INTEGRIUM, LLC
BIOSTATISTICS AND STATISTICAL PROGRAMMING DEPARTMENT

Clinical Study Protocol: DFD-07-CD-002

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

Statistical Analysis Plan (SAP) Documentation

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Statistical Analysis Plan for Clinical Study Protocol: DFD-07-CD-002

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Glossary of Abbreviations

AE	Adverse Event
AK	Actinic Keratosis
cm	Centimeter
CTR	Clinical Trial Report
eCRF	Electronic Case Report Form
EKG	Electrocardiogram
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary of Regulatory Activities
MI	Multiple Imputation
N	Sample Size
PP	Per Protocol
SAE	Serious Adverse Event
SAS®	Statistical Analysis Software
SD	Standard Deviation
WHO	World Health Organization

Table of Contents

1. Introduction

1.1. Scope

This document contains detailed information on the statistical analyses proposed to be performed on the data collected in the trial DFD-07-CD-002 ,to aid the production of the Clinical Trial Report (CTR) including summary tables and listings. The contents of this document were reviewed by the sponsor, Dr. Reddy's Laboratories, Ltd., and the trial biostatistician at Integrium.

1.2. Study Background/Plan

This is a multi-center, randomized, double-blind, parallel group, Vehicle-controlled study. The study products will be applied to a single continuous 5 cm x 5 cm ($25cm^2$) treatment area containing the target AK lesions once or twice daily for a duration of 12 weeks of treatment, followed by 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 four arms (60 subjects in each group).

Subjects will receive either 1.25% concentration once daily (with Vehicle once daily), 2.5% concentration once daily (with Vehicle once daily), 2.5% concentration twice daily or Vehicle twice daily.

The study consists of three phases: Screening (up to 60 days), Treatment (12 weeks) and Follow-Up (4 weeks).

1.3. Trial Objectives and Purpose

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.

1.3.1. 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.

1.3.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints for the study are:

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 Week 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 Week 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.

2. Detailed Statistical Methods

2.1. General Statistical Methods

Efficacy summaries will be provided for the Intention to Treat and Per Protocol Populations. Safety summaries will be provided for the Safety Population.

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 on the proportion of success and the difference compared to Vehicle Cream.

If the method to handle missing observations is not explicitly defined (i.e. Percent Change from Baseline in Actinic Keratosis Lesion Count), two principles will be applied to adjust for missing observations: last observation carried forward (LOCF) and multiple imputations (MI). Last observation carried forward will be derived in the analysis datasets while the multiple imputations method will be performed using SAS procedures PROC MI and PROC MIANALYZE.

If there are at least 5 observations in each cell in the 2 x 2 table (when comparing treatment groups to Vehicle), the Pearson's Chi Square test will be used. If there are not at least 5 observations in each cell in the 2 x 2 table (when comparing treatment groups to Vehicle), the Fisher's exact test will be used.

A Documentation of Statistical Decisions will be created, reviewed and signed (with appropriate signatures) prior to database lock. This document will document:

- On a subject level, which populations the subject is included in and reason for exclusion if a subject is excluded from a population.
- The details of any decision made (i.e. how data is handled in the analysis or the addition of any outputs) based on the actual data collected.
- Any known issues with the data quality and how that data is handled in the analysis, and
- Any other unexpected findings that require documentation prior to database lock.

2.2. Study Populations

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.

Intention- to -Treat Population (ITT)

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

If the method to handle missing observations is not explicitly defined (i.e. Percent Change from Baseline in Actinic Keratosis Lesion Count), two principles will be applied to adjust for missing observations: last observation carried forward (LOCF) and multiple imputations (MI). Last observation carried forward will be derived in the analysis datasets while the multiple imputations method will be performed using SAS procedures PROC MI and PROC MIANALYZE.

Per-Protocol Population (PP)

The per protocol (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, the dose, and duration of treatment with the concomitant medication, and its possible influence on the efficacy and safety assessments (from the known pharmacokinetic and pharmacodynamics interactions of the concomitant medication) prior to deeming a prohibited medication as a protocol violation that warrants exclusion from PP.
3. Completed the Week 16 visit within the allowed window (of ± 5 days).
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 of AK lesions. 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 in the Documentation of Statistical Decisions.

2.3. Subset Analyses

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

2.4. Study Conduct and Baseline Characteristics

2.4.1. Demographics and Subject Baseline Characteristics

Subject demographics and baseline data characteristics will be reported in descriptive summaries by treatment group for the Intention-to-Treat, Per Protocol and Safety populations. Data will also be shown in data listings by treatment group and subject.

Evaluation for significance of the comparisons of the individual baseline characteristics between treatment groups will be performed using an analysis of variance model (for continuous data) or Fisher's exact test (for categorical data).

2.4.2. Extent of Exposure

The extent of exposure to study product will be summarized as the total number of applications, the total number of days the subject was receiving drug (last dose date – first dose date + 1) 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.

2.4.3. Prior and Concomitant Medications

Prior and concomitant medications will be summarized by frequencies and percentages. All medications will be coded using the World Health Organization (WHO) Drug dictionary September 2016 version.

Prior medications will be defined as any medication that started prior to the first day of injection. Concomitant medications will be defined as any medication that starts or is ongoing on or after the first day of injection. A medication may qualify as both a prior and concomitant medication if it started prior to first dose and is ongoing or stopped after the day of dosing.

Medications will be summarized by treatment.

Section 2.10 describes the imputation rules for partial dates. All medications will be presented in a data listing.

2.5. Safety Evaluations

The following safety parameters will be tracked at designated intervals throughout the trial:

- Adverse Events
- Safety and Local Tolerability Evaluation
- Vital signs
- Physical examination
- Electrocardiogram
- Safety Laboratory Tests

2.5.1. Adverse Events (AEs)

Adverse events will be coded using the medical dictionary of regulatory activities (MedDRA Version 19.1) dictionary.

All reported treatment emergent AEs will be summarized by treatment group, the number of subjects reporting events and the no. of AEs reported, 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 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.

2.5.2. Safety and Local Tolerability Evaluation

A safety and local tolerability evaluation will be performed at baseline and each post-baseline visit. This evaluation will include: erythema, edema, weeping/exudate, flaking/scaling/dryness, scabbing/crusting, erosion/ulceration and vesiculation/blistering.

These results will be summarized as frequency and percentages for each evaluation by severity (None, Mild, Moderate and Severe) at each visit in which the evaluation took place.

This information will also be presented in subject data listings.

2.5.3. Vital Signs

Changes from Baseline in vital signs parameters (systolic and diastolic blood pressures, pulse rate) will be summarized at each evaluation. All vital signs data will be shown in subject data listings.

2.5.4. 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.

2.5.5. Safety Laboratory Values

Hematology/chemistry/urinalysis safety laboratory parameters will be performed for all subjects at Baseline (Visit 2), Week 4 (Visit 3), and Week 12 (Visit 5). Summary tables for the individual laboratory parameters will be presented showing observed value and change from baseline. Laboratory test results will be shown in subject data listings.

Urine pregnancy tests will be performed at all visits for female subjects of child bearing potential, and will be presented in subject data listings.

2.6. Efficacy

Primary endpoint

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

H_0: $p1 \leq p2$ vs. H_a: $p1 > p2$

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:

H_0: $p1 \leq p2$ vs. H_a: $p1 > p2$

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 the percent change from baseline in AK lesion counts, the Mann-Whitney U-test (Wilcoxon rank sum test) will be used to test for treatment differences compared to the Vehicle Cream preparation at a significance level of 0.05.

2.7. Interim Analyses and Database Lock

There are no planned interim analyses for this study.

2.7.1. Database Lock / Final Analysis

The final analysis will take place after database lock. The final analysis will unblind the subjects and contain all the outputs indicated in the table on contents.

2.8. Sample Size and Power Considerations

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 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.

2.9. Randomization Scheme and Codes

The details related to the randomization is documented in a separate Randomization Plan.

2.10. Handling Missing Data

Listings will be provided for all data. Descriptive statistics will be provided for all planned visits as provided on the eCRFs. No imputations for missing data will be used in the data displayed in the listings such that the listing will only show "observed data".

Dates related to the adverse events and medications will be imputed using the rules below in an effort to categorize them properly into the summary tables.

Imputing partial or missing start dates:

- If the year is unknown, then the start date will not be imputed. The date will remain missing.
- If the month is unknown and the year is the same as the first administration of study product date of the study, then impute the month and day of the date to be equal to the first administration of study product month and day. Otherwise, impute the month as January.
- If the day is unknown and the month and year are the same as the first administration of study product date of the study, then impute the day to be equal to the day of the first administration of study product. Otherwise, impute the day as '01'.

Impute partial or missing stop dates:

- If the year is unknown, then the stop date will not be imputed. The date will remain missing.

- If the month is unknown, impute the month as December.
- If the day is unknown, impute the day to be the last day of the month.

If an imputed stop date is greater than the date of study completion/discontinuation date of the study, then the imputed stop date will be set equal to the date of completion/discontinuation date.

The imputed dates will be stored in the analysis datasets along with the original dates as recorded by the sites.

2.11. Subject Withdrawals

Subject withdrawals will be summarized in a disposition table for all subjects by treatment. The reasons for discontinuation will also be tabulated. Withdrawals due to AEs will be tabulated as discussed in the Adverse Event section above. A listing of the subjects who withdrew due to an AE will be presented as well as a listing of the subjects' completion and/or discontinuation status.

2.12. Protocol Deviations

Protocol deviations will be displayed in a data listing as provided by the clinical team.

2.13. Computer Systems and Packages Used for Statistical Analyses

SAS® version 9.4 or higher on the Microsoft Windows 7 64 bit platform will be used for all analyses. All computations will be performed using SAS®. The exact form of the various algorithms will be the SAS® defaults. The output from any SAS® procedure will be used in the tables using SAS® macros.

3. Data Listing Shells

3.1. Data Listings Table of Contents

The following post-text listings will be generated.

Listing Number	Listing Title
16.1.7	Randomization Schedule
16.2.1	Subject Completion / Discontinuation
16.2.2	Protocol Deviations
16.2.3	Study Populations
16.2.4.1	Demographics and Baseline Characteristics
16.2.4.2	Subject Eligibility and Informed Consent
16.2.4.3	Substance Use
16.2.4.4	Actinic Keratosis History
16.2.4.5	Medical History / Surgical History / Procedures
16.2.4.6	Prior and Concomitant Medications
16.2.4.7	Non-Drug Treatment History
16.2.5.1	Study Drug Accountability
16.2.5.2	Study Drug Exposure
16.2.6.1	Actinic Keratosis Lesion Counts
16.2.6.2	Complete and Partial Clearance
16.2.7.1	Adverse Events
16.2.7.2	Adverse Events Leading to Discontinuation of Study
16.2.7.3	Serious Adverse Events
16.2.7.4	Adverse Events Related to Study Procedures Prior to Study Product Administration
16.2.8.1	Laboratory Results - Hematology
16.2.8.2	Laboratory Results - Chemistry
16.2.8.3	Laboratory Results - Urinalysis
16.2.9.1	Safety and Local Tolerability Evaluation
16.2.9.2	Vital Signs
16.2.9.3	Electrocardiogram Results
16.2.9.4	Physical Examination

3.2. Data Listings

All subjects and all data will be presented in the listings. The listings will be sorted by treatment and subject number with page breaks between treatments.

4. Summary Table and Figure Shells

4.1. Post-text Table of Contents

The following post-text tables will be generated.

Table Number	Table title
14.1.1.1	Summary of Subject Disposition – Intention-to-Treat Population
14.1.1.2	Summary of Subject Disposition –Safety Population
14.1.1.3	Summary of Subject Disposition – Per Protocol Population
14.1.2.1	Summary of Demographics and Baseline Characteristics – Intention-to-Treat Population
14.1.2.2	Summary of Demographics and Baseline Characteristics – Safety Population
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14.1.5.1	Summary of Extent of Exposure – Intention-to-Treat Population
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14.2.1.1	Proportion of Subjects with Complete Clearance by Visit – ITT Population
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14.2.1.3	Proportion of Subjects with Complete Clearance by Visit – Based on Age – ITT Population
14.2.1.4	Proportion of Subjects with Complete Clearance by Visit – Based on Median Age – ITT Population
14.2.1.5	Proportion of Subjects with Complete Clearance by Visit – By Gender – ITT Population
14.2.1.6	Proportion of Subjects with Complete Clearance by Visit – By Race – ITT Population
14.2.1.7	Proportion of Subjects with Complete Clearance by Visit – By Ethnicity – ITT Population

Table Number	Table title
14.2.1.8	Proportion of Subjects with Complete Clearance by Visit – By Location of Treated Lesion(s) – ITT Population
14.2.1.9	Proportion of Subjects with Complete Clearance by Visit- By Previous AK treatment –ITT population
14.2.2.1	Proportion of Subjects with Partial Clearance by Visit – Last Observation Carried Forward - ITT Population
14.2.2.2	Proportion of Subjects with Partial Clearance by Visit – Last Observation Carried Forward - PP Population
14.2.2.3	Proportion of Subjects with Partial Clearance by Visit – Based on Age – Last Observation Carried Forward - ITT Population
14.2.2.4	Proportion of Subjects with Partial Clearance by Visit – Based on Median Age – Last Observation Carried Forward - ITT Population
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14.2.2.9	Proportion of Subjects with Partial Clearance by Visit- By Previous AK treatment – Last Observation Carried Forward - ITT population
14.2.3.1	Proportion of Subjects with Partial Clearance by Visit – Multiple Imputation Method - ITT Population
14.2.3.2	Proportion of Subjects with Partial Clearance by Visit – Multiple Imputation Method - PP Population
14.2.3.3	Proportion of Subjects with Partial Clearance by Visit – Based on Age – Multiple Imputation Method - ITT Population
14.2.3.4	Proportion of Subjects with Partial Clearance by Visit – Based on Median Age – Multiple Imputation Method - ITT Population
14.2.3.5	Proportion of Subjects with Partial Clearance by Visit – By Gender – Multiple Imputation Method - ITT Population
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Table Number	Table title
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14.2.4.8	Percent Change from Baseline in Actinic Keratosis Lesion Count by Visit – By Location of Treated Lesion(s) – Last Observation Carried Forward - ITT Population
14.2.4.9	Percent Change from Baseline in Actinic Keratosis Lesion Count by Visit- By Previous AK treatment – Last Observation Carried Forward - ITT population
14.2.5.1	Percent Change from Baseline in Actinic Keratosis Lesion Count by Visit – Mulitple Imputation Method - ITT Population
14.2.5.2	Percent Change from Baseline in Actinic Keratosis Lesion Count by Visit – Mulitple Imputation Method - PP Population
14.2.5.3	Percent Change from Baseline in Actinic Keratosis Lesion Count by Visit – Based on Age – Mulitple Imputation Method - ITT Population
14.2.5.4	Percent Change from Baseline in Actinic Keratosis Lesion Count by Visit – Based on Median Age – Mulitple Imputation Method - ITT Population
14.2.5.5	Percent Change from Baseline in Actinic Keratosis Lesion Count by Visit – By Gender – Mulitple Imputation Method - ITT Population
14.2.5.6	Percent Change from Baseline in Actinic Keratosis Lesion Count by Visit – By Race – Mulitple Imputation Method - ITT Population
14.2.5.7	Percent Change from Baseline in Actinic Keratosis Lesion Count by Visit – By Ethnicity – Mulitple Imputation Method - ITT Population

Table Number	Table title
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14.2.6.6	Proportion of Subjects with Local Skin Reactions by Visit – By Race – ITT Population
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14.2.6.8	Proportion of Subjects with Local Skin Reactions by Visit – By Location of Treated Lesion(s) – ITT Population
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14.3.1.2	Summary of Treatment Emergent Adverse Events by Severity – Safety Population
14.3.1.3	Summary of Treatment Emergent Adverse Events by Relationship – Safety Population
14.3.1.4	Summary of Adverse Events Leading to Discontinuation – Safety Population
14.3.1.5	Summary of Serious Adverse Events – Safety Population
14.3.2.1	Summary of Lab Parameters – Hematology – Safety Population
14.3.2.2	Summary of Lab Parameters – Chemistry – Safety Population
14.3.2.3	Summary of Lab Parameters – Urinalysis – Safety Population
14.3.3	Summary of Safety and Local Tolerability Evaluation – Safety Population
14.3.4	Summary of Vital Signs – Safety Population

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14.2.2	Partial Clearance - Intention-to-Treat Population
14.2.3	Percent Change from Baseline in Actinic Keratosis Lesion Count - Intention-to-Treat Population

4.3. Table Shells

The table shells can be found in a separate zipped file. The following number of decimal places will be used when presenting summary statistics:

- N to 0 decimal places
- Minimum and maximum to 0 or 1 decimal places, depending on how the raw data was recorded
- Means and medians to 1 decimal place. Standard deviations to 2 decimal places
- Percentages to 1 decimal place

The precision may be changed for individual endpoints as needed.