CLINICAL STUDY PROTOCOL

A Randomized, Open-Label, Multiple Dose, Bioavailability Study of DFD-03 (Tazarotene Lotion, 0.1 %) Dosed Twice Daily Compared to Once Daily Tazorac® (tazarotene) Cream, 0.1% in Patients with Moderate Acne Vulgaris

Protocol Number: DFD-03-CD-007 **Version:** 3.0
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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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PROTOCOL APPROVAL

Protocol Number: DFD-03-CD-007

Title: A Randomized, Open-Label, Multiple Dose, Bioavailability Study of DFD-03 (Tazarotene Lotion, 0.1 %) Dosed Twice Daily Compared to Once Daily Tazorac® (tazarotene) Cream, 0.1% in Patients with Moderate Acne Vulgaris

We the undersigned declare that we have reviewed the protocol and approve it on behalf of Dr. Reddy's Laboratories Limited.

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SYNOPSIS

Title:

A Randomized, Open-Label, Multiple Dose, Bioavailability Study of DFD-03 (Tazarotene Lotion, 0.1%) Dosed Twice Daily Compared to Once Daily Tazorac® (tazarotene) Cream, 0.1% in Patients with Moderate Acne Vulgaris

Sponsor:	Dr. Reddy's Laboratories, Ltd 8-2-337, Road No. 3 Banjara Hills Hyderabad – 500034, Telangana, India
Study Centers: 2 sites	**Number of Subjects:** Approximately 62
Study Period: 21 days	Clinical Phase: Phase 2

Objectives:

The primary objective is to evaluate the comparative bioavailability of tazarotene and tazarotenic acid after twice-daily application of DFD-03 Lotion (Test product) versus once-daily application of Tazorac Cream (Reference product) for 21 days in subjects with moderate acne vulgaris.

The secondary objectives are

a) Assessment of disease severity at baseline and at the pharmacokinetic (PK) sampling days for each treatment.

b) To determine the safety and tolerability of each treatment.

Methods:

This will be a multicenter, randomized, multiple-dose, laboratory-blinded, open-label, 2-arm, parallel-arm study in subjects with moderate acne vulgaris.

Approximately 62 subjects will be randomized to receive either Test or Reference product, stratified by age (Adult subjects: 17 years or older; Pediatric subjects: 9 years to 16 years 11 months for the Test product and 12 years to 16 years 11 months for the Reference product) with approximately even distribution between males- and females in each age-strata. The study will be conducted in two parts, Part A and Part B in a sequential manner. Based on full PK profiles generated for adult subjects in Part A, the sparse PK sampling design in pediatric population has been established in Part B.

Part B (age 9 years to 16 years 11 months for DFD-03 Lotion arm and age 12 years to 16 years 11 months for Tazorac Cream arm) will enroll up to 38 subjects, which will include at least 6 subjects 9 to 11years of age, and among those at least 2 subjects between 9 and 10 years of age. Target enrollment is 32 subjects, but up to 6 additional subjects may be enrolled to reach a minimum of 16 evaluable subjects, who have sparse samples collected on Day 14 and Day 21, randomized to the Test treatment.

PK profiling will be performed on Day 14 and on Day 21. Day 14 is selected as the earliest time point at which the steady state is expected to be achieved in subjects with moderate acne vulgaris, before any significant improvement in skin barrier occurs.

In Part A, 24 adult subjects will be enrolled such that 12 subjects each will be assigned to receive either Test or Reference treatment. In Part B, up to 38 subjects will be enrolled where approximately 26 subjects will receive Test treatment and 12 subjects will receive Reference treatment. Enrollment will continue until at least 16 evaluable subjects randomized to the Test treatment in Part B complete the study.

For 21 days, study product will be applied on the face, neck, upper chest, shoulders and upper back region, not exceeding 15% of the body surface area. The Test product will be applied twice daily, 12 hours apart (morning and evening; 42 consecutive doses) and the Reference product will be applied once daily in the evening (21 consecutive doses).

Subjects will visit the clinical site daily prior to each dose application. Subjects will be confined at the clinic prior to the evening dose on Day 1, allowing sufficient time for all pre-dosing assessments to be performed, until after that dose, from Day 14 evening to Day 15 evening, and from Day 21 evening to Day 22 evening for dose application and/or PK sampling. The subjects will leave the clinic after completion of clinical activities. On Days 14 and 21, blood sampling for PK estimation will be performed over an interval of 24 hours. Adequate trough samples will be collected at the evening visit on Days 1 to assess baseline and on days12, 13, 14, 19, 20 and 21 to assess attainment of steady state. For the pediatric population in part B, the trough samples will not be collected on days 12, 13, 19 and 20. Any subject missing dosing of any one dose of Reference product and two consecutive doses of Test product between days 1 and 8, or between days 8 and 15 will be considered for steady state estimation at Day 14, or Day 21, respectively. Subject (s) missing either two consecutive dosing days (two doses for reference and four for test product) between day 1 and 8 or missing two non-consecutive dosing days between Day 2 and Day 11 will be assessed for steady-state estimation at Day 21. Subjects missing dosing between Days 12 and 14 and between Days 19 and 21 will not be considered for steady-state estimation or PK and statistical analysis.

For all dosing days (except confinement days), subjects will come to the clinical site ±1 hour of each dose application (e.g., around 7:00 pm and 7:00 am) for twice-daily application of Test product and (e.g. around 7:00 pm) for once daily application of Reference product. Subjects will leave the clinical site after completion of the scheduled activities. On Day 1, subjects will report to the clinical site prior to the first (evening) dose and on Day 14 and Day 21, subjects will report to the clinical site before the evening dose application allowing sufficient time for all pre-dosing assessments to be performed.

Blood samples for PK estimation will be collected at scheduled intervals over a period of 24 hours after the evening dose application for Test and Reference treatments on Day 14 and Day 21. On Day 22, for assessment of leave on exposure for 12 hours, the last dose application of Test product (morning dose on Day 22) will not be rinsed off.

Based on the full PK profile of Test and Reference treatments in Part A, the sparse sampling schedule for pediatric subjects in Part B has been decided (Table 3).

Number of Subjects:

Approximately 62 subjects across 2 study sites will be enrolled.

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. Male or female at least 9 years of age for the DFD-03 (Test) group and at least 12 years of age for the Tazorac Cream (Reference) group.
4. Female subjects must be having their menstrual period at Baseline (Day 1, as reported by the subject), except for subjects using hormonal contraceptives that preclude menstrual periods, if the subject is premenarcheal, 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 3 (moderate) at Baseline (Day 1).
6. Subjects should have acne lesions on at least 1 of the following regions at the Screening visit: neck, upper chest, upper back (including shoulders).
    - This criterion is not applicable to the 9-11 years and 11 months age group.
7. Inflammatory lesion count (papules and pustules) of at least 20 on the face, including the nose, at Baseline (Day 1).
    - This criterion is not applicable to the 9-11 years and 11 months age group.
8. Non-inflammatory lesion count (closed and open comedones) of at least 25 on the face, including the nose, at Baseline (Day 1).
    - This criterion is not applicable to the 9-11 years and 11 months age group.
9. No more than 2 nodulocystic lesions on the face, including the nose, at Baseline (Day 1).
10. Females, regardless of childbearing potential:
    a. Must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline (Day 1). Urine pregnancy 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 (Day 1); or partner has had a vasectomy at least 90 days prior to Baseline (Day 1); 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 (Day 1) 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 if 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.

11. 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.
12. 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 direct sunlight exposure time, and have no tanning bed use or use of other UV light sources during participation in the study.
13. 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).

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 (other 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 Baseline (Day 1), 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 Baseline (Day 1).
    c. Systemic retinoid use (including high-dose vitamin A > 10,000 units per day) in the 180 days prior to Baseline (Day 1).
    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 (Day 1). 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 Baseline (Day 1).

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, excessive hair on the neck, upper chest, shoulders and upper back region 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 Baseline (Day 1).
8. Subjects who have been in another investigational trial within 30 days of Baseline (Day 1).
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.
10. HIV Ag/Ab Combo, Hepatitis B (HBsAg (B)) and Hepatitis C (anti-HCV (C)) positive subjects

Investigational Product, Dose and Mode of Administration:

Test Product: DFD-03 (Tazarotene Lotion, 0.1 %), Manufacturer: Dr. Reddy's Labs. Ltd India

The Test product will be applied twice daily, 12 hours apart (± 1 hour) (morning and evening), for 21 days (42 consecutive doses). Before each dose application in the evening and morning, subjects will take a brief warm shower to wet their skin. Approximately 5 grams of the product will be applied by the subject to the face, neck, and upper chest and will be applied by a member of the clinical staff to the shoulders and upper back, and rubbed into the skin until foamy (approximately 30 seconds for the total application area). After being left on for about 1 minute, the subject will rinse off the Test product in the shower for about 1 minute. On Day 22, the last dose application in morning will not be rinsed off in the shower; the subject will be permitted to towel dry after the Test product has been on for approximately one minute. Twelve hours

following the last application, the subject will rinse off the Test product in the shower for 1 minute. The subject should bare their exposed body parts when the product is rinsed off and the clinical staff should ensure that no residues are left on the body.

Note: For age group 9-11 years 11 months, approximately 4 grams of test product will be applied considering their lesser BSA.

On each dosing day (except confinement days) the subject will come to the clinic ±1 hour of scheduled dose application and leave the facility after completion of clinical activities.

Reference Product, Dose and Mode of Administration:

Reference Product: Tazorac (tazarotene) Cream, 0.1%, Manufacturer: Allergan, Inc., USA

The Reference product will be applied to dry skin once daily in evening for 21 consecutive days. There should be a 24 hour interval between applications (± 1 hour). Approximately 5 grams of the product will be applied by the subject to the face, neck, and upper chest and will be applied by a member of the clinical staff to the shoulders and upper back. The applied cream will be left on for 12 hours and showering will not be permitted until at least 12 hours after the application.

Duration of Treatment and Study:

Study products will be applied daily for 21 days (twice daily for the Test product and once daily for the Reference product). The total study duration including the screening period will be approximately 6 weeks.

Housing: Subjects will be confined to clinic as per the following schedule:

Day 1: From prior to the first (evening) dose application of Test or Reference treatment at the Baseline visit, allowing sufficient time for all pre-dosing assessments to be performed, until after the evening dose application for assessing baseline disease severity, blood sampling, and dosing

Days 14-15: From prior to the Day 14 evening dose application of Test or Reference treatment, allowing sufficient time for all pre-dosing assessments to be performed, until after collection of the 24-hour PK sample, disease severity assessment, and the Day 15 evening dose application. For pediatric population in Part B of the study, the PK samples will be collected as per Table 3.

Days 21-22: From prior to the evening dose application of Test or Reference treatment, allowing sufficient time for all pre-dosing assessments to be performed, until after collection of the 24-hour PK sample on Day 22 and following disease severity assessment after the last dose application (evening dose application on Day 21 for Reference treatment or morning dose application on Day 22 for Test treatment). For pediatric population in Part B of the study, the PK samples will be collected as per Table 3.

Wash-out: None; parallel design

Bioanalysis: Tazarotene and tazarotenic acid plasma concentrations will be measured by a validated bioanalytical LC-MS/MS method.

Criteria for Evaluation:

Pharmacokinetics:

The absorption and disposition parameters will be determined using a noncompartmental approach, trapezoidal rule will be used to estimate the area under the curve. The PK parameters of interest for this study will be:

Day 14 and Day 21: $T_{max(ss)}$, $C_{max(ss)}$, $AUC_{0-12(ss)}$, $AUC_{0-24(ss)}$, $C_{min(ss)}$.

For Part B of study, plasma concentration data generated from sparse samples (maximum of 4 time points from each subject) on Day 14 and Day 21 will be used for calculation of PK parameters: $C_{max(ss)}$, $AUC_{(ss)}$, $C_{min(ss)}$.

Disease severity: Disease severity will be assessed by the Investigator's Global Assessment (IGA) score. Inflammatory and non-inflammatory lesion count (% change from baseline for both parameters) will also be done.

Safety:

Safety assessments will include adverse events (AEs), the investigator's assessment of application site reactions (dryness, non-lesional erythema, peeling, stinging, burning, and itching), clinical safety laboratory evaluations (chemistry, hematology, and urinalysis), and physical examination including vital signs (blood pressure and pulse rate).

Statistics:

Statistical analysis of all PK parameters will be based on analysis of variance (ANOVA) model. Two-sided 90% confidence intervals of the ratio of geometric least squares (LS) means will be presented from the natural log (ln)-transformed PK parameters ($C_{max(ss)}$, $AUC_{(ss)}$, $C_{min(ss)}$) for Test vs Reference on Day 14 and Day 21.

Achievement of steady state will be performed by treatment, using log-transformed $C_{min(ss)}$ (at Days 12, 13 and 14 and Days 19, 20 and 21) in a mixed effect model through repeated-measure ANOVA or through other appropriate statistical method.

Disease severity will be assessed between baseline and sampling days by paired t-test or other appropriate statistical test and will be presented by treatment.

Descriptive statistics will be presented for safety parameters.

Table 1: Overall Study Procedure and Schedule of Assessments

Procedure or Assessment	Screening Visit	Treatment Application (21 Days)									
	(Day -21 to Day -1)	Baseline Visit (Day 1)	2 to 6	7	8 to 11	12 to 13	14	15 to 19	20	21	22
Informed consent/assent	X										
Inclusion and exclusion criteria	X	X									
Medical history / prior medications	X	X[1]									
Randomization		X									
Demographics	X										
Study drug administration[2]		X	X	X	X	X	X	X	X	X	X[2]
Confinement[3]		X					X			X	
IGA assessment[4]	X	X						X		X	X[4]
Lesion count[5]	X	X						X		X	X[5]
Serology (HIV Ag/Ab Combo, Hepatitis B (HBsAg (B)) and Hepatitis C (anti-HCV (C), Serum Pregnancy Test.	X										
Urine pregnancy test[6]		X		X			X			X	
Drug screen (urine)	X	X		X			X			X	
Alcohol breath test	X	X		X		X	X	X (Day 19)	X	X	
Physical examination	X	X								X	
Height	X										
Weight	X	X									
Vital signs[7]	X	X	X	X	X	X	X[7]	X	X	X[7]	X[7]
12-Lead ECG	X	X								X	
Clinical safety blood sample	X	X								X	

Table 1 Continued: Overall Study Procedure and Schedule of Assessments

Procedure or Assessment	Screening Visit	Treatment Application (21 Days)									
	(Day -21 to Day -1)	Baseline Visit (Day 1)	2to 6	7	8 to 11	12 to 13	14	15 to 19	20	21	22
PK blood samples[8]		X				X[8]	X	X[8]	X	X	X
Disease Severity Assessment [9]		X						X		X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Assess for local cutaneous adverse reactions[10]		X	X	X	X	X	X	X	X	X	X
Adverse events[11]	X	X	X	X	X	X	X	X	X	X	X
End of study											X

1. Update medical history/prior medication
2. Test product: Twice daily morning and evening (12 hours apart, ± 1 hour), Reference product: Once daily in evening (24 hours apart, ± 1 hour).
3. All subjects will be confined at the clinical site on PK sample collection Day 14 and Day 21 (after evening dose application). On Day 15, the subjects will leave clinic after completion of evening dose application for Test Product and Reference product. On Day 22 subjects will leave clinic after collection of 24-hr blood sample. Test product last dose will be applied on Day 22 morning.
4. Evaluation by IGA score at Screening, prior to the evening dose application for Test and Reference treatment on Day 1, before evening dose application on Day 15 for Test and Reference treatments, and before evening dose application on Day 21 for Reference and before morning dose application on Day 22 for Test treatment.
5. Lesion count will be performed before evening dose application on Day 1 and Day 15 for Test, and Reference treatments and after evening dose application on Day 21 for Reference and morning dose application on Day 22 for Test treatment.
6. For females of childbearing potential on Day 7, Day 14 and Day 21.
7. Sitting blood pressure, pulse rate at pre-dose and at 1 and 8 hours after evening dose application with an allowable window of ±15 minutes on Day 14 and Day 21. On non-confinement days, sitting vital sign measurements will be done pre-evening dose (within 15 minutes of dosing) and within 1 hour after evening dose application.
8. Blood sampling for pharmacokinetics will be done at pre-specified time points (for Part A) and sparse sampling for Part B, as described in Table 2 and Table 3, respectively. Allowable sampling window is ± 15 minutes for each timepoint.
9. Disease severity assessment will be performed by Investigator's Global Assessment (IGA) score and lesion counts at baseline and at PK Sampling days.
10. Before each dose application, the investigator or designated trained site staff will visually inspect the skin and grade erythema and scaling/peeling. After each dose application (within 1 hour of dosing), the investigator or designated trained site staff will assess application site reactions of non-lesional erythema, peeling, dryness and ask the subject if any stinging, burning, or itching has occurred.

11. Adverse events will be collected from signing of the Informed Consent at Screening through end of the study and any adverse events spontaneously reported by subjects for a period of 30 days following the last blood sample of the study.

Table 2: Schedule of Blood Sample Collection for Pharmacokinetic Analysis

Day	Part A (Adults: 17 years or older)		Part B (Pediatrics)	
	Test Treatment	**Reference Treatment**	**Test Treatment (9 years to 16 years 11 months)**	**Reference Treatment (12 years to 16 years 11 months)**
1	Prior to evening dose	Prior to evening dose	Prior to evening dose	Prior to evening dose
12	Prior to evening dose	Prior to evening dose		
13	Prior to evening dose	Prior to evening dose		
14-15	Prior to evening dose and serial sampling at 1, 2, 4, 6, 8, 12, 14, 16, 18, and 24 hours post 1st evening dose application.	Prior to evening dose and serial samples at 1, 2, 4, 6, 8, 12, 14, 16, 18 and 24 hours post dose application.	Sparse[1] samples) as per sampling design in Table 3	Sparse[1] samples as per sampling design in Table 3.
19	Prior to evening dose	Prior to evening dose		
20	Prior to evening dose	Prior to evening dose		

21-22	Prior to evening dose and serial sampling at 1, 2, 4, 6, 8, 12, 14, 16, 18, and 24 hours after evening dose application.	Prior to evening dose and serial samples at 1, 2, 4, 6, 8, 12, 14, 16, 18 and 24 hours post dose application.	Sparse[1] sampling as per sampling design in Table 3	Sparse[1] sampling as per sampling design in Table 3

1 The sparse blood sampling schedule for Part B (pediatrics) has been decided after generation of PK profiles in adults in Part A. The schedule consists of two sets: Set 1 with sampling time points of 0, 2, and 8 hours and Set 2 with sampling time points of 4, 12, 18, and 24 hours. Half of the subjects will follow Set 1 and other half will follow Set 2 and this assignment will be in a serial order based on the sequence of randomization for test and reference treatments across the sites. The assignment of sets will cross over between the Day 14 and Day 21, such that each subject will provide a total of 8 PK samples including Day 1 pre-dose as presented in the table below.

Table 3: Sparse Blood Sample Collection for Pharmacokinetic Analysis

Sparse sampling schedule	Day 1	Time Points in Hours (Post evening dose: Day 14 and Day 21)							
		Day 14-15				Day 21-22			
Set 1	0 (Pre-dose)	0 (Pre-dose)	2	8		4	12	18	24
Set 2	0 (Pre-dose)	4	12	18	24	0 (Pre-dose)		2	8

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LIST OF ABBREVIATIONS

Abbreviations	Description
AE	adverse event
ANOVA	analysis of variance
βhCG	human chorionic gonadotropin
BP	blood pressure
CFR	Code of Federal Regulations
CRF	case report form
CRO	contract research organization
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IGA	Investigator's Global Assessment
IRB	institutional review board
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic(s)
PT	preferred term
SAE	serious adverse event
SOC	system organ class
TEAE	treatment-emergent adverse event

LIST OF DEFINITIONS

Term	Definition
Screening Visit	The day a subject is screened according to the protocol inclusion/exclusion criteria and screening procedures after having provided informed consent/assent.
Screened Subject	A subject who has signed informed consent/assent.
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).
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 compare the bioavailability of tazarotene and tazarotenic acid after twice-daily application of DFD-03 Lotion with that after once-daily application of Tazorac Cream, with products applied for 21 days.

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

2 ETHICAL CONSIDERATIONS

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.

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 if they are qualified to perform the task.

3 STUDY OBJECTIVES

The primary objective of this study is to evaluate the comparative bioavailability of tazarotene and tazarotenic acid after twice-daily application of DFD-03 Lotion (Test product) versus once-daily application of Tazorac Cream (Reference product) for 21 days in Patients with moderate acne vulgaris.

The secondary objectives are

a) Assessment of disease severity at baseline and at the pharmacokinetic (PK) sampling days for each treatment.

b) To determine the safety and tolerability of each treatment.

4 STUDY DESIGN

This will be a randomized, multiple-dose, laboratory-blinded, open-label, 2-arm, parallel-arm, multicenter study in subjects with moderate acne vulgaris.

Approximately 62 subjects will be randomized to receive either Test or Reference product, stratified by age (adult subjects:17 years or older; pediatric subjects: 9 years to 16 years 11 months for the Test product and 12 years to 16 years 11 months for the Reference product) with approximately even distribution between males and females in each age stratum. The study will be conducted in two parts, Part A and Part B in a sequential manner. Based on full PK profiles generated for adult subjects in Part A, the sparse PK sampling design in pediatric subjects has been established in Part B. Part B (age 9 years to 16 years 11 months for DFD-03 and 12 years to 16 years 11 months for Reference) will enroll up to 38 subjects, which will include at least 6 subjects 9 to 11years of age, and among those at least 2 subjects between 9 and 10 years of age. Target enrollment is 32 subjects, but up to 6 additional subjects may be enrolled to reach a minimum of 16 evaluable subjects, who have sparse samples collected on Day 14 and Day 21, randomized to the Test treatment.

PK profiling will be performed on Day 14 and on Day 21. Day 14 is selected as the earliest time point at which the steady state is expected to be achieved in subjects with moderate acne vulgaris, before any significant improvement in skin barrier occurs.

In Part A, 24 adult subjects will be enrolled such that 12 subjects each will be assigned to receive either Test or Reference treatment. In Part B, up to 38 subjects will be enrolled where approximately 26 subjects will receive Test treatment and 12 subjects will receive Reference treatment. Enrollment will continue until at least 16 evaluable subjects randomized to the Test treatment complete the study.

For 21 days, study product will be applied on the face, neck, upper chest, shoulders and upper back region, not exceeding 15% of the body surface area. The Test product will be applied twice daily, 12 hours apart (morning and evening; 42 consecutive doses), and the Reference product will be applied once daily in the evening (21 consecutive doses).

Subjects will visit the clinical site daily prior to each dose application. Subjects will be confined at the clinic on Day 1 from prior to the evening dose until after that dose, from prior to the evening dose on Day 14 to after the evening dose on Day, and from prior to the evening dose on Day 21 to after the 24-hour post dose PK sample collection on Day 22. Subjects will leave the clinic after completion of clinical activities. On Days 14 and 21, blood sampling for PK estimation will be performed over an interval of 24 hours. Adequate trough samples will be collected at the evening visit on Day 1 to assess baseline and on days 12, 13, 14, 19, 20 and 21 to assess attainment of steady state. For the pediatric population in part B, the trough samples will not be collected on days 12, 13, 19 and 20. Any subject missing dosing of any one dose of Reference product and two consecutive doses of Test product between days 1 and 8, or between days 8 and 15 will be considered for steady state estimation at Day 14, or Day 21, respectively. Subject (s) missing either two consecutive dosing days (two doses for reference and four for test product) between day 1 and 8 or missing two non-consecutive dosing days between Day 2 and Day 11 will be assessed for steady-state estimation at Day 21. Subjects missing dosing between Days 12 and 14 and between Days 19 and 21 will not be considered for steady-state estimation or PK and statistical analysis.

For all dosing days (except confinement days), subjects will come to the clinical site ±1 hour of each dose application (e.g., around 7:00 pm and 7:00 am) for twice-daily application of Test product and (e.g. around 7:00 pm) for once-daily application of Reference product. Subjects will leave the clinical site after completion of the scheduled activities. On Day 14 and Day 21, subjects will report to the clinical site before scheduled dosing, allowing sufficient time for all pre-dosing assessments to be performed.

Blood samples for PK estimation will be collected (within time window ± 15 minutes) at scheduled intervals over a period of 24 hours after the evening dose application for Test product and Reference product on Day 14 and Day 21. On Day 22, for assessment of leave on exposure for 12 hours, the last dose application of Test product (morning dose on Day 22) will not be rinsed off.

Plasma samples for analysis of tazarotene and tazarotenic acid plasma concentrations will be collected on the schedule described in Table 2. The PK parameters of interest will be $T_{max(ss)}$, $C_{max(ss)}$, $AUC_{(ss)}$, $C_{min(ss)}$.

For Part B of study, plasma concentration data generated from sparse samples (maximum of 4 time points from each subject, Table 3) on Day 14 and Day 21 will be used for calculation of PK parameters: $C_{max(ss)}$, $AUC_{(ss)}$, $C_{min(ss)}$.

Disease severity will be assessed by IGA score and inflammatory and non-inflammatory lesion count (% change from baseline for lesion counts) at Day 15 and Day 21/Day22.

Safety assessments will include adverse events (AEs), the investigator's assessment of application site reactions (dryness, non-lesional erythema, peeling, stinging, burning, and itching), clinical safety laboratory evaluations (chemistry, hematology, and urinalysis), and physical examination including vital signs (blood pressure and pulse rate).

5 SELECTION OF STUDY POPULATION

5.1 Number of Subjects

Approximately 62 subjects across 2 study sites will be enrolled.

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. Male or female at least 9 years of age for the DFD-03 (Test) group and at least 12 years of age for the Tazorac Cream (Reference) group.
4. Female subjects must be having their menstrual period at Baseline (Day 1, as reported by the subject), except for subjects using hormonal contraceptives that preclude menstrual periods, if the subject is premenarcheal, 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 3 (moderate) at Baseline (Day 1).
6. Subjects should have acne lesions on at least 1 of the following regions at the Screening visit: neck, upper chest, upper back(including shoulders).
   - This criterion is not applicable to the 9-11 years and 11 months age group.
7. Inflammatory lesion count (papules and pustules) of at least 20 on the face, including the nose, at Baseline visit (Day 1).
   - This criterion is not applicable to the 9-11 years and 11 months age group.
8. Non-inflammatory lesion count (closed and open comedones) of at least 25 on the face, including the nose, at Baseline (Day1).
   - This criterion is not applicable to the 9-11 years and 11 months age group.
9. No more than 2 nodulocystic lesions on the face, including the nose, at Baseline (Day 1).
10. Females, regardless of childbearing potential:
    a. Must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline (Day 1). Urine pregnancy test must have a sensitivity of at least 25 mIU/mL for beta human chorionic gonadotropin (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 (Day 1); or partner has had a vasectomy at least 90 days prior to Baseline (Day 1); 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 (Day 1) 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 if 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.
11. 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.

12. 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 direct sunlight exposure time, and have no tanning bed use or use of other UV light sources during participation in the study.
13. 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).

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 (other 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 Baseline (Day 1), 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 Baseline (Day 1).
    c. Systemic retinoid use (including high-dose vitamin A > 10,000 units per day) in the 180 days prior to Baseline (Day 1).
    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 (Day 1). 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 Baseline (Day 1).
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, excessive hair on the neck, upper chest, shoulders and upper back region 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 Baseline (Day 1).
8. Subjects who have been in another investigational trial within 30 days of Baseline (Day 1).
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.
10. HIV Ag/Ab Combo, Hepatitis B (HBsAg (B)) and Hepatitis C (anti-HCV (C)) positive subjects.

Subjects must not use the medications or procedures shown in Table 4 for the period specified before Baseline (Day 1). Table 4 also indicates whether the medications or procedures are allowed or prohibited during the study (after Day 1).

Table 4: Restriction Periods (Prior to Day -1)

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. Tazorac (tazarotene) Cream, 0.1%
   (60 g tube, Allergan, Inc., USA)

The study products will be provided by Dr. Reddy's Laboratories Ltd.

6.1.2 Labels and Packing

Bottles will be packed individually. Labels on the bottles will be in English and Spanish and include the protocol number, a unique bottle number, site number and PI name, 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 clinical site staff must be maintained at the study site.

6.1.4 Dispensing

All applications of study product will be performed at the clinical site. Clinical site staff will dispense bottles of Test product or tubes of Reference cream as assigned to the subject.

At the end of the trial, all used and unused bottles and tubes must be held at the clinic for eventual destruction by the sponsor or designee.

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).

6.1.6 Storage of Retention Samples

At the conclusion of the study, samples of study product will be stored at the investigational sites (or other Sponsor-approved storage facility) per FDA Guidance for Handling and Storage of Retention of BA and BE Testing Samples, which states that a sufficient number of samples for five times of release testing should be stored across the study sites.

6.2 Treatment Regimen

For all dosing days (except confinement days), subjects will come to the clinical site ±1 hour of each dose application (e.g., around 7:00 pm and 7:00 am) for twice-daily application of Test product and (e.g. around 7:00 pm) for once-daily application of Reference product. Subjects will leave the clinical site after completion of the scheduled activities. On Day 1, subjects will come to the clinical site prior to the evening dose application (the first study treatment) and on Day 14 and Day 21 subjects will come to the clinical site before scheduled dosing allowing sufficient time for all pre-dosing assessments to be performed. The daily application time should be set based on the time of Day 1 application and should be followed for all applications through Day 22.

For each treatment arm, approximately 5 grams of Test or Reference product will be applied by the subject to the face, neck, and upper chest and will be applied by a member of the clinical staff to the shoulders and upper back (with the total area not exceeding 15% of the body surface area) over 21 consecutive days (Days 1 to 21). The study product should be applied to all affected areas [face, neck, upper chest, and/or upper back (including shoulders)] avoiding contact with the eyes, eyelids, and mouth. Subjects will be asked to refrain from applying emollients (moisturizers, creams) to the application areas at least an hour before dose application.

Note: For age group 9-11 years 11 months, approximately 4 grams of test product will be applied considering their lesser BSA.

The following steps should be taken to ensure consistent product application across time points and subjects:

1. Weigh the empty boat and record weight (e.g. 2.38g)
2. Dispense 5g of product into the boat and record total weight (e.g. 7.38g) [For age group 9-11 years 11 months, dispense 4g of test product into the boat and record total weight (e.g. 6.38g)]
3. Dose the subject
4. Put the empty boat on the scale and record the final weight (e.g. 2.41g)
5. Subtract the full boat weigh from the final weight to get the total weight of product applied (7.38-2.41 = 4.97g) [For age group 9-11 years 11 months, subtract the full boat weight from the final weight to get the total weight of product applied (e.g. 6.38-2.41 = 3.97g)]

Study staff should wear gloves at all times while handling or applying the study product. If powdered gloves are worn, they should be rinsed and dried prior to handling study product.

Test Product

The Test product will be applied twice daily, 12 hours apart (± 1 hour) (morning and evening), for 21 days (42 consecutive doses). Before each dose application, subjects will take a brief warm shower to wet their skin. Approximately 5 grams of the product will be applied by the subject to the face, neck, and upper chest and will be applied by a member of the clinical staff to the shoulders and upper back, and rubbed into the skin until foamy (approximately 30 seconds for the total application area). After being left on for about 1 minute, the subject will rinse off the Test product in the shower for about 1 minute. On Day 22, the last dose application in morning will not be rinsed off in the shower; however, the subject will be permitted to towel dry after the Test product has been on for approximately one minute. Twelve hours following the last application,, the subject will rinse off in the shower for 1 minute. The subject should bare their exposed body parts when the product is rinsed off and the clinical staff should ensure that no residues are left on the body.

Note: For age group 9-11 years 11 months, approximately 4 grams of test product will be applied considering their lesser BSA.

Reference Product

The Reference product will be applied to dry skin once daily in the evening for 21 consecutive days. There should be a 24 hour interval between applications (± 1 hour). Approximately 5 grams of the product will be applied by the subject to the face, neck, and upper chest and by a

member of the clinical staff to the shoulders and upper back. The applied cream will be left on for 12 hours and showering will not be permitted until at least 12 hours after the application.

All Subjects

The times of dose applications should be recorded on the case report form (CRF).

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.

Subjects will be instructed not to use any other topical medicated treatments or products on the face (sunscreens are allowed); and to avoid contact with eyes, eyelids, and mouth. 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. Subjects will be asked to refrain from applying emollients (moisturizers, creams) to the application areas at least an hour before dose application. For subjects receiving the Reference product, they will be reminded to leave the applied cream on their skin for 12 hours and showering will not be permitted until at least 12 hours after the application. The Subject Instructions will be reviewed with each subject.

At each visit, the investigator will 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 CRF and will be identified programmatically during data analysis for purposes of reporting. The sponsor should be consulted before discontinuing a subject due to protocol deviations unless safety is a concern.

Any subject missing dosing > 1 day (more than one dose of Reference product or two consecutive doses of Test product) from Days 7 to 14 and missing dosing between Days 12 and 14 will be removed from steady-state estimation at Day 14 but will be assessed for steady-state estimation at Day 21, provided the subject does not miss dosing between Days 19 and 21. Subjects missing dosing between Days 12 and 14, and between Days 19 and 21 will not be considered for steady-state estimation or PK and statistical analysis.

6.4 Method of Assigning Subjects to Treatment Groups

Each subject will be assigned a unique identification number upon screening. Subjects who complete the study screening assessments and meet all eligibility criteria will receive the treatment as per randomization, the order of which will be according to randomization scheme generated for each site.

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

6.5 Blinding

Study treatment will be open-label during the study conduct. However, the plasma samples provided to the designated laboratory for determination of tazarotene and tazarotenic acid will be coded to ensure that the identity of the treatments is not known when the plasma samples are analyzed.

6.6 Prior and Concomitant Therapy and Procedures

Chronic medications being used at the time of the Screening and Baseline Visit, except for 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 CRF.

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 CRF.

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

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

See Table 4 for a list of medications and procedures that are prohibited during the study.

6.7 Study Restrictions

Only the assigned study product and investigator-approved sunscreen/moisturizer with SPF, gentle cleanser, face wash, and non-medicated 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 investigator-approved sunscreen and/or hats, have limited sun exposure time, and have no tanning bed use.

Subjects should abstain from alcohol for 72 hrs prior to first dosing and during study duration. Subjects who are smokers should be reminded to smoke no more than 10 cigarettes per day (or the equivalent for other nicotine containing products) during non-confinement days (except Day 13 and Day 20). They should also be instructed to abstain from smoking or using any products containing nicotine (including electronic cigarettes) 1 day prior to confinement days (Day 13 and Day 20) and during confinement.

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

An initial Screening visit should be scheduled to occur approximately 19 days (Day -21 to Day -1) prior to the Baseline visit (Day 1). The subject number, date of visit, date of consent, reason for screen failure, and study status (screen failure) will be captured in the CRF for every screen failure subject. 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 CRF. Acne history will be collected and recorded in the CRF.

A history of tobacco, alcohol and drug use should be reviewed and collected. Presence of alcoholism (i.e. alcohol in excess of 14 glasses/units per week, with one unit = 150 ml of wine or 360 ml of beer or 45 ml of 45% alcohol) and a history of drug abuse within 2 years prior to first dose will be determined and recorded.

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 Day 1 date), race, ethnicity, and sex. Baseline characteristics include IGA and lesion counts of the face.

7.4 Acne Evaluation

7.4.1 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 Screening/Baseline to determine study eligibility. 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 accurate counts. The investigator will perform lesion count at Screening and the baseline visit (Day1) and at PK sampling days at Day 15 (prior to evening dose application), Day 21 (post last evening dose application for Reference treatment) and Day 22 (post last morning dose application for Test treatment).

Disease severity will be assessed by IGA, inflammatory and non-inflammatory lesion count (% change from baseline for lesion count) at Day 15 and Day 21/Day22.

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

The IGA will be performed by the investigator, with best attempts made to assign the same evaluator for a subject throughout the study to obtain consistency in grading scores. The IGA will be performed at Screening and the baseline visit (Day1) and at PK sampling days at Day 15 (prior to evening dose application), Day 21 (post last evening dose application for Reference treatment) and Day 22 (post last morning dose application for Test treatment).

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 5). The grades on the scale have been sufficiently defined to appropriately and unambiguously represent each severity grade on the scale. The investigator will perform IGA scoring at Screening and the baseline visit (Day 1).To be enrolled, subjects had to have an IGA score of 3 at Baseline (Day 1). Disease severity will be assessed by the Investigator's Global Assessment (IGA) score at baseline and PK sampling days.

Table 5: 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

7.5 Pharmacokinetic Assessments

On the schedule shown in Table 2 and Table 3, blood samples (6 mL) for Part A (adult subjects) and 4 mL for Part B (pediatric subjects) will be collected in sodium fluoride and potassium oxalate (NaFKO) anticoagulant for analysis of tazarotene and tazarotenic acid plasma concentrations. If vital sign measurements and PK blood samples are scheduled at the same time, the PK blood samples are to be collected before blood pressure and heart rate are recorded. At each specified time, 2 aliquots of plasma will be prepared and stored until the part of the study is completed and will then be sent to designated analytical laboratory (Algorithme) for analysis.

The PK assessment for Part A has been conducted prior to Part B. Based on the full PK profile of Test and Reference treatments in Part A, the sparse sampling schedule for pediatric subjects in Part B has been decided.

The procedures for blood sample collection, plasma separation, storage and sample shipment to each clinical site will be described in a sample processing instruction supplied by the bioanalytical facility.

Tazarotene and tazarotenic acid plasma concentrations will be determined at a designated laboratory from the blinded samples using a validated bioanalytical method.

7.6 Safety Assessments

Safety assessments include visual inspection of the skin (erythema, scaling [peeling]) prior to dose application, assessment of application site reactions (dryness, non-lesional erythema, peeling, stinging, burning, and itching) after dose application, clinical safety laboratory evaluations (chemistry, hematology, and urinalysis), and physical examinations including vital signs (blood pressure and pulse rate). A 12-lead ECG will be performed at the Screening Visit, Baseline visit (Day 1) and Day 21. For females of childbearing potential serum pregnancy tests will be conducted at the Screening Visit and urine pregnancy tests will be conducted at Day 1, Day 7, Day 14 and Day 21. Adverse events will be collected by spontaneous reports from subjects, 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 CRF.

Before each dose application, the investigator or designated trained site staff will visually inspect the skin and grade erythema and scaling using the scales shown in Table 6 and Table 7, respectively.

After each dose application, the investigator or designated trained site staff will assess application site reactions 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 CRF. Assessments will be recorded separately for the face and (if applicable) neck, chest and/or back (including shoulders). The investigator or designated trained site staff will also ask the subject if any stinging (Table 9), burning (Table 10), or itching (Table 11) has occurred on the face (neck, chest and/or back (including shoulders), if applicable since the previous drug application. Day 1 assessments are made prior to first application. An AE should be recorded if the severity is worse than at Day 1. In addition, overall cutaneous tolerance should be graded at Day 21, 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 neck, chest and/or back (including shoulders) using the same scales below and should be performed within 1 hour of dose application.

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/Scaling

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.		

7.7 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 who were later discovered to not have met exclusion criteria 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. 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.
5. At the time of study discontinuation, the investigator will record the reason for early withdrawal, date of last dose application, date of last visit or contact, collect AE data, and, if possible, perform all Day 21 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.
6. Subjects who withdraw early will not be replaced.

7.8 Modification of Protocol

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

7.9 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.

7.10 Study Schedule

The study schedule chart is provided in Table 1.

7.10.1 Screening Visit (Day -21 to Day -1)

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 assign subject number. 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. Collect demographic data - date of birth, sex, race, and ethnicity.
4. 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 CRF. Acne history will be collected and recorded in the CRF. Review and record alcohol, drug and smoking history, to include history or presence of alcoholism (i.e. alcohol in excess of 14 glasses/unit per week, with 1 unit=150 ml of wine or 360 ml of beer or 45 ml of 45% alcohol) and history of drug abuse within 2 years prior to first dose.

5. Perform acne evaluation (IGA and lesion count). IGA scoring will be done prior to lesion count.
6. Perform urine drug screen, alcohol breath test.
7. Perform physical examination.
8. Collect sitting vital signs (blood pressure and pulse), height, and weight.
9. Perform 12-lead electrocardiogram (ECG).
10. Collect blood sample for safety laboratory evaluations (chemistry, hematology, and serology including serum pregnancy test and urinalysis).
11. Collect AEs.
12. Screen subject according to the study inclusion/exclusion criteria to determine tentative eligibility.
13. Initiate any protocol-required washout, if applicable.
14. Schedule Day 1 visit. Inform subject that he or she will come to the clinical site on Day 1 from at least 6 hours prior to the evening dose until after the evening dose application.
15. 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 CRF.
16. Remind the subjects to abstain from alcohol for 72 hrs prior to first dosing and during study duration. Subjects who are smokers will be reminded to smoke no more than 10 cigarettes per day (or the equivalent for other nicotine containing products) during non-confinement days (except Day 13 and Day 20). They should also be instructed to abstain from smoking or using any products containing nicotine (including electronic cigarettes) 1 day prior to confinement days (Day 13 and Day 20) and during confinement.

7.10.2 Day 1

Subjects will be come to the clinical site prior to the first (evening) study dose application on Day 1, allowing sufficient time for all pre-dosing activities to be performed. Baseline assessments will be followed by evening dose application of Test or Reference treatment (as per randomization). Subjects will leave the clinic after the Day 1 evening dose application.

The procedures will be followed as per the study schedule.

1. Update the medical history and concomitant medications. Any medical event (not related to a protocol intervention) that occurred after the “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 CRF.
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. Assess severity of acne using IGA and measurement of lesion count. IGA scoring will be done prior to lesion count prior to first dose. IGA scoring will be done prior to lesion count.
4. Perform a urine pregnancy test for female subjects of childbearing potential. Record method of contraception, as applicable, on source only.
5. Perform urine drug screen and alcohol breath test. Any subject with a positive alcohol breath test and/or positive drug screen should not be randomized.
6. Perform physical examination.
7. Collect sitting vital signs (blood pressure and pulse), and weight prior to first dose.
8. Perform 12-lead electrocardiogram (ECG) pre-dose.
9. Collect blood sample for safety laboratory evaluations (chemistry, hematology, and urinalysis).
10. Confirm eligibility according to inclusion/exclusion criteria.
11. Randomize subject.
12. Prior to first evening dose, visually inspect the skin and grade erythema, scaling/peeling.
13. Collect pre-dose pK blood sample.
14. Administer first dose.
15. After administering first dose, collect sitting vital signs within 1 hour post-dose.
16. Perform local cutaneous safety evaluation for dryness, non-lesional erythema, and peeling. The investigator or designated trained site staff should also ask the subject if any burning, stinging, or itching has occurred. These evaluations should be recorded separately for the face and, if applicable, neck, chest and/or back (including shoulders).
17. Complete the CRF for randomized subjects.

7.10.3 Daily, Day 2 Through Day 20

Subjects will come to the clinical site ±1 hour of each dose application (except Day 14). Subjects assigned to Test product will come to the clinical site for evening and morning twice-daily application and subjects assigned to Reference product will come to the clinical site for evening application. Subjects will leave clinic after completion of clinical activities for each dose application.

Subjects will be confined to the clinic from prior to evening dose application of Test or Reference on Day 14, allowing sufficient time for all pre-dosing assessments to be performed, until after the 24-hour PK sample collection and evening dose application on Day 15.

1. On Day 7 and Day 14, prior to evening dose application, perform urine pregnancy test for female subjects, urine drug screen and alcohol breath test. Any subject with a positive alcohol breath test and/or positive drug screen should be discontinued from the study.
2. Alcohol breath test will be additionally performed on Days 12, 13, 19 and 20. Any subject with a positive alcohol breath test and/or positive drug screen should be discontinued from

the study.

3. On Day 14, collect sitting vital signs (blood pressure and pulse) pre-evening dose and at 1, and 8 hours after evening dose application for Test and Reference product.
4. On non-confinement days (Days 2-13 and Days 15-20), collect sitting vital signs (blood pressure and pulse) pre-evening dose (within 15 minutes of dosing) and within 1 hour after evening dose application for Test and Reference.
5. On Days 12 and 13 (steady state), collect PK blood sample. Additionally trough samples will be collected at Day 19 and Day 20. For the pediatric population in Part B, trough samples will not be collected on days 12, 13, 19 and 20.
6. On Day 15, prior to the evening dose application for Test and Reference products, assess severity of acne by IGA scoring and measurement of lesion count. IGA scoring will be done prior to lesion count.
7. Prior to each dose application, visually inspect the skin and record erythema and scaling (peeling) grades.
8. Apply assigned study product (morning and evening applications for subjects assigned to the Test product, evening application for subjects assigned to Reference product).
9. After each dose application, perform local cutaneous safety evaluation for dryness, non-lesional erythema, and peeling within 1 hour of dosing. The investigator or designated trained site staff should also ask the subject if any burning, stinging, or itching has occurred on the face since the last application. These evaluations should be recorded separately for the face and, if applicable, chest/back (including shoulders).
10. Collect AE data.
11. Update concomitant medications data.
12. Subjects will leave the clinical site after completion of the clinical activities except as noted below for Days 14 to 15.
13. On Day 14 subjects will be housed at the clinical site from prior to the evening dose application, allowing sufficient time for all pre-dosing assessments to be performed, until after the 24-hour PK sample has been collected on Day 15. The morning dose application for Test treatment will be performed on the morning of Day 15. The 24-hour PK sample collection will be followed by the Day 15 evening dose application for Test and Reference product.
14. On Days 14 to 15, PK blood sample collection will occur at the following times:

    In Part A (adult subjects, age 17 years or older), blood samples will be collected prior (pre-dose) to the Day 14 evening dose application for Test and Reference treatments and at 1, 2, 4, 6, 8, 12, 14, 16, 18, and 24 hours post dose application.
15. In Part B for Test treatment (subjects age 9 years to 16 years 11 months) and Reference treatment (subjects 12 years to 16 years 11 months), a maximum of 4 blood samples will be collected as per the sparse sample design (Table 3)Complete the CRF.

7.10.4 Days 21 and 22

Subjects will be confined to clinic prior to evening dose application of Test or Reference treatment, allowing sufficient time for all pre-dosing assessments to be performed on Day 21 until the completion of clinical activities per schedule on Day 22.

1. On Day 21, perform physical examination.
2. On Day 21, update concomitant medications.
3. On Day 21 prior to evening dose application in evening for Test and Reference treatments, perform urine pregnancy test for female subjects, urine drug screen and alcohol breath test. Any subject with a positive alcohol breath test and/or positive drug screen should be discontinued.
4. On Day 21, perform 12-lead ECG pre-dose.
5. Prior to dosing on evening of Day 21 for Reference treatment and morning treatment of Day 22 for Test treatment, assess severity of acne by IGA scoring and measurement of lesion count. IGA scoring will be done prior to lesion count.
6. Prior to each dose application, visually inspect the skin and record erythema and scaling grades.
7. Apply assigned study product for the Day 21 evening dose application for Test and Reference treatments. For subjects assigned to Test treatment, the morning dose application will be performed the morning of Day 22 and this last dose application will not be rinsed off in the shower.
8. After each dose application, perform local cutaneous safety evaluation for dryness, non-lesional erythema, and peeling within 1 hour of dosing. The investigator or designated trained site staff should also ask the subject if any burning, stinging, or itching has occurred on the face since the last application. These evaluations should be recorded separately for the face and, if applicable, chest/back (including shoulders).
9. On Day 21, collect sitting vital signs (blood pressure and pulse) pre-evening dose and at 1 and 8 hours after evening dose application for Test and Reference treatments. (Note that the 8-hour post dose vital sign will occur on the morning of Day 22).
10. On Days 21 to 22, PK blood sample collection will occur at the following times:

    In Part A (adults, age 17 years or older), blood samples will be collected prior (pre-dose) to the Day 21 evening dose application for Test and Reference treatments and at 1, 2, 4, 6, 8, 12, 14, 16, 18, and 24 hours post dose application.

    In Part B for Test treatment (subjects age 9 years to 16 years 11 months) and Reference treatment (subjects 12 years to 16 years 11 months), a maximum of 4 blood samples will be collected as per the sparse sample design (Table 3).
11. On Day 21, collect blood sample for safety laboratory evaluations (chemistry, hematology, and urinalysis).
12. Collect AE data.
13. Complete CRF.

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 CRF 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 CRF.

8.1 Adverse Event Reporting Period

Adverse event data must be collected from the time of signing of Informed Consent 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 CRF. 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 CRF. Standard medical terminology should be used when describing AEs. Whenever possible a diagnosis should be made and recorded on the CRF 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 CRF:

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

Laboratory and Vital Signs Variables

Vital signs and laboratory abnormalities (except at the Screening and Day -1 visits and pre-dose on Day 1) should be reported as AEs if they are out of range and considered to be clinically significant, as per the investigator's judgment. If an abnormal laboratory value is associated with clinical signs and symptoms, the sign/symptom should be reported as an AE, and the associated abnormal laboratory result should be considered additional information.

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 to the Sponsor's medical monitor and appointed Pharmacovigilance person. 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.

All serious and unexpected suspected SAEs will be reported to the Agency by the Sponsor.

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 CRFs) 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 screening date, subject number, and date of enrollment, which is when ICF is signed, where applicable.

9.4 Case Report Forms

CRFs for individual subjects will be provided by Symbio. CRFs must be legible and complete. CRFs for this study will be maintained in a study binder and data recorded on 2-part NCR paper. One copy will be kept by the investigator and the other copy will be collected by the study monitor. All forms should be completed using a black ballpoint pen. Errors should be lined out, *but not obliterated,* and the correction inserted, initialed, and dated by designated study personnel. Further data corrections will be performed on special "data correction forms" (DCFs) that will be provided to the investigator in case of erroneous or unclear data. The investigator will make the correction on the DCF and sign the DCF. The original will be sent to Symbio and a copy retained with the CRFs.

A CRF must be completed and signed by the investigator for each subject enrolled, including those discontinued from the study for any reason. The reason for discontinuation must be noted on a subject's study termination form.

CRFs must be kept current to reflect the subject's status at each phase during the study. Subjects are not to be identified on CRFs by name; appropriately coded identification and the subject's initials must be used. The investigator must keep a separate log of the subjects' names and addresses

A Data Management Plan, which describes the programming of database structure, will be prepared.

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 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 and outlier testing, will be provided as a separate document prior to database lock and unblinding of the study treatments.

11.1 Sample Size

Approximately 62 subjects will be enrolled in the study. Since the study is not aimed to meet the bioequivalence criteria, proper powering of the study is not required. The sample size chosen for the study attempts adequate representation of pediatric and adult population and was considered adequate to meet the study objectives.

11.2 Analysis Data Sets

11.2.1 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.

11.2.2 Pharmacokinetic Analysis Population

Samples from all subjects who provide evaluable data will be assayed; these subjects will be included in the PK and statistical analysis. In order to be considered evaluable, a subject must have PK samples collected on both Day 14 and Day 21. An unequal number of subjects per arm will be used.

11.3 Demographic and Baseline Data

Subject demographic and baseline characteristics will be summarized descriptively by treatment group for the safety and PK populations.

11.4 Pharmacokinetic Analyses

Tazarotene and tazarotenic acid plasma concentrations produced by the application of the study products will be determined to establish the PK profile of each treatment regimen. Below limit of quantitation concentrations (coded BLQ) will be treated as zero for all statistical analyses. The PK parameters will be derived from the plasma concentrations versus time profiles. All reported sampling time deviations following application for test and Reference will be taken into consideration for evaluation of PK parameters.

In the case where concentrations of tazarotene and tazarotenic acid cannot be determined due to bioanalytical or clinical reasons, these values will be set to missing for the PK and statistical analysis.

In the case where less than 3 consecutive measurable concentrations of tazarotene and tazarotenic acid are observed, the area under the curve (AUC) parameters will not be estimated for that specific study period.

The following PK parameters will be calculated for tazarotene and tazarotenic acid on Day 14 and Day 21 using a noncompartmental approach. The linear trapezoidal rule will be used to estimate the AUC.

$C_{max(ss)}$:	Maximum observed maximum plasma concentration during a dosing interval at steady state
$AUC_{0-12(ss)}$	Area under the concentration–time curve from time zero to 12 hours post-dose, at steady state
$AUC_{0-24(ss)}$	Area under the concentration–time curve from time zero to 24 hours post-dose, at steady state
$T_{max(ss)}$	Time to reach observed maximum plasma concentration, at steady state
$C_{min(ss)}$	Minimum observed plasma concentration during a dosing interval at steady state

The absorption and disposition parameters will be determined using a noncompartmental approach, the trapezoidal rule will be used to estimate the area under the curve. The PK parameters of interest for this study will be:

Day 14 and Day 21: $T_{max(ss)}$, $C_{max(ss)}$, $AUC_{0-12(ss)}$, $AUC_{0-24(ss)}$, $C_{min(ss)}$,

For Part B, plasma concentration data generated from sparse samples (maximum 4 time points from each subject) on Day 14 and Day 21 will be used for calculation of PK parameters: $C_{max(ss)}$, $AUC_{(ss)}$, $C_{min(ss)}$.

Descriptive statistics will be calculated for plasma concentrations at each individual time point and for all PK parameters. The individual plasma concentration/time profiles will be presented using the actual sampling times whereas the mean plasma concentration/time profiles will be presented using the theoretical sampling times. Concentration/time profiles will be presented on linear and semi-log scales.

Pharmacokinetic analyses will be generated using validated PK software (e.g. Phoenix® WinNonlin® Version 6.3 or higher and Phoenix® Connect™ version 1.3.1 or higher).

A statistical plan will prepared. Statistical analysis of all PK parameters will be based on a parametric analysis of variance (ANOVA) model. Two-sided 90% confidence intervals of the ratio of geometric least squares (LS) means will be presented from the natural log (ln)-transformed PK parameters ($C_{max(ss)}$, $AUC_{0-24(ss)}$, $Cmin_{(ss)}$) for Treatment 1 vs Treatment 2.

Achievement of steady state will be performed by treatment, using log-transformed $C_{min(ss)}$ (at Days 12, 13 and 14 and 19, 20 and 21) in a mixed effect model through repeated-measure ANOVA or through other appropriate statistical methods.

Disease severity will be assessed between baseline and sampling days by paired t-test or any other appropriate statistical test and will be presented by treatment.

Descriptive statistics will be presented for safety parameters.

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.

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 Electrocardiogram

A 12-lead Electrocardiogram (ECG) will be performed and must be without clinically significant abnormality.

11.5.6 Physical Examination

The physical examination will include measurement of vital signs (blood pressure, pulse rate and body temperature) and a review of the following: Head, Eyes, Ears, Nose, Throat (HEENT), neck, chest, back, abdomen, extremities, skin (face, neck, shoulders, upper chest and upper back) and neurological function.

Demographic data (age, gender, race, body weight adjusted for indoor clothing, height, BMI), and alcohol and smoking habits will be recorded.

11.5.7 Safety Laboratory Values

General Biochemistry: Sodium, potassium, chloride, glucose, blood urea nitrogen (BUN), creatinine, bilirubin total, alkaline phosphatase, AST, ALT and albumin

Hematology: White cell count with differential (absolute values of neutrophil, lymphocyte, monocyte, eosinophil, and basophil), red cell count, hemoglobin, hematocrit, mean corpuscular volume (MCV), and platelets count

Urinalysis: Color, clarity, specific gravity, pH, leukocyte, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen. Microscopic examination will only be performed if the dipstick test is outside of the reference range for leukocyte, blood, nitrite or protein

Additional laboratory tests may be also performed by the medical laboratory as part of larger standard tests panels although not required for the subject's safety. All test results will be

assessed by physician for clinical significance. Only test results required by the protocol will be entered in the clinical database and reported in the Clinical Study Report.

Results of urine pregnancy tests will be provided in a data listing.

12 REFERENCES

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Fabior (tazarotene) Foam, 0.1%. Prescribing Information. Stiefel Laboratories, 2013.

Menter A. Pharmacokinetics and safety of tazarotene. J Am Acad Dermatol 2000;43:S31-35.

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