A Multi-Center, Randomized, Double-Blind, Parallel-Group, Controlled Study to Assess the Efficacy, Safety and Tolerability of Oral DFD-29 Extended Release Capsules for the Treatment of Inflammatory Lesions of Rosacea over 16 weeks

Protocol No.: DFD-29-CD-002

STATISTICAL ANALYSIS PLAN

Version: 2.0
Date: 06.NOV.2018
Biostatistician: John Chen

Approval of Statistical Analysis Plan
Protocol No : DFD-29-CD-002

The undersigned approved the SAP Version 2.0, dated 06-Nov-2018 as final.
Programming of the tables and listings based upon the specifications within this document can proceed.

Dr. Reddy's Laboratories Ltd., India Approval:

	USHA RANGANATHAN	6 Nov 2018
Signature (Title:)	Print Name	**Date**

QPS-Qualitix Approval:

	Jo Chen	07 Nov 2018
Signature (Lead Statistician)	Print Name	**Date**

Please Note:
QPS-Qualitix will not notify Dr. Reddy's Laboratories Ltd., India of modification of column width, title or typo of tables, listings or figures that are different from SAP when generating data-driven tables, listings or figures after database lock.

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LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/ Explanation
AE	Adverse Event
ANOVA	**Analysis of Variance**
ATC	**Anatomical Therapeutic Chemical (ATC) Classification System**
CEA	**Clinician's Erythema Assessment**
DFD-29	**Minocycline HCl (formulated as Extended Release Capsules)**
eCRF	**Electronic Case Report Form**
FAS	**Full analysis set**
HCl	**Hydrochloride**
hs-CRP	**high sensitivity C-reactive protein**
ITT	**Intention to treat**
MedDRA	**Medical Dictionary for Regulatory Affairs**
PP	**Per protocol**
PT	**Preferred Term**
QoL	**Quality of Life**
RosaQoL	**Rosacea Quality of Life**
SAE	**Serious Adverse Event**
SAP	**Statistical Analysis Plan**
SOC	**System Organ Class**
TEAE	**Treatment Emergent Adverse Event**
WHO	**World Health Organization**

1. INTRODUCTION

This Statistical Analysis Plan (SAP) is based on the final protocol No. DFD-29-CD-002 amendment IV date 02-Oct-2018. The SAP provides details of data handling procedures and statistical analysis methods for efficacy and safety evaluations. It also outlines statistical programming specifications for tables and listings, and other details on the analyses not provided in the study protocol.

2. STUDY OBJECTIVE

Primary Objectives

- To evaluate the efficacy of oral DFD-29 (minocycline HCl 40 mg capsules) in comparison to placebo in the treatment of inflammatory lesions of rosacea for 16 weeks.
- To evaluate the safety and tolerability of oral DFD-29 (minocycline HCl 40 mg capsules) in comparison to placebo in the treatment of inflammatory lesions of rosacea for 16 weeks.

Secondary Objectives

- To evaluate the efficacy of oral DFD-29 (minocycline HCl 20 mg capsules) in comparison to placebo in the treatment of inflammatory lesions of rosacea for 16 weeks.
- To evaluate the efficacy of the two dosage strengths of oral DFD-29 (minocycline HCl 20 mg and 40 mg capsules) in comparison to Oraycea® (doxycycline 40 mg capsules) in the treatment of inflammatory lesions of rosacea for 16 weeks.
- To evaluate the safety and tolerability of oral DFD-29 (minocycline HCl 20 mg capsules) in comparison to placebo in the treatment of inflammatory lesions of rosacea for 16 weeks.
- To evaluate the safety and tolerability of the two dosage strengths of oral DFD-29 (minocycline HCl 20 mg and 40 mg capsules) in comparison to Oraycea® (doxycycline 40 mg capsules) in the treatment of inflammatory lesions of rosacea for 16 weeks.
- To evaluate the efficacy of oral DFD-29 (minocycline HCl 40 mg capsules) in comparison to oral DFD-29 (minocycline HCl 20 mg capsules) in the treatment of inflammatory lesions of rosacea for 16 weeks.
- To evaluate the safety and tolerability of oral DFD-29 (minocycline HCl 40 mg capsules) in comparison to DFD-29 (minocycline HCl 20 mg capsules) in the treatment of inflammatory

lesions of rosacea for 16 weeks.

3. STUDY DESIGN

3.1. Overall Study Design and Plan

This is a 16-week, multicenter, controlled, randomized, parallel group, double-blind study. Subjects, who are at least 18 years old and diagnosed with papulopustular rosacea will be randomized to 4 different treatment groups.

After assessing eligibility during an up to 28-days screening period, 200 subjects will be enrolled in the study and subjects visits are scheduled at Screening, Baseline (Day 1), and Week 4, 8, 12 and 16.

Clinical assessments of efficacy will be conducted based on Investigator's Global Assessment (IGA, modified scale without erythema), Clinician's Erythema Assessment (CEA), RosaQoL Score, Telangiectasia Score and on inflammatory lesion counts at Weeks 4, 8, 12 and 16 in comparison to Baseline. Additionally, high sensitivity C-reactive protein (hs-CRP) in the blood will be assessed at Baseline, and at Week 16 to explore any impact of the treatment on the inflammatory pathology.
Laboratory assessments on blood (hematology and biochemistry) and urine (routine tests) will be conducted at Screening, Week 4 and Week 16 (End of the study) to assess for any changes in the safety parameters. Other safety assessments include vital signs, physical examination, urine pregnancy tests (only for females with child bearing potential), and collection of adverse event data.
Impact of the treatment on the Quality of Life (QoL) of the subjects will be done using a rosacea specific tool RosaQoL at Baseline, and at Weeks 4, 8, 12 and 16.
A detailed description of the scheduled tasks at each visit can be found in Section 3.5.

3.2. Study Medication

Subjects will be randomized to one of the following treatments assigned in a 1:1:1:1 fashion.

1. DFD-29 (minocycline HCl) Extended Release Capsules (40 mg) once daily for 16 weeks.
2. DFD-29 (minocycline HCl) Extended Release Capsules (20 mg) once daily for 16 weeks
3. Oraycea® (doxycycline) Modified Release Hard Capsules (40 mg) once daily for 16 Weeks
4. Placebo capsules once daily for 16 weeks

The investigational products will be taken orally at a fixed time of the day once a day (± 2 hours), for 16 consecutive weeks.

3.3. Selection of Study Population

3.3.1. Study Population

Two hundred (200) male and female subjects with papulopustular rosacra will be enrolled in the study (fifty (50) subjects each in groups 1 to 4) in order to get 176 completed subjects (forty four (44) completers each in group).

3.3.2. Blinding

This study is performed in a double-blind fashion. The investigator and study staff (including lab personnel), the subjects, the monitors, medical monitors, the CRO personnel involved in clinical operations and the sponsor's staff will remain blinded to the treatment until study closure.

The randomization code will be kept strictly confidential. It is accessible only to authorized personnel, who are not involved in the conduct and analysis of the study, and will keep the randomization schema strictly confidential.

Only if the subject experiences a medical emergency whose management would be improved by the knowledge of the blinded treatment assignment, the identity of the study drug may be revealed.

Documentation about any code break must be documented and attached to the eCRF.

3.3.3. Randomization

Subjects will be randomized to any of the treatments assigned in a 1:1:1:1 fashion. Block size will be determined by the statistician of QPS Netherlands. The randomization code will be generated by a computer program (OpenClinica) and controlled by the study drug packaging.

The number on the subject kit equals the randomization number. The kits will be allocated to the sites. The randomization number will be un-blinded and made available for data analysis only after study closure.

3.4. Interim Analysis

Not applicable.

3.5. Flow Chart of Timing of Assessments

The schedule of events is provided in ***Table 1***.

Table 1 Flow Chart of Study Assessment

	Visit 1	**Visit 2**	**Phone call**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
	Screening	**Baseline**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16 Early termination**
Study Day	**Day -30 to Day -3**	**Day 1**	**Day 15 (+/- 2 days)**	**Day 29 (+/- 5 days)**	**Day 57 (+/- 5 days)**	**Day 85 (+/- 5 days)**	**Day 113 (+/- 5 days)**
Informed Consent	X						
Demographic Data including Fitzpatrick Skin Type	X						
Inclusion and Exclusion Criteria	X						
Eligibility Conclusion		X	X	X	X	X	X
Weight	X	X					X
Height	X						
Medical History/ Prior Medications	X	X					
Vital Signs (BP, Pulse rate)	X	X		X	X	X	X
Urine Pregnancy Test (for females of childbearing potential)	X	X		X	X	X	X
IGA	X	X		X	X	X	X
CEA	X	X		X	X	X	X
Lesion count	X	X		X	X	X	X
Telangiectasia	X	X		X	X	X	X
RosaQoL Score	X	X		X	X	X	X

	Visit 1	**Visit 2**	**Phone call**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
	Screening	**Baseline**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16 Early termination**
Study Day	**Day -30 to Day -3**	**Day 1**	**Day 15 (+/- 2 days)**	**Day 29 (+/- 5 days)**	**Day 57 (+/- 5 days)**	**Day 85 (+/- 5 days)**	**Day 113 (+/- 5 days)**
Physical Examination	X						X
Laboratory assessments (Blood & Urine)	X			X			X
hs-CRP		X					X
Randomization		X					
Dispense Study Drug		X		X	X	X	
Dispense/Review/Collect Study Diary		X		X	X	X	X
Discussion of Subject Instructions		X		X	X	X	
Collect Study Drug				X	X	X	X
Evaluate Study Drug Compliance			X	X	X	X	X
Adverse Event (Assessment/Collection)		X	X	X	X	X	X
Concomitant Medication			X	X	X	X	X
End of Study							X
Telephonic enquiry of wellbeing and medication compliance			X				

3.6. Study Parameters

3.6.1. Efficacy Endpoints

The following parameters have been defined as parameters regarding efficacy.

Co-Primary Endpoints

- Proportion of subjects with IGA (modified scale without erythema) 'treatment success' – Grade 0 or 1 at the end of study with at least 2 grade reduction from Baseline to Week 16.
- Total inflammatory lesion count (sum of papules, pustules, and nodules) reduction from Baseline to Week 16.

Secondary Endpoints

- Proportion of subjects with at least a 2 grade reduction in IGA (modified scale without erythema) score from Baseline to Week 16
- Median change in total RosaQoL score from Baseline to Week 16.

Exploratory Endpoints

- Proportion of subjects with IGA (modified scale without erythema) 'treatment success' from Baseline to Weeks 4, 8 and 12.
- Total inflammatory lesion count (sum of papules, pustules, and nodules) reduction from Baseline to Weeks 4, 8 and 12.
- Proportion of subjects with at least a 2 grade reduction in IGA (modified scale without erythema) score from Baseline to Week 4, 8 and 12.
- Median change in total RosaQoL score from Baseline to Weeks 4, 8 and 12.
- Mean change in high sensitivity C-reactive protein (hs-CRP) levels from Baseline compared to Week 16.
- Change in Telangiectasia score from Baseline compared to Week 16.
- Proportion of subjects meeting CEA 'treatment success' criteria (i.e. a two grade improvement in the CEA scale) at Weeks 4, 8, 12 and 16

3.6.2. Safety and Tolerability Endpoints

The following parameters have been defined as parameters regarding safety and tolerability:

- Change from Baseline to each scheduled time point up to EOS for vital signs.
- Change from Screening up to EOS for physical examination.
- Change from Screening up to EOS for clinical laboratory tests.
- Treatment-emergent AEs up to EOS.
- Treatment-emergent AEs leading to premature discontinuation of study drug.

- Treatment-emergent SAEs up to EOS.

3.6.3. Sample Size Estimation

The sample size calculation was based on the assumption that basis of comparable pharmacokinetic parameters of orally administered minocycline hydrochloride to doxycycline, it is assumed that DFD-29 (minocycline hydrochloride) will demonstrate an efficacy either similar or better than that reported with ORACEA® (doxycycline) 40 mg in the treatment of inflammatory lesions of papulopustular rosacea The sizes of the treatment effect of doxycycline 40 mg in comparison to placebo that were reported from the two pivotal efficacy and safety clinical trials, that formed the basis of approval of ORACEA® for the treatment of only inflammatory lesion of rosacea, interms of the two co-primary endpoints in this study.

The sample size required is calculated to be 44 subjects per group to achieve 70% power in the study, and considered an expected subject discontinuation rate of 10%, the required sample size is rounded off to 50 subjects per group.

The determined sample size of 44 subjects per treatment group was also seen to ensure an adequately powered analysis (87%) for demonstrating non-inferiority of DFD-29 40 mg and DFD-29 20 mg treatments against the active comparator Oraycra ® while assuming the lower limit of the 90% CI for concluding non-inferiority to be ≤ 3 for the absolute change in total inflammatory lesion count from Baseline at Week 16 for the individual DFD-29 treatment arms versus Oraycea® arm, a common standard deviation of 5 lesion counts, the expected difference of treatment means to be 0 and alpha of 0.05 (one sided). Similarly, this sample size will also achieve 91% power to detect a non-inferiority margin difference of 0.5 points on the RosaQoL, assuming a common standard deviation of 0.77 points.

4. GENERAL STATISTICAL ISSUES

Summary statistics (mean, median, standard deviation, min, max, number of available observations) will be provided for continuous variables (e.g., age, height, weight). Qualitative variables (e.g., gender, race) will be summarized by counts and percentages.

Appropriate rounding will be performed for the summary statistics of both safety and efficacy parameters: mean, median will be presented with one decimal more than the original data; standard deviation will be presented with two decimals more than the original data; minimum and maximum values will be presented with the same precision as the original data; Percentages will be presented with 2 decimals.

Additional measurements (such as unscheduled or repeat assessments) will not be included in the

descriptive statistics, but will be included in subject listings only.

For the analyses, baseline is defined as the last value measured prior to the first intake of assigned study drug.

Subjects who withdraw from the study, or who have missing data, will be included in the statistical analyses provided that they are eligible for inclusion in the analysis population.

All statistical tests used will be two-sided, with α=0.05 as level of significance.

5. DATA HANDLING PROCEDURES

5.1. Coding System

The medical history, adverse events (AEs) and serious adverse events (SAEs) will be coded using the most recent Medical Dictionary for Regulatory Activities (MedDRA) version.

Previous and concomitant medications will be coded by the World Health Organization (WHO) drug code and the ATC (Anatomical Therapeutic Chemical) class code.

5.2. Missing Data Handling

All safety analyses will be performed on data available at the time point considered. In summary tables, the number of subjects with missing data will be presented unless otherwise specified. In calculation of percentages, subjects with missing data will not be considered in numerator or denominator unless otherwise specified.
For the efficacy data; in case of missing measurements, multiple imputation (MI) will be used to impute the missing values. For the MI of the inflammatory lesion count test and CRP, a MIXED model will be used, with visit as a factor and subject as random variable. For success rate, a logistic model will be used.

6. ANALYSIS POPULATION

Full Analysis Set (FAS)

This analysis population includes all subjects who have been randomized and had at least one post baseline efficacy assessment. The FAS population will be the primary population for the efficacy analyses.

Intention To Treat (ITT) Population

This analysis population includes all subjects who have been randomized and dispensed the study

drug.

Safety Population

This analysis population includes subjects who had at least one safety assessment post-baseline. The safety population will be employed in the analysis of tolerability and safety variables.

Per-Protocol (PP) Population

This analysis population comprises all subjects who did not violate the protocol in a way that might affect the evaluation of the effect of the study drug(s) on the primary endpoint, i.e., without major protocol violations or deviations.

The safety population will be used to perform all safety analyses and efficacy endpoints (primary/secondary/exploratory) will be analyzed by FAS, ITT and PP population.

All subjects who excluded from analysis will be listed in Listing 16.2.3.

7. DISPOSITION OF PATIENTS AND STUDY COMPLETION

Data on the completion status and reason for study discontinuation will be provided in Listing 16.2.1.1 and 16.2.1.2. The subject disposition and completion status will be summarized by cohort in Table 14.1.1.

Individual subject eligibility at screening and other scheduled visits will be provided in Listing 16.2.1.3 and 16.2.1.4. All minor and major protocol deviation(s) will be listed in Listing 16.2.2.

8. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Individual subject listings of demographics will be provided in Listing 16.2.4.1. Descriptive tabulations of the screening data of demographics and other baseline characters will be presented by different treatment groups for both ITT and safety population, in Table 14.1.2.1 and Table 14.1.2.2, respectively.

The subject demographics and baseline characteristics including height, weight, body mass index (BMI), inflammatory lesion counts, IGA score, CEA score, RosaQoL score, Telangiectasia score and hs-CRP will be summarized using mean, median, standard deviation, min, max, number of available observations and number of subjects with missing data. Fitzpatric Skin Type, Gender, Race and Ethnicity will be summarized by counts (frequencies) and percentages.

The results of IGA score, total inflammatory lesion count, CEA score, RosaQoL score, hs-CRP, and Telangiectasia score will be compared between different treatment groups in both ITT and

safety population, using T-test or Wilcoxon rank sum test. The 'Overall' group will not be one of the comparison groups for the analysis.

Previous medications will be summarized by tabulating the number and percentages of subjects treated.

8.1. Medical History

The medical history will be coded by the most recent MedDRA version and listed in Listing 16.2.4.2.

9. EFFICACY ANALYSIS

For all efficacy endpoints, the comparison of oral DFD-29 (40 mg capsule) versus placebo will be the primary objective of the study. All other comparisons viz, between oral DFD-29 (20 mg capsule) and placebo, between oral DFD-29 (40 and 20 mg capsules) and Oraycea® and between oral DFD-29 40 mg capsules and DFD-29 20 mg capsules, will be treated as secondary.
For exploratory analyses for the following subgroups will be performed:

- Male versus Female
- Mild (score 2), Moderate (score 3) and Severe (score 4) IGA score
- Normal hs-CRP versus Abnormal hs-CRP at Baseline

9.1. Investigator's Global Assessment Modified Scale Without Erythema (IGA Scale)

The IGA is carried out by visual inspection by the Investigator at every study visit from Screening up to Week 16. The IGA grades for individual subject will be listed by each visit in Listing 16.2.6.3.

The proportion of subjects with IGA 'treatment success' and those who have at least 2 grade reduction from baseline will be analyzed using Chi-square test. IGA 'treatment success' is described as having at least 2 grade reduction in IGA score from baseline and achieving an IGA score of 0 or 1 at week 16.

Table 14.2.1.1 through 14.2.1.3 will summarize the proportion of subjects with IGA 'treatment success' at week 16 over baseline and present the results by comparison groups.

Table 14.2.3.1 through 14.2.3.3 will summarize the proportion of subjects achieving a 2 grade reduction in their IGA score at week 16 over baseline, between the comparison groups.

Table 14.2.5.1.1 through 14.2.5.1.3 will summarize the proportion of subjects with IGA 'treatment success' at weeks 4, 8, and 12 over baseline and present the results by comparison

groups. Table 14.2.5.2.1 through 14.2.5.4.3 will summarize the subgroup analyses of the proportions of subjects with IGA 'treatment success' at weeks 4, 8, 12 and 16 over baseline, between comparison groups, separated by gender, IGA grade at baseline and the evaluation (Normal versus Abnormal) of hs-CRP at baseline.

Table 14.2.7.1.1 through 14.2.7.1.3 will summarize the proportion of subjects achieving a 2 grade reduction in their IGA score at week 4, 8, and 12 over baseline and present the results by comparison groups. Table 14.2.7.2.1 through 14.2.7.4.3 will summarize the subgroup analyses of the proportions of subjects achieving a 2 grade reduction in their IGA score at weeks 4, 8, 12 and 16 over baseline, between comparison groups, separated by gender, IGA score at baseline and the evaluation (Normal versus Abnormal) of hs-CRP at baseline.

9.2. Total Inflammatory Lesion Count

The total inflammatory lesion count is carried out by visual inspection by the Investigator at every study visit from Screening up to Week 16 (or at early termination). Inflammatory lesions will be recorded on a diagram of a human face, divided in 4 quadrants. The number of lesions of pustules, papules and/or nodules/cysts, as well as the total number of lesions for individual subject will be listed by each visit and quadrant on the face in Listing 16.2.6.4.

The total inflammatory lesion count will be account for the individual type of inflammatory lesion (i.e., papule or pustule or nodule/cyst) in each of the 4 quadrants and the total inflammatory lesion count will be calculated automatically. The change in the total inflammatory lesion count from baseline will be analyzed using MIXED model, with the investigator as a random factor.

Table 14.2.2.1 through 14.2.2.3 will summarize the difference between the comparison groups in terms of the change in total inflammatory lesion counts at week 16 over baseline.

Table 14.2.6.1.1 through 14.2.6.1.3 will summarize the difference between the comparison groups in terms of the change in total inflammatory lesion counts at week 4, 8, and 12 over baseline. Table 14.2.6.2.1 through 14.2.6.4.3 will summarize the subgroup analyses of the changes in the total inflammatory lesion counts at weeks 4, 8, 12 and 16 over baseline, between the comparison groups, separated by gender, IGA grade, and the evaluation (Normal versus Abnormal) of hs-CRP.

9.3. Clinician's Erythema Assessment (CEA)

The CEA is carried out by visual inspection by the Investigator at every study visit from Screening up to Week 16 (or at early termination). The erythema assessment will be carried out

separately at 5 locations on the face- forehead, nose, chin, right cheek and left cheek. The scores from all 5 locations will be totaled to yield the final CEA grade. The CEA grades on different part of face (forehead, nose, chin, right cheek, and left cheek) and final CEA grade (total score) for individual subject will be listed by each visit in Listing 16.2.6.2.

Proportions of subjects meeting CEA 'treatment success' criteria (i.e. a two grade improvement in the CEA scale) in the comparison groups at weeks 4, 8, 12 and 16 over baseline, will be analyzed using Chi-square test in Table 14.2.11.1.1 through 14.2.11.1.3. Table 14.2.11.2.1 through 14.2.11.4.3 will summarize the subgroup analyses of subjects meeting CEA 'treatment success' criteria at weeks 4, 8, 12, and 16 over baseline, between comparison groups, separated by gender, IGA grade at baseline and the evaluation (Normal versus Abnormal) of hs-CRP at baseline.

Mean change in CEA score for subjects who met 'treatment success' criteria in comparison groups at week 4, 8, 12, and 16 over baseline, will be analyzed using ANOVA in Table 14.2.12.1.1 through 14.2.12.1.3.

Table 14.2.12.2.1 through 14.2.12.4.3 will summarize the subgroup analyses of the mean change in CEA score for subjects who met 'treatment success' criteria at week 4, 8, 12, and 16 over baseline, between comparison groups, separated by gender, IGA grade at baseline and the evaluation (Normal versus Abnormal) of hs-CRP at baseline.

The graphs of mean change in CEA score for subjects who met 'treatment success' criteria at week 4, 8, 12 and 16 over baseline will be provided in Figure 14.2.12.1.1 through 14.2.12.1.3, and the subgroup analyses will be provided in Figure 14.2.12.2.1 through 14.2.12.4.3.

9.4. Rosacea Quality-of-Life Instrument (RosaQoL)

The RosaQoL assessment is carried out by the Investigator by asking questions as per the validated RosaQoL questionnaire instrument, at every study visit from Screening up to Week 16 (or at early termination). The subjects will have to rate on a 5 grade scale their perception of the impact that Rosacea has on various dimensions influencing their quality of life. The total score of RosaQoL will be listed by individual subject at every visit in Listing 16.2.6.1.

The median change of RosaQoL score at week 16 over baseline in the comparison groups will be analyzed using Kruskal-Wallis test in Table 14.2.4.1 through 14.2.4.3.

Table 14.2.8.1.1 through 14.2.8.1.3 will summarize the median change of RosaQoL score at week 4, 8 and 12 over baseline using Kruskal-Wallis test, in the comparison groups. Table 14.2.8.2.1 through 14.2.8.4.3 will summarize the subgroup analyses of the median change of RosaQoL at week 16 over baseline, between comparison groups, separeated by gender, IGA grade at baseline

and the evaluation (Normal versus Abnormal) of hs-CRP at baseline.

9.5. High sensitive C-reactive Protein (hs-CRP)

Blood will be drawn for the analysis of hs-CRP at Baseline and Week 16, and the assessment of hs-CRP will be collected in laboratory exam.

The mean change in hs-CRP at week 16 over baseline in the comparison groups will be analyzed using ANOVA in Table 14.2.9.1.1 through 14.2.9.1.3.

Table 14.2.9.2.1 through 14.2.9.4.3 will summarize the subgroup analyses of the difference of mean change in hs-CRP between comparison groups at week 16 over baseline, using ANOVA and the subgroup analyses will be performed by gender, IGA grade at baseline and the evaluation (Normal versus Abnormal) of hs-CRP at baseline.

9.6. Telangiectasia Score

Telangiectasia will be graded by visual inspection by the Investigator at every study visit from Screening up to Week 16 (or at early termination) and all scores will be listed by individual subject and visit in Listing 16.2.6.5.

Change in Telangiectasia score at week 16 over baseline, will be analyzed using ANOVA and the subgroup analyses will be performed by gender, IGA grade at baseline and the evaluation (Normal versus Abnormal) of hs-CRP at baseline in Table 14.2.10.1.1 through 14.2.10.4.3.

10. EXTENT OF EXPOSURE AND DRUG COMPLIANCE

10.1. Study Drug Description

All accurate records of dose administration date, the amount of study drug dispensed/returned and compliance for each subject will be listed in Listing 16.2.5.1.1 through 16.2.5.2.2.

The patient diary including the information of study drug usage instruction will be listed only in Listing 16.2.5.3.1 and 16.2.5.3.2.

10.2. Prior and Concomitant Medication

The verbatim prior and concomitant medications will be coded by WHO drug code and ATC class code and listed by subject, subject medical history condition which it is used to treat, formulation, dose, regimen, route of administration, starting and stopping dates, and whether the medication

was ongoing at the time of randomization in Listing 16.2.5.4.

11. SAFETY ANALYSIS

11.1. Adverse Events

A treatment-emergent adverse event (TEAE) is defined as any AE temporally associated with the use of a study drug or worsened following the start of dosing, whether or not considered related to the study drug.

All AEs recorded in the CRF/source document will be listed by subject in Listing 16.2.7.1 and 16.2.7.2.

AEs will be coded using the most recent MedDRA version, but only TEAEs will be tabulated by "system organ class (SOC)", and individual "preferred terms (PT)" within SOC by treatment group. The number and percentage of subjects who experienced AEs coded with the same PT and SOC will be summarized by treatment group.

As defined in the CRF/source document, all adverse events will be assigned an intensity of: Mild, Moderate or Severe.

For purposes of the summary tables, AEs will be classified as either related or not related to study drug. A study drug-related AE is defined as any TEAE that is assessed as 'Definitely Related, 'Probably Related' or 'Possibly Related' to study drug. An AE not related to study drug is defined as any AE that is assessed as 'Not Related' to study drug.

A general summary of all TEAEs and SAEs by treatment groups will be provided in Table 14.3.1.1.1 and Table 14.3.1.1.2. This summary will present the numbers and percentages of subjects according to the following categories:

- Subject with Any AE
- Subjects with Any SAE
- Intensity
- Serious AE
- Reason for SAE
- Relationship to Study Drug
- Outcome
- Action Taken
- Unexpected AE
- Concomitant Medication Given

Other summary tables for adverse events will include:

- Table 14.3.1.2: Treatment-Emergent Adverse Events - MedDRA
- Table 14.3.1.3.1: Treatment-Emergent Adverse Events by Intensity – MedDRA (Placebo and Oraycea)
- Table 14.3.1.3.2: Treatment-Emergent Adverse Events by Intensity – MedDRA (DFD-29 and Overall)
- Table 14.3.1.4: Treatment-Emergent Adverse Events by Relationship to Study Drug – MedDRA
- Table 14.3.1.5: Treatment-Emergent Adverse Events with Concomitant Medication Given – MedDRA
- Table 14.3.1.6: Treatment-Emergent Adverse Events by Therapeutic Procedures – MedDRA
- Table 14.3.1.7: Treatment-Emergent Adverse Events Leading to Premature Discontinuation
- Table 14.3.1.8: Non-Treatment-Emergent Adverse Events - MedDRA
- Table 14.3.1.9: Treatment-Emergent Serious Adverse Events - MedDRA
- Table 14.3.1.10.1: Treatment-Emergent Serious Adverse Events by Intensity – MedDRA (Placebo and Oraycea)
- Table 14.3.1.10.2: Treatment-Emergent Serious Adverse Events by Intensity – MedDRA (DFD-29 and Overall)
- Table 14.3.1.11: Treatment-Emergent Serious Adverse Events by Relationship to Study Drug – MedDRA
- Table 14.3.1.12: Treatment-Emergent Serious Adverse Events with Concomitant Medication Given – MedDRA
- Table 14.3.1.13: Treatment-Emergent Serious Adverse Events by Therapeutic Procedures – MedDRA
- Table 14.3.2.1: List of Subjects with Death Due to Treatment-Emergent Serious Adverse Event
- Table 14.3.2.2.1: List of Subjects Withdrew Due To Treatment-Emergent Adverse Event - Start Date, Stop Date, Intensity, Serious AE, and Relationship to Study Drug
- Table 14.3.2.2.2: List of Subjects Withdrew Due To Treatment-Emergent Adverse Event - Outcome, Action Taken, and Expectedness

11.2. Clinical Safety Laboratory Tests

Clinical laboratory data (Hematology, Chemistry, Serology, Urinalysis, Urine Pregnancy Test and hs-CRP) will be listed in Listing 16.2.8.2 through 16.2.8.7 and the related comment will be listed in Listing 16.4.3.

Observations of hematology, chemistry and hs-CRP outside the normal range will be flagged. The abnormal values will be flagged with ‘L’ (low) for values below the lower limit of the laboratory’s

normal range, 'H' (high) for values above the upper limit of the laboratory's normal range or 'A' (abnormal) for values out of normal range. All clinically significant laboratory results will be marked as well.

Abnormal laboratory values of hematology, chemistry, serology, urinalysis, urine pregnancy test and hs-CRP will be listed in Listing 16.2.8.1 and Table 14.3.4.

The results of hematology, chemistry and urinalysis will be summarized for each measurement between the treatment groups in Table 14.3.5.1 through 14.3.5.3. If applicable, change from screening will be calculated. The shift table of evaluation including 'Normal', 'Abnormal NCS', and 'Abnormal CS' for all laboratory exam terms will be presented in Table 14.3.5.4.1 and Table 14.3.5.4.2, respectively.

11.3. Other Safety Evaluations

11.3.1. Vital Signs

Individual subject listings of vital signs data (weight, systolic blood pressure, diastolic blood pressure, and pulse rate) will be listed in Listing 16.4.1 and the related comment will be listed in Listing 16.4.3. All the vital signs data will be summarized using descriptive statistics for each time point in Table 14.3.6.1. If applicable, change from baseline will be calculated. The shift table including 'Normal', 'Abnormal NCS', and 'Abnormal CS' for all vital signs will be presented in Table 14.3.6.2.1 and Table 14.3.6.2.2, respectively.

11.3.2. Physical Examination

Individual subject physical examination will be listed in Listing 16.4.2 and the results will be summarized as a shift table of evaluation including both 'Normal' and 'Abnormal', as well as 'Not Done' if the physical examination was not performed in Table 14.3.7.

12. COMPUTER METHODS

All statistical analyses will be conducted using SAS® software, Version 9.3 of the SAS System for Windows 7. Copyright © 2013 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA