CLINICAL STUDY PROTOCOL

A Multicenter, Randomized, Double-Blind, Parallel-Group, Vehicle-Controlled Study of the Safety and Efficacy of DFD-03 Lotion in the Treatment of Acne Vulgaris for 12 Weeks

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CONFIDENTIAL

COMPLIANCE STATEMENT

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312) and ICH E6; 62 Federal Register 25691 (1997).

SIGNATURES

The signatures below provide the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

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SYNOPSIS

Title:

A Multicenter, Randomized, Double-Blind, Parallel-Group, Vehicle-Controlled Study of the Safety and Efficacy of DFD-03 Lotion in the Treatment of Acne Vulgaris for 12 Weeks

Sponsor:	Dr. Reddy's Laboratories, Ltd 8-2-337, Road No. 3 Banjara Hills Hyderabad – 500034, Telangana, India

Study Centers:	25 to 35 sites	**Number of Subjects:**	Approximately 550
Study Period:	12 weeks	**Clinical Phase:**	Phase 3

Objective:

The objectives of this study are to compare the efficacy and safety of DFD-03 Lotion to Vehicle Lotion in subjects with acne vulgaris after 12 weeks of topical treatment.

Methods:

This will be a multicenter, randomized, double-blind, parallel group, vehicle-controlled study.

Subjects with mild to moderate facial acne vulgaris will be randomized to either of the two arms in a 1:1 ratio:

Arm 1: DFD-03 Lotion

Arm 2: Vehicle Lotion

Enrollment of subjects with mild acne (IGA Grade 2) at each site will be restricted to no more than 20% of total enrollment at that site. Subjects with acne lesions of any severity on the chest and/or back (including shoulders) may be enrolled provided they have mild to moderate acne on the face. During the 12-week treatment period subjects will use the study product twice daily with approximately 12 hours between applications. Subjects will be instructed to treat the entire face (and chest and/or back including shoulders, if applicable). The investigator will assess efficacy by using an Investigator's Global Assessment scale (IGA 5-point scale) and by counting the number of inflammatory and non-inflammatory lesions on the face at Baseline and Weeks 4, 8, and 12. Lesion counts will also be done for the chest and/or back (including shoulders), where applicable. The IGA should always be done prior to lesion counts.

Safety assessments will include the investigator's assessment of local cutaneous tolerance of the treated skin (dryness, non-lesional erythema, peeling, stinging, burning, and itching; assessed separately on the chest and/or back including shoulders (if applicable), vital signs (blood pressure and pulse rate), and adverse events (AEs). Urine pregnancy tests will be performed at Baseline and at every visit through Week 12 for all female subjects. A physical examination will be performed at the Baseline Visit.

The Cardiff Acne Disability Index (CADI) will be used to assess the quality of life in all subjects at Baseline (Day 1) and at Weeks 4, 8 and 12.

Subjects will assess the severity of their facial acne using the Subject's Global Assessment scale (SGA) at Baseline and at every visit through Week 12. Subject quality of life and treatment satisfaction will also be evaluated using the Dermatology Life Quality Index (DLQI) at Baseline, Weeks 4, 8, and 12. For subjects ≤ 16 years of age the children's DLQI will be used. At up to 4-6 selected study centers, consenting subjects will have lesions on the face photographed at Baseline and Weeks 4, 8, and 12.

Number of Subjects:

Approximately 550 subjects will be enrolled in about 25 to 35 centers.

Diagnosis and Criteria for Inclusion / Exclusion:

Inclusion:

1. Subject understands the study procedures, is willing to comply with the study procedures and required visits, and agrees to participate by giving written informed consent. Subjects under the legal age of consent must provide written assent and must have the written informed consent of their legal guardian.
2. Subject (or legal guardian) must be willing to authorize use and disclosure of protected health information collected for the study.
3. Subject must be at least 9 years of age.
4. Female subjects must be having their menstrual period at the Baseline Visit (as reported by the subject), except for subjects using hormonal contraceptives that preclude menstrual periods, if the subject is premenarchal, is postmenopausal for at least 12 months prior to baseline, is surgically sterilized (i.e. tubal ligation) or if the subject is without a uterus and /or both ovaries.
5. A clinical diagnosis of facial acne vulgaris with a facial Investigator's Global Assessment (IGA) score of 2 (mild) to 3 (moderate) at Baseline. Subjects with acne lesions on the chest and/or back (including shoulders) in addition to those on the face have the option of treating their back and/or chest (including shoulders) in addition to their face.
6. Inflammatory lesion count (papules and pustules) of at least 20 on the face, including the nose, at Baseline.
7. Non-inflammatory lesion count (closed and open comedones) of at least 25 on the face, including the nose, at Baseline.
8. No more than 2 nodulocystic lesions on the face, including the nose, at Baseline.
9. Females, regardless of childbearing potential:
    a. Must have a negative urine pregnancy test at Screening and Baseline. Test must have a sensitivity of at least 25 mIU/mL for βhCG.

b. If sexually active, must be on or use an acceptable method of birth control.

Acceptable methods of birth control include:

- hormonal methods* or intrauterine device in use ≥ 90 days prior to Baseline; or
- partner has had a vasectomy at least 90 days prior to Baseline; or
- barrier methods plus spermicide; or
- Essure® that has been in place for at least 3 months before the screening visit with radiograph confirmation of fallopian tube blockage.

***Hormonal methods:** If on hormonal contraceptives, must have been on the same hormonal contraceptive product for 3 months (90 days) prior to Baseline and continued on same method and dose throughout the duration of the study. If subject had used hormonal birth control and had stopped, this should have occurred more than 6 months prior to Baseline.

Exception: Sexually inactive female subjects are not required to practice a reliable method of contraception and may be enrolled at the investigator's discretion provided that they are counseled to remain sexually inactive for the duration of the study and understand the possible risks involved in getting pregnant during the study. An abstinent female must agree that if she becomes sexually active during the study she will use an acceptable form of contraception such as a barrier method with spermicide. Females who are surgically sterilized [e.g. hysterectomy, bilateral tubal ligation, bilateral oophorectomy] at least 1 year prior to Baseline or have been postmenopausal for at least 1 year prior to Baseline are not required to practice a reliable method of contraception.

10. Subjects agree not to use any product on the face during the entire course of study except for non-medicated, investigator-approved cleanser, sunscreen, face wash, and make-up. Subjects should continue to use these investigator-approved products for the duration of the study and should avoid any changes in these consumer products.
11. Subjects must be willing to comply with sun avoidance measures for the face (as well as back/chest and shoulders, if applicable) including use of investigator-approved sunscreen and/or hats, have limited sun exposure time, and have no tanning bed use.
12. Subject must be in good general health as determined by the investigator and supported by the medical history, physical examination, and normal or not clinically significant abnormal vital signs (blood pressure and pulse). Subjects are eligible if:

    — Systolic blood pressure (BP) < 160 and > 85 mmHg
    — Diastolic BP < 100 and > 50 mmHg
    — Pulse 50 to 100 bpm inclusive for adults; up to 110 bpm for subjects < 18 years of age

Exclusion:

1. Females who are pregnant or lactating or planning to become pregnant during the study period.
2. Treatment with the following products:

a. Topical acne treatments (retinoids, antibiotics, benzoyl peroxide, azelaic acid, resorcinol, salicylates, α-hydroxy/glycolic acid), or other topical facial medication (antifungals, steroids, anti-inflammatories) on the treatment area in the 14 days prior to the Baseline Visit, including prescription and non-prescription products.

b. Systemic corticosteroids, systemic acne treatments including systemic antibiotics used for treatment of acne, potential photosensitizing agents (thiazides, phenothiazines), spironolactone, flutamide, or immunosuppressant drugs in the 30 days prior to the Baseline Visit.

c. Systemic retinoid use (including high dose vitamin A > 10,000 units per day) in the 180 days prior to the Baseline Visit.

d. Undertaken certain facial procedures such as chemical peel, laser treatment, photodynamic therapy, acne surgery, cryodestruction or chemodestruction, x-ray therapy, intralesional steroids, dermabrasion, or depilation (except eyebrow shaping) in the 30 days prior to the Baseline Visit. After the subject is enrolled in the study, eyebrow shaping (except for tweezing) is prohibited.

e. Treatment with a medication or procedure that, in the opinion of the investigator, would put the subject at unacceptable risk for participation in the study or may interfere with evaluations in the study.

f. Treatment with an investigational product or device in the 30 days prior to the Baseline Visit.

3. Known allergic reaction to retinoids or tazarotene or any of the other ingredients of these products. The inactive ingredients are sodium lauryl sulphate, stearyl alcohol, cetyl alcohol, gluconolactone, Vitamin E polyethylene glycol succinate, glycerin, carbomer P 971, propylparaben, methylparaben, edetate disodium, butylated hydroxytoluene, medium-chain triglyceride, trolamine, and purified water.
4. Presence of any facial skin disease or condition that would interfere with the study or place the subject at unacceptable risk including sunburn, rosacea, seborrheic dermatitis, perioral dermatitis, lupus, dermatomyositis, psoriasis, eczema, squamous cell carcinoma, acneiform eruptions caused by medications, steroid acne, steroid folliculitis, bacterial folliculitis or any other facial disease or condition.
5. Excessive facial hair (i.e., heavy beard or mustache), facial tattoos or facial disfigurement that would interfere with study assessments.
6. Subjects with a serious and/or chronic medical condition such as chronic or active liver disease, renal impairment, heart disease, severe respiratory disease, rheumatoid arthritis, current malignancies, immunocompromised conditions, or any other disease that, in the opinion of the investigator, would interfere with the study or place the subject at unacceptable risk.
7. Subjects who have been treated for alcohol dependence or alcohol or drug abuse in the year prior to the Baseline Visit.
8. Subjects who have been in another investigational trial within 30 days of the Baseline Visit.

9. Subjects may not have a personal relationship with any member of the study staff or be part of the staff at the medical practice.

Investigational Product, Dose and Mode of Administration:

DFD-03 Lotion (0.1% tazarotene)

Subjects will apply a quarter (U.S coin) size amount of the study product all over the moistened face and rub it into the skin until foamy. Care should be taken to avoid the areas around the eyes, mouth, and nostrils. An additional 1-2 quarter size amount of the study product may be used over other affected areas (chest and/or back, including shoulders). After being left on for 1 minute, the subject will rinse off the product by thoroughly rinsing with warm water for about 30 seconds. This procedure will be followed twice daily, in the morning and at bedtime, approximately 12 hours apart.

Duration of Treatment and Study:

Subjects will treat the entire face, including the nose (and chest and/or back, including shoulders, if applicable) twice daily for 12 weeks. The total study duration including the screening period will be approximately 12 to 20 weeks.

Reference and Control Products, Dose and Mode of Administration:

Vehicle: DFD-03 Vehicle Lotion (0% tazarotene)

The control product will be applied similarly to the study product as described above.

Criteria for Evaluation:

Safety criteria:
The primary safety endpoint will be treatment-emergent adverse events (TEAEs). Other safety variables include local cutaneous tolerance evaluation (dryness, non-lesional erythema, peeling, stinging, burning, and itching) and vital signs (blood pressure and pulse rate).

Efficacy criteria:
The co-primary endpoints are:

- The absolute change from Baseline to Week 12 in the inflammatory (papules and pustules) lesion counts on the face
- The absolute change from Baseline to Week 12 in the non-inflammatory (open and closed comedones) lesion counts on the face
- Proportion of subjects with a clinical response of "success" at Week 12 for lesions on the face. Success based on IGA is defined as an IGA score of 0 (Clear) or 1 (Almost clear) at Week 12 with at least a 2-grade reduction from Baseline.

The secondary endpoints are:

1. Percent change from Baseline to Week 12 in inflammatory lesion counts on the face.
2. Percent change from Baseline to Week 12 in non-inflammatory lesion counts on the face.

The exploratory endpoints are:

1. Time to 50% reduction in total lesion counts on the face.
2. Absolute change from Baseline in inflammatory, non-inflammatory and total lesion counts on the face at Weeks 4 and 8.
3. Percent change from Baseline in inflammatory, non-inflammatory, and total lesion counts on the face at Weeks 4 and 8.
4. Proportion of subjects with an IGA score of 0 or 1 with at least a 2-grade reduction (for the face) from Baseline at Weeks 4 and 8.
5. Change from Baseline in Children's DLQI total score in subjects 16 years of age or younger at Weeks 4, 8 and 12.
6. Change from Baseline in DLQI score in subjects >16 years of age at Weeks 4, 8 and 12.
7. Percent change from Baseline in inflammatory, non-inflammatory and total lesion counts on the chest and/or back including shoulders (in relevant subjects) at Weeks 4, 8, and 12.
8. Time to 50% reduction in total lesion counts on the chest and/or back (including shoulders).
9. Proportion of subjects with at least a 2-grade improvement from Baseline in the SGA at Week 12.
10. Change from Baseline in CADI score at Weeks 4, 8 and 12.

If the statistical analysis for all the co-primary endpoints achieves $p<0.05$, statistical analysis for the secondary endpoints will use a sequential approach according to a pre-specified order: percent change in inflammatory lesion counts on the face, and then percent change in non-inflammatory lesion counts on the face. If $p<0.05$ is achieved for a higher ranking secondary variable, then success will be declared for the variable, and statistical comparisons will be performed for the lower ranking variable. If $p<0.05$ is not achieved for a higher ranking variable, then statistical comparisons will be considered descriptive (non-inferential) for this variable and for the lower ranking secondary variable.

The sample size was estimated based on the primary study endpoints and statistics available from the Summary Basis of Approval for Tazorac® (tazarotene) Gel (NDA 20-600). The total sample size of 550 will provide an overall power of at least 90% based on a 2-tailed alpha of 0.05.

Approximately 550 subjects (275 for each treatment arm) will be randomized and about 25 to 35 sites will participate in the study.

Table 1: Study Schedule

	Visit 1[1]	Visit 2[1]	Visit 3	Visit 4	Visit 5
	Screen Day -60 to 0	**Day 1** Baseline	**Week 4**[2] Day 28	**Week 8**[3] Day 56	**Week 12**[3] Day 84
Informed consent/assent	X				
Inclusion and exclusion criteria	X	X			
Medical (including acne) history / prior & concomitant medications	X	X			
Collect Demographic Data	X				
Fitzpatrick Skin Type Assessment		X			
Physical Examination (including height and weight)		X			
Vital signs assessment (Blood Pressure & Pulse Rate)	X	X	X	X	X
Update concomitant medications			X	X	X
Urine pregnancy test[4]	X	X	X	X	X
Randomization		X			
Dispense/redispense study product		X	X	X	
Weigh study product bottles prior to dispensing and used bottles upon return		X	X	X	X
Initiate treatment		X			
Dispense/review/ collect study diary		X	X	X	X
Review subject instructions		X	X	X	
Collect empty bottles			X	X	X
Evaluate IGA on face	X	X	X	X	X
Count inflammatory and non-inflammatory lesions on face	X	X	X	X	X
Count inflammatory and non-inflammatory lesions on the chest and/or back including shoulders (if applicable)		X	X	X	X
Assess for local cutaneous tolerance [5] on face, and chest and/or back including shoulders (if applicable)		X	X	X	X
Evaluate Subject's Global Assessment (SGA) on face		X	X	X	X
Photography[6]		X	X	X	X
DLQI or Children's DLQI		X	X	X	X
CADI Questionnaire		X	X	X	X
Evaluate compliance			X	X	X
Adverse event assessment		X	X	X	X
End of study					X

[1] Visit 1 and Visit 2 may be combined if no washout is required, but should not be separated by more than 60 days
[2] Visit window ± 3 days
[3] Visit window ± 5 days
[4] For all females regardless of reproductive potential
[5] Dryness, non-lesional erythema, peeling, stinging, burning, itching
[6] Photography of the face at selected sites

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LIST OF ABBREVIATIONS

Abbreviations	Description
AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
BP	blood pressure
CADI	Cardiff Acne Disability Index
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel
eCRF	electronic case report form
CRO	contract research organization
DLQI	Dermatology Life Quality Index
EDC	electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
IGA	Investigator's Global Assessment
IRB	institutional review board
ITT	intent-to-treat
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
PHI	protected health information
PP	per-protocol
PT	preferred term
SAE	serious adverse event
SGA	Subject's Global Assessment
SOC	system organ class
TEAE	treatment-emergent adverse event

LIST OF DEFINITIONS

Term	Definition
EDC	Electronic Data Capture is a computerized system designed for the collection of clinical data in electronic format including the eCRF.
IWRS	Interactive Web-Based Response System that manages randomization, subject enrollment, and drug supply.
Screening Visit (Visit 1)	The day a subject is screened according to the protocol inclusion/exclusion criteria after having provided informed consent/assent. The screening visit may occur on the same day as Visit 2 (Baseline) for this study.
Screened Subject	A subject who has signed informed consent/assent.
Baseline Visit (Visit 2/Day 1)	The day of randomization and the first study product application. The first study product application is done at the site by the subject during the visit.
Subject Number	A unique number assigned to a screened subject. The number consists of the 3-digit unique site number followed by a 3-digit sequential number for each subject in chronological order (e.g., 206001, 206002, where the site number is 206 and the first and second screened subjects at site 206 are 001 and 002, respectively). The subject number will be assigned by way of Interactive Web-Based Response System.
Study product(s)	Investigational product(s)

1 INTRODUCTION

Tazarotene, an acetylenic retinoid, is a prodrug that undergoes rapid and complete metabolism to its active metabolite tazarotenic acid (Chandraratna, 1996). Retinoids are a class of keratolytic drugs derived from retinoic acid used for the treatment of acne and psoriasis. Several synthetic retinoids have been developed for topical treatment of acne.

Tazarotene was initially developed in gel formulation and subsequently in cream and foam formulations. Products containing tazarotene have been proven to be effective in the treatment of acne vulgaris and psoriasis, as well as being effective in the mitigation (palliation) of facial fine wrinkling, facial mottled hyper- and hypopigmentation, and benign facial lentigines.

Dr. Reddy's Laboratories has developed DFD-03 Lotion, a new formulation containing 0.1% tazarotene for the topical treatment of acne vulgaris. This new product is intended to be used as a face wash twice daily. Treatment use will begin by applying a generous amount of product to moistened affected skin, rubbing until foamy, and then rinsing with water after 1 minute.

Acne vulgaris is characterized by a mixture of inflammatory lesions (papules, pustules, and nodular cystic lesions) and non-inflammatory lesions (open and closed comedones) (Shalita, 2004). The four primary factors contributing to acne are abnormal follicular epithelial desquamation, hyperactivity of the sebaceous glands, proliferation of *Propionibacterium acnes*, and perifollicular inflammation.

Currently available treatments for acne vulgaris include oral and topical antibiotics, topical benzoyl peroxide, topical salicylic acid, topical adapalene, topical azelaic acid, topical dapsone, oral and topical retinoids (including tazarotene), and phototherapy.

Tazarotene is a well-characterized active ingredient, and many studies have been conducted on its pharmacology, toxicology and clinical efficacy and safety (Fabior Prescribing Information, Tazorac Cream Prescribing Information).

Tazarotene is characterized by the FDA as a Category X drug, indicating that it may or can cause fetal harm when administered to a pregnant woman and is contraindicated in women who are or may become pregnant (Menter, 2000). At least 6 women are known to have become pregnant during clinical studies with tazarotene and all reported the birth of healthy babies, although the timing and extent of exposure in relation to the gestation time are unknown in these cases.

The purpose of this study is to assess the safety and efficacy of DFD-03 Lotion for topical treatment of acne vulgaris over 12 weeks of treatment.

More information about DFD-03 Lotion can be found in the Investigator's Brochure.

2 ETHICALCONSIDERATIONS

2.1 Institutional Review Board Review

The protocol, protocol amendments, subject recruiting materials, the informed consent form, and any other materials provided to subjects must be approved by an institutional review board (IRB) operating in compliance with 21 Code of Federal Regulations (CFR) Part 56. A copy of the approval letter must be received by the sponsor or contract research organization (CRO) prior to shipment of drug supplies to the site.

Records of the IRB's review and approval of all documents pertaining to the study must be kept on file by the investigator and are subject to sponsor and Food and Drug Administration (FDA) inspection at any time.

2.2 Ethical Conduct of Study

The investigator will ensure that this study is conducted in full conformity with the principles set forth in 21 CFR Part 50 – Protection of Human Subjects and in the Declaration of Helsinki (2013) (see Appendix 1).

2.3 Informed Consent

Written informed consent must be obtained before a subject can participate in the study, prior to performing any study related procedures, and before withdrawal of any therapies prohibited during the study. Informed consent is a process that is initiated prior to the subject's agreement to participate in the study and continuing throughout the subject's study participation. The process involves an extensive discussion with the subject about the study procedures and the risks and possible benefits of participation in the study.

For subjects under the age of majority in the state they are enrolled, the subject's parent or legal guardian will be required to sign the informed consent form and the subject will sign an IRB-approved 'information and assent' form before the subject is enrolled into the study.

At selected study centers, consenting subjects will have lesions on the face photographed at Baseline and Weeks 4, 8 and 12. Neither the subject nor the investigator is permitted to refer to the photographs at any subsequent visit for the purposes of grading. The informed consent form will contain a section on photography with statement that the photographs may be used for commercial promotion.

A copy of the signed consent form and 'information and assent' form (when applicable) will be given to every subject and the original will be maintained with the subject's records.

2.4 Selection of Investigators

Investigators for the study should be board-certified dermatologists licensed in the state where the study is being conducted, with knowledge and understanding of Good Clinical Practice (GCP) and experience in treating acne vulgaris. In some cases, qualified physicians who are not board-certified dermatologists may participate based on training and experience in the treatment

of acne vulgaris. Sub-investigators may be licensed physicians, physician assistants, or nurse practitioners with experience in treating acne vulgaris or in dermatology and a good understanding of GCP. Investigators may delegate study tasks to other site personnel as long as they are qualified to perform the task.

3 STUDY OBJECTIVES

The objectives of this study are to compare the efficacy and safety of DFD-03 Lotion to Vehicle Lotion in subjects with acne vulgaris after 12 weeks of topical treatment.

4 STUDY DESIGN

This will be a multicenter, randomized, vehicle-controlled, double-blind, parallel-group study. Approximately 550 subjects with mild to moderate facial acne vulgaris will be randomized in a 1:1 ratio to treatment with either DFD-03 Lotion or Vehicle Lotion. Enrollment of subjects with mild acne (IGA Grade 2) at each site will be restricted to no more than 20% of total enrollment at that site. During the 12-week treatment period subjects will use the study drug twice daily with approximately 12 hours between applications. Subjects will be instructed to treat the entire face (and chest and/or back (including shoulders), if applicable). The investigator will assess efficacy by using an Investigator's Global Assessment scale (IGA, 5-point scale) and by counting the number of inflammatory and non-inflammatory lesions on the face at Baseline and Weeks 4, 8, and 12. Lesion counts will also be done for the chest and/or back (including shoulders), where applicable.

The primary safety endpoint will be treatment-emergent adverse events (TEAEs). Other safety assessments will include the investigator's assessment of local cutaneous tolerance (dryness, non-lesional erythema, peeling, stinging, burning, and itching) and vital signs (blood pressure and pulse rate). A physical examination will be performed at Baseline. Urine pregnancy tests will be performed at Baseline and at every visit through Week 12 for all female subjects.

The co-primary efficacy endpoints are:

1. The absolute change from Baseline to Week 12 in the inflammatory (papules and pustules) lesion counts on the face
2. The absolute change from Baseline to Week 12 in the non-inflammatory (open and closed comedones) lesion counts on the face
3. Proportion of subjects with a clinical response of "success" at Week 12 for lesions on the face. Success based on IGA is defined as an IGA score of 0 (Clear) or 1 (Almost clear) at Week 12 with at least a 2-grade reduction from Baseline.

The secondary endpoints are:

1. Percent change from Baseline to Week 12 in inflammatory lesion counts on the face
2. Percent change from Baseline to Week 12 in non-inflammatory lesion counts on the face.

The exploratory endpoints are:

1. Time to 50% reduction in total lesion counts on the face
2. Absolute change from Baseline in inflammatory, non-inflammatory and total lesion counts on the face at Weeks 4 and 8.
3. Percent change from Baseline in inflammatory, non-inflammatory, and total lesion counts on the face at Weeks 4 and 8.
4. Proportion of subjects with an IGA score of 0 or 1 with at least a 2-grade reduction (for the face) from Baseline at Weeks 4 and 8.
5. Change from Baseline in Children's DLQI total score in subjects 16 years of age or younger at Weeks 4, 8 and 12.
6. Change from Baseline in DLQI score in subjects >16 years of age at Weeks 4, 8 and 12.
7. Percent change from Baseline in inflammatory, non-inflammatory and total lesion counts on the chest and/or back including shoulders (in relevant subjects) at Weeks 4, 8, and 12.
8. Time to 50% reduction in lesion counts on the chest and/or back including shoulders.
9. Proportion of subjects with at least a 2-grade improvement from Baseline in the SGA at Week 12.
10. Change from Baseline in CADI score at Weeks 4, 8 and 12.

5 SELECTION OF STUDY POPULATION

5.1 Number of Subjects

Approximately 550 subjects will be randomized and about 25 to 35 sites will participate in the study.

5.2 Inclusion Criteria

1. Subject understands the study procedures, is willing to comply with the study procedures and required visits, and agrees to participate by giving written informed consent. Subjects under the legal age of consent must provide written assent and must have the written informed consent of their legal guardian.
2. Subject (or legal guardian) must be willing to authorize use and disclosure of protected health information collected for the study.
3. Subject must be at least 9 years of age.
4. Female subjects must be having their menstrual period at the Baseline Visit (as reported by the subject), except for subjects using hormonal contraceptives that preclude menstrual periods, if the subject is premenarchal, is postmenopausal for at least 12 months prior to baseline, is surgically sterilized (i.e. tubal ligation) or if the subject is without a uterus and /or both ovaries.
5. A clinical diagnosis of facial acne vulgaris with an Investigator's Global Assessment (IGA) score of 2 (mild) to 3 (moderate) at Baseline. Subjects with acne lesions on the chest and/or back (including shoulders) in addition to those on the face have the option of treating their back and/or chest (including shoulders) in addition to their face.

6. Inflammatory lesion count (papules and pustules) of at least 20 on the face, including the nose, at Baseline.
7. Non-inflammatory lesion count (closed and open comedones) of at least 25 on the face, including the nose, at Baseline.
8. No more than 2 nodulocystic lesions on the face, including the nose, at Baseline.
9. Females, regardless of childbearing potential:
   a. Must have a negative urine pregnancy test at Screening and Baseline. Test must have a sensitivity of at least 25 mIU/mL for βhCG.
   b. If sexually active, must be on or use an acceptable method of birth control.

   Acceptable methods of birth control include:

   - hormonal methods* or intrauterine device in use ≥ 90 days prior to Baseline; or
   - partner has had a vasectomy at least 90 days prior to Baseline; or
   - barrier methods plus spermicide; or
   - Essure® that has been in place for at least 3 months before the screening visit with radiograph confirmation of fallopian tube blockage.

   ***Hormonal methods:** If on hormonal contraceptives, must have been on the same hormonal contraceptive product for 3 months (90 days) prior to Baseline and continued on same method and dose throughout the duration of the study. If subject had used hormonal birth control and had stopped, this should have occurred more than 6 months prior to Baseline.

   Exception: Sexually inactive female subjects are not required to practice a reliable method of contraception and may be enrolled at the investigator's discretion provided that they are counseled to remain sexually inactive for the duration of the study and understand the possible risks involved in getting pregnant during the study. An abstinent female must agree that if she becomes sexually active during the study she will use an acceptable form of contraception such as a barrier method with spermicide. Females who are surgically sterilized [e.g. hysterectomy, bilateral tubal ligation, bilateral oophorectomy] at least 1 year prior to Baseline or have been postmenopausal for at least 1 year prior to Baseline are not required to practice a reliable method of contraception.
10. Subjects agree not to use any product on the face during the entire course of study except for non-medicated, investigator-approved cleanser, sunscreen, face wash, and make-up. Subjects should continue to use these investigator-approved products for the duration of the study and should avoid any changes in these consumer products.
11. Subjects must be willing to comply with sun avoidance measures for the face (as well as back/chest and shoulders, if applicable) including use of investigator-approved sunscreen and/or hats, have limited sun exposure time, and have no tanning bed use.
12. Subject must be in good general health as determined by the investigator and supported by the medical history, physical examination, and normal or not clinically significant abnormal vital signs (blood pressure and pulse). Subjects are eligible if:

- Systolic blood pressure (BP) < 160 and > 85 mmHg
- Diastolic BP < 100 and > 50 mmHg
- Pulse 50 to 100 bpm inclusive for adults; up to 110 bpm for subjects < 18 years of age;

5.3 Exclusion Criteria

1. Females who are pregnant or lactating or planning to become pregnant during the study period.
2. Treatment with the following products:
   a. Topical acne treatments (retinoids, antibiotics, benzoyl peroxide, azelaic acid, resorcinol, salicylates, α-hydroxy/glycolic acid), or other topical facial medication (antifungals, steroids, anti-inflammatories) on the treatment area in the 14 days prior to the Baseline Visit, including prescription and non-prescription products.
   b. Systemic corticosteroids, systemic acne treatments including systemic antibiotics used for treatment of acne, photosensitizing agents (thiazides, phenothiazines), spironolactone, flutamide, or immunosuppressant drugs in the 30 days prior to the Baseline Visit.
   c. Systemic retinoid use (including high dose vitamin A > 10,000 units per day) in the 180 days prior to the Baseline Visit.
   d. Undertaken certain facial procedures such as chemical peel, laser treatment, photodynamic therapy, acne surgery, cryodestruction or chemodestruction, x-ray therapy, intralesional steroids, dermabrasion, or depilation (except eyebrow shaping) in the 30 days prior to Baseline visit. After the subject is enrolled in the study, eyebrow shaping (except for tweezing) will also be prohibited.
   e. Treatment with a medication or procedure that, in the opinion of the investigator, would put the subject at unacceptable risk for participation in the study or may interfere with evaluations in the study.
   f. Treatment with an investigational product or device in the 30 days prior to the Baseline Visit.
3. Known allergic reaction to retinoids or tazarotene or any of the other ingredients of these products. The inactive ingredients are sodium lauryl sulphate, stearyl alcohol, cetyl alcohol, gluconolactone, Vitamin E polyethylene glycol succinate, glycerin, carbomer P 971, propylparaben, methylparaben, edetate disodium, butylated hydroxytoluene, medium-chain triglyceride, trolamine, and purified water.
4. Presence of any facial skin disease or condition that would interfere with the study or place the subject at unacceptable risk including sunburn, rosacea, seborrheic dermatitis, perioral dermatitis, lupus, dermatomyositis, psoriasis, eczema, squamous cell carcinoma, acneiform eruptions caused by medications, steroid acne, steroid folliculitis, bacterial folliculitis or any other facial disease or condition.
5. Excessive facial hair (i.e., heavy beard or mustache), facial tattoos or facial disfigurement that would interfere with study assessments.

6. Subjects with a serious and/or chronic medical condition such as chronic or active liver disease, renal impairment, heart disease, severe respiratory disease, rheumatoid arthritis, current malignancies, immunocompromised conditions, or any other disease that, in the opinion of the investigator, would interfere with the study or place the subject at unacceptable risk.
7. Subjects who have been treated for alcohol dependence or alcohol or drug abuse in the year prior to the Baseline Visit.
8. Subjects who have been in another investigational trial within 30 days of the Baseline Visit.
9. Subjects may not have a personal relationship with any member of the study staff or be part of the staff at the medical practice.

Subjects must not use the medications or procedures shown in Table 2 for the period specified before the Baseline Visit (Visit 2). Table 2 also indicates whether the medications or procedures are allowed or prohibited during the study (after the Baseline Visit).

Table 2: Washout Periods (Prior to Baseline - Visit 2)

Product	Washout Period	During Study
Topical acne treatments (retinoids, antibiotics, benzoyl peroxide, azelaic acid, resorcinol, salicylates, α-hydroxy/glycolic acid), or other topical facial medication (antifungals, steroids, anti-inflammatories) on the treatment area, including prescription and non-prescription products	14 days	Prohibited
Systemic corticosteroids, systemic acne treatments including systemic antibiotics used for acne treatment, photosensitizing agents (thiazides, phenothiazines), spironolactone, flutamide, or immunosuppressant drugs Other investigational product or device	30 days	Prohibited
Systemic antibacterials	Allowed except systemic antibiotics used for acne treatment which will require a 30-day washout period	Up to 10 days allowed for indications other than acne
Facial procedures such as chemical peel, laser treatment, photodynamic therapy, acne surgery, cryodestruction or chemodestruction, x-ray therapy, intralesional steroids, dermabrasion, or depilation (except eyebrow shaping)	30 days	Prohibited [Eyebrow shaping (except for tweezing) is prohibited during the study]
Systemic retinoid (including high dose vitamin A > 10,000 units per day)	180 days	Prohibited

6 SUBJECT TREATMENT

6.1 Investigational Products

6.1.1 Description

The investigational products are:

1. DFD-03 Lotion (0.1% tazarotene)
   (60 mL bottle containing 50 ml of study product, Dr. Reddy's Laboratories Ltd.)

2. Vehicle Lotion (0% tazarotene)
   (60 mL bottle containing 50 ml of study product, Dr. Reddy's Laboratories Ltd.)

The study products will be provided by Dr. Reddy's Laboratories Ltd., Hyderabad, India. The study products are white to off-white lotions. The ingredients of the Vehicle Lotion are identical to DFD-03 Lotion except for omission of tazarotene.

6.1.2 Labels and Packing

Bottles will be packed individually. Labels on the bottles will be in English and include the protocol number, a unique bottle number, investigational use warning, storage conditions, brief instructions for use, and sponsor name and address. In addition, there will be a place to write the subject number and subject initials. The bottle label will also have a tear-off panel that includes the protocol number and unique bottle number. The tear-off panel is to be affixed to the source document and filed in subject's chart.

6.1.3 Accountability

Documentation of receipt, study product inventory, and return shipments of the study product must be maintained at each study site. Upon receipt of the study product supplies, an inventory must be performed. It is important that site personnel count and verify that the shipment contains all the items noted in the shipment record and that they are in good condition. At study completion, all bottles of study product, used and unused, must be returned to the sponsor or designee.

In addition, an Investigational Product Dispensing Record showing dispensing to and return by subjects must be maintained at each study site. Any dispensed bottles that are not returned to the clinic must be documented on the log.

6.1.4 Dispensing and Return

At the Baseline Visit (Visit 2), 2 bottles of study product will be assigned by the interactive web-based system (IWRS) and will be dispensed to subjects who will apply to the face only and 4 bottles will be dispensed to subjects who will apply to the face and chest and/or back (including shoulders). At subsequent visits, additional bottles will be assigned by the IWRS and dispensed as needed from the same assigned treatment. Partially used bottles can be re-dispensed to the subject. The specific study product bottle to be dispensed for each subject will be identified by using IWRS. The tear-off panel is to be affixed to the source document and filed in the subject's chart. Subject initials and subject number must be written on the bottle label. Study staff will then dispense and instruct the subject on study product use. The subject will be provided with a copy of the subject instructions.

Dispensing and return of study product must be documented on the Investigational Product Dispensing Record.

Subjects must return the used bottles even if empty throughout the trial. At the end of the trial, all used and unused bottles must be returned to the clinic for eventual destruction by the sponsor or designee. Any dispensed bottles that are not returned to the clinic must be documented on the log.

6.1.5 Storage

Study product must be kept in a secure room temperature-controlled/monitored space at 20°-25°C (68°-77°F); excursions are permitted to 15°-30°C (59°-86°F).

6.2 Treatment Regimen

Subjects will use the study product twice daily with approximately 12 hours between applications for 12 weeks starting on Day 1 during the study visit. The first application will be done at the clinic and supervised by site staff. If the first on-site application occurs later in the afternoon (e.g. at or after 4 pm), this application will be considered the pm dose. Treatment use will begin by moistening facial skin with lukewarm tap water. Subjects will then be instructed to dispense a quarter (U.S. coin) size amount of study product into the palm of their hand and then apply over the entire face, delineated by the hairline, jaw-line and ears and including the nose (avoiding the areas around the eyes, mouth and nostrils), with the tip of a finger. For subjects with acne on chest and/or back (including shoulders), an additional 1-2 quarter size amount of the study treatment will be similarly applied. Subjects should then rub the treated areas for 5 to 10 seconds until foamy, wait approximately 1 minute (a timer will be provided), and then rinse thoroughly with lukewarm tap water for about 30 seconds, being careful to close eyes tightly. A washcloth should not be used on the face but can be used for the chest and/or back including shoulders.

The first and last dates of treatment and the number of study product applications made on these dates should be recorded on the electronic case report form (eCRF). The total number of applications (including those on the first and last days) and the number of missed applications should also be recorded by reference to the diary. By definition there are no missed applications before the first date of treatment or after the last date of treatment.

Heavy make-up used to cover-up blemishes and sunscreen should be removed before study product application using a gentle cleanser approved by the investigator, such as Cetaphil Gentle Skin Cleanser, etc.

Subjects will be allowed to use an investigator-approved cleanser, face wash, sunscreen, and/or non-comedogenic moisturizer with SPF daily on the face. Subjects will be instructed to continue to use their investigator- approved products for the duration of the study and should avoid any changes in these consumer products.

6.3 Treatment and Protocol Compliance

Subjects will be provided an instruction sheet. Study staff should review the instruction sheet with the subjects to ensure protocol compliance.

At each visit, the investigator or designee will interview subjects concerning treatment compliance and ask if any doses have been missed. The study product bottles will be weighed prior to being dispensed and weighed again when the bottle is returned. If the study product bottle still contains study product it should be re-dispensed to the subject after it is weighed. Additional bottles should be dispensed as needed. The investigator will also ask about

compliance with protocol requirements. Protocol deviations will be recorded in the subject's chart and Protocol Deviation Form and included in the study report. A Protocol Deviation Form is not needed for missed visits, missed applications, out-of-window visits, or missing data. These items will be apparent from the missing data on the eCRF and will be identified programmatically during data analysis for purposes of reporting. The sponsor should be consulted before discontinuing subjects due to protocol deviations unless safety is a concern.

In addition, subjects will be provided a diary card for documenting the time and dates of applications. The subjects will review the diary card with the investigator or designee at each visit. The number of applied and missed applications will be recorded on the eCRF.

6.4 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned randomly to one of the two treatment groups in a 1:1 ratio (275 for DFD-03 Lotion and 275 for Vehicle Lotion).

IWRS will randomize each subject to a treatment group by site based on the subject's IGA score in order for each site to maintain a 1:1 ratio within each IGA stratum. IWRS will assign a bottle (designated by a number) to be dispensed, based on the treatment assignment from the inventory available at the site. IWRS will restrict each site from enrolling no more than 20% of enrolled subjects with IGA score of 2 (mild). The date and time of randomization and the bottle number should be entered on the eCRF.

The investigator shall ensure that study products are only used by subjects under the investigator's personal supervision or under the supervision of a sub-investigator responsible to the investigator and in accordance with the protocol.

6.5 Blinding

6.5.1 Method of Blinding

This is a double-blind, vehicle-controlled study. The primary and secondary containers and the product appearance of the DFD-03 Lotion and Vehicle Lotion will be identical. All subjects, study site, CRO personnel, statisticians, and sponsor staff will be completely blinded.

6.5.2 Unblinding

The blind should be broken for all SAE IND safety reports that are judged to be expedited reports for submission to FDA. The unblinding procedures and follow-up will be performed in accordance with the protocol and the CRO's standard operating procedures (SOPs). The blind should not be broken at the study site level except in a medical emergency (where knowledge of the study medication received would affect the treatment of the emergency). For a medical emergency, the blind must only be broken following discussion on a case-by-case basis, at the discretion of the Investigator/treating physician/Sponsor.

If the blind is broken, the date, time, and reason must be recorded in the subject's source record, eCRF, and any associated AE report. If an Investigator, site personnel performing assessments, or subject is unblinded, the unblinding incident and unblinded subject must be listed as a major

protocol deviation. A subject for whom the blind is broken will discontinue study medication and be scheduled for a safety follow-up visit and then discontinued from the study. The subject will be encouraged to stay in the study until the AE is resolved or stabilized. All Investigators and the IRB will receive blinded reports. However, on the request of the IRB, the Sponsor will send unblinded reports directly to the IRB.

6.6 Prior and Concomitant Therapy and Procedures

Chronic medications being used at the time of the Screening and Baseline Visit, with the exception of those specified as prohibited, may be continued at the discretion of the investigator. History of medications, therapies, and procedures is collected from the prior 6-month period for determination of eligibility. Only medications, therapies and procedures in use during the study should be entered on the eCRF.

New medications used after baseline required for another medical condition, that in the opinion of the investigator will have no material impact on the study, are permitted. The addition of such a new medication during the study will be documented as a concomitant medication and the associated medical need must be recorded as an AE, if applicable.

All medications (topical, oral, prescription, over-the-counter, and herbal medications) and medical therapies or procedures that are used during the study for other diseases/conditions must be recorded on the eCRF.

Subjects will only be allowed to use a non-medicated investigator-approved gentle cleanser, facial wash, sunscreen, and/or non-comedogenic moisturizer with SPF, and make-up.

Subjects should be instructed to refrain from making any significant change in the use of consumer products during the course of the study. Any changes will be captured in the source documents and eCRF. The name and the date that the new product was started will be recorded.

See Table 2 for a list of medications and procedures that are prohibited during the study.

6.7 Study Restrictions

Only the assigned study product and non-medicated investigator-approved sunscreen/moisturizer with SPF, gentle cleanser, face wash, and make-up should be applied to the face during the study.

Subjects must be willing to comply with sun avoidance measures for the face (and chest and/or back (including shoulders), if applicable) including use of non-medicated investigator-approved sunscreen and/or hats, have limited sun exposure time, and have no tanning bed use.

7 STUDY PROCEDURES AND EVALUATIONS

7.1 Informed Consent Process

Informed consent must be obtained before a subject can participate in the study, prior to performing any study related procedures and before withdrawal of any therapies prohibited during the study. The investigator must discuss the study fully with the subject (and legal guardian, as applicable). Subjects must demonstrate their willingness to participate in the study and comply with the study procedures by giving written informed consent or written assent, as applicable. The consent form and 'information and assent' form must be signed and dated by the subject or legal guardian, as applicable. A copy of the consent form (and 'information and assent' form, as applicable) must be given to the subject and/or legal guardian, and the date of the consent process and who conducted the consent process must be documented in the source documents.

7.2 Screening

A separate Screening Visit (Visit 1) may be performed when a washout period is required or for scheduling purposes. Alternatively, Visits 1 and 2 may be combined if no washout period is required. The subject number, date of visit, date of consent, reason for screen failure, and study status (screen failure) will be captured in the eCRF for every screen failure subject. The Baseline Visit 2 must occur no later than 60 days after the Screening Visit. Medical history and acne history should be collected for the prior 1-year period and concomitant medications, therapies, and procedures collected for the prior 6-month period. Only ongoing medical conditions and ongoing concomitant medications should be entered on the eCRF. Acne history will be collected and recorded in the eCRF.

A screen failure is a subject who received information about the study, including signing an informed consent and possibly performing some study-related procedures, but was not randomized and/or did not use study product.

7.3 Demographic and Baseline Characteristics

Demographic variables include age (computed from date of birth and Baseline Visit date), race, ethnicity, and sex. Baseline characteristics are the baseline values for the efficacy variables – inflammatory lesion count, non-inflammatory lesion count, and IGA. The IGA should always be done prior to lesion counts.

7.4 Fitzpatrick Skin Type Assessment

The Fitzpatrick skin scale (Fitzpatrick, 1988; Table 3) classifies a person's complexion and tolerance of sunlight. It is commonly used by many practitioners to determine how someone will respond or react to facial treatments, and how likely they are to get skin cancer.

The Fitzpatrick Classification Scale will be performed at Day 1 (Baseline) prior to the first application of study medication and will be recorded in the subject's source document and CRF.

Table 3: Fitzpatrick Classification Scale

Skin Type	Skin Color	Characteristics
I	White; very fair; red or blond hair; blue eyes; freckles	Always burns, never tans
II	White; fair; red or blond hair; blue, hazel, or green eyes	Usually burns, tans with difficulty
III	Cream white; fair with any eye or hair color; very common	Sometimes mild burn, gradually tans
IV	Brown; typical Mediterranean Caucasian skin	Rarely burns, tans with ease
V	Dark Brown; mid-eastern skin types	very rarely burns, tans very easily
VI	Black	Never burns, tans very easily

7.5 Standardized Photography

This assessment will be performed at up to 4-6 selected sites. Photographs will be taken of each consenting subject's face, to document all acne lesions that are present at Baseline/Day 1 and Weeks 4, 8, and 12/Visit 5. Photographs will be stored electronically and considered part of the subject's source documents. Neither the subject nor the investigator is permitted to refer to the photographs at any subsequent visit for the purposes of grading.

Equipment, supplies, training and detailed instructions for obtaining and managing the photographs will be provided to the sites prior to the initiation of subject enrollment.

7.6 Efficacy Assessments

The investigator will be responsible for all clinical evaluations, with best attempts made to assign the same evaluator for a subject throughout the study to obtain consistency in grading scores and measurements.

Efficacy assessments will be conducted using IGA for overall disease severity and inflammatory and non-inflammatory lesion counts on the face. The IGA should always be done prior to lesion counts.

7.6.1 Investigator's Global Assessment (IGA) of the Face

The IGA scale to be used in the study is a measure of static evaluation of qualitative overall acne severity. IGA is an ordinal scale with five severity grades (reported only in integers, e.g., 0 to 4). Each grade is defined by a distinct and clinically relevant morphologic description to minimize inter-observer variability (Table 4). The grades on the scale have been sufficiently defined to appropriately and unambiguously represent each severity grade on the scale. The investigator is required to perform IGA scoring at each visit. The IGA should always be done prior to lesion counts.

Table 4: IGA Scale for Facial Acne Vulgaris*

Grade	Description
0	Clear skin with no inflammatory or non-inflammatory lesions
1	Almost clear; rare non-inflammatory lesions with no more than rare papules
2	Mild severity; some non-inflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions)
3	Moderate severity; up to many non-inflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion
4	Severe; up to many non-inflammatory and inflammatory lesions, but no more than a few nodular lesions

* Areas other than the face and nose are not included in assessment

Enrollment of subjects with mild acne (IGA Grade 2) at each site will be restricted to no more than 20% of total enrollment at that site; management of this requirement will be handled by the IWRS.

7.6.2 Lesion Counts of the Face

Non-inflammatory lesions (closed comedones and open comedones), inflammatory lesions (papules and pustules), and nodulocystic lesions (nodules and cysts) on the face (above the mandibular line), including the nose, will be counted and recorded separately at each visit from Screening/Baseline through Week 12. Non-inflammatory lesions of acne are the open (blackheads) or closed (whiteheads) comedones. Closed comedones may be more difficult to detect visually and may require stretching of the skin to aid in visualization. Inflammatory lesions are divided into papules, pustules, and nodules/nodulocystic lesions, depending on the severity and location of the inflammation within the dermis. Nodulocystic lesions will be counted separately from inflammatory lesions of papules and pustules. The papules and pustules have surrounding halos of erythema allowing for their characterization as inflammatory. Nodules are typically erythematous and often tender and/or painful. Additionally, they are deep-seated in the skin (i.e., centered in the dermis or subcutis). Nodules have been defined as being greater than 5 mm in diameter. The borders of these lesions may be difficult to determine because of the associated erythema/inflammation. The investigator/evaluator should use standard, good lighting to visualize lesions and a systematic counting procedure to ensure consistent and accurate counts.

7.6.3 Subject's Global Assessment (SGA) of the Face

The SGA of the facial skin will be conducted by the subjects at Baseline, Weeks 4, 8, and 12 using a standardized scale shown in the table below:

Table 5: SGA Scale for Facial Acne Vulgaris*

Grade	Description
0	My face is basically free of acne, with only an occasional blackhead and/or whitehead
1	My face has several blackheads and/or whiteheads and small pimples, but there are no tender deep-seated bumps or cysts
2	My face has several to many blackheads and/or whiteheads and small to medium-sized pimples, and may have one deep-seated bump or cyst
3	My face has many blackheads and/or whiteheads, many medium- to large-sized pimples, and perhaps a few deep-seated bumps or cysts
4	My face has blackheads and/or whiteheads, and several to many medium- to large-sized pimples, and deep-seated bumps or cysts dominate
* Areas other than the face and nose are not included in assessment	

7.6.4 Lesion Counts of the Chest and/or Back (including shoulders)

Non-inflammatory lesions (closed comedones and open comedones), inflammatory lesions (papules and pustules), and nodulocystic lesions (nodules and cysts) on the chest and/or back including shoulders (if applicable) will be counted and recorded separately at each visit from Baseline through Week 12. Nodulocystic lesions will be counted separately from inflammatory lesions of papules and pustules. The back area is from most prominent cervical spinous process superiorly to the superior aspect of iliac crest inferiorly and the shoulder area will also be included. The chest area is from the manubrium of the sternum superiorly to the xiphiod process inferiorly. The lesion types are as described above. The investigator/evaluator should use standard, good lighting to visualize lesions and a systematic counting procedure to ensure consistent and accurate counts.

7.6.5 DLQI

The DLQI is a quality of life instrument that has ten questions addressing symptoms and feelings (Questions 1 and 2), daily activities (Questions 3 and 4), leisure (Questions 5 and 6), work and school (Question 7), personal relationships (Questions 8 and 9), and treatment (Question 10). Each is rated from 0 to 3, such that the maximum score is 30. The higher the score, the more quality of life is impaired. The usual clinical interpretation of the total score is as follows:

0 to 1 = no effect at all on subject's life
2 to 5 = small effect on subject's life
6 to 10 = moderate effect on subject's life
11 to 20 = very large effect on subject's life
21 to 30 = extremely large effect on subject's life

The adult and children's versions of the DLQI are provided in Appendix 2 and Appendix 3, respectively.

7.6.6 Cardiff Acne Disability Index (CADI)

The CADI is a short 5 item questionnaire that will be conducted by all subjects at Baseline, Week 4, 8, and 12. The questionnaire rapidly assesses the disability caused by the acne. It consists of 5 questions. The scoring for each question is done from 0 to 3 (a=3, b=2, c=1, d=0). The CADI score is calculated by summing the score of each question resulting in a possible maximum of 15 and a minimum of 0. The higher the score, the more the quality of life is impaired.

The CADI questionnaire is provided in Appendix 4.

7.7 Safety Assessments

Safety assessments include vital signs, local cutaneous tolerance evaluation of the treated skin, and AEs. Vital signs (blood pressure and pulse) will be collected at each visit. A physical examination will be performed at Baseline (Day 1). Urine pregnancy tests for all female subjects (regardless of childbearing potential) will be conducted at Screening and Baseline (Day 1) and at each subsequent visit. Adverse events will be collected by spontaneous reports from subjects (either verbal or recorded in the subject diary), by directed questioning of subjects, and by observation (see Section 8 for details about AEs). Adverse events, whether believed by the investigator to be related or unrelated to treatment, will be recorded on the eCRF.

At Visits 2 through 5 the investigator will assess local cutaneous tolerance by examining treated areas for clinically significant non-lesional erythema, peeling, and dryness that will be graded as shown below (Table 6, Table 7, Table 8) and recorded on the eCRF. Assessments will be recorded separately for the face and (if applicable) chest and/or back (including shoulders). The investigator will also ask the subject if any stinging (Table 9), burning (Table 10), or itching (Table 11) has occurred on the face (chest and/or back (including shoulders), if applicable since the last visit (for Visit 2 in the last 2 weeks). Visit 2 assessments are made prior to first application. An AE should be recorded if the severity is worse than at Baseline. In addition, overall cutaneous tolerance should be graded at the Week 12 visit, or the last visit if earlier, using the grading shown in Table 12. The local cutaneous tolerance signs and symptoms will be assessed separately for the face and chest and/or back (including shoulders) using the same scales below.

Table 6: Scoring of Non-Lesional Erythema

Severity	Score	Description
None	0	No erythema
Mild	1	Light pinkness present
Moderate	2	Definite redness, easily recognized
Severe	3	Intense redness

Table 7: Scoring of Peeling

Severity	Score	Description
None	0	No peeling
Mild	1	Barely perceptible shedding, noticeable only on light scratching or rubbing
Moderate	2	Obvious but not profuse shedding
Severe	3	Heavy scale production

Table 8: Scoring of Dryness

Severity	Score	Description
None	0	No dryness
Mild	1	Slight barely perceptible fine superficial scale
Moderate	2	Clearly perceptible fine scale giving skin a powdery appearance
Severe	3	Marked roughness, cracked skin with fissures

Table 9: Scoring of Stinging

Severity	Score	Description
None	0	No stinging
Mild	1	Slight sharp, tingling/stinging sensation; not really bothersome
Moderate	2	Definite sharp, tingling/stinging sensation; that is somewhat bothersome
Severe	3	Sharp, tingling/stinging sensation that has caused definite discomfort

Table 10: Scoring of Burning

Severity	Score	Description
None	0	No burning
Mild	1	Slight warm, burning sensation; not really bothersome
Moderate	2	Definite warm, burning sensation; that is somewhat bothersome
Severe	3	Hot, burning sensation that has caused definite discomfort

Table 11: Scoring of Itching

Severity	Score	Description
None	0	No itching
Mild	1	Slight itching; not really bothersome
Moderate	2	Definite itching that is somewhat bothersome, without loss of sleep
Severe	3	Intense itching that has caused pronounced discomfort; night rest interrupted and excoriation of the skin from scratching may be present

Table 12: Overall Tolerance

Grades	Score	Description
Excellent	0	No signs of irritation during the study
Good	1	Slight signs of irritation during the study, which resolved by the end of the study
Fair	2	Signs of irritation throughout the study
Poor	3	Subject discontinued due to irritation
Irritation is defined as any sign or symptom of intolerance.		

7.8 Early Withdrawal of Subjects

1. Subjects should be withdrawn from the study if they no longer wish to participate, are being uncooperative, or if the investigator feels that it is in the best interest of the subject to withdraw.
2. Subjects with protocol deviations or for whom it is discovered should have been excluded should not be withdrawn unless there is a safety concern. The protocol deviation should be recorded in the subject's chart and Protocol Deviation Form and included in the study report.
3. Subjects who experience an AE resulting in or requiring discontinuation of study product use should be encouraged to be followed in the study until the AE is resolved or stabilized.
4. Subjects whose treatment randomization is unblinded at the study site should be withdrawn.
5. If a female subject becomes pregnant during the study, study product will be discontinued immediately and she will be followed through the pregnancy and delivery. Details of the pregnancy, delivery and health of the infant should be recorded on the Pregnancy Report Form and the sponsor notified immediately.
6. At the time of study discontinuation, the investigator will record the reason for early withdrawal, date of last study product application, date of last visit or contact, collect AE data, and, if possible, perform all Week 12 visit-specific evaluations. Every attempt should be made to contact subjects who are lost-to-follow-up for a final safety assessment. At least three attempts must be documented in the subject's chart including the use of at least 1 certified letter. Any contact, either direct or indirect, should be made with the purpose to document the final status of the subject with regard to safety.

7. Subjects who withdraw early will not be replaced.

7.9 Modification of Protocol

No amendments to this protocol can be made without consultation with and agreement of the sponsor, the FDA, and IRB. Amendments must be made in writing. Modifications needed for the safety of subjects will be made immediately with notifications made as soon as possible.

7.10 Early Termination of Study

If it is determined by the sponsor or investigators that the study presents an unreasonable and significant risk to subjects, the study will be terminated as soon as possible, and in no event later than 5 working days following the determination that the study should be discontinued. The IRB and FDA must be notified as soon as possible about early termination of the study due to safety concerns.

7.11 Study Schedule

A Study Schedule chart can be found as Table 1. There are approximately 5 study visits: Screening (Visit 1), Baseline (Visit 2, Day 1), Week 4 (Visit 3), Week 8 (Visit 4), and Week 12 (Visit 5). The visit window is ± 3 days for Week 4 and ± 5 days for Weeks 8 and 12. Visit 1 and Visit 2 should not be separated by more than 60 days.

The Screening Visit (Visit 1) and the Baseline Visit (Visit 2) may be combined into a single visit if no washout is required. In that case, complete the required procedures for each visit as listed below.

7.11.1 Visit 1 - Screening Visit

1. Obtain written assent and/or informed consent prior to initiating any study procedures. Provide subject with signed copy of 'information and assent'/consent form. Document assent and/or informed consent in the subject's study record.
2. List subject on Screening/Enrollment Log and obtain subject number via IWRS. Subject numbers consist of the 3-digit site number followed by sequential 3-digit numbers usually starting with 001 (e.g., 206001, 206002, 206003). All subjects including screen failures will also be assigned a subject number.
3. Perform a urine pregnancy test on all female subjects.
4. Collect demographic data – date of birth, sex, race, and ethnicity.
5. Review and record medical history, acne history (including naïve vs previous therapy, acne treatment received 12 months prior to screening, onset date for acne and first acne treatment, previous use of Tazorac and any issue with Tazorac use), and concomitant medications, therapies, and procedures. Medical history and acne history should be collected for the prior 1-year period and concomitant medications, therapies, and procedures collected from the prior 6-month period. Only ongoing medical history items and ongoing concomitant medications should be entered on the eCRF. Acne history will be collected and recorded in the eCRF.

6. Assess severity of acne using IGA (record on source only). IGA assessments should always be done prior to lesion counts.
7. Conduct inflammatory and non-inflammatory lesion counts of the face (record on source only).
8. Collect vital signs (blood pressure and pulse) (record on source only).
9. Screen subject according to the study inclusion/exclusion criteria to determine tentative eligibility.
10. Initiate any protocol-required washout, if applicable.
11. Schedule Visit 2.
12. Complete eCRF for randomized subjects. For every screen failure subject, record the subject number, date of visit, date of consent, reason for screen failure, and study status (screen failure) in the eCRF.

7.11.2 Visit 2 - Day 1, Baseline Visit

If no washout is required, Screening and Baseline may occur on the same day.

1. Update the medical history and concomitant medications. Any medical event (not related to a protocol intervention) that occurred since 'information and assent'/informed consent form was signed should be recorded as medical history. Only ongoing medical conditions and ongoing concomitant medications should be entered on the eCRF.
2. Collect AEs. Any new medical event or need for medication caused by a protocol procedure performed at the Screening Visit should be considered an AE except for worsening of acne.
3. Confirm eligibility according to inclusion/exclusion criteria.
4. Conduct urine pregnancy test on all female subjects. Record method of contraception, as applicable, on source only.
5. Perform a physical examination.
6. Collect vital signs (blood pressure and pulse), height and weight, and record Fitzpatrick skin type.
7. Conduct clinical assessments:
    a. IGA for the face (Table 4). IGA assessments should always be done prior to lesion counts.
    b. Count inflammatory and non-inflammatory lesions on face and, if applicable, on chest and/or back (including shoulders). These counts should be recorded separately for the face and, if applicable, chest and/or back (including shoulders).
    c. Local cutaneous safety evaluation for dryness, non-lesional erythema, and peeling. The investigator should also ask the subject if any burning, stinging, or itching has occurred on the face in the last 14 days. These evaluations should be recorded separately for the face and, if applicable, chest and/or back (including shoulders).

8. Have the subject perform the SGA for the face (Table 5).
9. Perform photography of the face on consenting subjects at selected sites.
10. Administer the DLQI or Children's DLQI.
11. Administer the CADI questionnaire.
12. Randomize subject by using IWRS.
13. Weigh and then dispense 2 bottles of study product to subjects who will apply to the face only, or 4 bottles to subjects who will apply to the face and chest and/or back (including shoulders). The tear-off panel is to be affixed to the source document and filed in subject's chart. Instruct subject on study product use. Review the Subject Instructions with subject.
14. When the subject performs the first application of study product at the site, ensure that it is done correctly.
15. Remind subject to bring all bottles of study product to next visit.
16. Dispense and review use of diary. Remind subject to report missed applications and/or potential AEs as well as any medication used in the diary and to bring diary to each visit.
17. Schedule next visit.
18. Complete eCRF for randomized subjects. For every screen failure subject, record the subject number, date of visit, date of consent, reason for screen failure, and study status (screen failure) in the eCRF.

7.11.3 Visit 3 – Week 4/Day 28 (Visit Window ± 3 Days)

1. Evaluate treatment and protocol compliance and record any deviations. This includes a review of the diary card for number of applications and missed applications.
2. Conduct clinical assessments:
    a. IGA for the face (Table 4). IGA assessments should always be done prior to lesion counts.
    b. Count inflammatory and non-inflammatory lesions on face and, if applicable, on chest and/or back (including shoulders). These counts should be recorded separately for the face and, if applicable, chest and/or back (including shoulders).
    c. Local cutaneous safety evaluation for dryness, non-lesional erythema, and peeling. The investigator should also ask the subject if any burning, stinging, or itching has occurred on the face since the last visit. These evaluations should be recorded separately for the face and, if applicable, chest and/or back (including shoulders).
3. Have the subject perform the SGA for the face (Table 5).
4. Perform photography of the face on consenting subjects at selected sites.
5. Administer the DLQI or Children's DLQI.
6. Administer the CADI questionnaire.
7. Collect vital signs (blood pressure and pulse).

8. Conduct a urine pregnancy test for all females.
9. Collect AE data. This includes a review of the diary card for potential AEs.
10. Update concomitant medications data.
11. Dispense diary and review instructions. Remind subject to bring all bottles of study product to each visit.
12. If subject requires more study product, weigh and then dispense study product as needed from IWRS assignment and collect empty or nearly empty bottles. Weigh bottles when they are collected and prior to re-dispensing. Re-dispense partially filled bottles.
13. Schedule next visit.
14. Complete eCRF.

7.11.4 Visit 4 - Week 8/Day 56 (Visit Window ± 5 Days)

1. Evaluate treatment and protocol compliance and record any deviations. This includes a review of the diary card for number of applications and missed applications.
2. Conduct clinical assessments:
   a. IGA for the face (Table 4). IGA assessments should always be done prior to lesion counts.
   b. Count inflammatory and non-inflammatory lesions on face and, if applicable, on chest and/or back (including shoulders). These counts should be recorded separately for the face and, if applicable, chest and/or back (including shoulders).
   c. Local cutaneous safety evaluation for dryness, non-lesional erythema, and peeling. The investigator should also ask the subject if any burning, stinging, or itching has occurred on the face since the last visit. These evaluations should be recorded separately for the face and, if applicable, chest and/or back (including shoulders).
3. Have the subject perform the SGA for the face (Table 5).
4. Perform photography of the face on consenting subjects at selected sites.
5. Administer the DLQI or Children's DLQI.
6. Administer the CADI questionnaire.
7. Collect vital signs (blood pressure and pulse).
8. Conduct a urine pregnancy test for all female subjects.
9. Collect AE data. This includes a review of the diary card for potential AEs.
10. Update concomitant medications data.
11. Dispense diary and review instructions. Remind subject to bring all bottles of study product to each visit.

12. If subject requires more study product, weigh and then dispense study product as needed from IWRS assignment and collect empty or nearly empty bottles. Weigh bottles when they are collected and prior to re-dispensing. Re-dispense partially filled bottles.
13. Schedule next visit.
14. Complete eCRF.

7.11.5 Visit 5 – Week 12/Day 84/ End of Treatment (Visit Window ± 5 Days)

1. Evaluate treatment and protocol compliance and record any deviations. This includes a review of the diary card for number of applications and missed applications.
2. Conduct clinical assessments:
    a. IGA for face (Table 4). IGA assessments should always be done prior to lesion counts.
    b. Count inflammatory and non-inflammatory lesions on face and, if applicable, on chest and/or back (including shoulders). These counts should be recorded separately for the face and, if applicable, chest and/or back (including shoulders).
    c. Local cutaneous safety evaluation for dryness, non-lesional erythema, and peeling. The investigator should also ask the subject if any burning, stinging, or itching has occurred on the face since the last visit. These evaluations should be recorded separately for the face and, if applicable, chest and/or back (including shoulders).
3. Have the subject perform the SGA for the face (Table 5).
4. Perform photography of the face on consenting subjects at selected sites.
5. Administer the DLQI or Children's DLQI.
6. Administer the CADI questionnaire.
7. Collect vital signs (blood pressure, pulse).
8. Collect AE data. This includes a review of the diary card for potential AEs.
9. Update concomitant medications data.
10. Conduct a urine pregnancy test for all female subjects.
11. Collect study diary.
12. Collect and weigh all study product bottles.
13. Complete eCRF.

7.11.6 Unscheduled Visit (If Applicable)

Conduct the following, as needed.

1. Evaluate treatment and protocol compliance and record any deviations.
2. Collect vital signs (blood pressure and pulse).
3. Collect AE data. This includes a review of the diary card for potential AEs.
4. Update concomitant medications data.

5. Weigh and then dispense study product, as needed, according to IWRS assignment.
6. Conduct a urine pregnancy test for all females.
7. Complete eCRF.

8 ADVERSE EVENTS

Adverse events will be collected by spontaneous reports from subjects, either verbal or recorded in the subject diary, by directed questioning of subjects, and by observation.

The most common frequently reported adverse reactions during clinical trials with tazarotene cream 0.1% for the treatment of acne were desquamation, dry skin, erythema, and burning sensation, occurring in 10% to 30% of subjects. Adverse reactions occurring in 1% to 5% of treated subjects included pruritus, irritation, face pain, and stinging.

The investigator is to pay special attention at each visit to any signs of clinically significant dryness, non-lesional erythema, and peeling and report as an AE subsequent to the Baseline Visit if worse than at Baseline.

An AE is any untoward medical occurrence in a subject participating in a clinical trial. The event does not necessarily have to have a causal relationship with the study product. An AE can therefore be any sign, symptom, or disease, or any worsening of an existing sign, symptom, or disease, whether or not considered related to the study product or trial procedures, including injuries.

Any medical condition that is present at the time of Screening or Baseline should be considered as medical history and reported on the medical history eCRF and should not be reported as an AE except for AEs observed at the Baseline Visit due to study procedures performed at the Screening visit, which should be reported. Anticipated day-to-day fluctuations of pre-existing conditions should not be reported as AEs. Unexpected worsening of pre-existing conditions should be reported as AEs. The disease or condition being studied or expected progression, signs, or symptoms of the disease or condition being studied such as worsening of acne should not be reported as an AE unless it is more severe than expected, results in discontinuation from the study or requires alternative therapy.

All serious adverse events (SAEs), all study product-related events, and all AEs leading to study product discontinuation must be followed until the clinical outcome is determined or until all attempts to determine resolution of the event are exhausted (not recovered is not an acceptable outcome for acute conditions). For other AEs, the status at the last visit can be entered into the eCRF.

8.1 Adverse Event Reporting Period

Adverse event data must be collected from the time treatment is initiated until study product treatment is discontinued except for spontaneously reported SAEs, which should be reported up to 30 days after discontinuing study product use and entered into the eCRF. Adverse events

occurring from the time of the Screening Visit until the Baseline Visit associated with study procedures should also be reported for all subjects, including screen failures.

8.2 Recording Adverse Events

The investigator will record all AEs, regardless of relationship to study product on the AE eCRF. Standard medical terminology should be used when describing AEs. Whenever possible a diagnosis should be made and recorded on the eCRF rather than listing signs and symptoms. Intermittent AEs can be recorded once. The anatomical location of the AE must be specified when applicable. The following information should be recorded on the eCRF:

1. Description, including whether on treated area or not
2. Start date
3. Stop date or date of death, ongoing, or unknown
4. Severity of the event (see Section 8.3.1 Severity for details)
5. Study product use continued or not
6. Outcome of the event (recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, unknown, fatal)
7. Relationship to study product (see Section 8.3.2 Relationship to Study Product [Causality] for details)
8. Indication of whether the event is serious (see Section 8.3.3 Seriousness for details)
9. Actions taken including treatment with concomitant medication

Vital Signs Variables

Vital signs (except at Visits 1 & 2) should be reported as AEs if they are considered to be clinically significant, as per the Investigator's judgment.

8.3 Assessment of Adverse Events

8.3.1 Severity

It is the investigator's responsibility to assess the severity of each AE. Descriptions of severity are as follows:

1. Mild: Awareness of sign or symptom, but easily tolerated. Not likely to interfere with normal activity or require medical attention.
2. Moderate: Discomfort enough to cause interference with usual activity. May require medical intervention.

3. Severe: Incapacitating such that normal activity is prevented. Likely requires medical intervention and/or close follow-up.

8.3.2 Relationship to Study Product (Causality)

It is the investigator's responsibility to assess the relationship between the study product and the AE. The degree of "relatedness" of the AE to the study product should be described using the following categories:

1. Not Related: The event is clearly due to extraneous causes (e.g., diseases, environment, etc.). Specify if known. Or, the event is most probably produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant therapy and does not follow a known response pattern to the study product.

2. Possibly Related: The event is temporally related to study product use but can be explained by another etiology. Information on the effect of study product withdrawal may be lacking.

3. Probably Related: The event is temporally related to study product use and is consistent with known effects of the study product and/or improves upon withdrawal of the study product.

4. Definitely Related: The event follows a reasonable temporal sequence from the time of study product administration and/or follows a known response pattern to the study product, and could not have been produced by other factors such as the subject's clinical state, therapeutic intervention, or concomitant therapy, and either occurs immediately following study product administration or improves on stopping the product, or there is a positive reaction at the application site.

8.3.3 Seriousness

It is the investigator's responsibility to determine the "seriousness" of an AE. A serious adverse event (SAE) is any AE occurring at any dose that results in any of the following outcomes:

1. Death
2. Life-threatening (subject at immediate risk of death)
3. Inpatient hospitalization or prolongation of hospitalization
4. Results in persistent or significant disability/incapacity
5. Results in congenital anomaly/birth defect

Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.4 Reporting Serious Adverse Events

SAE information must be faxed or emailed within 24 hours of becoming aware of the event. The minimum *initial* information required to be reported on the Serious Adverse Event Form is: the subject number, subject initials, the event, the causality, the date of the event, and the name of the person reporting the event. This initial report should be promptly followed up with a *completed* Serious Adverse Event Form.

Serious Adverse Events: Shahida Hasan, MD, MS
Associate Director
Clinical Pharmacovigilance, NA
Fax: 908-450-1510
Email: SAE@drreddys.com

The initial information must include a causality assessment that is provided by the primary investigator or other medically qualified individual. The causality assessment can be amended as more information is available. Significant new information about ongoing SAEs should be reported promptly to the sponsor.

Serious adverse events will be evaluated by the medical monitor within 24 hours of receipt and plans for management and further reporting (i.e., FDA) determined.

It is the responsibility of the CRO, Symbio LLC, to promptly notify the IRB and other Investigators involved in this study about serious and unexpected SAEs for which there is a reasonable possibility of their being related to the investigational product.

Follow-up of Serious Adverse Events

All follow-up reports will be subject to the same reporting timelines as the Initial Reports. Within 24 hours of receipt of new information, the updated follow-up SAE form, along with any supporting documentation (e.g., patient discharge summary or autopsy reports), should be faxed or emailed to the Sponsor.

8.5 Discontinuation Due to an Adverse Event

The sponsor must be notified within 5 days if any subject is withdrawn or discontinues study product use due to an AE if the event is related to the study product (see title page for contact information).

8.6 Exposure *in utero* (Pregnancy)

If a female subject becomes pregnant during the study, study product must be discontinued immediately and she must be followed through the pregnancy and delivery. The investigator should report the event to the sponsor immediately (see contact information on title page) and complete the Pregnancy Report Form. The expected date of delivery or expected date of the end of the pregnancy should be included in this information. The investigator is instructed to contact the subject every 3 months until the end of her pregnancy and report the outcome to the sponsor. Details of the pregnancy, delivery and health of the infant should be recorded on the Pregnancy Report Form.

The following outcomes of pregnancy fall under the criteria for SAEs and should be reported as such: delivery complications prolonging hospitalization, spontaneous abortion, stillbirth, death of newborn baby, congenital anomaly, and anomaly in a miscarried fetus.

9 DATA HANDLING AND RECORD KEEPING

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act. This regulation requires a signed authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use/disclosure of their PHI.
- Expiration of authorization

If a subject revokes authorization to collect and use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of authorization. For subjects who have revoked authorization to collect and use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Investigators must keep accurate separate records (other than eCRFs) of all subject visits that include all pertinent study-related information, including original signed/dated informed consent/ information and assent forms. Source documents for this study include all written records of study data. All study data must have a paper source document, including investigator assessments.

9.3 Screening/Enrollment Log

A subject Screening/Enrollment Log, noting reasons for screen failure where applicable, must be maintained for all subjects who are consented. The log should also include subject initials, screening date, subject number, and date of enrollment, which is when ICF is signed, where applicable.

9.4 Case Report Forms

Database set-up will be performed by Symbio in collaboration with the electronic data capture (EDC) vendor, using an appropriate fully validated, 21 CFR Part 11 compliant EDC system. eCRFs will be provided to each site via a secured web link. All applicable study data collected on each subject will be recorded by approved site personnel into the eCRF. Only authorized site personnel will be able to enter/modify/correct data to the eCRF.

Approved staff at Symbio will verify all data entered into eCRFs for completeness and accuracy with reference to the source documents and records and will issue manual data queries to correct missing data or discrepancies found against the source within the EDC system.

Data validation will consist of automated and manual edit checks that are created directly into the EDC. Automated edit checks will be executed on all data points defined and documented by the study team and data management. Study metrics will be reported from the EDC system. After all data have been verified by approved staff at Symbio, an investigator or sub-investigator (listed on Form FDA 1572) is required to review and approve all eCRFs prior to database lock and breaking of the blind.

After database lock, each site will receive the eCRF data for their site in an electronic format for local archival purposes.

Quality assurance verification via a 10% database audit of eCRF data will be conducted before database lock and before the treatment assignment code is broken.

9.5 Archiving of Study Documentation

The investigator must retain study records for 2 years following the date a marketing application is approved for the investigational product; or, if the application is not filed or is not approved, until 2 years after the investigation is discontinued and the FDA is notified.

The sponsor will inform the investigator, in writing, as to when these documents no longer need to be maintained.

All study documents, original source documents, correspondence, IRB documents, etc. are subject to sponsor and FDA inspection at any time.

10 MONITORING AND DATA QUALITY ASSURANCE

Only persons who are appropriately trained and who have the scientific and clinical knowledge to adequately monitor the study will be selected for monitoring this study. The monitor must have at least 1 year of previous experience in monitoring clinical studies. The monitor should be familiar with the etiology and signs and symptoms of acne and the treatment options that are currently available.

Before study initiation, the investigator and site personnel will receive protocol training from the sponsor's representatives to ensure collection of accurate, consistent, complete, and reliable data. This training will take place either at a web-based Investigator Meeting or individually on-site.

During the course of the study, a monitor will make multiple site visits to check the progress of the study, review consent forms, review protocol compliance, assess drug accountability, and ensure that the study is being conducted according to the protocol and GCP. Any review of the subjects' original medical records will be performed in a manner to ensure that subject confidentiality is maintained. The investigator will ensure that the monitor or other compliance auditor is given access to all study-related documents and has adequate time and space to conduct the monitoring visit including availability of the investigator and site personnel to discuss findings.

Data capture methods will be designed to ensure accurate transfer of data to electronic media.

The sponsor's Quality Assurance representative may conduct QA audits randomly or if needed at 5% to 10% of the investigator sites.

11 STATISTICAL CONSIDERATIONS

All statistical processing will be performed using SAS® unless otherwise stated. Two-sided hypothesis testing will be conducted for all inferential analyses using a significance level of 0.05. Efficacy analyses performed using the intent-to-treat (ITT) population will be considered primary. Efficacy analyses performed using the per-protocol (PP) population will be considered supportive. Safety analyses will be performed on the safety population (all subjects who receive study product and provide any post-baseline safety information). Study populations are defined in Section 11.2.

A Statistical Analysis Plan, describing all statistical analyses, will be provided as a separate document prior to database lock and unblinding of the study treatments.

11.1 Sample Size

The sample size was estimated based on the primary study endpoints and statistics available from the Summary Basis of Approval for Tazorac® (tazarotene) Gel (NDA 20-600). The total sample size of 550 will provide an overall power of at least 90% based on a 2-tailed alpha of 0.05.

Approximately 550 subjects (275 for each treatment arm) will be randomized and about 25 to 35 sites will participate in the study.

Table 13: Assumptions for Sample Size Calculation

Endpoint	Statistics	DFD-03	Vehicle
Absolute change from Baseline to Week 12 in number of inflammatory lesions	Mean (SD)	10.06 (9.45)	6.32 (11.23)
Absolute change from Baseline to Week 12 in number of non-inflammatory lesions	Mean (SD)	29.12 (27.64)	17.18 (25.4)
Proportion of subjects with a clinical response of "success" at Week 12	%	27%	15%

Table 14: Estimated Sample Size

Endpoint	Number of ITT subjects (DFD-03: Vehicle)	Power of showing superiority
Inflammatory Lesions	(275:275)	At least 98%
Non-inflammatory Lesions	(275:275)	At least 99%
Clinical response of "success"	(275:275)	At least 93%
		Power of showing study success: At least 90%

Sample sizes estimated based on a two-tailed alpha of 0.05 using nQuery Advisor.

11.2 Analysis Data Sets

11.2.1 Intent-to-Treat

The ITT population will be the primary efficacy analysis data set and consists of all subjects who are randomized and dispensed study medication.

11.2.2 Per-Protocol

The PP population will include all subjects in the ITT population who complete the Week 12 evaluation without any major protocol violations (i.e., any subject or investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy).

Specifically, the PP population will include subjects in the ITT population who meet all of the following criteria:

1. Subject met all inclusion/exclusion criteria.
2. Subject did not take any prohibited concomitant medications during the evaluation period. The concomitant medication usage will be reviewed during the population determination review, remaining blinded to treatment designation, to determine prohibited medication usage that warrants exclusion from the PP population if they met the entrance criteria without any protocol violations. This review will take into consideration the timing, duration of treatment with the concomitant medication, and influence on the efficacy and safety assessments prior to deeming a prohibited concomitant medication as a protocol violation that warrants exclusion from PP.
3. Completed the Week 12 visit within the allowed window.
4. Subject was compliant with the dosing regimen. A subject will be considered compliant if the subject applied at least 80% but no more than 120% of the expected applications (168 applications expected) during the entire evaluation period.

Subjects who prematurely discontinue from the study due to documented lack of efficacy, worsening condition, or a treatment-related AE will be included in the PP population.

Other additional criteria may be added to the list to accommodate for unforeseen events that occurred during the conduct of the trial that result in noteworthy study protocol violations. These criteria will be documented with appropriate signature at the time subject populations are finalized, prior to database lock.

11.2.3 Safety Population

All subjects who receive at least one confirmed dose of study product and provide any post-baseline safety information will be included in the safety population. No imputation will be made for missing safety data.

11.3 Demographic and Baseline Data

Subject demographic and baseline characteristics will be summarized descriptively by treatment group for the ITT, Safety, and PP populations.

11.4 Efficacy Analyses

Efficacy summaries will be provided for both the ITT and PP populations.

11.4.1 Primary Efficacy Analysis

The three co-primary efficacy endpoints will be analyzed as follows on the ITT population:

- IGA success at Week 12 (an IGA score of 0 (Clear) or 1 (almost clear) with at least a 2-grade reduction from baseline) – will be analyzed using the Cochran-Mantel-Haenszel (CMH) test for general association with treatment, stratified by site/analysis center and baseline IGA. Homogeneity of treatment effect across sites / analysis centers will be assessed at the 0.15 significance level using the Breslow-Day test.
- Change in inflammatory lesion counts on the face from baseline to Week 12 – will be analyzed using a two-way analysis of covariance (ANCOVA) model with factors of treatment group, site/analysis center, treatment*center interaction, baseline IGA and a covariate of baseline inflammatory lesion count.
- Change in non-inflammatory lesion counts on the face from baseline to Week 12 – will be analyzed using the same ANCOVA model as for the inflammatory lesion counts (with covariate of baseline non-inflammatory lesion count instead of inflammatory).

In the above analyses, any significant Breslow-Day or treatment*center interactions ($P<0.15$) will be examined, and if outlier centers are identified, the analysis may be repeated, excluding those centers.

To claim success of the study, the analysis of all three co-primary endpoints must show DFD-03 Lotion significantly superior to the vehicle lotion (at the 5% level, 2-sided). No multiplicity adjustments will be applied.

11.4.2 Primary Sensitivity Analysis

To assess the sensitivity of the above primary methods to missing data, analysis will also be conducted for the ITT population with missing values being imputed by the following two methods:

1) The last-observation-carried-forward (LOCF) approach: Where a co-primary endpoint (IGA, inflammatory and non-inflammatory lesion counts) has missing Week 12 value, the most recent value available for that endpoint will be imputed in its place.
2) Multiple imputation (MI) approach with the Markov Chain Monte Carlo (MCMC) method: The variables to be imputed will be the three co-primary efficacy endpoints (IGA and the inflammatory and non-inflammatory lesion counts) at all visits. The MI regression model (used to create the imputations) will include the following factors: treatment, age, gender,

baseline inflammatory lesion counts, baseline non-inflammatory lesion counts, and the results of the same variable from previous visits. A first-stage MI with MCMC will be performed using SAS PROC MI (seed=14805) to produce a single imputed dataset with a monotone missingness pattern. Subsequently, a second-stage MI will be performed (seed=26174) using the logistic regression method to produce 5 imputed datasets with all visit values filled in. The primary analysis described above will then be performed on each of the 5 imputed datasets (for each of the 3 primary endpoints), which will produce estimates of treatment difference (DFD-03 minus vehicle; in the case of IGA success, it will be the estimate of difference in logodds and will be back-transformed to odds ratio and corresponding CI at the end) and the standard error of that estimate. Finally, the set of estimates and standard errors will be analyzed by PROC MIANALYZE to produce overall estimates, confidence intervals, and P-values for the treatment effect.

11.4.3 Secondary Efficacy Analysis

The secondary endpoints are:

1. Percent change from Baseline to Week 12 in inflammatory lesion counts on the face
2. Percent change from Baseline to Week 12 in non-inflammatory lesion counts on the face

The secondary endpoints will be analyzed as follows:

The percent change from Baseline to Week 12 in inflammatory and non-inflammatory lesion counts on the face will be analyzed using a two-way analysis of covariance (ANCOVA) model with factors of treatment group, site/analysis center, and baseline IGA and a covariate of baseline lesion count.

To control for overall Type I error rate for testing multiple secondary endpoints, statistical analysis for the secondary endpoints will be performed if $p<0.05$ has been achieved for all the co-primary endpoints, using a sequential approach according to the following order: percent change in inflammatory lesion counts on the face, and then percent change in non-inflammatory lesion counts on the face. In details, if $p<0.05$ is achieved for a higher ranking secondary variable, then success will be declared for the variable, and statistical comparisons will be performed for the lower ranking variable. If $p<0.05$ is not achieved for a higher ranking variable, then statistical comparisons will be considered descriptive (non-inferential) for this variable and for the lower ranking secondary variable.

11.4.4 Other Efficacy Analyses

Descriptive statistics will be presented for the ITT population for the following efficacy endpoints

1) Time to 50% reduction in total lesion counts on the face

2) Absolute change from Baseline in inflammatory, non-inflammatory and total lesion counts on the face at Weeks 4 and 8
3) Percent change from Baseline in inflammatory, non-inflammatory, and total lesion counts on the face at Weeks 4 and 8.
4) Proportion of subjects with an IGA score of 0 or 1 with at least a 2-grade reduction (for the face) from Baseline at Weeks 4 and 8.
5) Change from Baseline in Children's DLQI total score in subjects 16 years of age or younger at Weeks 4, 8 and 12.
6) Change from Baseline in DLQI score in subjects >16 years of age at Weeks 4, 8 and 12.
7) Percent change from Baseline in inflammatory, non-inflammatory and total lesion counts on the chest and/or back including shoulders (in relevant subjects) at Weeks 4, 8, and 12.
8) Time to 50% reduction in total lesion counts on the chest and/or back (including shoulders).
9) Proportion of subjects with at least a 2-grade improvement from Baseline in the SGA at Week 12.
10) Change from Baseline in CADI score at Weeks 4, 8 and 12.

Sample size, frequency counts and percentages will be used to summarize categorical endpoints. Sample size, mean, median, standard deviation, minimum, and maximum will be used to summarize continuous endpoints. Sample size, median, and frequency and percent of censored subjects will be used to summarize time-to-event variables.

11.4.5 Secondary Sensitivity Analyses

To assess the potential impact of protocol violations, analysis of the primary and secondary efficacy endpoints described above will be repeated on the PP population.

For the PP population, number of subjects who are discontinued prematurely due to documented lack of efficacy, worsening condition, or a treatment-related AE is expected to be small. For these subjects the efficacy data from their termination visit will be assigned to the nearest corresponding scheduled visit that has been missed, and carried forward to the subsequent visits for the analysis.

11.4.6 Pooling Analyses

For the purpose of analysis, a small site is defined as a site with < 4 ITT subjects in either treatment arm. Small sites will be ranked in descending order based on the total number of ITT subjects of the sites. The first small site will be pooled with the next small site, or with more sites if needed, until the pooled site/analysis center has at least 4 ITT subjects in both the arms. The algorithm will continue down the list, and if the last few small sites are pooled but fail to be adequately large, they will be combined with the previously pooled smallest site/analysis center.

11.5 Safety Analyses

11.5.1 Extent of Exposure

The extent of exposure to study product on the face in each treatment group will be summarized as the total number of applications and number and percentage of subjects who are compliant

for the Baseline to Week 12 evaluation period. A subject will be considered compliant with the dosing regimen if the subject has applied at least 80% but no more than 120% of the expected applications for the respective evaluation period. The total number of applications will be taken from the subject diaries. The number and percentage of subjects who use study product for less than 28 days, 28 to 56 days, 57 to 84 days and more than 84 days will be summarized.

11.5.2 Local Cutaneous Safety Evaluation

Non-lesional erythema, peeling, dryness, burning, stinging, and itching scores will be summarized by treatment group and visit including sample size, frequency count and percentage for each visit. A similar summary will be provided excluding subjects with signs or symptoms present at Baseline.

11.5.3 Adverse Events

All AEs occurring during the study will be recorded and classified on the basis of Medical Dictionary for Regulatory Activities (MedDRA) terminology. Treatment-emergent adverse events (TEAEs) are AEs with an onset on or after the date of the first study product administration. For the safety population, all reported TEAEs will be summarized by treatment group, the number and percent of subjects reporting events, system organ class (SOC), preferred term (PT), severity, relationship to study product, and seriousness. When summarizing TEAEs by causality and severity, each subject will be counted only once within a system organ class or a preferred term by using the event with the greatest relationship and highest severity within each classification.

Additionally, treatment-related TEAEs will be summarized for each treatment group by SOC and PT, and further by severity. A TEAE will be considered treatment-related if it is reported as possibly, probably, or definitely related to study treatment.

SAEs will be listed by subject. In addition, a list of subjects who prematurely discontinued from the study due to an AE will be provided.

All information pertaining to AEs noted during the study will be listed by subject, detailing verbatim term given by the investigator, preferred term, system organ class, onset date, resolution date, maximum severity, seriousness, action taken regarding study product, corrective treatment, outcome, and drug relatedness. The event onset will also be shown relative (in number of days) to date of first administration.

AEs related to study procedures done before study product administration will be provided in a data listing.

11.5.4 Vital signs

Changes from Baseline in vital signs (blood pressure and pulse) will be summarized by treatment group at each evaluation visit using descriptive statistics.

11.5.5 Safety Laboratory Values

Urine pregnancy tests will be performed at all visits, and results will be provided in a data listing.

11.6 Analysis of Drug Concentrations

None

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Shalita A, Berson D, Thiboutot D, Leyden J, Parizadeh D, Sefton J, Walker P, Gibson J. Effects of tazarotene 0.01% cream in the treatment of facial acne vulgaris: pooled results from two multicenter, double-blind, randomized, vehicle-controlled, parallel-group trials. Clin Ther 2004;26(11):1865-1873.

Tazorac (tazarotene) Cream, 0.05%/0.1%. Prescribing Information. Allergan, 2013.

APPENDIX 1: DECLARATION OF HELSINKI (2013)

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

A. PREAMBLE

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.
   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.
2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

B. GENERAL PRINCIPLES

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the international Code of Medical Ethics declares that "A physician shall act in the patient's best interest when providing medical care."
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimizes possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy

volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

C. RISK, BURDENS AND BENEFITS

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

D. VULNERABLE GROUPS AND INDIVIDUALS

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.
20. Medical Research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

E. SCIENTIFIC REQUIREMENTS AND RESEARCH PROTOCOLS

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

F. RESEARCH ETHICS COMMITTEES

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

G. PRIVACY AND CONFIDENTIALITY

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

H. INFORMED CONSENT

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed. All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such

representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

I. USE OF PLACEBO

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    a. Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    b. Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of no receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option.

J. POST-TRIAL PROVISIONS

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

K. RESEARCH REGISTRATION AND PUBLICATION AND DISSEMINATION OF RESULTS

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

October 2013

APPENDIX 2: DLQI

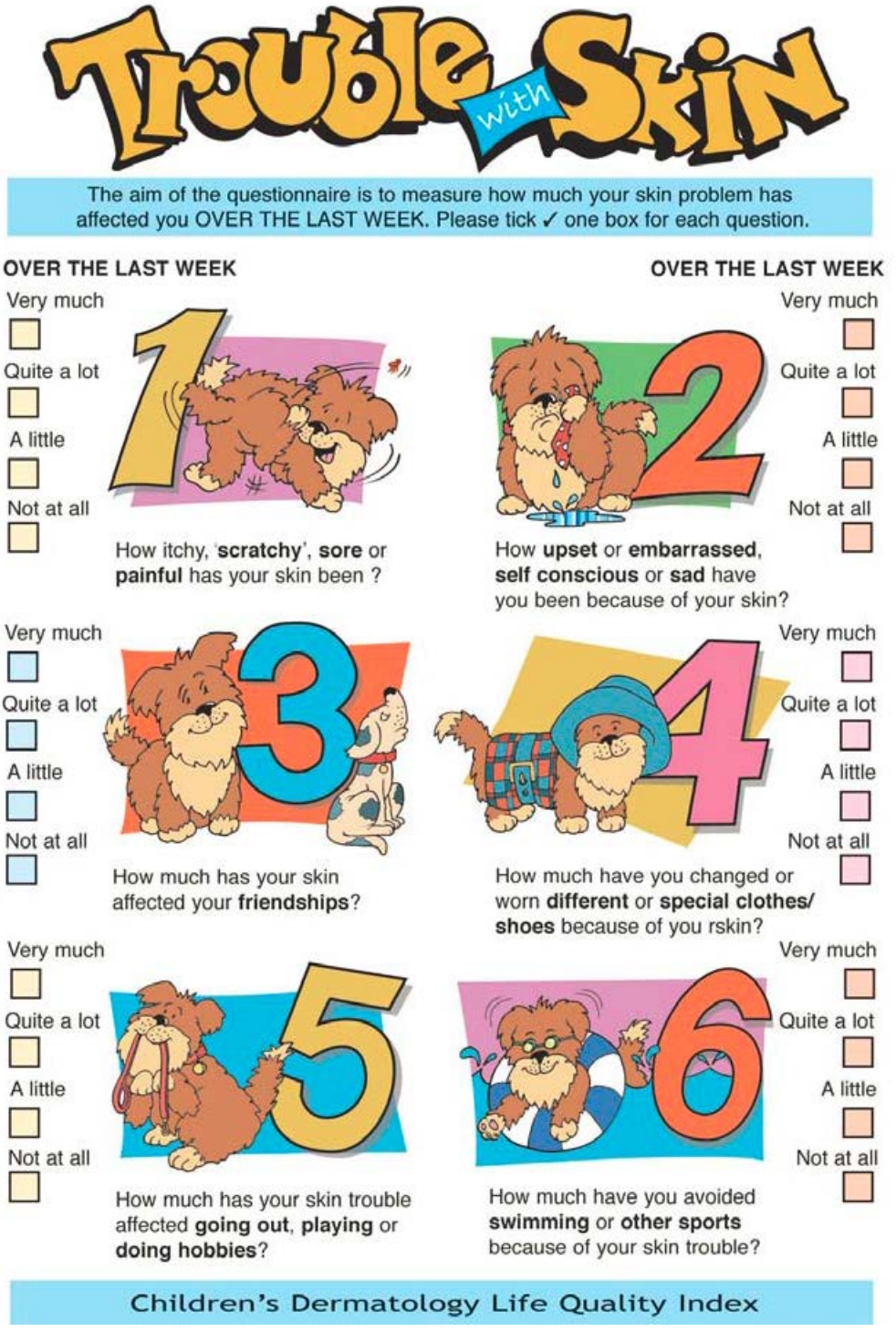
The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all Not relevant	❒ ❒ ❒ ❒ ❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all Not relevant	❒ ❒ ❒ ❒ ❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all Not relevant	❒ ❒ ❒ ❒ ❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all Not relevant	❒ ❒ ❒ ❒ ❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No Not relevant	❒ ❒ ❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒

8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all Not relevant	❒ ❒ ❒ ❒ ❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all Not relevant	❒ ❒ ❒ ❒ ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all Not relevant	❒ ❒ ❒ ❒ ❒

Please check you have answered EVERY question. Thank you.

APPENDIX 3: CHILDREN'S DLQI



OVER THE LAST WEEK

EITHER

Very much ☐
Quite a lot ☐
A little ☐
Not at all ☐

If school time: How much did your skin affect your **school work**?

OR

If holiday time: How has your skin problem interfered with your **holiday plans**?

OVER THE LAST WEEK

Very much ☐
Quite a lot ☐
A little ☐
Not at all ☐

How much trouble have you had because of your skin with other people **calling you names**, **teasing**, **bullying**, **asking questions** or **avoiding you**?

OVER THE LAST WEEK

Very much ☐
Quite a lot ☐
A little ☐
Not at all ☐

How much has your **sleep** been affected by your skin problem ?

Hospital No.:
Name :
Age:
Address:

Diagnosis:

Date:

CDLQI SCORE:

Very much ☐
Quite a lot ☐
A little ☐
Not at all ☐

How much of a problem has the **treatment** for your skin been ?

Please check that you have answered EVERY question. Thank you.

APPENDIX 4: THE CARDIFF ACNE DISABILITY INDEX

1. As a result of having acne, during the last month have you been aggressive, frustrated or embarrassed?	☐ ☐ ☐ ☐	(a) Very much indeed (b) A lot (c) A little (d) Not at all
2. Do you think that having acne during the last month interfered with your daily social life, social events or relationships with members of the opposite sex?	☐ ☐ ☐ ☐	(a) Severely, affecting all activities (b) Moderately, in most activities (c) Occasionally or in only some activities (d) Not at all
3. During the last month have you avoided public changing facilities or wearing swimming costumes because of your acne?	☐ ☐ ☐ ☐	(a) All of the time (b) Most of the time (c) Occasionally (d) Not at all
4. How would you describe your feelings about the appearance of your skin over the last month?	☐ ☐ ☐ ☐	(a) Very depressed and miserable (b) Usually concerned (c) Occasionally concerned (d) Not bothered
5. Please indicate how bad you think your acne is now:	☐ ☐ ☐ ☐	(a) The worst it could possibly be (b) A major problem (c) A minor problem (d) Not a problem