CLINICAL STUDY PROTOCOL

A Multi-Center, Randomized, Double-Blind, Parallel-Group, Vehicle-Controlled Study to Evaluate the Dose-Response Relationship of the Efficacy and Safety of Two Concentrations of DFD-07 (celecoxib) Cream, in Subjects with Actinic Keratosis (AK) of the Face and/or Scalp Over a 12-week Treatment Period

Protocol Number: DFD-07-CD-002

Version: 2.0
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Date: 02 March 2017

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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.

Site Investigator: **Site Number:** _____

Signature: _____ Date: _____

Name: _____
Title: _____
Address: _____
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Sponsor:

Signature: _____ Date: 02 March 2017

Name: Srinivas Sidgiddi, MD
Title: Director, Clinical Development Dermatology

SYNOPSIS

Title: A Multi-center, Randomized, Double-Blind, Parallel-group, Vehicle-Controlled Study to Evaluate the Dose-Response Relationship of the Efficacy and Safety of Two Concentrations of DFD-07 (celecoxib) Cream, in Subjects with Actinic Keratosis (AK) of the Face and/or Scalp Over a 12-week Treatment Period

Sponsor: Dr. Reddy's Laboratories Ltd.
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Telangana, India

Study Centers:	**20**	**Number of Subjects: 240**
Study Treatment:	12 Weeks	**Clinical Phase:** Phase 2b

Objectives:

The objective of this study is:

To evaluate the dose response relationship of the efficacy and safety of two strengths, of topical DFD-07 (celecoxib) Cream, 1.25% and 2.5% when used once or twice daily compared to Vehicle in the treatment of AK of the face and/or scalp over a 12-week period with a 4-week follow up.

Methods:

This is a multi-center, randomized, double-blind, parallel group, Vehicle-controlled study. The study products will be applied to the target lesions once or twice daily for a duration of 12 weeks of treatment, with a 4-week treatment-free follow-up. Subjects, who are at least 18 years old, diagnosed with AK of the face and/or scalp will be randomized to treatment in one of the following four arms (60 subjects in each group):

Treatment Group	Dose Strength	Dose Duration	DFD-07 Cream		Vehicle Cream	
			AM	PM	AM	PM
1	1.25%	12 Weeks	-	√	√	-
2	2.5%	12 Weeks	√	√	-	-
3	2.5%	12 Weeks	-	√	√	-
4	Vehicle	12 Weeks	-	-	√	√

The study consists of three phases: Screening (up to 60 days), Treatment (12 weeks) and Follow-Up (4 weeks). In Groups 2 and 4, the randomized investigational products will be applied twice daily for 12 weeks to cover the entire single contiguous 5 cm x 5 cm ($25cm^2$) lesional area on the face and/or scalp. In Groups 1 and 3, the randomized active product will be

applied only in the evening, while the Vehicle will be applied in the morning to keep the blinding between groups.

Subjects in all the groups will undergo a further 4-week treatment-free period from Week 12 to Week 16 (End of Study).

Subject visits are scheduled at Screening (Visit 1), Baseline (Visit 2 - Day 1), and Weeks 4 (Visit 3), 8 (Visit 4), 12 (Visit 5) and 16 (Visit 6). Clinical determinations of efficacy will be conducted based on clinically visible or palpable lesions of AK in the treated areas at Weeks 4, 8, 12 and 16 in comparison to Baseline. Comparisons will be made between the different strengths and dosing regimens of DFD-07 (celecoxib) Cream and Vehicle Cream.

Local cutaneous tolerability will be determined at Baseline (Visit 2 –Day 1) and visits 3 – 6 for all treated areas. Other safety assessments include physical examinations (HEENT, lungs, heart, abdomen, skin, neurologic) laboratory assessments, electrocardiogram (EKG), vital signs (blood pressure, pulse rate), urine pregnancy tests, and collection of adverse event data.

Number of Subjects:

A total of approximately 240 subjects with actinic keratosis of the face and/or scalp will be randomized into four groups in a 1:1:1:1 ratio (60 subjects in each group) at approximately 20 centers.

Diagnosis and Criteria for Inclusion / Exclusion:

Inclusion:

1. Subject understands the study procedures, is willing to comply with the study procedures and required visits, and agrees to participate by giving written informed consent. Subjects with a legal guardian, must have the written informed consent of the legal guardian.
2. Subject (or legal guardian) must be willing to authorize use and disclosure of protected health information collected for the study.
3. Subjects must have 5 or more AK lesions that are non-hypertrophic and non-hyperkeratotic contained within a single contiguous approximate 5 cm x 5 cm (25 cm^2) region of face and/or scalp.
4. Subjects must be 18 years of age or older. Male and female subjects can be enrolled.
5. Female subjects of childbearing potential must agree to use contraception during the study which can include abstinence with an adequate secondary option should the subject become sexually active. All women of childbearing potential must complete a urine pregnancy test (test must have a sensitivity of at least 25mIU/ml for human chorionic gonadotropin) at the Baseline Visit (Visit 2) and the test result must be negative to be eligible for enrollment.

   A female is considered of childbearing potential unless she is:
   - postmenopausal for at least 12 months prior to study product administration;
   - without a uterus and/or both ovaries; or has been surgically sterile (i.e., tubal ligation) for at least 6 months prior to study product administration.

Reliable methods of contraception are:

- hormonal methods or intrauterine device in use ≥ 90 days prior to study product administration; or
- barrier methods plus spermicide in use at least 14 days prior to study product administration.
- partner has had a vasectomy at least 3 months previous to study product administration.
- Essure®

Exception: Sexually inactive female subjects of childbearing potential are not required to practice a reliable method of contraception and may be enrolled at the investigator's discretion provided that they are counseled to remain sexually inactive for the duration of the study and understand the possible risks involved in getting pregnant during the study. An abstinent female must agree that if she becomes sexually active during the study she will use an acceptable form of contraception.

6. Subjects must be able to have ≥ 60 days washout from prohibited medications:
    - Masoprocol
    - 5-Fluorouracil
    - Cyclosporin
    - Retinoids (oral and topical)
    - Trichloroacetic Acid/Lactic Acid Peel
    - 50% Glycolic Acid Peel
    - Topical or systemic diclofenac, celecoxib or any other NSAID (however daily low-dose aspirin is allowed, as long as the subject has been on a stable dose, ≤ 100 mg once a day, for 60 days prior to the start of the study.) Note: Subjects may use acetaminophen/paracetamol as needed
    - Photodynamic therapy
    - Topical or systemic immunomodulating agents
    - Systemic, topical or intralesional interferon
    - Imiquimod (Aldara, Zyclara)
    - Topical ingenol mebutate (Picato)
    - Topical tacrolimus
    - Topical pimecrolimus
    - Sirolimus
    - Intralesional BCG
    - Topical coal tar products
    - Topical or systemic corticosteroids (nasal and inhaled steroids are allowable)
7. Subjects must agree not to use any product on the treatment area during the entire course of study except for Investigator-approved cleanser, sunscreen, wash, and non-medicated 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.
8. Subjects must be willing to comply with sun avoidance measures for the face including use of Investigator-approved sunscreen and/or hats, have limited sun exposure time, and have no tanning bed use.

9. Subjects must be in good general health as determined by the Investigator and supported by the medical history, and normal or not clinically significant abnormal vital signs (blood pressure and pulse). Subjects are eligible if:

   -Systolic blood pressure (BP) < 160 and > 85 mmHg
   -Diastolic BP < 100 and > 50 mmHg

Exclusion:

1. Known or suspected hypersensitivity to any non-steroidal anti-inflammatory drugs (NSAID) or any component of the formulation of the study medication, including a history of asthma, urticarial, or other allergic-type reactions after taking aspirin or other NSAIDs.
2. Known or suspected allergy to sulfonamides.
3. Clinical evidence of severe, uncontrolled autoimmune, cardiovascular, gastrointestinal, hematological, hepatic, neurologic, pulmonary or renal disease.
4. Recent (within 6 months) or planned coronary artery bypass graft surgery.
5. Significant history (within the past year) of alcohol or drug abuse.
6. Participation in any clinical research study within 30 days of the Baseline Visit.
7. Concomitant use of cosmetics or other topical drug products on or near the selected treatment area except for Investigator-approved cleanser, sunscreen, wash, and non-medicated makeup.
8. Cosmetic or therapeutic procedures (e.g. laser, peeling, photodynamic therapy) within 2 weeks and within 2 cm of the selected treatment area.
9. Other skin conditions within the selected treatment area (e.g. rosacea, psoriasis, atopic dermatitis, eczema, basal or squamous cell carcinoma or albinism).
10. Use of sun lamps, tanning beds, and tanning booths during the 14 days prior to the Baseline Visit or planned use during the study.
11. Any systemic cancer therapy or diagnosis within 6 months of the Baseline Visit.
12. Females who are pregnant or lactating or planning to become pregnant during the study period.
13. Subjects may not have a personal relationship with any member of the study staff or be part of the staff at the medical practice.
14. Subjects who are unable to comply with the study requirements for any reason.

Investigational Product, Dose and Mode of Administration:

This is a multi-center, randomized, double-blind, parallel group, Vehicle-controlled study. Subjects, who are at least 18 years old, diagnosed with AK of the face and/or scalp will be randomized to treatment with one of the following:

1. DFD-07 (celecoxib) Cream, 1.25% once daily in the evening/PM and Vehicle for DFD-07 (celecoxib) Cream, 0% once daily in the morning/AM for 12 weeks.
2. DFD-07 (celecoxib) Cream, 2.5% once daily in the morning/AM and evening/PM for 12 weeks.
3. DFD-07 (celecoxib) Cream, 2.5% once daily in the evening/PM and Vehicle for DFD07 (celecoxib) Cream, 0% once daily in the morning/AM for 12 weeks.
4. Vehicle (celecoxib) Cream, 0% once daily in the morning/AM and evening/PM for 12 weeks.

The investigational products will be applied twice daily for 12 weeks to cover the entire lesional area on the face and/or scalp. The maximum amount of study product applied will be 0.5 g per application to a 5 cm x 5 cm area (single contiguous area) on the face and/or scalp for a maximum dose of 1.0 g per day.

Duration of Treatment and Study:

Subjects will treat the affected area for a maximum of 12 weeks. The total expected study duration is 24 weeks including the Screening and Follow-Up Visits.

Reference and Control Products, Dose and Mode of Administration:

Subjects will be treated with either topical DFD-07 (celecoxib) Cream containing 1.25% or 2.5% or the matching topical Vehicle Cream.

Criteria for Evaluation:

Safety criteria:
Safety assessments will be performed at each visit to include vital signs (blood pressure, pulse rate), urine pregnancy tests for women of child bearing potential, local cutaneous tolerability evaluation (including erythema, edema, weeping/exudate, flaking/scaling/dryness, scabbing/crusting, erosion/ulceration, vesiculation/blistering), and collection of adverse event data.

For the safety analysis, only treatment-emergent adverse events (TEAEs) will be analyzed. Treatment-emergent adverse events will include any adverse event (AE) occurring during the treatment period. For pre-existing conditions, any condition that worsens during treatment will be considered treatment-emergent.

Efficacy Endpoints:

Primary Endpoint:
The proportion of subjects with complete clearance of AK lesions at the End of Study Visit, at 16 weeks (absence of clinically visible or palpable AK lesions in the treatment area) for DFD-07 (celecoxib) Cream, 2.5% BID compared to Vehicle Cream.

Secondary Endpoints:

1. Proportion of subjects with complete clearance of AK lesions at the End of Study Visit, for DFD-07 (celecoxib) Cream, 2.5% QD compared to Vehicle Cream.
2. Proportion of subjects with complete clearance of AK lesions at the End of Study Visit, for DFD-07 (celecoxib) Cream, 1.25% QD compared to Vehicle Cream.
3. Proportion of subjects with complete clearance of AK lesions at Week 12 in the different treatment groups.
4. Proportion of subjects with complete clearance of AK lesions at Week 8 in the different treatment groups.

5. Proportion of subjects with partial clearance of AK lesions at Weeks 4, 8, 12, and 16 in the different treatment groups (partial clearance defined as at least a 75% reduction in the number of AK lesions in the treatment area compared to Baseline).
6. Percent change from baseline in AK lesion count at Weeks 4, 8, 12 and 16 in the different treatment groups.
7. Number and proportion of subjects with local skin reactions in the different treatment groups.

Study Schedule

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6[b]
	Screen[a]	**Day 1 Baseline**	**Week 4**[b]	**Week 8**[b]	**Week 12**[b] (End of Treatment Visit)	**Week 16** (End of Study Visit)
Informed Consent	X					
Collect Demographic Data	X					
Inclusion and Exclusion Criteria	X	X				
Medical History/ Prior Medications	X	X				
Physical Examination		X			X	
Vital Signs (BP, Pulse rate)	X[c]	X	X	X	X	X
12-Lead EKG		X	X		X	
Hematology/Chemistry/Urinalysis		X	X		X	
Urine Pregnancy Test[d]	X	X	X	X	X	X
AK lesion count and measurements	X	X	X	X	X	X
Safety and Local Tolerability Evaluation		X	X	X	X	X
Randomization		X				
Dispense Study Product (as needed)		X	X	X		
Dispense/Review/Collect Study Diary		X	X	X	X	X
Diagram Affected Areas to be Treated[c]		X	X	X		
Review Subject Instructions		X	X	X	X	
Initiate Treatment Subjects will treat the affected areas under supervision for the first time		X				
Collect Study Product			X	X	X	
Evaluate Compliance			X	X	X	
Adverse Event Assessment/Collection		X	X	X	X	X
Concomitant Medications		X	X	X	X	X
End of Study						X

[a]Up to 60 days before Visit 2.
[b]Allowed visit window ± 5 days.
[c]Record on source only. Only a single contiguous 5 cm x 5 cm area will be treated per subject.
[d]For female subjects of childbearing potential.

TABLE OF CONTENTS

List of Abbreviations

Abbreviations	Description
AK	Actinic keratosis
AE	Adverse event
AM	Morning
BID	Twice in a Day
BP	Blood pressure
CFR	Code of Federal Regulations
COX	Cyclooxygenase (Enzyme)
eCRF	Electronic case report form
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DFD	Differentiated Formulation Dermatology
EDC	Electronic Data Capture
EKG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IRB	Institutional review board
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	No adverse effect level
NSAID	Non-steroidal anti-inflammatory drug
PHI	Protected health information
PK	Pharmacokinetic
PP	Per protocol
PT	Preferred term
PM	Evening

QD	Once Daily
SAE	Serious adverse event
SOC	System organ class
SUSAR	Suspected unexpected adverse reaction
TEAEs	Treatment emergent adverse events
UPT	Urine pregnancy test

List of Definitions

Term	Definition
EDC	Electronic Data Capture is a computerized system designed for the collection of clinical data in electronic format including the eCRF.
IWRS	Interactive Web-Based Response System that manages randomization, subject enrollment, and drug supply.
Screening Visit (Visit 1)	The day a subject is screened according to the protocol inclusion/exclusion criteria after having provided informed consent. The screening visit may occur on the same day as Visit 2 (Baseline) for this study.
Screened Subject	A subject who has signed informed consent.
Baseline Visit (Visit 2/Day 1)	The day of randomization and the first study product application. The first study product application is done at the site by the subject during the visit.
Subject Number	A unique number assigned to a screened subject. The number consists of the 2-digit unique site number followed by a 3-digit sequential number for each subject in chronological order (e.g., 01-001, 01-002, where the site number is 01 and the first and second screened subject at site 01 are 001 and 002, respectively). The subject number is assigned by clinical sites.
Study product(s)	Investigational products, that include the active and Vehicle products.

1 INTRODUCTION

Actinic keratosis (AK) is caused by sun exposure and considered squamous cell carcinoma (SCC) *in situ*. It is the most common carcinoma *in situ* of the skin. For Europe, prevalence was reported to be up to 49% among males and 28% among females (Flohil *et al*., 2013). Prevalence increases with increasing age (Memon *et al*., 2000). AK occurs most commonly in fair skinned individuals (Fitzpatrick skin types I and II and, to a lesser extent, III).

The standard of care is to remove AK when diagnosed, which can be achieved either by physical ablation (e.g. cryosurgery, curettage), chemotherapeutic agents (e.g. topical 5-fluorouracil, imiquimod, diclofenac, ingenol mebutate) or photodynamic therapy (PDT) with aminolevulinic acid or methylaminolevulinate.

Solaraze®, which is widely used in the treatment of AK, contains 3% diclofenac in a gel formulation. The preparation is self-applied by the subject over a period of 90 days.

Diclofenac and celecoxib (the substance used in this clinical trial) are non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs act against inflammation primarily by inhibiting cyclooxygenase (COX) enzyme activity. The mechanism of action of topical diclofenac 3% gel (Solaraze) against AK lesions is unknown.

Results of multiple *in vitro* studies in cancer cell lines and in human tumor xenograft mouse models have indicated that the type 2 isoform of the enzyme cycloxygenase is induced and plays critical roles in virtually all stages of tumorigenesis and proliferation (including tumor initiation, promotion, progression, survival, invasion and metastases) in several pre-malignant conditions and malignancies, including those of the colon, breast, lung, skin, mouth, esophagus, stomach, pancreas, liver, prostate and blood (Sobolewski *et al*., 2010). However, inhibition of enzyme activity alone cannot explain the anti-tumor potential of the selective COX-2 inhibitor, celecoxib. In recent cell culture studies assessing the anti-proliferative effect in HaCat keratinocytes, celecoxib has shown a 9-fold higher potency compared to diclofenac in terms of growth inhibition (unpublished data). There is accumulating evidence of COX-2 independent pathways contributing to the anti-tumor effect of celecoxib. These include enhancing tumor sensitivity to apoptosis and inhibition of cell proliferation (Sobolewski *et al*., 2010).

Topical diclofenac 3% gel, although better tolerated than many of the currently approved topical treatment modalities, requires twice a day treatment for 60 to 90 days and has limited efficacy as shown in Table 1:

Table 1: Efficacy of Solaraze Gel (Diclofenac 3%) in the Treatment of AK Lesions

Complete Clearance of Actinic Keratosis Lesions 30 Days Post-Treatment with Diclofenac 3% Gel (all locations)			
	Solaraze Gel	Vehicle	*p*-value
Study 1 (90 days treatment)	27/58 (47%)	11/59 (19%)	<0.001
Study 2 (90 days treatment)	18/53 (34%)	10/55 (18%)	0.061
Study 3 (60 days treatment)	15/48 (31%)	5/49 (10%)	0.021
(30 days treatment)	7/49 (14%)	2/49 (4%)	0.221

(http://www.drugs.com/pro/solaraze.html; adapted)

Therefore, there is still a need for a topical treatment option for AK, with one or more of the following attributes: once a day convenient application, faster onset of action, increased lesion clearance rate, and/ or fewer, or less severe, side effects. DFD-07, a cream formulation containing celecoxib, has shown promise of fulfilling this need in *in vitro* cell culture studies (unpublished data). These *in vitro* cell culture studies indicate that celecoxib is approximately 9 times as potent as diclofenac in inhibiting the growth of HaCaT (human keratinocyte) cell lines.

In a 13-week dermal toxicity study in rats, daily application of prototype DFD-07 cream formulations containing celecoxib concentrations of 0.3%, 0.6%, 1.25%, and 2.5% (corresponding to absolute celecoxib dose levels of 6, 12, 25 or 50 mg/kg /day, respectively), for 90 consecutive days was well tolerated. No celecoxib-related dermal or systemic effects were noted. The reversible epidermal hyperplasia noted at the application site was attributed to Vehicle, and was considered non-adverse. Based on the results of this study, the NOAEL of DFD-07 for systemic and local effect was considered to be more than 50 mg/kg/day in both sexes under the conditions of testing in this study.

In a study in minipigs, dermal administration of prototype DFD-07 cream formulations containing celecoxib concentrations of 0.6%, 1.25%, and 2.5% (corresponding to absolute celecoxib dose levels of 12, 25, or 50 mg/kg/day, respectively) was well tolerated. Reversible, non-adverse, dermal irritation was observed without any correlating microscopic changes in all animals of the placebo group and DFD-07-treated groups and was attributed to constituent(s) of the formulation other than the active ingredient celecoxib. There was no evidence of celecoxib-related systemic toxicity and no target organs were identified. Accordingly, the NOAEL was considered to be more than 50 mg/kg/day under the conditions of this study.

Celecoxib, a selective COX-2 inhibitor, is expected to have similar, if not better efficacy in clearing AK lesions than topical diclofenac.

2 ETHICAL CONSIDERATIONS

2.1 Institutional Review Board Review

The protocol, protocol amendments, subject recruiting materials, the informed consent form (ICF) and any other materials provided to subjects must be approved by an Institutional Review Board operating in compliance with 21 CFR Part 56. A copy of the approval letter must be received by the sponsor or CRO prior to shipment of drug supplies to the site.

Records of the Institutional Review Board'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 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 from the subject 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 (including the wash-out period, if needed). Informed consent is a process that is initiated prior to the subject's agreement to participate in the study and continues 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.

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 AK. In some cases, qualified physicians who are not board certified dermatologists may participate based on training and experience in the treatment of AK. Sub-investigators may be licensed physicians, physician assistants, or nurse practitioners with experience in AK or dermatology and a good understanding of GCP. Investigators may delegate study tasks to other site personnel as long as they are qualified to perform the task and the delegation is documented.

3 STUDY OBJECTIVE

To evaluate the dose-response relationship of the efficacy and safety of two strengths, of topical DFD-07 (celecoxib) Cream, 1.25% and 2.5% when used once or twice daily compared to Vehicle in the treatment of AK of the face and/or scalp over a 12-week period with a 4-week follow up.

3.1 Primary Efficacy Endpoint:

The proportion of subjects with complete clearance of AK lesions at the End of Study Visit, at 16 weeks (absence of clinically visible or palpable AK lesions in the treatment area) for DFD-07 (celecoxib) Cream, 2.5% BID compared to Vehicle Cream.

3.2 Secondary Efficacy Endpoints:

1. Proportion of subjects with complete clearance of AK lesions at the End of Study Visit, for DFD-07 (celecoxib) Cream, 2.5% QD compared to Vehicle Cream.
2. Proportion of subjects with complete clearance of AK lesions at the End of Study Visit, for DFD-07 (celecoxib) Cream, 1.25% QD compared to Vehicle Cream.
3. Proportion of subjects with complete clearance of AK lesions at Week 12 in the different treatment groups.
4. Proportion of subjects with complete clearance of AK lesions at Week 8 in the different treatment groups.
5. Proportion of subjects with partial clearance of AK lesions at Weeks 4, 8, 12, and 16 in the different treatment groups (partial clearance defined as at least a 75% reduction in the number of AK lesions in the treatment area compared to Baseline).
6. Percent change from baseline in AK lesion count at Weeks 4, 8, 12 and 16 in the different treatment groups.

7. Number and proportion of subjects with local skin reactions in the different treatment groups.

4 STUDY DESIGN

4.1 Overall Plan

This is a multi-center, randomized, double-blind, parallel group, Vehicle-controlled study. The study products will be applied to a single contiguous 5 cm x 5 cm (25 cm^2) treatment area containing the target lesions once or twice daily for a duration of 12 weeks of treatment with a 4-week treatment-free follow-up. Subjects, who are at least 18 years old, diagnosed with AK of the face and/or scalp will be randomized to treatment in one of the following four arms (60 subjects in each group):

Treatment Group	Dose Strength	Dose Duration	DFD-07 Cream		Vehicle Cream	
			AM	PM	AM	PM
1	1.25%	12 Weeks	-	√	√	-
2	2.5%	12 Weeks	√	√	-	-
3	2.5%	12 Weeks	-	√	√	-
4	Vehicle	12 Weeks	-	-	√	√

4.2 Discussion of Design

The study consists of three phases: Screening (up to 60 days), Treatment (12 weeks) and Follow-Up (4 weeks). In Groups 2 and 4, the randomized investigational products will be applied twice daily for 12 weeks to cover the entire single contiguous 5 cm x 5 cm (25 cm^2) lesional area on the face and/or scalp. In Groups 1 and 3, the randomized active DFD-07 (celecoxib) Cream product will be applied only in the evening, while the Vehicle for DFD-07 Cream will be applied in the morning to keep the blinding between groups.

Subjects in all the groups will undergo a further 4-week treatment-free period from Week 12 to Week 16 (End of Study).

The investigational products will be applied twice daily for 12 weeks to cover the entire lesional area (5 cm x 5 cm) on the face and/or scalp identified by the Investigator for treatment. The dose for the study product will be a maximum of 0.5 g per application to the entire 5 cm x 5 cm area on the face and/or scalp for a maximum dose of 1.0 g per day.

Subject visits are scheduled at Screening (Visit 1), Baseline (Visit 2 - Day 1), and Weeks 4 (Visit 3), 8 (Visit 4), 12 (Visit 5) and 16 (Visit 6). Clinical determinations of efficacy will be conducted based on clinically visible or palpable lesions of AK in the treated areas at Weeks 4, 8, 12 and 16 in comparison to Baseline. Comparisons will be made between the different strengths and dosing regimens of DFD-07 (celecoxib) Cream and Vehicle Cream.

Local cutaneous tolerability will be determined at Visits 2 – 6 for the entire treated area. Other safety assessments include physical examinations (HEENT, lungs, heart, abdomen, skin,

neurologic), laboratory assessments, electrocardiogram (EKG), vital signs (blood pressure, pulse rate), urine pregnancy tests, and collection of adverse event data.

5 SELECTION OF STUDY POPULATION

5.1 Number of Subjects

A total of approximately 240 subjects with actinic keratosis of the face and/or scalp will be randomized into four groups in a 1:1:1:1 ratio (60 subjects in each group) at approximately 20 centers.

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 with a legal guardian, must have the written informed consent of the legal guardian.
2. Subject (or legal guardian) must be willing to authorize use and disclosure of protected health information collected for the study.
3. Subjects must have 5 or more AK lesions that are non-hypertrophic and non-hyperkeratotic, contained within a single contiguous approximately 5 cm x 5 cm (25 cm^2) region of face and/or scalp.
4. Subjects must be 18 years of age or older. Male and female subjects can be enrolled.
5. Female subjects of childbearing potential must agree to use contraception during the study which can include abstinence with an adequate secondary option should the subject become sexually active. All women of childbearing potential must complete a urine pregnancy test (test must have a sensitivity of at least 25mIU/ml for human chorionic gonadotropin) at the Baseline Visit (Visit 2) and the test result must be negative to be eligible for enrollment.

   A female is considered of childbearing potential unless she is:
   - postmenopausal for at least 12 months prior to study product administration;
   - without a uterus and/or both ovaries; or has been surgically sterile (i.e., tubal ligation) for at least 6 months prior to study product administration.

   Reliable methods of contraception are:
   - hormonal methods or intrauterine device in use $\geq$ 90 days prior to study product administration; or
   - barrier methods plus spermicide in use at least 14 days prior to study product administration.
   - partner has had a vasectomy at least 3 months previous to study product administration.
   - Essure®

   Exception: Sexually inactive female subjects of childbearing potential are not required to practice a reliable method of contraception and may be enrolled at the investigator's discretion provided that they are counseled to remain sexually inactive for the duration of the study and understand the possible risks involved in getting pregnant during the

study. An abstinent female must agree that if she becomes sexually active during the study she will use an acceptable form of contraception.

6. Subjects must be able to have ≥ 60 days washout from prohibited medications:
    - Masoprocol
    - 5-Fluorouracil
    - Cyclosporin
    - Retinoids (oral and topical)
    - Trichloroacetic Acid/Lactic Acid Peel
    - 50% Glycolic Acid Peel
    - Topical or systemic diclofenac, celecoxib or any other NSAID (however daily low-dose aspirin is allowed, as long as the subject has been on a stable dose, ≤ 100 mg once a day, for 60 days prior to the start of the study.) Note: Subjects may use acetaminophen/paracetamol as needed
    - Photodynamic therapy
    - Topical or systemic immunomodulating agents
    - Systemic, topical or intralesional interferon
    - Imiquimod (Aldara, Zyclara)
    - Topical ingenol mebutate (Picato)
    - Topical tacrolimus
    - Topical pimecrolimus
    - Sirolimus
    - Intralesional BCG
    - Topical coal tar products
    - Topical or systemic corticosteroids (nasal and inhaled steroids are allowable)
7. Subjects must agree not to use any product on the treatment area during the entire course of study except for Investigator-approved cleanser, sunscreen, wash, and non-medicated 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.
8. Subjects must be willing to comply with sun avoidance measures for the face including use of Investigator-approved sunscreen and/or hats, have limited sun exposure time, and have no tanning bed use.
9. Subjects must be in good general health as determined by the Investigator and supported by the medical history, and normal or not clinically significant abnormal vital signs (blood pressure and pulse rate). Subjects are eligible if:
    - Systolic blood pressure (BP) < 160 and > 85 mmHg
    - Diastolic BP < 100 and > 50 mmHg

5.3 Exclusion Criteria

1. Known or suspected hypersensitivity to any non-steroidal anti-inflammatory drugs (NSAID) or any component of the formulation of the study medication, including a history of asthma, urticarial, or other allergic-type reactions after taking aspirin or other NSAIDs.
2. Known or suspected allergy to sulfonamides.

3. Clinical evidence of severe, uncontrolled autoimmune, cardiovascular, gastrointestinal, hematological, hepatic, neurologic, pulmonary or renal disease.
4. Recent (within 6 months) or planned coronary artery bypass graft surgery.
5. Significant history (within the past year) of alcohol or drug abuse.
6. Participation in any clinical research study within 30 days of the Baseline Visit.
7. Concomitant use of cosmetics or other topical drug products on or near the selected treatment area, except for Investigator-approved cleanser, sunscreen, wash, and non-medicated makeup.
8. Cosmetic or therapeutic procedures (e.g. laser, peeling, photodynamic therapy) within 2 weeks and within 2 cm of the selected treatment area.
9. Other skin conditions within the selected treatment area (e.g. rosacea, psoriasis, atopic dermatitis, eczema, basal or squamous cell carcinoma or albinism).
10. Use of sun lamps, tanning beds, and tanning booths during the 14 days prior to the Baseline Visit or planned use during the study.
11. Any systemic cancer therapy or diagnosis within 6 months of the Baseline Visit.
12. Females who are pregnant or lactating or planning to become pregnant during the study period.
13. Subjects may not have a personal relationship with any member of the study staff or be part of the staff at the medical practice.
14. Subjects who are unable to comply with the study requirements for any reason.

6 SUBJECT TREATMENT

6.1 Investigational Products

6.1.1 Description

DFD-07 (celecoxib) Cream, 1.25% and 2.5% and Vehicle for DFD-07 Cream will be provided by Dr. Reddy's Laboratories, Ltd.

Each investigational product of Active and Vehicle will be supplied as 30 grams in a collapsible aluminum tube. The study product is a white to off-white cream. The active and Vehicle creams will be similar in appearance and packaging.

6.1.2 Labels

Tubes will be packed two to a kit. Labels on the tubes will be in English and include protocol number, randomized kit number, investigational use warning, storage conditions, brief instructions for use, including whether the tube is for AM or PM use, and Sponsor name and address. Subjects will be asked to return the tubes of study medication in the kits.

In addition, there will be a place to write the subject number and subject initials on the kit label. The kit label will also have a tear-off panel that includes the protocol number, randomized kit number, subject number and initials. The tear-off panel is to be affixed to the source document (drug dispensing record).

6.1.3 Dispensing and Return

Tubes of study product will be dispensed to subjects at the Baseline Visit (Visit 2) by study staff. The study medication kits will be assigned by the interactive web-based system (IWRS). The weight of the tube(s) should be recorded before dispensing. Additional kits will be

dispensed as needed. Tubes will be weighed upon return and the weight will be recorded in the source documents. Partially filled tubes can be re-dispensed back to the subject after they have been weighed and the weight has been recorded in the source document. The tear-off panel is to be affixed to the source document. Subject initials and subject number must be written on the kit label. Study staff will then dispense and instruct subject on study product use.

Dispensing and return of study product must be documented in the Investigational Product Site Dispensing and Return Log.

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

6.1.4 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 containers of study product, used and unused, must be returned to the Sponsor or designee, or destroyed with the Sponsor's approval.

In addition, a study product accountability log showing dispensing to and return by subjects must be maintained at each study site. Any dispensed tubes that are not returned to the clinic must be documented on the log.

6.1.5 Storage

The study product must be stored at controlled room temperature 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F).

The Investigator agrees to use the study product only within the framework of this clinical study and in accordance with this study protocol. Any unused, partially used or empty containers of the study product will be returned to the Sponsor or destroyed with the Sponsor's approval after drug accountability has been done at the termination of the study.

Receipt, distribution and return of the study product must be properly documented on the drug accountability form.

6.2 Treatment Regimen

Subjects will use assigned study product twice daily (i.e. in the morning and in the evening, after any bathing or showering) with approximately 12 hours between applications for 12 consecutive weeks starting from Baseline/Day 1 (Visit 2) during the study visit. After randomization during the Baseline/Day 1 Visit (Visit 2), subjects will apply the first dose of study medication in the Investigator's office under supervision. The area(s) of application must be washed (with an Investigator-approved cleanser) before the study product is applied. Subjects should be instructed to apply a dime size amount of study product to the Investigator identified single contiguous treatment area (5 cm x 5 cm). Subjects will be provided with a diary to record the timing of application of the study medication on a daily basis. Starting with the first application during the Day 1 Visit, all applications will be recorded in the subject diary, which

will be checked by the Investigator or designee for compliance and potential safety-related data at Visits 3-6.

6.3 Treatment Precautions

Study products should not be used by any subject with known or suspected hypersensitivity to any non-steroidal anti-inflammatory drugs (NSAIDs) or any component of the formulation of the study medication. Indications of hypersensitivity include a history of asthma, uticarial, or other allergic-type reactions after taking aspirin or other NSAIDs or known or suspected allergy to sulfonamides.

6.4 Treatment and Protocol Compliance

Subjects will be provided an instruction sheet for the study product along with a diagram of affected areas to be treated. Study staff should review the instruction sheet and diagram with the subjects at every visit to ensure protocol compliance. AK lesions are to be counted and updated within the treatment area on the diagram at each post-Baseline visit. The first and last application of study product will be performed by the subjects at the site under supervision.

At each post-Baseline visit until Visit 5, the Investigator or designee will interview subjects concerning treatment compliance and ask if any doses have been missed. The Investigator will also ask about compliance with protocol requirements. Protocol deviations will be recorded in the subject's study record, and on a protocol deviation form that will be provided to the site. These items may also 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 subjects due to protocol deviations unless safety is a concern.

Subjects will be provided a diary card for documenting the dates of applications. The subjects will review the diary card with the Investigator or designee at each visit. The number of applications applied and the number of missed applications will be recorded on the source documents. By definition, there are no missed applications after the last date of treatment even if recorded on the diary.

In addition, tubes of study product will be weighed before dispensing and after the return of the investigational products. At the last visit, the tube should be weighed before and after the application to determine the amount of study product applied for the last dose. These weights should be entered into the CRF.

6.5 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned randomly via IWRS to one of four treatment groups in a 1:1:1:1 ratio (60 subjects per treatment group). A study medication assignment schedule will be created that is stratified by site, with kit numbers randomly assigned to study products. A randomization schedule will be produced for each site independently for use in randomization by the IWRS. The date and time of randomization, as well as the kit number, will be entered on the eCRF.

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

6.6 Blinding

6.6.1 Method of Blinding

This is a multi-center, randomized, double-blind, parallel group, Vehicle-controlled study. The DFD-07 (celecoxib) Cream and Vehicle Cream are white to off-white in color, and are similar in appearance, smell, and feel. The study medication kits (active and vehicle) will be marked for AM and PM use, so as to ensure blinding of the QD versus BID arms of the study. In the QD arms for the active product, the active product marked PM will be applied in the evening while the vehicle product marked AM will be applied in the morning. Since the active and vehicle product are similar, the study blind is expected to be preserved by this approach.

6.6.2 Unblinding

This is a double-blind study so neither Investigator nor subject will know which medication they receive. DFD-07 (celecoxib) Cream, 1.25% and 2.5%, and its matching Vehicle for DFD-07 Cream will be similar in appearance and have identical packaging.

The blind should be broken for all subjects suffering serious adverse events (SAEs) in which knowledge of the treatment assignment is critical to the subject's management. The blind for the subject may be broken by the Investigator, or designee, by contacting the IWRS. The blind should not be broken at the study site level except in a medical emergency (where knowledge of the study medication received would affect the treatment of the emergency). For a medical emergency, the blind must only be broken following discussion with Sponsor medical monitor, on a case-by-case basis, at the discretion of the Investigator/treating physician/Sponsor.

If the blind is broken, the date, time, and reason must be recorded in the subject's source record, eCRF, and any associated adverse event (AE) report. If an Investigator, site personnel performing assessments, or subject is unblinded, the unblinding incident and unblinded subject must be listed as a major protocol deviation. A subject for whom the blind is broken will discontinue study medication and be scheduled for an End of Study safety follow-up visit and then discontinued from the study. The subject will be encouraged to stay in the study until the AE is resolved or stabilized. All Investigators and the IRB will receive blinded safety reports. However, on the request of the IRB, the Sponsor will send unblinded reports directly to the IRB.

6.7 Prior and Concomitant Therapy

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

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

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

The following medications are not permitted within the 60 days prior to the Baseline Visit (Visit 2) and during the conduct of the study until EOS (Visit 6):

- Masoprocol
- 5-Fluorouracil
- Cyclosporin
- Retinoids
- Trichloroacetic Acid/Lactic Acid Peel
- 50% Glycolic Acid Peel
- Topical or systemic diclofenac, celecoxib or any other NSAID (however daily low-dose aspirin is allowed, as long as the subject has been on a stable dose, ≤ 100 mg once a day, for 60 days prior to the start of the study.) Note: Subjects may use acetaminophen/paracetamol as needed
- Photodynamic therapy
- Topical or systemic immunomodulating agents including:
- Systemic, topical or intralesional interferon
- Imiquimod (Aldara, Zyclara)
- Topical ingenol mebutate (Picato)
- Topical tacrolimus
- Topical pimecrolimus
- Sirolimus
- Intralesional BCG
- Topical coal tar products
- Topical or systemic corticosteriods (nasal and inhaled steroids are allowable)

No pharmaceutical therapy, physical therapy or cosmetic must be applied to the selected study area throughout the entire study from Visit 1 to Visit 5, except for Investigator-approved cleanser, sunscreen, wash, and non-medicated makeup.

7 STUDY PROCEDURES AND EVALUATIONS

7.1 Screening

A separate Screening Visit (Visit 1) may be performed when a washout period is required or for scheduling purposes. Alternatively, Visits 1 (Screening) and 2 (Baseline/Day 1) may be combined if no washout period is required. The subject number, date of visit, date of informed consent, reason for screen failure (if applicable) and study status will be captured in the eCRF for every screen failure subject. The Baseline/Day 1 (Visit 2) Visit must occur no later than 60 days after the Screening Visit. Medical 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 into the eCRF.

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

7.2 Demographic and Baseline Characteristics

Demographic variables include age (computed from date of birth and Baseline Visit date), race, ethnicity, weight, height and sex.

7.3 Efficacy Variables

Definition of the treatment area

Prior to the first application of the study medication at Visit 2, the Investigator will define the treatment area. The subject must have 5 or more AK lesions within a single contiguous 5 cm x 5 cm (25 cm^2) area of the face and/or scalp . Only a single 25 cm^2 area will be treated per subject. If the subject has extensive lesions in an area spread over the face and scalp, the lesional area on the face will be preferably selected for treatment. In order to determine and identify the position of the treatment area at each Visit, a plastic grid foil will be laid on the treatment area(s) and the contours of the treatment area(s) will be circumscribed. The lesions in the area will be circumscribed as well. Furthermore, facial features like eyebrows, ears, etc. will be circumscribed and marked. The foil will be labelled with the subject number and filed in the source document. It will be used again at Visits 3 to 6 (EOS).

The subject will need to be instructed where the treatment area is located. For this purpose, the Investigator will insert a drawing into the diary depicting the location of the treatment area. Subjects will be instructed to apply the study product to the entire area as defined by this drawing.

Efficacy assessment

The treated area will be inspected visually and by palpation. This will always be done by the same Investigator at each investigational site (unless the Investigator has delegated it to a trained designee, with proper documentation). The number of AK lesions being either visible or palpable in the defined treatment area will be assessed at all study visits. All lesions in the treatment area will be included in the lesion count even if the lesion is a new lesion that was not identified during the first Visit.

7.4 Safety Variables

Safety assessments include physical examinations (HEENT, lungs, heart, abdomen, skin, neurologic), vital signs (blood pressure, pulse rate), 12-lead EKGs, hematology/chemistry/urinalysis laboratory tests (Appendix 2), urine pregnancy tests for women of child bearing potential, local tolerability evaluation of the treated skin (including erythema, edema, weeping/exudate, flaking/scaling/dryness, scabbing/crusting, erosion/ulceration, vesiculation/blistering), and collection of adverse events (AEs) data. Adverse events will be collected by spontaneous reports from subject, either verbal or recorded in the subject diary, by directed questioning of subject, and by observation (see Section 8 for details about AEs). For female subjects of child bearing potential, urine pregnancy tests will be conducted at Screening, Baseline, and every subsequent visit. The test must have a sensitivity of at least 25 mIU/mL for human chorionic gonadotropin.

Adverse events, whether believed by the Investigator to be related or unrelated to treatment, will be recorded on the CRF.

7.5 Drug Concentration Measurements

Study drug concentration measurements will not be conducted in this study.

7.6 Early Withdrawal of Subjects

1. Subjects should be withdrawn from the study if they no longer wish to participate, are being uncooperative, or if the Investigator feels that it is in the best interest of the subject to withdraw.
2. Subjects with protocol deviations or for whom it is discovered should have been excluded should not be withdrawn unless there is a safety concern. The protocol deviation should be recorded in the subject's source documents and the eCRF.
3. If during the course of treatment a subject experiences a cardiovascular or hematologic AE (including abnormal laboratory values) of Common Terminology Criteria for Adverse Events (CTCAE) Version 4.02 Grade 2 or higher, the study product will be discontinued and the subject will be withdrawn from the study.
4. Subjects who experience an AE resulting in or requiring discontinuation of study product use should be encouraged to be followed until the AE is resolved or stabilized.
5. If a female subject becomes pregnant during the study, study product will be discontinued immediately and she will be followed through the pregnancy and delivery. Details of the pregnancy, delivery and health of the infant should be recorded on the Pregnancy Surveillance Form. The Sponsor will be notified immediately after the subject is detected to be pregnant.
6. At the time of study discontinuation, the Investigator will record the reason for early withdrawal, date of last study product application, date of last visit or contact, collect adverse event data, and, if possible, perform all End of Study Visit specific evaluations. Every attempt should be made to contact subjects who are lost-to-follow-up. At least three attempts must be documented in the subject's source document, including the use of at least one 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. Subjects who withdraw early will not be replaced.

7.7 Modification of Protocol

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

7.8 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.

7.9 Data Safety Monitoring Board

A Data Safety Monitoring Board will not be utilized in this study.

7.10 Study Schedule

A Study Schedule Chart can be found on page 9. There are at least 5 study visits; Screening (Visit 1), Baseline (Visit 2, Day 1), Week 4 (Visit 3), Week 8 (Visit 4), Week 12 (Visit 5-End of Treatment) and 4 Weeks Post-Treatment (Visit 6 – End of Study). The Screening Visit and Baseline/Day 1 Visit may be combined into a single visit if no wash-out is required. The visit window is ±5 days for Weeks 4, 8, 12 and 16. Visits 1 and 2 cannot be separated by more than 60 days.

7.10.1 Visit 1 - Screening Visit

The Screening Visit should occur no more than 60 days before the Baseline Visit.

1. Obtain written informed consent prior to initiating any study procedures or before withdrawing any of the therapies prohibited during the study (including the wash-out period, if needed). Provide subject with signed copy of consent form. Document informed consent in the subject's study record.
2. List the subject on the Screening/Enrollment Log and assign a subject number. Subject numbers consist of the 2-digit site number followed by sequential 3-digit numbers usually starting with 001 (e.g., 01-001, 01-002 etc.). All subjects including screen failures should be assigned a subject number.
3. Perform a urine pregnancy test on all female subjects of child bearing potential.
4. Collect demographic data – date of birth, sex, race, ethnicity, height and weight. Review and record medical history, AK history (including naïve vs previous therapy, AK treatment received 12 months prior to screening, onset date for AK and first AK treatment), and concomitant medications, therapies, and procedures. Medical history (including any cosmetic or therapeutic procedures, such as laser, peeling, and photodynamic therapy, within 2 cm of the selected treatment area and within the 2 weeks prior to the Baseline Visit) and AK history should be collected for the prior 1-year period and concomitant medications, therapies, and procedures collected from the prior 6-month period. Only ongoing medical history items and ongoing concomitant medications should be entered on the eCRF. AK history will be collected and recorded in the eCRF.
5. Assess AK lesions (counting the visible and palpable lesions and measuring total area of lesions) to confirm that the subject has a single contiguous 5cm x 5cm area that qualifies for treatment on the face and/or scalp. If the subject has extensive lesions in an area spread over the face and scalp, the lesional area on the face will be preferably selected for treatment.
6. Documentation of size and location of selected treatment area on grid foil
7. Collect vital signs (blood pressure and pulse rate).
8. Screen subjects according to the study inclusion/exclusion criteria to determine tentative eligibility. Initiate any protocol-required washout, if applicable.
9. Schedule Visit 2 (Baseline/Day 1). If no washout is required, Visit 1 and Visit 2 may be combined.

7.10.2 Visit 2 - Day 1 - Baseline Visit

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

1. Update the medical history and concomitant medications. Any medical event (not related to a protocol intervention) that occurred since informed consent form was signed should be recorded as medical history. Only ongoing medical conditions and ongoing concomitant medications should be entered on the eCRF.
2. Collect data on 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 AK.
3. Confirm eligibility according to inclusion/exclusion criteria.
4. Collect blood (2/3 tablespoon) and urine for hematology/chemistry/urinalysis safety labs.
5. Conduct urine pregnancy test on all female subjects of child bearing potential. Record method of contraception, as applicable, on source only.
6. Collect vital signs (blood pressure and pulse rate), height and weight.
7. Perform a physical examination (HEENT, lungs, heart, abdomen, skin, and neurologic).
8. Perform a 12-lead EKG.
9. Conduct clinical assessments:
    a. Investigator is to identify a treatment area on the face and/or scalp (if not already done at screening).
    b. Investigator is to document the number and location of the lesions with in the treatment area and on a grid foil. One copy of the grid foil should be inserted into the subject's source document and the other should be given to the subject for use at home.
    c. Investigator is to count the visible and palpable AK lesions in treatment areas
    d. Confirm size and location of selected treatment area on grid foil
10. Randomize subject by using IWRS.
11. Weigh and then dispense tubes of study product to subject. The tear-off panel from the box of the investigational products is to be affixed to the source document and filed in subject's chart. Instruct subject on study product use. Review the Subject Instructions with the subject.
12. When the subject performs the first application of study product at the site, ensure that it is done correctly.
13. Remind subject to bring all tubes of study product to next visit.
14. Dispense and review use of diary. Remind subject to report missed applications and/or potential AEs as well as any medication used in the diary and to bring diary to each visit.
15. Schedule next visit.
16. Complete eCRF for randomized subjects. For every screen failure subject, record the subject number, date of visit, date of consent, reason for screen failure, and study status (screen failure) in the eCRF.

7.10.3 Visit 3- Week 4 (Allowed visit window is ± 5 days)

1. Evaluate treatment and protocol compliance and record any deviations. This includes a review of the diary card for number of applications and missed applications.
2. Investigator is to document the number and location of the lesions within the treatment area on a grid foil. One copy of the grid foil should be inserted into the subject's source document and the other should be given to the subject for use at home.
3. Collect vital signs (blood pressure and pulse rate).
4. Perform a 12-lead EKG.

5. Collect blood (2/3 tablespoon) and urine for hematology/chemistry/urinalysis safety labs.
6. Conduct a urine pregnancy test for all females of child bearing potential.
7. Collect AE data. This includes a review of the diary card for potential AEs.
8. Update concomitant medications data.
9. Dispense diary and review instructions. Remind subject to bring all tubes of study product to each visit.
10. If subject requires more study product, weigh and then dispense study product as needed from IWRS assignment and collect empty or nearly empty tubes. Weigh tubes when they are collected and prior to re-dispensing. Re-dispense partially filled tubes.
11. Schedule next visit.
12. Complete eCRF.

7.10.4 Visit 4 – Week 8 (Allowed visit window is ± 5 days)

1. Evaluate treatment and protocol compliance and record any deviations. This includes a review of the diary card for number of applications and missed applications.
2. Investigator is to document the number and location of the lesions with in the treatment area and on a grid foil. One copy of the grid foil should be inserted into the subject's source document and the other should be given to the subject for use at home.
3. Collect vital signs (blood pressure and pulse rate).
4. Conduct a urine pregnancy test for all females of child bearing potential.
5. Collect AE data. This includes a review of the diary card for potential AEs.
6. Update concomitant medications data.
7. Dispense diary and review instructions. Remind subject to bring all tubes of study product to each visit.
8. If subject requires more study product, weigh and then dispense study product as needed from IWRS assignment and collect empty or nearly empty tubes. Weigh tubes when they are collected and prior to re-dispensing. Re-dispense partially filled tubes.
9. Schedule next visit.
10. Complete eCRF.

7.10.5 Visit 5 – Week 12/End of Treatment Visit (Allowed visit window is ± 5 days)

1. Evaluate treatment and protocol compliance and record any deviations. This includes a review of the diary card for number of applications and missed applications.
2. Investigator is to document the number and location of the lesions with in the treatment area and on a grid foil. One copy of the grid foil should be inserted into the subject's source document.
3. Collect vital signs (blood pressure and pulse rate).
4. Perform a physical examination (HEENT, lungs, heart, abdomen, skin, and neurologic).
5. Perform a 12-lead EKG.
6. Collect blood (2/3 tablespoon) and urine for hematology/chemistry/urinalysis safety labs.
7. Conduct a urine pregnancy test for all females of child bearing potential.
8. Collect AE data. This includes a review of the diary card for potential AEs.
9. Update concomitant medications data.
10. Dispense diary and review instructions. Advise subjects that if they still have unreturned tubes of study product, they are not to use any of the study products after this visit.

11. Weigh tubes when they are collected.
12. Schedule next visit.
13. Complete eCRF.

7.10.6 Visit 6 – Week 16/End of Study Visit (Allowed visit window is ± 5 days)

1. Evaluate protocol compliance and record any deviations.
2. Investigator is to document the size and location of the lesions with in the treatment area and on a grid foil. One copy of the grid foil should be inserted into the subject's source document.
3. Collect vital signs (blood pressure and pulse rate).
4. Conduct a urine pregnancy test for all females of child bearing potential.
5. Collect AE data. This includes a review of the diary card for potential AEs.
6. Complete eCRF.

7.10.7 Early Withdrawal

If a subject is withdrawn from the study according to any of the criteria defined in Section 7.6, the following procedures will be performed:

1. Evaluate treatment and protocol compliance and record any deviations. This includes a review of the diary card for number of applications and missed applications.
2. Investigator is to document the number and location of the lesions with in the treatment area and on a grid foil. One copy of the grid foil should be inserted into the subject's source document.
3. Collect vital signs (blood pressure and pulse rate).
4. Perform a physical examination (HEENT, lungs, heart, abdomen, skin, and neurologic).
5. Perform a 12-lead EKG.
6. Collect blood (2/3 tablespoon) and urine for hematology/chemistry/urinalysis safety labs.
7. Conduct a urine pregnancy test for all females of child bearing potential.
8. Collect AE data. This includes a review of the diary card for potential AEs.
9. Update concomitant medications data.
10. Weigh tubes when they are collected.
11. Complete eCRF.

8 ADVERSE EVENTS

Adverse Events will be documented at Visits 2 to 6. The definitions as laid down in GCP-V § 3 (6) – (9) will be the basis for the safety assessments in this clinical study.

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.

Baseline assessments are made prior to first application. For medical conditions present at Baseline, an adverse event should be recorded at subsequent visits if the severity is worse than Baseline.

An adverse event 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 adverse event 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 adverse event except for adverse events 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 adverse events. Unexpected worsening of pre-existing conditions should be reported as adverse events. The disease or condition being studied or expected progression, signs, or symptoms of the disease or condition being studied should not be reported as an adverse event unless more severe than expected.

All serious adverse events, all study-product-related adverse events and all adverse events 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 adverse events, 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 treatment is initiated until the Week 16/End of Study Visit takes place. 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

All AEs will be documented including

- Severity (see 8.3.1: Severity for details)
- Start and stop date
- Causality assessment with study medication
- Measures / action taken
- Serious AE (yes/no)

All AEs will be followed-up until resolution or the End of Study Visit and documented in CRF and subject's medical file.

SAEs will be documented in the subject's medical file, the CRF and on the SAE-form. A copy of the SAE form will be emailed or faxed to the Sponsor and filed in the Investigator's File.

Local Reactions in the treatment area will be documented separately. The following local reactions will be assessed and documented:

a. Erythema
b. Edema
c. Weeping/exudate
d. Flaking/scaling/dryness

e. Scabbing/crusting
f. Erosion/ulceration
g. Vesiculation/blistering

Per definition, all Local Reactions are causally related to the study treatment.

All Local Reactions will be documented including

- Severity
- Start and stop date

The severity of the local reactions is graded as follows:

Grades	Score	Description
None	0	No signs of reaction
Mild	1	Slight signs of reaction
Moderate	2	Definite signs of reaction
Severe	3	Subject discontinues study product due to reaction

The Investigator will record all adverse events, regardless of relationship to study product, on the adverse event CRF. Standard medical terminology should be used when describing adverse events. Whenever possible a diagnosis should be made and recorded on the CRF rather than listing signs and symptoms. Intermittent adverse events can be recorded once. The anatomical location of the adverse event must be specified, when applicable, as well as whether the location is a treatment area. The following information should be recorded on the CRF:

1. Description
2. Start date
3. Stop date or date of death, ongoing, or unknown
4. Severity of the event (see 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 8.3.2: Relationship to Study Product (Causality) for details)
8. Indication of whether the event is serious (see 8.3.3: Seriousness for details)
9. Action taken including treatment with concomitant medication

8.3 Assessment of Adverse Events

8.3.1 Severity

It is the Investigator's responsibility to assess the severity of each adverse event. 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 adverse event. The degree of "relatedness" of the adverse event 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 adverse event. A serious adverse event (SAE) is any adverse event 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 e-mailed within 24 hours of becoming aware of the event. The minimum *initial* information required to be reported on the Serious Adverse Event Form is: the protocol number, site number, subject number, subject initials, the event, the causality, the date of the event and the name and contact information (email, phone number) 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, M.D., M.S.
Fax: 908-450-1510
Email: SAE@drreddys.com

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

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

It is the responsibility of the CRO, Integrium, LLC® to promptly notify the other Investigators involved in this study and they in turn notify their respective IRBs 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., subject 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 adverse event if AE 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 as described in Section 8.4 above and complete a pregnancy surveillance 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 a pregnancy surveillance form.

The following outcomes of pregnancy fall under the criteria for serious adverse events and should be reported as such: delivery complications prolonging hospitalization, spontaneous abortion, still birth, 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 the authorization for use/disclosure of subject's PHI
- Expiration of authorization

In the event that 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 that have revoked authorizations 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 which include all pertinent study related information including original signed/dated informed consent forms. Source documents for this study include all written records of study data. All study data must have a paper source document including Investigator assessments.

9.3 Screening/Enrollment Log

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

9.4 Case Report Forms

All data requested on the CRF must be recorded on source documentation. The CRF cannot be the source document for any data. Detailed instructions and training for completing the CRF will be provided to the sites.

Study subjects are not to be identified by name on CRFs, but rather by coded identifiers (subject number and initials). The Investigator or Sub-investigator must review all CRF pages for each subject and approve the group of CRFs pages for each subject.

9.5 Data Capture

Study data will be entered into and maintained in a 21 CFR Part 11 compliant database.

9.6 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 one year previous experience in monitoring clinical studies. The monitor should be familiar with the etiology and signs and symptoms of Actinic Keratosis 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 an Investigator Meeting or individually on-site.

During the course of the study, a monitor will make multiple site visits to check the progress of the study, review consent forms, review protocol compliance, assess drug accountability, and ensure that the study is being conducted according to the protocol and Good Clinical Practice. 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 will conduct QA audits randomly or if needed at 5-10% of the investigational sites.

11 STATISTICAL CONSIDERATIONS

11.1 Sample Size

The sample size estimation of this trial is based on the assumption that the Active product exhibits a complete clearance of the AK lesions in 45% of the subjects, while the Vehicle does so in 20% of the subjects (a difference of 25% between the Active and Vehicle treatment groups). Assuming a power of 80% and α of 0.05, in order to demonstrate the statistical significance of such an effect difference, 54 patients per treatment group would be needed.

Considering the exploratory dose-response character of the trial, and assuming a drop-out rate of 10%, 60 subjects need to be recruited in each treatment group. With 4 treatment groups in the study, it is planned to recruit approximately 240 subjects in the study.

11.2 Analysis Data Set

11.2.1 Intent to Treat

The intent-to-treat population (ITT) will be the primary efficacy analysis data set and consists of all subjects who are randomized and dispensed study medication.

Missing data for efficacy analysis will be replaced using last observation carried forward (LOCF). If a subject withdraws early from the study, that subject's efficacy assessments captured at the early termination visit will be assigned to the nearest corresponding scheduled visit that has been missed.

11.2.2 Per Protocol

The PP population will include all subjects in the ITT population who complete the Week 16 evaluation without any major protocol violations (i.e., any subject or Investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy).

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

1. Subject met all inclusion/exclusion criteria.
2. Subject did not take any prohibited concomitant medications during the evaluation period. The concomitant medication usage will be reviewed during the population determination review, remaining blinded to treatment designation, to determine prohibited medication usage that warrants exclusion from the PP population if they met the entry criteria without any protocol violations. This review will take into consideration the timing, duration of treatment with the concomitant medication, and influence on the efficacy and safety assessments prior to deeming a prohibited concomitant medication as a protocol violation that warrants exclusion from PP.
3. Completed the Week 16 visit within the allowed window.
4. Subject was compliant with the dosing regimen. A subject will be considered compliant if the subject applied at least 80%, but no more than 120% of the expected number of applications during the entire treatment period.

Subjects who prematurely discontinue from the study due to documented lack of efficacy, worsening condition, or a treatment-related AE will be included in the PP population. These subjects will be considered failures for all subsequent visits in the analysis of the primary and secondary endpoints of complete and partial clearance. Other than this, no imputations for missing data will be made for the PP populations.

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

11.2.3 Safety Population

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

11.3 Demographic and Baseline Data

Subject demographic and baseline data characteristics will be reported in descriptive summaries by treatment group for the Intent to Treat, Per Protocol and Safety populations.

11.4 Efficacy Analyses

Efficacy summaries will be provided for the Intent to Treat and Per Protocol populations.

Descriptive statistics (N, arithmetic means, SD, minimum, median, maximum) for all continuous values and frequency tables for categorical variables will be created. With regard to primary and secondary objectives as descriptive statistical evaluation, absolute and relative frequencies of number of observations will be presented together with 95 %- confidence intervals.

In case of missing values the last-observation-carried forward principle shall be applied.

A statistical testing procedure Chi-Quadrat test or alternatively a binomial testing procedure will be applied. In case of small sample sizes alternatively Fisher's exact test may be applied. Other tests may be applied as required and these will be enumerated in the Statistical Analysis Plan (SAP).

Further details of the statistical evaluation procedure will be presented in the Statistical Analysis Plan (SAP). Analysis sets (ITT population, safety population, per-protocol population, rational for exclusion from any population) will also be specified in the SAP.

Primary endpoint

For statistical assessment of the primary endpoint with a significance level of 0.05% the following underlying hypotheses are used:

H0: $p1 \leq p2$ vs. H1: $p1 > p2$

where p1 is the treatment effect of 2.5% DFD-07 (celecoxib) Cream twice daily and p2 is the treatment effect of the Vehicle Cream preparation.

Secondary endpoints

For statistical assessment of all product comparisons after certain period of treatment (i.e. at Visits 3, 4, 5 and 6) with a significance level of 0.05% the following underlying hypotheses are used:

H0: $p1 \leq p2$ vs. H1: $p1 > p2$

where p1 is the treatment effect of 1.25% or 2.5% DFD-07 (celecoxib) Cream once daily and p2 is the treatment effect of the Vehicle Cream preparation.

For product and time point comparisons of medians, Mann-Whitney U-test and Wilcoxon-test may be applied.

11.5 Safety Analyses

All subjects who receive at least one dose of study product and provide any post-baseline safety information will be included in the Safety analysis.

11.5.1 Extent of Exposure

The extent of exposure to study product will be summarized as the total number of applications and the total amount of study product used based on tube weights. The amount of the last dose will be provided based on tube weight before and after treatment. Also the calculated mean amount of drug used per application will be provided.

11.5.2 Local Safety Evaluation

Erythema, edema, weeping/exudate, flaking/scaling/dryness, scabbing/crusting, erosion /ulceration and vesiculation/blistering will be summarized by visit.

11.5.3 Adverse Events

All reported treatment-emergent AEs will be summarized by treatment group, the number of subjects reporting events, system organ class, preferred term, severity, relationship to study product, and seriousness. When summarizing AEs 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.

Serious adverse events (SAEs) will be summarized by severity and relationship to study product, and 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, pulse rate) will be summarized at each evaluation.

11.5.5 Physical Examination and EKG

Physical examinations (HEENT, lungs, heart, abdomen, skin, and neurologic) will be performed for all subjects at Baseline (Visit 2) and Week 12 (Visit 5). EKGs will be performed for all subjects at Baseline (Visit 2), Week 4 (Visit 3), and Week 12 (Visit 5). Results will be presented in subject data listings.

11.5.6 Safety Laboratory Values

Hematology/chemistry/urinalysis safety labs will be performed for all subjects at Baseline (Visit 2), Week 4 (Visit 3), and Week 12 (Visit 5). Urine pregnancy tests will be performed at all visits for female subjects of child bearing potential, and will be presented in subject data listings.

Subset Analyses

Subgroup analyses will be done based on age (above 65 years vs below 65 years), median age, gender, race, ethnicity, location of treated lesion(s) on the face and/or scalp and previous treatment of AK (naïve vs experienced).

11.6 Analysis of Drug Concentrations

Analysis of drug concentration will not be done in this study.

11.7 Statistical Analysis Plan

A Statistical Analysis Plan, describing all statistical analyses, will be provided as a separate document prior to database lock.

12 REFERENCES

1. DFD-07 (celecoxib) Cream [Investigator's Brochure]. Promius Pharma LLC, Princeton NJ, 2015

2. Celebrex (capsules) 200 mg and 400 mg Prescribing Information.http://www.drugs.com/pro/celebrex.html (last accessed on 01 SEP 2015)

3. Solaraze Prescribing Information (Diclofenac sodium 3% gel): http://www.drugs.com/pro/solaraze.html (last accessed on 01 SEP 2015)

4. World Medical Association, Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. Last amended by the 64th WMA General Assembly, Fortaleza, October 2013.

5. International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Good Clinical Practice. CPMP/ICH/135/35. 17 January 1997.

6. Flohil SC, van der Leest RJ, Dowlatshahi EA et al. Prevalence of actinic keratosis and its risk factors in the general population: the Rotterdam Study. J Invest Dermatol. 2013Aug; 133(8):1971-1978

7. Memon AA, Tomenson JA, Bothwell J et al. Prevalence of solar damage and actinic keratosis in a Merseyside population. Br J Dermatol. 2000 Jun; 142(6): 1154-1159

8. Sobolewski C, Cerella C, Dicato M, Ghibelli L and Diederich M. The Role of Cyclooxygenase-2 in Cell Proliferation and Cell Death in Human Malignancies. Int J Cell Biology. 2010: Article ID 215158 accessed from http://dx.doi.org/10.1155/2010/215158 on 19 June 2010

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 patients, 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 patients 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 patients.
6. The primary purpose of medical research involving human patients 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 patient to ethical standards that promote and ensure respect for all human patients 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 patients.
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 patients. The responsibility for the protection of research patients must always rest with the physician or other health care professionals and never with the research patients, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human patients 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 patients 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 patients 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 patients.
15. Appropriate compensation and treatment for patients 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 patients may only be conducted if the importance of the objective outweighs the risks and burdens to the research patients.
17. All medical research involving human patients 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 patients 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 patients 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 patients 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 patients and information regarding provisions for treating and/or compensating patients 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 patients 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 patients and the confidentiality of their personal information.

H. INFORMED CONSENT

25. Participation by individuals capable of giving informed consent as patients 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 patients capable of giving informed consent, each potential patient 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 patient 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 patients as well as to the methods used to deliver the information. After ensuring that the potential patient has understood the information, the physician or another appropriately qualified individual must then seek the potential patient'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 patients 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 patient 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 patient 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 patient, 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 patient 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 patient's dissent should be respected.
30. Research involving patients 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 patients 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 patient 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 patient to additional risks of serious or irreversible harm as a result of not 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 patients must be registered in a publicly accessible database before recruitment of the first patient.
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 patients 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.

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APPENDIX 2 – Hematology, Chemistry, and Urinalysis List of Laboratory Tests

Hematology	Hemoglobin, Hematocrit, RBC, WBC (total count and differential count), Platelets Count, Mean Platelet Volume (MPV), MCV, MCH, MCHC, RDW, Neutrophils (absolute value and %), Bands (ABS CNT), Bands, Lymphocytes (absolute value and %), Monocytes (absolute value and %), Eosinophils (absolute value and %), Basophils (absolute value and %), RBC Morphology
Comprehensive Metabolic Panel	Sodium, Potassium, Glucose, BUN, Creatinine, BUN/Creatinine, Chloride, Calcium, Protein, Albumin, Globulin (total), A/G Ratio, SGOT (AST), SGPT (ALT), Bilirubin (total), Alkaline Phosphatase, Basic Metabolic Panel
Urinalysis	Color, Character, Specific Gravity, pH, Protein, Glucose, Ketone, Urobilinogen, Bilirubin, Blood, Mucous Threads, Leukocyte Esterase, Amorphous Sediment, Nitrite, Urine Comment, RBC, WBC, Epithelial Cells, Crystals, Casts, Bacteria