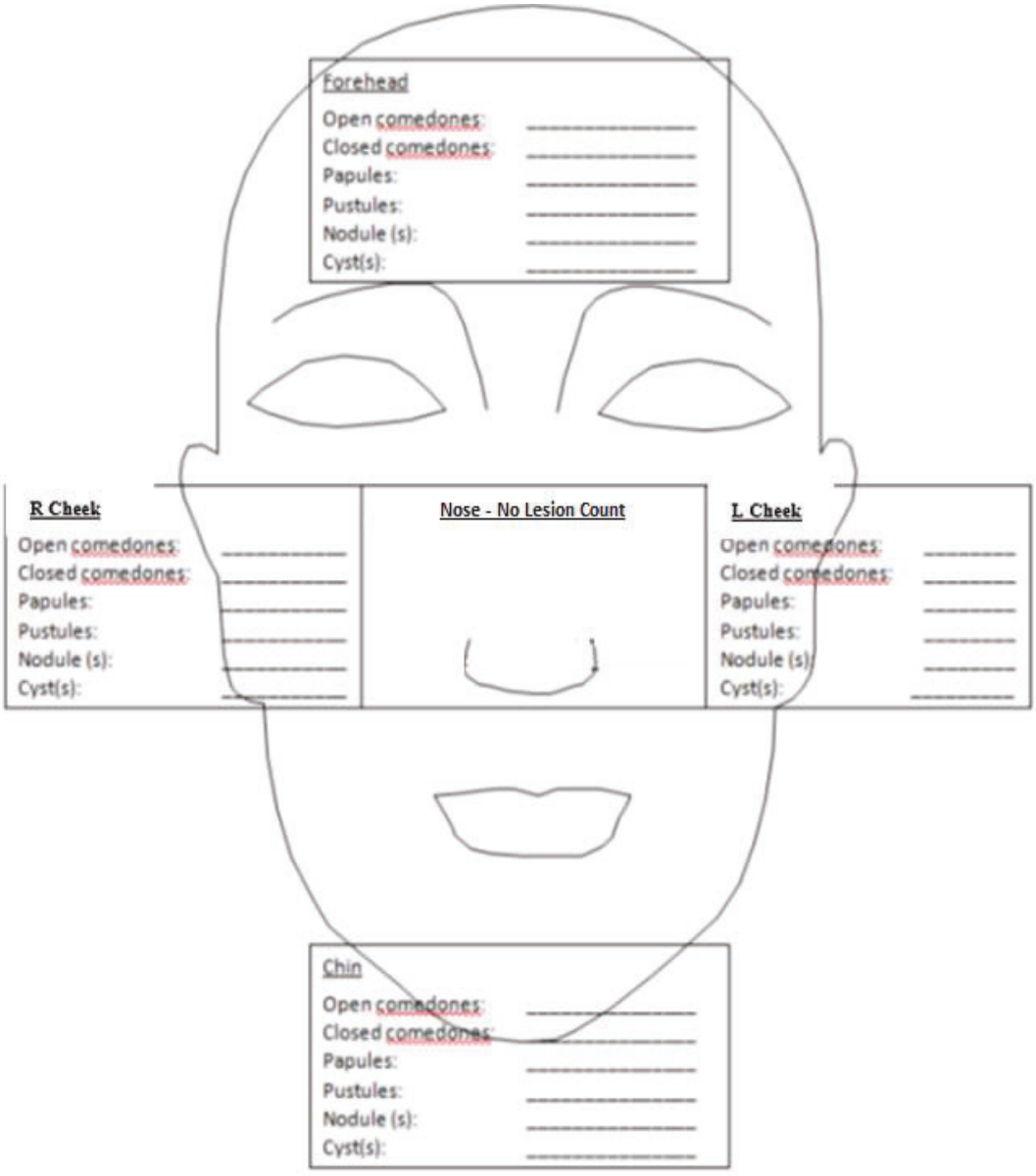
14.4 Fitzpatrick Skin Classification

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

14.5 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): _____

14.6 Investigator Notification of Ingredient Patch Test Results

Dear <u>Investigator,</u>

The accompanying form provides results of the ingredient patch testing for the topical study drug in Galderma clinical protocol: 202394.

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.: **202394** 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 202394, " ***A Multi-Center, Randomized, Double-Blind, Placebo Controlled Study To Compare Efficacy and Safety of Trifarotene (CD5789) When Used with an Oral Antibiotic for the Treatment of Severe Acne Vulgaris***"

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:

Advanced Clinical Pharmacovigilance: DrugSafetyPV@advancedclinical.com

Please mention the study ID (RD.06.SPR.202394) 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

14.7 DORYX MPC Prescribing Information

DORYX MPC- doxycycline hyclate tablet, delayed release
Mayne Pharma

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

DORYX MPC (doxycycline hyclate delayed-release tablets), for oral use.
Initial U.S. Approval: 1967

INDICATIONS AND USAGE

DORYX MPC is a tetracycline class drug indicated for:

- Rickettsial Infections (1.1)
- Sexually Transmitted Infections (1.2)
- Respiratory Tract Infections(1.3)
- Specific Bacterial Infections (1.4)
- Ophthalmic Infections (1.5)
- Anthrax, Including Inhalational Anthrax (Post-Exposure) (1.6)
- Alternative Treatment for Selected Infections when Penicillin is Contraindicated (1.7)
- Adjunctive Therapy in Acute Intestinal Amebiasis and Severe Acne (1.8)
- Prophylaxis of Malaria (1.9)

Usage
To reduce the development of drug-resistant bacteria and maintain the effectiveness of doxycycline hyclate, DORYX MPC and other antibacterial drugs, DORYX MPC Tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. (1.10)

DOSAGE AND ADMINISTRATION

- Important Dosage and Administration Instructions:
  - DORYX MPC is not substitutable on a mg per mg basis with other oral doxycyclines. (2.1)
  - Do not chew or crush tablets. (2.1)
- Dosage in Adult Patients
  - The usual dosage of DORYX MPC is 240 mg on the first day of treatment (administered 120 mg every 12 hours) followed by a maintenance dose of 120 mg daily. (2.3)
  - In the management of more severe infections (particularly chronic infections of the urinary tract), 120 mg every 12 hours is recommended. (2.3)
- Dosage in Pediatric Patients
  - For all pediatric patients weighing less than 45 kg with severe or life threatening infections (e.g., anthrax, Rocky Mountain spotted fever), the recommended dosage of DORYX MPC is 2.6 mg per kg of body weight administered every 12 hours. Pediatric patients weighing 45 kg or more should receive the adult dose. (2.4)
  - For pediatric patients with less severe disease (greater than 8 years of age and weighing less than 45 kg), the recommended dosage schedule of DORYX MPC is 5.3 mg per kg of body weight divided into two doses on the first day of treatment, followed by a maintenance dose of 2.6 mg per kg of body weight (given as a single daily dose or divided into twice daily doses). For pediatric patients weighing over 45 kg, the usual adult dose should be used. (2.4)

- See Full Prescribing Information for additional indication specific dosage information and important administration instructions for DORYX MPC. (2.2, 2.5, 2.6)

DOSAGE FORMS AND STRENGTHS

DORYX MPC Delayed-Release Tablets 120 mg (3)

CONTRAINDICATIONS

Doxycycline is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines. (4)

WARNINGS AND PRECAUTIONS

- The use of drugs of the tetracycline-class during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). (5.1)
- *Clostridium difficile*-associated diarrhea. Evaluate patients if diarrhea occurs. (5.2)
- Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Limit sun exposure. (5.3)
- Overgrowth of non-susceptible organisms, including fungi, may occur. If such infections occur, discontinue use and institute appropriate therapy. (5.4)

ADVERSE REACTIONS

Adverse reactions observed in patients receiving tetracyclines include anorexia, nausea, vomiting, diarrhea, rash, photosensitivity, urticaria, and hemolytic anemia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Mayne Pharma at 1-844-825-8500 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage (7.1)
- Avoid co-administration of tetracyclines with penicillin (7.2)
- Absorption of tetracyclines, including DORYX MPC is impaired by antacids containing aluminum, calcium, or magnesium, bismuth subsalicylate and iron-containing preparations (7.3)
- Concurrent use of tetracyclines, including DORYX MPC may render oral contraceptives less effective (7.4)
- Barbiturates, carbamazepine, and phenytoin decrease the half-life of doxycycline (7.5)

USE IN SPECIFIC POPULATIONS

- Tetracycline-class drugs can cause fetal harm when administered to a pregnant woman, but data for doxycycline are limited. (5.6, 8.1)
- Tetracyclines are excreted in human milk; however, the extent of absorption of doxycycline in the breastfed infant is not known. DORYX MPC use during nursing should be avoided if possible. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 7/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Rickettsial Infections

DORYX MPC is indicated for treatment of Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox, and tick fevers caused by *Rickettsiae*.

1.2 Sexually Transmitted Infections

DORYX MPC is indicated for treatment of the following sexually transmitted infections:

- Uncomplicated urethral, endocervical or rectal infections in adults caused by *Chlamydia trachomatis.*
- Nongonococcal urethritis caused by *Ureaplasma urealyticum*.
- Lymphogranuloma venereum caused by *Chlamydia trachomatis.*
- Granuloma inguinale caused by *Klebsiella granulomatis.*
- Uncomplicated gonorrhea caused by *Neisseria gonorrhoeae.*

- Chancroid caused by *Haemophilus ducreyi*.

1.3 Respiratory Tract Infections

DORYX MPC is indicated for treatment of the following respiratory tract infections:

- Respiratory tract infections caused by *Mycoplasma pneumoniae*.
- Psittacosis (ornithosis) caused by *Chlamydophila psittaci*.
- Because many strains of the following groups of microorganisms have been shown to be resistant to doxycycline, culture and susceptibility testing are recommended.
- Doxycycline is indicated for treatment of infections caused by the following microorganisms, when bacteriological testing indicates appropriate susceptibility to the drug:
  - Respiratory tract infections caused by *Haemophilus influenzae*.
  - Respiratory tract infections caused by *Klebsiella* species.
  - Upper respiratory infections caused by *Streptococcus pneumoniae*.

1.4 Specific Bacterial Infections

DORYX MPC is indicated for treatment of the following specific bacterial infections:

- Relapsing fever due to *Borrelia recurrentis*.
- Plague due to *Yersinia pestis*.
- Tularemia due to *Francisella tularensis*.
- Cholera caused by *Vibrio cholerae*.
- Campylobacter fetus infections caused by *Campylobacter fetus*.
- Brucellosis due to *Brucella* species (in conjunction with streptomycin).
- Bartonellosis due to *Bartonella bacilliformis*.

Because many strains of the following groups of microorganisms have been shown to be resistant to doxycycline, culture and susceptibility testing are recommended.

DORYX MPC is indicated for treatment of infections caused by the following gram-negative microorganisms, when bacteriological testing indicates appropriate susceptibility to the drug:

- Escherichia coli
- Enterobacter aerogenes
- Shigella species
- Acinetobacter species
- Urinary tract infections caused by Klebsiella species.

1.5 Ophthalmic Infections

DORYX MPC is indicated for treatment of the following ophthalmic infections:

- Trachoma caused by *Chlamydia trachomatis*, although the infectious agent is not always eliminated as judged by immunofluorescence.
- Inclusion conjunctivitis caused by *Chlamydia trachomatis*.

1.6 Anthrax Including Inhalational Anthrax (Post-Exposure)

DORYX MPC is indicated for treatment of Anthrax due to *Bacillus anthracis*, including inhalational anthrax (post-exposure): to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*.

1.7 Alternative Treatment for Selected Infections when Penicillin is Contraindicated

DORYX MPC is indicated as an alternative treatment for the following selected infections when penicillin is contraindicated:

- Syphilis caused by *Treponema pallidum*.
- Yaws caused by *Treponema pallidum* subspecies *pertenue*.
- Listeriosis due to *Listeria monocytogenes*.
- Vincent's infection caused by *Fusobacterium fusiforme*.
- Actinomycosis caused by *Actinomyces israelii*.
- Infections caused by *Clostridium* species.

1.8 Adjunctive Therapy for Acute Intestinal Amebiasis and Severe Acne

In acute intestinal amebiasis, DORYX MPC may be a useful adjunct to amebicides.

In severe acne, DORYX MPC may be useful adjunctive therapy.

1.9 Prophylaxis of Malaria

DORYX MPC is indicated for the prophylaxis of malaria due to *Plasmodium falciparum* in short-term travelers (less than 4 months) to areas with chloroquine and/or pyrimethamine-sulfadoxine resistant strains [*see Dosage and Administration (2.2) and Patient Counseling Information (17)*].

1.10 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of DORYX MPC and other antibacterial drugs, DORYX MPC should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

- DORYX MPC is not substitutable on a mg per mg basis with other oral doxycyclines. To avoid prescribing errors, do not substitute DORYX MPC for other oral doxycyclines on a mg per mg basis because of differing bioavailability.
- Do not chew or crush tablets.
- The recommended dosage, frequency of administration and weight-based dosage recommendations of DORYX MPC differ from that of the other tetracyclines [*see Dosage and Administration (2.2, 2.3, 2.4)*]. Exceeding the recommended dosage may result in an increased incidence of adverse reactions.
- Administer DORYX MPC with an adequate amount of fluid to wash down the drug and reduce the risk of esophageal irritation and ulceration [*see Adverse Reactions (6)*].
- If gastric irritation occurs, DORYX MPC may be given with food or milk *[see Clinical Pharmacology (12.3)]*.

2.2 Switching from DORYX to DORYX MPC

When switching from DORYX to DORYX MPC*:*

- A 120 mg dose of DORYX MPC will replace a 100 mg dose of DORYX

2.3 Dosage in Adult Patients

- The usual dosage of DORYX MPC is 240 mg on the first day of treatment (administered 120 mg every 12 hours) followed by a maintenance dose of 120 mg daily. The maintenance dose may be administered as a single dose.
- In the management of more severe infections (particularly chronic infections of the urinary tract), 120 mg every 12 hours is recommended.
- For certain selected specific indications, the recommended duration or dosage and duration of

DORYX MPC in adult patients are as follows:

1. Streptococcal infections, therapy should be continued for 10 days.
2. Uncomplicated urethral, endocervical, or rectal infection caused by *C. trachomatis*: 120 mg, by mouth, twice-a-day for 7 days.
3. Uncomplicated gonococcal infections in adults (except anorectal infections in men): 120 mg, by mouth, twice-a-day for 7 days. As an alternate single visit dose, administer 360 mg followed in one hour by a second 360 mg dose.
4. Nongonococcal urethritis (NGU) caused by *C. trachomatis* and *U. urealyticum*: 120 mg, by mouth, twice-a-day for 7 days.
5. Syphilis – early: Patients who are allergic to penicillin should be treated with doxycycline 120 mg, by mouth, twice-a-day for 2 weeks.
6. Syphilis of more than one year's duration: Patients who are allergic to penicillin should be treated with doxycycline 120 mg, by mouth, twice-a-day for 4 weeks.
7. Acute epididymo-orchitis caused by *N. gonorrhoeae*: 120 mg, by mouth, twice-a-day for at least 10 days.
8. Acute epididymo-orchitis caused by *C. trachomatis*: 120 mg, by mouth, twice-a-day for at least 10 days

2.4 Dosage in Pediatric Patients

- For all pediatric patients weighing less than 45 kg with severe or life threatening infections (e.g., anthrax, Rocky Mountain spotted fever), the recommended dosage of DORYX MPC is 2.6 mg per kg of body weight administered every 12 hours. Pediatric patients weighing 45 kg or more should receive the adult dose *[see Warnings and Precautions (5.1)]*.
- For pediatric patients with less severe disease (greater than 8 years of age and weighing less than 45 kg), the recommended dosage schedule of DORYX MPC is 5.3 mg per kg of body weight divided into two doses on the first day of treatment, followed by a maintenance dose of 2.6 mg per kg of body weight (given as a single daily dose or divided into twice daily doses). For pediatric patients weighing over 45 kg, the usual adult dose should be used.

2.5 Dosage for Prophylaxis of Malaria

For adults, the recommended dose of DORYX MPC is 120 mg daily.

For pediatric patients 8 years of age and older, the recommended dosage of DORYX MPC is 2.4 mg per kg of body weight administered once daily. Pediatric patients weighing 45 kg or more should receive the adult dose.

Prophylaxis should begin 1 or 2 days before travel to the malarious area. Prophylaxis should be continued daily during travel in the malarious area and for 4 weeks after the traveler leaves the malarious area.

2.6 Dosage for Inhalational Anthrax (Post-Exposure)

For adults, the recommended dosage is 120 mg, of DORYX MPC, by mouth, twice-a-day for 60 days.

For pediatric patients weighing less than 45 kg, the recommended dosage of DORYX MPC is 2.6 mg per kg of body weight, by mouth, twice-a-day for 60 days. Pediatric patients weighing 45 kg or more should receive the adult dose.

3 DOSAGE FORMS AND STRENGTHS

DORYX MPC (doxycycline hyclate delayed-release tablets), 120 mg are white, oval tablets containing yellow pellets and debossed on one face with "DC" and plain on the other. Each tablet contains doxycycline 120 mg (equivalent to doxycycline hyclate 138.8 mg).

4 CONTRAINDICATIONS

DORYX MPC is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

5 WARNINGS AND PRECAUTIONS

5.1 Tooth Development

The use of drugs of the tetracycline-class during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long-term use of the drugs but it has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Use DORYX MPC in pediatric patients 8 years of age or less only when the potential benefits are expected to outweigh the risks in severe or life-threatening conditions (e.g., anthrax, Rocky Mountain spotted fever), particularly when there are no alternative therapies.

5.2 Clostridium difficile Associated Diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including DORYX MPC Tablets, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

5.3 Photosensitivity

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema.

5.4 Potential for Microbial Overgrowth

DORYX MPC may result in overgrowth of non-susceptible organisms, including fungi. If such infections occur, discontinue use and institute appropriate therapy.

5.5 Severe Skin Reactions

Severe skin reactions, such as exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in patients receiving doxycycline [See Adverse Reactions (6)]. If severe skin reactions occur, doxycycline should be discontinued immediately and appropriate therapy should be instituted.

5.6 Intracranial Hypertension

Intracranial hypertension (IH, pseudotumor cerebri) has been associated with the use of tetracycline including DORYX MPC. Clinical manifestations of IH include headache, blurred vision, diplopia, and vision loss; papilledema can be found on fundoscopy. Women of childbearing age who are overweight

or have a history of IH are at greater risk for developing tetracycline associated IH. Avoid concomitant use of isotretinoin and DORYX MPC because isotretinoin is also known to cause pseudotumor cerebri.

Although IH typically resolves after discontinuation of treatment, the possibility for permanent visual loss exists. If visual disturbance occurs during treatment, prompt ophthalmologic evaluation is warranted. Since intracranial pressure can remain elevated for weeks after drug cessation patients should be monitored until they stabilize.

5.7 Skeletal Development

All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in prematures given oral tetracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was discontinued. [*See Use in Specific Populations (8.1)*].

5.8 Antianabolic Action

The antianabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur with the use of doxycycline in patients with impaired renal function.

5.9 Malaria

Doxycycline offers substantial but not complete suppression of the asexual blood stages of *Plasmodium* strains.

Doxycycline does not suppress *P. falciparum's* sexual blood stage gametocytes. Subjects completing this prophylactic regimen may still transmit the infection to mosquitoes outside endemic areas.

5.10 Development of Drug-Resistant Bacteria

Prescribing DORYX MPC in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

5.11 Laboratory Monitoring for Long-Term Therapy

In long-term therapy, periodic laboratory evaluation of organ systems, including hematopoietic, renal, and hepatic studies should be performed.

6 ADVERSE REACTIONS

The following adverse reactions have been identified during post-approval use of doxycycline. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Due to oral doxycycline's virtually complete absorption, side effects to the lower bowel, particularly diarrhea, have been infrequent. The following adverse reactions have been observed in patients receiving tetracyclines:

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, inflammatory lesions (with monilial overgrowth) in the anogenital region, and pancreatitis. Hepatotoxicity has been reported. These reactions have been caused by both the oral and parenteral administration of tetracyclines. Superficial discoloration of the adult permanent dentition, reversible upon drug discontinuation and professional dental cleaning has been reported. Permanent tooth discoloration and enamel hypoplasia may occur with drugs of the tetracycline class when used during tooth development [See Warnings and Precautions (5.1)]. Esophagitis and esophageal ulcerations have been reported in patients receiving capsule and tablet forms of drugs in the tetracycline-class. Most of these patients took medications immediately before going to bed [*see Dosage and Administration (2.1)*].

Skin: Maculopapular and erythematous rashes, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, and erythema multiforme have been reported. Photosensitivity is discussed above [*see Warnings and Precautions (5.3)*].

Renal: Rise in BUN has been reported and is apparently dose-related [*see Warnings and Precautions (5.8)*].

Hypersensitivity reactions: Urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, serum sickness, pericarditis, and exacerbation of systemic lupus erythematosus, and drug reaction with eosinophilia and systemic symptoms (DRESS).

Blood: Hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia have been reported.

Intracranial Hypertension: Intracranial hypertension (IH, pseudotumor cerebri) has been associated with the use of tetracycline [*See Warnings and Precautions (5.6)*]

Thyroid Gland Changes: When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function are known to occur.

7 DRUG INTERACTIONS

7.1 Anticoagulant Drugs

Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

7.2 Penicillin

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracyclines, including DORYX MPC in conjunction with penicillin.

7.3 Antacids and Iron Preparations

Absorption of tetracyclines including DORYX MPC is impaired by antacids containing aluminum, calcium, or magnesium, bismuth subsalicylate, and iron-containing preparations.

7.4 Oral Contraceptives

Concurrent use of tetracyclines, including DORYX MPC may render oral contraceptives less effective.

7.5 Barbiturates and anti-epileptics

Barbiturates, carbamazepine, and phenytoin decrease the half-life of doxycycline.

7.6 Penthrane

The concurrent use of tetracycline and Penthrane® (methoxyflurane) has been reported to result in fatal renal toxicity.

7.7 Drug/Laboratory Test Interactions

False elevations of urinary catecholamines may occur due to interference with the fluorescence test.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate studies on the use of doxycycline in pregnant women. The vast majority of

reported experience with doxycycline during human pregnancy is short-term, first trimester exposure. There are no human data available to assess the effects of long-term therapy of doxycycline in pregnant women such as that proposed for the treatment of anthrax exposure. An expert review of published data on experiences with doxycycline use during pregnancy by TERIS - the Teratogen Information System - concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as limited to fair), but the data are insufficient to state that there is no risk.[1] In the U.S. general population the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively [*see Data*].

Clinical Considerations

Embryo/Fetal Risk

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity also has been noted in animals treated early in pregnancy. If any tetracycline is used during pregnancy or if the patient becomes pregnant while taking these drugs, the patient should be apprised of the potential hazard to the fetus. [*see Warnings and Precautions (5.1, 5.6)*].

Data

Human Data

A case-control study (18,515 mothers of infants with congenital anomalies and 32,804 mothers of infants with no congenital anomalies) shows a weak but marginally statistically significant association with total malformations and use of doxycycline anytime during pregnancy. Sixty-three (0.19%) of the controls and 56 (0.30%) of the cases were treated with doxycycline. This association was not seen when the analysis was confined to maternal treatment during the period of organogenesis (i.e., in the second and third months of gestation), with the exception of a marginal relationship with neural tube defect based on only two-exposed cases.[2]

A small prospective study of 81 pregnancies describes 43 pregnant women treated for 10 days with doxycycline during early first trimester. All mothers reported their exposed infants were normal at 1 year of age.[3]

8.2 Lactation

Risk Summary

Tetracyclines are excreted in human milk, however, the extent of absorption of tetracyclines including doxycycline, by the breastfed infant is not known. Short-term use by lactating women is not contraindicated. The effects of prolonged exposure to doxycycline on breast milk production and breast fed neonates, infants and children are unknown.[4] The developmental and health benefits of breast feeding should be considered along with the mother's clinical need for DORYX MPC and any potential adverse effects on the breast fed child from DORYX MPC or from the underlying maternal condition [*see Warnings and Precautions (5.1, 5.6)*].

8.4 Pediatric Use

Because of the effects of drugs of the tetracycline-class on tooth development and growth, use DORYX MPC in pediatric patients 8 years of age or less only when the potential benefits are expected to outweigh the risks in severe or life-threatening conditions (e.g., anthrax, Rocky Mountain spotted fever), particularly when there are no alternative therapies [*see Warnings and Precautions (5.1, 5.6) and Dosage and Administration (2.1, 2.4)*].

8.5 Geriatric Use

Clinical studies of DORYX MPC did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience

has not identified differences in responses between the elderly and younger patients. DORYX MPC Tablets each contain less than 10 mg of sodium.

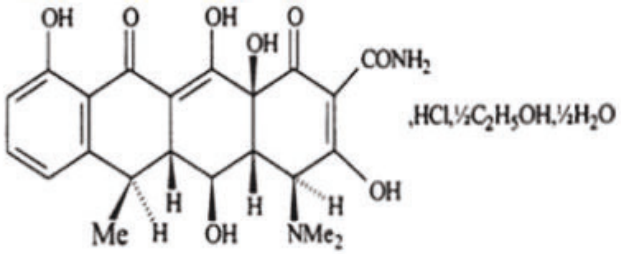
10 OVERDOSAGE

In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures. Dialysis does not alter serum half-life and thus would not be of benefit in treating cases of overdosage.

11 DESCRIPTION

Doryx MPC (doxycycline hyclate delayed-release tablets) for oral use, contain doxycycline hyclate, a tetracycline class drug synthetically derived from oxytetracycline, in a delayed-release formulation consisting of pellets with a modified polymer enteric coat that has increased acid resistance.

The structural formula for doxycycline hyclate is:



with a molecular formula of $C_{22}H_{24}N_2O_8$, HCl, ½ C_2H_6O, ½ H_2O and a molecular weight of 512.9. The chemical name for doxycycline hyclate is [4S(4aR,5S,5aR,6R,12aS)]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-deoxonaphthacene-2-carboxamide monohydrochloride, compound with ethyl alcohol (2:1), monohydrate. Doxycycline hyclate is a yellow crystalline powder soluble in water and in solutions of alkali hydroxides and carbonates. Doxycycline has a high degree of lipid solubility and a low affinity for calcium binding. It is highly stable in normal human serum. Doxycycline will not degrade into an epianhydro form.

Each tablet contains doxycycline 120 mg (equivalent to doxycycline hyclate 138.8 mg). Inactive ingredients in the tablet formulation are: lactose monohydrate; microcrystalline cellulose; sodium lauryl sulfate; sodium chloride; talc; anhydrous lactose; corn starch; crospovidone; magnesium stearate; cellulosic polymer coating.

Each DORYX MPC 120 mg Tablet contains 7.2 mg (0.313 mEq) of sodium.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Doxycycline is a tetracycline-class antimicrobial drug [*see Microbiology (12.4)*].

12.3 Pharmacokinetics

Absorption

Following administration of a single dose of DORYX MPC under fasting conditions, the AUC_{inf} and C_{max} were 26.7 mcg-h/mL and 1.6 mcg/mL, respectively. The Tmax was 2.8 hours. In a single-dose study to evaluate the relative bioavailability in healthy adult subjects under fasted conditions, DORYX MPC 120 mg Tablets were found to be bioequivalent to Doryx 100 mg Tablets. When a single dose of DORYX MPC 120 mg Tablet was administered with a standardized high-fat high-calorie meal, (937kcal consisting of approximately 55% fat, 30% carbohydrate and 15% protein), the C_{max} was approximately 30% lower, but there was no significant difference in the AUC_{inf} compared to administration under

fasting conditions *[see Dosage and Administration (2.1)]*.

Excretion

Tetracyclines are concentrated in bile by the liver and excreted in the urine and feces at high concentrations and in a biologically active form. Excretion of doxycycline by the kidney is about 40%/72 hours in individuals with a creatinine clearance of about 75 mL/min. This percentage may fall as low as 1-5%/72 hours in individuals with a creatinine clearance below 10 mL/min.

Studies have shown no significant difference in the serum half-life of doxycycline (range 18 to 22 hours) in individuals with normal and severely impaired renal function. Hemodialysis does not alter the serum half-life.

12.4 Microbiology

Mechanism of Action

Doxycycline inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit. Doxycycline has bacteriostatic activity against a broad range of Gram-positive and Gram-negative bacteria.

Resistance

Cross-resistance between tetracyclines is common.

Antimicrobial Activity

Doxycycline has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections [see *Indications and Usage (1)*].

Gram-negative Bacteria

Acinetobacter species
Bartonella bacilliformis
Brucella species
Campylobacter fetus
Enterobacter aerogenes
Escherichia coli
Francisella tularensis
Haemophilus ducreyi
Haemophilus influenzae
Klebsiella granulomatis
Klebsiella species
Neisseria gonorrhoeae
Shigella species
Vibrio cholerae
Yersinia pestis

Gram-positive Bacteria

Bacillus anthracis
Listeria monocytogenes
Streptococcus pneumoniae

Anerobic Bacteria

Clostridium species
Fusobacterium fusiforme
Propionibacterium acnes

Other Bacteria

Norcardiae and other aerobic *Actinomyces* species

Borrelia recurrentis
Chlamydophila psittaci
Chlamydia trachomatis
Mycoplasma pneumonia
Rickettsiae
Treponema pallidum
Treponema pallidum subspecies *pertenue*
Ureaplasma urealyticum

Parasites

Balantidium coli
Entamoeba species
Plasmodium falciparum[1]

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC.

[1] Doxycycline has been found to be active against the asexual erythrocytic forms of *Plasmodium falciparum* but not against the gametocytes of *P. falciparum.* The precise mechanism of action of the drug is not known.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential of doxycycline have not been conducted. However, there has been evidence of oncogenic activity in rats in studies with the related antibiotics, oxytetracycline (adrenal and pituitary tumors) and minocycline (thyroid tumors). Likewise, although mutagenicity studies of doxycycline have not been conducted, positive results in *in vitro* mammalian cell assays have been reported for related antibacterials (tetracycline, oxytetracycline).

Doxycycline administered orally at dosage levels as high as 250 mg/kg/day had no apparent effect on the fertility of female rats. Effect on male fertility has not been studied.

13.2 Animal Toxicology and/or Pharmacology

Hyperpigmentation of the thyroid has been produced by members of the tetracycline-class in the following species: in rats by oxytetracycline, doxycycline, tetracycline PO_4, and methacycline; in minipigs by doxycycline, minocycline, tetracycline PO_4, and methacycline; in dogs by doxycycline and minocycline; in monkeys by minocycline.

Minocycline, tetracycline PO_4, methacycline, doxycycline, tetracycline base, oxytetracycline HCl, and tetracycline HCl, were goitrogenic in rats fed a low iodine diet. This goitrogenic effect was accompanied by high radioactive iodine uptake. Administration of minocycline also produced a large goiter with high radioiodine uptake in rats fed a relatively high iodine diet.

Treatment of various animal species with this class of drugs has also resulted in the induction of thyroid hyperplasia in the following: in rats and dogs (minocycline); in chickens (chlortetracycline); and in rats and mice (oxytetracycline). Adrenal gland hyperplasia has been observed in goats and rats treated with oxytetracycline.

Results of animal studies indicate that tetracyclines cross the placenta and are found in fetal tissues.

15 REFERENCES

1. Friedman JM, Polifka JE. *Teratogenic Effects of Drugs. A Resource for Clinicians (TERIS).* Baltimore, MD: The Johns Hopkins University Press: 2000: 149-195. The TERIS (Teratogen Information System) is available at: http://www.micromedexsolutions.com/ (cited: 2016 Jan).

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3. Horne HW Jr. and Kundsin RB. The role of mycoplasma among 81 consecutive pregnancies: a prospective study. *Int J Fertil* 1980; 25: 315-317.
4. Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD): National Library of Medicine (US); [Last Revision Date 2015 March 10; cited 2016 Jan]. Doxycycline; LactMed Record Number: 100; [about 3 screens]. Available from: http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm

16 HOW SUPPLIED/STORAGE AND HANDLING

DORYX MPC (doxycycline hyclate delayed-release tablets), 120 mg are white, oval tablets containing yellow pellets and debossed on one face with "DC" and plain on the other. Each tablet contains doxycycline 120 mg (equivalent to doxycycline hyclate 138.8 mg).

The 120 mg tablet is supplied in bottles of 30 tablets. NDC 51862-559-30

Store at 25° C (77° F); excursions permitted to 15°C to 30° C (59°F to 86° F) [see USP Controlled Room Temperature]. Dispense in a tight, light-resistant container (USP).

17 PATIENT COUNSELING INFORMATION

Advise patients taking DORYX MPC for malaria prophylaxis:

- that no present-day antimalarial agent, including doxycycline, guarantees protection against malaria.
- to avoid being bitten by mosquitoes by using personal protective measures that help avoid contact with mosquitoes, especially from dusk to dawn (for example, staying in well-screened areas, using mosquito nets, covering the body with clothing, and using an effective insect repellent).
- that doxycycline prophylaxis:
  - should begin 1 to 2 days before travel to the malarious area,
  - should be continued daily while in the malarious area and after leaving the malarious area,
  - should be continued for 4 further weeks to avoid development of malaria after returning from an endemic area,
  - should not exceed 4 months.

Advise all patients taking DORYX MPC:

- to avoid excessive sunlight or artificial ultraviolet light while receiving doxycycline and to discontinue therapy if phototoxicity (for example, skin eruptions, etc.) occurs. Sunscreen or sunblock should be considered [*see Warnings and Precautions (5.3)*]
- to drink fluids liberally along with DORYX MPC to reduce the risk of esophageal irritation and ulceration [*see Adverse Reactions (6)*]
- that the absorption of tetracyclines is reduced when taken with foods, especially those that contain calcium. [*see Drug Interactions (7.3)*]
- that if gastric irritation occurs, DORYX MPC may be given with food or milk [*see Clinical Pharmacology (12.3)*]
- that the absorption of tetracyclines is reduced when taken with antacids containing aluminum, calcium or magnesium, bismuth subsalicylate, and iron-containing preparations [*see Drug Interactions (7.3)*].
- that the use of doxycycline might increase the incidence of vaginal candidiasis.

Advise patients that diarrhea is a common problem caused by antibacterial drugs which usually ends when the antibacterial is discontinued. Sometimes after starting treatment with antibacterial drugs, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of antibacterial. If this occurs, patients should contact their physician as soon as possible.

Counsel patients that antibacterial drugs including DORYX MPC should only be used to treat bacterial infections. They do not treat viral infections (for example, the common cold). When DORYX MPC is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by DORYX MPC or other antibacterial drugs in the future.

Manufactured by:
Mayne Pharma International Pty Ltd
1538 Main North Road
Salisbury South, SA 5106 Australia

Distributed by:
Mayne Pharma USA
Greenville, NC 27834

Rev. 07/2018
61596

14.8 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)]*.

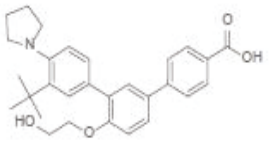
Safety and effectiveness of AKLIEF Cream have not been established in pediatric subjects under the age of 9 years.

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.

14 CLINICAL STUDIES

AKLIEF Cream applied once daily in the evening was evaluated in the treatment of moderate facial and truncal acne vulgaris in two randomized, multicenter, parallel group, double-blind, vehicle-controlled trials of identical design, Study 1 (NCT02566369) and Study 2 (NCT02556788). The trials were conducted in a total of 2420 subjects aged 9 years and older, who were treated for up to 12 weeks with either AKLIEF Cream (1214 subjects) or vehicle cream (1206 subjects). Subjects were encouraged to use a moisturizer as desired, while allowing an interval of approximately 1 hour before or after the study treatment application.

Acne severity was evaluated using a 5-point Investigator's Global Assessment (IGA) scale for the face and a 5-point Physician's Global Assessment (PGA) scale for the trunk with moderate acne vulgaris defined as a score of 3. Overall, 87% of subjects were Caucasian and 55% were female. Thirty-four (1.4%) subjects were 9 to 11 years of age, 1128 (47%) subjects were 12 to 17 years of age, and 1258 (52%) subjects were 18 years and older. All subjects had moderate acne vulgaris on the face and 99% of subjects had moderate acne vulgaris on the trunk. At baseline, subjects had between 7 and 200 (average 36) inflammatory lesions on the face and between 0 and 220 (average 38) on the trunk. Additionally, subjects had 21 to 305 (average 52) non-inflammatory lesions on the face and 0 to 260 (average 46) on the trunk.

Success on the IGA/PGA scale was defined as achieving a score of 0 (clear) or 1 (almost clear) and at least a 2-grade improvement from baseline. The co-primary endpoints (evaluated on the face) were the percentage of subjects achieving success on the IGA scale, the mean absolute change in facial inflammatory lesion count from baseline, and the mean absolute change in facial non-inflammatory lesion count from baseline, all evaluated at Week 12. The co-secondary endpoints (evaluated on the trunk) were the percentage of subjects achieving success on the PGA scale, the mean absolute change in truncal inflammatory lesion count from baseline, and the mean absolute change in truncal non-inflammatory lesion count from baseline, all evaluated at Week 12. Efficacy results for acne on the face and trunk after 12 weeks of treatment are presented in Tables 3 and 4 respectively.

Table 3. Acne of the Face Efficacy Results at Week 12 (Intent-to-Treat; Multiple Imputation)

	Study 1		Study 2	
	AKLIEF Cream	Vehicle Cream	AKLIEF Cream	Vehicle Cream
	(N= 612)	(N= 596)	(N= 602)	(N=610)
IGA Success At least a 2-grade improvement and "Clear" (0) or "Almost Clear" (1)	29.4%	19.5%	42.3%	25.7%
Inflammatory Lesions Mean* Absolute (Percent) Change from Baseline	-19.0 (-54.4%)	-15.4 (-44.8%)	-24.2 (-66.2%)	-18.7 (-51.2%)
Non-inflammatory Lesions Mean* Absolute (Percent) Change from Baseline	-25.0 (-49.7%)	-17.9 (-35.7%)	-30.1 (-57.7%)	-21.6 (-43.9%)

*Means presented in table are Least Square (LS) means

Table 4. Acne of the Trunk Efficacy Results at Week 12 (Intent-to-Treat on the Trunk; Multiple Imputation)

	Study 1		Study 2	
	AKLIEF Cream	Vehicle Cream	AKLIEF Cream	Vehicle Cream
	(N= 600)	(N=585)	(N= 598)	(N=609)
PGA Success At least a 2-grade improvement and "Clear" (0) or "Almost Clear" (1)	35.7%	25.0%	42.6%	29.9%
Inflammatory Lesions Mean* Absolute (Percent) Change from Baseline	-21.4 (-57.4%)	-18.8 (-50.0%)	-25.5 (-65.4%)	-19.8 (-51.1%)
Non-inflammatory Lesions Mean* Absolute (Percent) Change from Baseline	-21.9 (-49.1%)	-17.8 (-40.3%)	-25.9 (-55.2%)	-20.8 (-45.1%)

*Means presented in table are Least Square (LS) means

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

GALDERMA is a registered trademark.

INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Multi-Center, Randomized, Double-Blind, Placebo Controlled Study To Compare Efficacy and Safety of Trifarotene (CD5789) Cream When Used with an Oral Antibiotic for the Treatment of Severe Acne Vulgaris

Protocol Number: RD.06.SPR.202394

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.

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Investigator Signature Date

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Printed Name