STATISTICAL ANALYSIS PLAN

DFD-29 (Minocycline Hydrochloride Extended Release Capsules) 40 mg

DFD-29-CD-005

Final 3.0
06 June 2023

A Multicenter, Randomized, Double-Blind, Parallel-Group, Active and Placebo-Controlled Study to Assess the Safety, Efficacy, and Tolerability of Oral DFD-29 Extended Release Capsules for the Treatment of Inflammatory Lesions of Rosacea Over 16 Weeks

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

Journey Medical Corporation
9237 East Via De Ventura Boulevard, Suite 105
Scottsdale, AZ 85258, USA

Approved By:

Craig W. Wesselman — Digitally signed by Craig W. Wesselman
Date: 2023.06.07 15:48:27 -06'00'

Craig W. Wesselman, MS — Date
Director of Statistics
Symbio LLC

DocuSigned by:
3F61889E01B6430...
08-Jun-2023 | 1:59 AM IST

Srinivas Shenoy B., M.D. — Date
Director, Clinical Development
Dr. Reddy's Laboratories, Ltd.

DocuSigned by:
Srinivas Sidgiddi
8E2E89622B4B495...
07-Jun-2023 | 2:18 PM PDT

Srinivas Sidgiddi, M.D. — Date
Vice President, Clinical Development
Journey Medical Corporation

Table of Contents

List of Abbreviations and Definitions of Terms

Term	Definition
AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AR(1)	Autoregressive first order
ARH(1)	Heterogeneous Autoregressive first order
ATC	Anatomical Therapeutic Chemical
CEA	Clinician's Erythema Assessment
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CS	Compound Symmetry
CSH	Heterogenous Compound Symmetry
DFD-29	Minocycline Hydrochloride Extended Release Capsules 40 mg
DLQI	Dermatology Life Quality Index
EOS	End of Study
ET	Early Termination
IGA	Investigator's Global Assessment
IQR	Interquartile Range
ITT	Intent-to-Treat
LOCF	Last-Observation-Carried-Forward
LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed Model Repeated Measures
PP	Per-Protocol
PT	Preferred Term
QoL	Quality of Life
RosaQoL	Rosacea-specific Quality of Life (tool)
SAE	Serious Adverse Event

Term	Definition
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
TEAEs	Treatment-Emergent Adverse Events
UN	Unstructured
US	United States
WHO-DD	World Health Organization Drug Dictionary

Version Summary

Version	Date	Changes
1.0	26Jul2022	Initial Version
2.0	10Nov2022	1. Defined intercurrent events for the estimands and how they will be handled. 2. Added pooling of small sites language. 3. Updated multiple imputation language to impute each treatment separately. 4. Updated multiple imputation language for categorical data to impute using original scale. 5. Updated efficacy data collected during remove visits to be excluded from the intent-to-treat and per-protocol analyses for the co-primary and secondary endpoints 6. Updated multiple imputation and analysis methods to use world region (United States and Europe) as factors. 7. Added the difference between DFD-29 and Doxycycline capsules 40 mg in percentage change from Baseline in total inflammatory lesion count at Week 16 to secondary endpoints. 8. Removed Dermatology Life Quality Index from secondary endpoints. 9. Removed sensitivity analysis for Rosacea-specific Quality of Life tool. 10. Added possible exploratory analysis for efficacy data collected during remote visits. 11. Added possible sensitivity analysis for site outliers.
3.0	06Jun2023	Section 4.2 Per-protocol criteria updated to include subjects who are out of window at Visit 7 but continued treatment with investigational product.

Statistical Analysis Plan

1 Purpose of Statistical Analysis Plan

The purpose of the statistical analysis plan is to describe in detail all the data, statistical methods, and summary tables required to implement the statistical analysis of Clinical Study Protocol DFD-29-CD-004 (Section 9 in the study protocol version 3.0, dated 01 November 2022).

2 Study Objectives

2.1 Primary Objective

To evaluate the safety, efficacy, and tolerability of oral DFD-29 compared to placebo in the treatment of papulopustular rosacea for 16 weeks.

2.2 Secondary Objective

To evaluate the safety, efficacy, and tolerability of oral DFD-29 compared to Doxycycline capsules 40 mg (*an authorized generic of Oracea® in the United States*) in the treatment of papulopustular rosacea for 16 weeks.

3 Study Design

For the purpose of exploring the above objectives, the study will be conducted as a 16-week, multicenter, randomized, parallel-group, double-blind, placebo and active controlled study.

Approximately 320 subjects at least 18 years old who are diagnosed with moderate to severe papulopustular rosacea will be randomized in a ratio of 3:3:2 stratified by site to one of the following groups:

- DFD-29 (Minocycline Hydrochloride Extended Release Capsules), 40 mg once daily for 16 weeks
- Doxycycline capsules 40 mg once daily for 16 weeks
- Placebo capsules once daily for 16 weeks.

Subject visits are scheduled for Screening (Visit 1), Baseline (Visit 2, Day 1), and Week 2 (Day 14 ± 3 days, Visit 3), Week 4 (Day 29 ± 3 days, Visit 4), Week 8 (Day 57 ± 5 days, Visit 5), Week 12 (Day 85 ± 5 days, Visit 6), and Week 16 (Day 113 ± 5 days, Visit 7).

Clinical assessments of efficacy will be conducted based on Investigator's Global Assessment modified scale without erythema (IGA), Clinician's Erythema Assessment (CEA), and total inflammatory lesion count at Weeks 2, 4, 8, 12, and 16 compared to Baseline. Total inflammatory lesion count will be the sum of papules, pustules, and nodules.

Laboratory assessments of blood (hematology and biochemistry) and urine (routine tests) will be conducted at Screening and Week 16 (end of study [EOS] or early termination [ET]) to assess for any changes in the safety parameters. Other safety assessments include vital signs, physical examination, urine pregnancy results (for females of childbearing potential), and collection of adverse event (AE) data.

The impact of the treatment on the quality of life (QoL) of the subjects will be assessed using the rosacea-specific quality of life (RosaQoL) tool in addition to the Dermatology Life Quality Index (DLQI) at Baseline and Weeks 2, 4, 8, 12, and 16.

4 Analysis Populations

4.1 Intent-to-treat

The intent-to-treat (ITT) analysis population includes all randomized subjects. The ITT population will be the primary population for the efficacy analysis.

4.2 Per-protocol

The per-protocol population (PP): This analysis population includes all ITT subjects who completed the Week 16 evaluation and did not have any protocol violations or major protocol deviations in a way that might affect the evaluation of the effect of the study medication on the co-primary endpoints. Specifically, the PP population will include subjects who meet all the following criteria:

1. Subject met all inclusion/exclusion criteria.
2. Subject did not take any prohibited concomitant medications during the evaluation period.
3. Subject completed the Week 16 visit within the allowed visit window (Day 113 ± 5 days) or subject completed Week 16 visit outside the allowed visit window and the visit happened within 1 calendar day after the final dose of IP.
4. Subject was compliant with the dosing regimen. Subjects will be considered compliant if they administer at least 80% and no more than 120% of doses and do not miss 7 or more consecutive doses of study medication. See Section 5.6.1 for the derivation of the compliance rate.
5. Subjects whose co-primary endpoint assessments were conducted in-person at Baseline and Week 16.

The concomitant medication usage will be reviewed during the population determination review, remaining blinded to treatment assignment, to determine prohibited medication usage that warrants exclusion from the PP population. Other additional criteria may be added to the list to accommodate unforeseen events that occurred during the conduct of the trial that result in noteworthy study protocol violations or major protocol deviations. These criteria will be documented with appropriate signature when subject populations are finalized, prior to database lock and unblinding.

4.3 Safety

The safety analysis population includes subjects who have received at least one dose of study medication and had at least one post-Baseline safety assessment. The safety population will be used for the summary and analysis of tolerability and safety variables.

5 Planned Analyses

5.1 Methodological Considerations

All statistical processing will be performed using SAS® unless otherwise stated. Two-sided hypothesis testing will be conducted for all inferential analyses using a significance level of 0.05. No interim analyses are planned. Efficacy analyses performed using the ITT population will be considered primary. Efficacy analyses performed using the PP population will be considered supportive. Tolerability and safety analyses will be performed on the safety population.

The type I error will be controlled using a fixed-sequence method using the order of the endpoints listed in Sections 5.5.1and 5.5.2. If both co-primary endpoints are significant, then the first secondary endpoint can be tested at $\alpha < 0.05$. If the first secondary endpoint is significant, the next secondary endpoints will use the approach described above. A similar approach will be used for subsequent testing of secondary endpoints. Testing of exploratory endpoints will not be included in the type 1 error control method and inferences will not have any confirmatory value.

Efficacy will be demonstrated if DFD-29 is superior to placebo for both IGA treatment success and change from Baseline in the total inflammatory lesion count at Week 16.

Sample size, frequency counts, and percentages will be used to summarize categorical endpoints. Sample size, mean, median, standard deviation (SD), minimum, and maximum will be used to summarize continuous endpoints.

Baseline for safety and efficacy data is the last observation prior to the first dose of study drug. Study day will be derived for Baseline and post-Baseline visits using Visit Date – Baseline Date + 1. Study day prior to Baseline will be derived using Visit Date – Baseline Date.

5.1.1 Estimands

The following patient level data descriptions are required for defining the pre-specified analyses:

Estimand-endpoint specific	**Description**
Primary Estimand (composite strategy) – continuous endpoint	Population: Randomized subjects with moderate to severe papulopustular rosacea as defined by inclusion criteria to reflect the targeted population. Variable: change from baseline in total inflammatory lesion count at Week 16. Intercurrent events: Adverse Events (AEs) leading to treatment discontinuation, including study discontinuation; withdrawal from the study due to lack of efficacy; or prohibited medication use during the treatment period. Population-level summary: Treatment differences between DFD-29 and placebo at Week 16. Percentage change from Baseline in total inflammatory lesion counts at Week 16 and change from Baseline in total inflammatory lesions counts at Week 16 comparing DFD-29 and Doxycycline will follow the same structure as defined above.

	For subjects with any of the above defined intercurrent events, missing data will have the last observation prior to the occurrence of the intercurrent event carried forward for all subsequent visits. Otherwise, missing continuous data will be imputed using a multiple imputation (MI) approach.
Primary Estimand (composite strategy) – categorical endpoint	Population: Randomized subjects with moderate to severe papulopustular rosacea as defined by inclusion criteria to reflect the targeted population. Variable: Success based on the IGA score of 0 or 1 and at least a 2-grade reduction from Baseline. Intercurrent events: Adverse Events (AEs) leading to treatment discontinuation, including study discontinuation; withdrawal from the study due to lack of efficacy; or prohibited medication use during the treatment period. Population-level summary: Treatment differences between DFD-29 and placebo at Week 16 Success based on the IGA comparing DFD-29 and Doxycycline and success based on the CEA comparing DFD-29 and placebo will follow the same structure defined above. Subjects with any of the above defined intercurrent events will have observations for each visit after the occurrence of the intercurrent event defined as a treatment non-responder. Otherwise, missing categorical data will be imputed using an MI approach using the original scale.
Secondary Estimand –continuous and categorical endpoints	Population: Randomized subjects with moderate to severe papulopustular rosacea as defined by inclusion criteria and have no protocol violations or major protocol deviations. Variable: change from baseline in total inflammatory lesion count at Week 16. Intercurrent event: All data collected for the population will be utilized. Population-level summary: Treatment differences between DFD-29 and placebo at Week 16. All primary and secondary endpoints will follow the same structure. No imputations for missing data will be made.

5.1.2 Pooling of Sites

Analysis centers which include adequately large original sites and pooled centers of small sites will be created. A site is considered small if it has less than 8 ITT subjects. An adequately large site is one that produces at least 8 ITT subjects. While adequately large sites remain as they originally are, small sites will be pooled to form adequately large centers for the analyses. The small sites will be pooled from biggest to smallest until the pooled center is adequately large. If the last few small sites are pooled but fail to be adequately large, they will be pooled with the

smallest analysis center. Sites in the United States (US) and sites in Europe will be pooled separately.

5.2 Handling of Dropouts or Missing Data

5.2.1 Early Termination Visit

For subjects with an ET visit, efficacy data collected during the ET visit will be reallocated for the ITT analyses to the closest visit using the visit windows below:

- Week 2 (Day 14, Visit 3)—Day 1 post-dose to Day 22
- Week 4 (Day 29, Visit 4)—Day 23 to Day 43
- Week 8 (Day 57, Visit 5)—Day 44 to Day 71
- Week 12 (Day 85, Visit 6)—Day 72 to Day 99
- Week 16 (Day 113, Visit 7)—Day 100 to EOS

Subjects who terminated early will be excluded from the PP analyses. For safety data collected during the ET visit, the data will remain at the Week 16/ET visit.

5.2.2 Missing Data

Missing data for the primary estimands will be replaced using an MI approach. Seed numbers for each endpoint will use the randomly generated 4-digit numbers from the table below. Other variables that are included in the imputation models will include treatment, world region (US and Europe), analysis center, and key baseline characteristics such as age, gender, and race. Depending on the pattern of missingness, a 2-step process may be employed. If missing data points occur for an intermediate visit, which is often unlikely, they will be imputed first using a Markov Chain Monte Carlo (MCMC) method for each treatment separately. As a result, a monotone missingness pattern will be obtained for the data to be fully imputed. The subsequent imputation will use general regression for continuous variables and logistic regression for categorical variables under the assumption data are missing at random to produce 200 imputed datasets where the remaining missing data are filled in using 200 separate sets of values. For categorical variables, imputations will occur using the original scale (e.g, IGA score). When a variable with missing values at a given visit is imputed, its assessments at all previous visits will be included as predictors in the imputation model. For example, for a subject with missing IGA data at Week 16, the IGA data from Baseline and Weeks 2, 4, 8, and 12 for the subject will be included in the imputation model.

	Random Seed Number		
Endpoint	DFD-29	Vehicle	Doxycycline
IGA	4561	7829	8902
Total inflammatory lesion count	8505	6665	1689
CEA	7855	0140	4537

For each copy of the imputed datasets, both the primary and secondary endpoints involving the same endpoint variable will be analyzed in the same way as described in the primary and secondary analyses in Sections 5.5.1 and 5.5.2, respectively. Results from the copies of the imputed datasets will be synthesized using SAS Proc MIANALYZE.

No imputation for missing data will be used for safety.

5.2.3 COVID-19 Impacted Visits

Efficacy data collected during remote visits at Baseline and Week 16 visits are considered major protocol deviations and will be excluded from the ITT and PP analyses for the coprimary and secondary endpoints. Such data would be included in supportive/exploratory analyses for the ITT & PP populations. Efficacy data collected during remote visits due to COVID-19 issues for interim visits will be used as collected. Any missing data that arise due to COVID-19 issues will be handled using the methods described in Sections 5.2.1 and 5.2.2. Subjects with COVID-19 impacted visits will be listed with the type of visit that resulted due to the impact.

5.3 Demographics, Medical History, and Baseline Characteristics

Subject demographics and Baseline characteristics will be summarized by treatment group for the ITT, PP, and Safety populations. For continuous variables, (e.g., age and total inflammatory lesion counts), comparisons between the treatment groups will be conducted using a 2-way analysis of variance (ANOVA) model with fixed factors of treatment group, world region, and analysis center. The Cochran-Mantel-Haenszel (CMH) test for general association stratified by world region and analysis center will be used for analyzing the categorical variables (e.g., gender, and IGA).

The medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.1. Medical history will be summarized by system organ class (SOC) and preferred term (PT). If a subject has more than one medical history event in an SOC or PT, the subject will be counted only once within the term.

5.4 Subject Accountability

A summary of subject disposition will be provided for all subjects. Descriptive summaries of subject disposition, reason for discontinuation, and analysis populations will be provided by treatment group. Subject disposition and population status will also be tabulated for each site. Major protocol deviations will be summarized by deviation type for all sites and by site. Protocol deviations and protocol violations will be listed by subject.

5.5 Efficacy Variables and Analyses

For all endpoints, the comparison of DFD-29 versus placebo will be the primary objective of the study. Comparison between DFD-29 and Doxycycline capsules 40 mg will be treated as secondary. All efficacy summaries and analyses will be provided for the ITT population. The co-primary and secondary efficacy endpoint summaries and analyses will also be provided for the PP population.

5.5.1 Primary Efficacy Analyses

- The proportion of subjects with IGA treatment success at Week 16 comparing DFD-29 to placebo will be tested using a CMH test for general association adjusted for world region and analysis center. Treatment success is defined as IGA = 0 or 1 and at least a 2-grade reduction from Baseline. The frequency and proportion of subjects with IGA treatment success for each treatment group will be displayed along with the difference in proportions between DFD-29 and placebo with a corresponding 95% confidence interval (CI). The primary analysis will be performed using the primary estimand for categorical data and a supportive analysis will be performed using the secondary estimand.

- The difference between DFD-29 and placebo in change from Baseline in total inflammatory lesion count at Week 16 will be tested using an analysis of covariance (ANCOVA) model with treatment, world region, and analysis center included in the model as fixed effects and Baseline total inflammatory lesion count as a covariate. Least squares (LS) means and standard errors (SE) for each treatment group will be displayed along with the difference in LS means with the corresponding SE and 95% CI. The primary analysis will be performed using the primary estimand for continuous data and a supportive analysis will be performed using the secondary estimand.

5.5.2 Secondary Efficacy Analyses

- The difference between DFD-29 and placebo in percentage change from Baseline in total inflammatory lesion count at Week 16 will be tested using an ANCOVA model with treatment, world region, and analysis center included as fixed effects and Baseline total inflammatory lesion counts as a covariate. LS means and standard errors (SE) for each treatment group will be displayed along with the difference in LS means with the corresponding SE and 95% CI. The primary estimand for continuous data will be used and a supportive analysis will be performed using the secondary estimand.
- The proportion of subjects with IGA treatment success at Week 16 comparing DFD-29 to Doxycycline capsules 40 mg will be tested using a CMH test for general association adjusted for world region and analysis center. The frequency and proportion of subjects with IGA treatment success for each treatment group will be displayed along with the difference in proportions between DFD-29 and Doxycycline capsules with a corresponding 95% CI. The primary estimand for categorical data will be used and a supportive analysis will be performed using the secondary estimand.
- The difference between DFD-29 and Doxycycline capsules 40 mg in change from Baseline in total inflammatory lesion count at Week 16 will be tested using an ANCOVA model with treatment, world region, and analysis center included as fixed effects and Baseline total inflammatory lesion counts as a covariate. LS means and standard errors (SE) for each treatment group will be displayed along with the difference in LS means with the corresponding SE and 95% CI. The primary estimand for continuous data will be used and a supportive analysis will be performed using the secondary estimand.
- The difference between DFD-29 and Doxycycline capsules 40 mg in percentage change from Baseline in total inflammatory lesion count at Week 16 will be tested using an ANCOVA model with treatment, world region, and analysis center included as fixed effects and Baseline total inflammatory lesion counts as a covariate. LS means and standard errors (SE) for each treatment group will be displayed along with the difference in LS means with the corresponding SE and 95% CI. The primary estimand for continuous data will be used and a supportive analysis will be performed using the secondary estimand.
- The CEA erythema assessment will be carried out separately on the forehead, nose, chin, right cheek, and left cheek. The Baseline score will be considered from location(s) with the maximum CEA severity out of the 5 locations assessed. If CEA assessment is missing for one or more locations at Baseline, then the Baseline score will be considered for the location(s) having the maximum CEA severity out of the available assessments. Assessments with the same maximum severity will be averaged for the Baseline score. A ≥ 2-grade improvement is

defined as a ≥ 2-grade reduction in the same location(s) as the Baseline score. If more than one location was used for Baseline, the same locations will be averaged for the post-baseline score. Subject with a ≥ 2-grade reduction in the worst affected area(s), who show worsening (i.e., increases) by > 1 grade over Baseline in one or more of the other facial locations, will be considered treatment non-responders for the primary analysis of this endpoint and considered treatment responders for the supportive analyses. If a post-Baseline assessment is missing for the location(s) which was considered for Baseline score, the CEA score will be handled as missing data and imputed according to the estimand of interest. The proportion of subjects with ≥ 2-grade reduction in CEA score from Baseline to Week 16 comparing DFD-29 to placebo will be tested using a CMH test for general association adjusted for world region and analysis center. The frequency and proportion of subjects with at least a 2-grade reduction for each treatment group will be displayed along with the difference in proportions between DFD-29 and placebo with a corresponding 95% CI. The primary estimand for categorical data will be used and a supportive analysis will be performed using the secondary estimand.

5.5.3 Exploratory Efficacy Analyses

The following exploratory analyses will be performed and will not have any confirmatory value and will compare DFD-29 to placebo and Doxycycline capsules 40 mg. There will be no Type 1 error control or missing data imputation for these analyses.

The mixed model repeated measures (MMRM) analyses below will use the following methods: 1) Treatment, world region, analysis center, visit, and treatment by visit interaction will be included as fixed effects, Baseline of the parameter of interest as a covariate, and subject as a random factor. 2) The first variance/covariance structure to converge will be used following this hierarchy: a) unstructured (UN), b) heterogenous first order autoregressive [ARH(1)], c) first order autoregressive [AR(1), d) heterogenous compound symmetry (CSH), and compound symmetry (CS). LS means and standard errors (SE) for each treatment group will be displayed along with the difference in LS means with the corresponding SE and 95% CI.

- The proportion of subjects with IGA treatment success at Weeks 2, 4, 8, and 12 comparing treatments will be tested using a CMH test for general association adjusted for world region and analysis center for each time point. The frequency and proportion of subjects with IGA treatment success for each treatment group will be displayed along with the difference in proportions between the DFD-29 and Placebo/doxycycline groups with a corresponding 95% CI.
- The difference between treatments in change from Baseline in total inflammatory lesion count at Weeks 2, 4, 8, and 12 will be tested using MMRM.
- The difference between treatments in percentage change from Baseline in total inflammatory lesion count at Weeks 2, 4, 8, and 12 will be tested using MMRM.
- The proportion of subjects with at least a 2-grade reduction in IGA score from Baseline to Weeks 2, 4, 8, 12, and 16 comparing treatments will be tested using a CMH test for general association adjusted for world region and analysis center for each time point. The frequency and proportion of subjects with at least a 2-grade reduction for each treatment group will be displayed along with the difference in proportions between DFD-29 and placebo with a corresponding 95% CI.

- The RosaQoL consists of 21 questions that subjects will rate using a 5-grade scale. The total RosaQoL score will be the sum of the individual ratings. If an individual rating is missing, the total score will also be missing. The difference between treatments in change from Baseline in total RosaQoL score at Weeks 2, 4, 8, 12, and 16 will be tested using MMRM.
- The DLQI questionnaire consists of 10 questions scored from 0 to 3. The total from all questions is the DLQI score. If one or more of the 10 questions is missing a score, the DLQI score will be considered missing. The difference between treatments in change from Baseline in DLQI score at Weeks 2, 4, 8, 12, and 16 will be tested using MMRM.
- The proportion of subjects with at least a 2-grade improvement in the CEA score from Baseline to Weeks 2, 4, 8, and 12 comparing treatments will be tested using a CMH test for general association adjusted for world region and analysis center at each time point. Week 16 will be included for the DFD-29 versus Doxycycline capsules 40 mg comparison. The frequency and proportion of subjects with at least a 2-grade reduction for each treatment group will be displayed along with the difference in proportions between DFD-29 and placebo with a corresponding 95% CI.

Exploratory analyses using descriptive statistics for the following subgroups will be performed for the co-primary endpoints using the ITT population:

- Males versus females
- Baseline rosacea severity: moderate (IGA = 3) versus severe (IGA = 4)
- Baseline total inflammatory lesion count below or equal to the median count versus above the median count.
- Fitzpatrick skin types I-III versus IV-VI
- Baseline body weight below or equal to median weight versus above median weight
- Subjects enrolled in the US versus subjects enrolled in Europe

If > 5% of subjects have remote visits at either Baseline or Week 16, then an exploratory analysis will be performed for the co-primary endpoints for the ITT population. The data collected from the remote visits will be used as it is and other missing data will be estimated using the MI approach.

5.5.4 Sensitivity Analyses

Last Observation Carried Forward: To assess the potential impact of the MI method for handling missing data, the primary and secondary endpoints will be analyzed in the ITT population with missing data replaced using a last observation carried forward (LOCF) approach.

Tipping Point: A tipping point MI analysis using the ITT population will also be performed for the primary and secondary endpoints for the primary estimand for continuous variables. Ten percent of the treatment difference from the original model will be added to the non-DFD-29 treatment arm results. If the DFD-29 versus placebo comparison is still significant, an additional 10% will be added to subsequent analyses until the comparison is not significant. For the DFD-29 versus Doxycycline comparison, a similar approach will be used.

A tipping point analysis for the primary and secondary endpoints for the primary estimand for categorical variables will also be performed. The number of missing values for each endpoint

will be determined for each treatment. For DFD-29 versus placebo and DFD-29 versus Doxycycline comparisons, all missing values will be imputed using various proportions of success. The extremes for this analysis are:

- Worst case DFD-29: All missing data from the non-DFD-29 arm are imputed as treatment responder and all missing data from the DFD-29 arm are imputed as treatment non-responder
- Best case DFD-29: All missing data from the non-DFD-29 arm are imputed as treatment non-responder and all missing data from the DFD-29 arm are imputed as treatment responder

The tipping point analysis will use a CMH test for general association adjusted for site for the above cases and every possible proportion of treatment responder from imputed missing values between the 2 cases. A table will be developed to display the resultant response rates for each treatment and associated p-values. Depending on the number of missing values, not every permutation may be displayed.

Site outliers: For the difference between DFD-29 and placebo in change from Baseline in total inflammatory lesion count at Week 16, the analysis center by treatment group interaction will be evaluated. If the p-value for the interaction term is < 0.10, then an investigation for outlier sites will be conducted. For the proportion of subjects with IGA treatment success at Week 16 comparing DFD-29 to placebo, the Breslow-Day test will be performed to assess homogeneity of treatment effect across analysis centers. If the p-value for the Breslow-Day test is < 0.10, then an investigation for outlier sites will be conducted. Outlier analysis centers will be identified by treatment group using Tukey's method. The interquartile range (IQR) will be determined from the mean values of the endpoint under investigation by analysis center and treatment group. Any analysis centers whose mean value is < the first quartile – 1.5*IQR or > the third quartile + 1.5*IQR for any treatment group will be considered an analysis center outlier. If outlier analysis centers are identified, a sensitivity analysis will be performed excluding the outliers.

5.6 Safety Variables and Analyses

5.6.1 Extent of Exposure

The extent of exposure to study product in each treatment group will be summarized as mean number of doses, mean days of exposure, and number and percentage of subjects who are compliant for the treatment period. A subject will be considered compliant with the dosing regimen if the subject took at least 80% but no more than 120% of the expected doses from the subject's first dose date to last dose date and missed no more than 6 consecutive doses. The total number of doses will be taken from the subject diaries. The compliance rate is equal to 100 * (total # doses / days of exposure). Days of exposure is equal to date of the last dose – date of the first dose + 1.

5.6.2 Adverse Events

AEs will be coded in the MedDRA, version 24.1. Treatment-Emergent Adverse Event (TEAE) is defined as any AE occurs on or after taking the first dose of study drug. Number and percent of subjects reporting TEAEs, treatment emergent serious AEs, and TEAEs that led to treatment interruption or discontinuation will be tabulated by treatment group. Summaries will be

presented by SOC and PT in descending order according to the incidence in the DFD-29 treatment group, and further by severity and relationship to study medication. In summaries of severity and relationship, subjects who report more than one event that is mapped to the same preferred term will be counted only once under the strongest severity and relationship, accordingly.

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.

Treatment-Emergent Serious Adverse Events, TEAEs that led to treatment interruption or discontinuation, pre-dose AEs, and reasons for death will be presented in data listings.

5.6.3 Physical Examination

Physical examination findings will be summarized by body system displaying the number and percentage of subjects with abnormalities at Baseline and Week 16/ET. Physical examination findings will also be presented in data listings.

5.6.4 Vital Signs

Vitals signs include pulse rate, diastolic and systolic blood pressure, and body weight. Observed values and change from Baseline in vital sign measurements will be summarized at each time point using number of available observations, mean, SD, median, minimum and maximum. Subject level vital sign data will be presented in listings.

5.6.5 Laboratory Parameters

The individual hematology, chemistry, urinalysis, and hepatic transaminases parameters with Baseline and post-Baseline numeric results will be summarized. Observed values and change from Baseline in laboratory parameters will be summarized at each time point using number of available observations, mean, SD, median, minimum, and maximum. All subject level laboratory data including serology, anti-nuclear-Ab, and hepatic transaminases will be presented in listings.

5.6.6 Prior and Concomitant Medications

Medications taken prior to start of study treatment and during the study will be classified according to the World Health Organization Drug Dictionary (WHO-DD; version September 2021 Q). Prior medications are any taken 30 days or less before signing the informed consent form and will be presented in data listings. Concomitant medications are any taken after first dose of study treatment through the end of study participation and will be summarized by WHO-DD Anatomical Therarapeutic Chemical (ATC) level 2 and ATC level 4 for each treatment group. A subject will be counted only once in each unique ATC level if the subject has multiple medications of the same level.

6 Appendices

6.1 Handling of Missing or Incomplete Dates for Adverse Events and Concomitant Medications

Handling of partial dates is only considered for the start date. An adverse event with a partial start date is considered treatment emergent if:

- only the day is missing and the start month/year is the same or after the month/year of the first dose

- the day and month are missing and the start year is the same or greater than the year of the first dose date

- the start date is completely missing

Concomitant Medications

Handling of partial dates is only considered for the stop date. A medication with a partial stop date is considered concomitant if:

- only the day is missing and the stop month/year is the same or after the month/year of the first dose

- the day and month are missing and the stop year is the same or greater than the year of the first dose date

- the stop date is completely missing or the medication is ongoing

6.2 Summary of Assessments (Study Visit Schedule)

	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**
	Screening	**Baseline**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16 EOS/ET**
Study Day	**Day -30 to Day -3**	**Day 1**	**Day 14 (± 3 days)**	**Day 29 (± 3 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	X					
Eligibility Conclusion	X	X					
Weight	X	X					X
Height	X						
Medical History/Prior Medications	X	X					
Vital Signs (blood pressure, pulse rate)	X	X	X	X	X	X	X
Urine Pregnancy Test (for females of childbearing potential)	X	X	X	X	X	X	X
IGA	X	X	X	X	X	X	X
CEA	X	X	X	X	X	X	X
Lesion count	X	X	X	X	X	X	X
RosaQoL & DLQI Score		X	X	X	X	X	X
Physical Examination[a]	X						X
Laboratory assessments (Blood & Urine tests)	X[b]						X[c]
Randomization		X					
Dispense/ Re-dispense Study Drug		X	X[e]	X	X	X	
Dispense/Review/Collect Study Diary		X	X	X	X	X	X
Discussion of Subject Instructions		X	X	X	X	X	
Collect Study Drug			X[e]	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

CEA = Clinician's Erythema Assessment; DLQI = Dermatology Life Quality Index; EOS = end of study;
IGA = Investigator's Global Assessment modified scale without erythema; RosaQoL = Rosacea Quality of Life

[a] A complete physical examination will be performed. Height and weight will be measured at Screening. Weight will also be measured at Baseline and Visit 7 (EOS or ET)
[b] Serology assessments will be performed only at Screening.
[c] Laboratory assessments (except Serology) for all subjects will be done at their EOS visit (Week 16).
[d] Collect and Re-dispense at Visit 3

6.3 Tables and Listings

Include shell tables, figures (if applicable) and data listings.

Following are some examples for tables and listings.

6.3.1 Summary Tables*

Table Number	Title	Population(s)	Listing Reference
Baseline			
14.1.1	Subject Enrollment	Intent-to-Treat	16.2.1.1
14.1.2	Subject Discontinuations by Reason	Intent-to-Treat	16.2.1.2
14.1.3	Subject Enrollment and Disposition by Study Site	Intent-to-Treat	16.2.1.1, 16.2.1.2
14.1.4.1	Demographics	Intent-to-Treat	16.2.4.1
14.1.4.2	Demographics	Safety	16.2.4.1
14.1.4.3	Demographics	Per-Protocol	16.2.4.1
14.1.5.1	Baseline Characteristics	Intent-to-Treat	16.2.4.1, 16.2.6.1, 16.2.6.2
14.1.5.2	Baseline Characteristics	Safety	16.2.4.1, 16.2.6.1, 16.2.6.2
14.1.5.3	Baseline Characteristics	Per-Protocol	16.2.4.1, 16.2.6.1, 16.2.6.2
14.1.6	Medical History by MedDRA System Organ Class and Preferred Term	Safety	16.2.4.2
14.1.7	Major Protocol Deviations	Intent-to-treat	16.2.2.1
Efficacy			
14.2.1.1.1	Analyses of the Co-Primary Efficacy Endpoint: Proportion of Subjects with IGA Treatment Success at Week 16 Visit	Intent-to-Treat and Per-Protocol	16.2.6.1
14.2.1.1.2	Analyses of the Co-Primary Efficacy Endpoint: Change from Baseline in Total Inflammatory Lesion Count at Week 16 Visit	Intent-to-Treat and Per-Protocol	16.2.6.2
14.2.1.2.1	Sensitivity (Tipping Point and LOCF) Analyses of the Co-Primary Efficacy Endpoint: Proportion of Subjects with IGA Treatment Success at Week 16 Visit	Intent-to-Treat	16.2.6.1
14.2.1.2.2	Sensitivity (Tipping Point and LOCF) Analyses of the Co-Primary Efficacy Endpoint: Change from Baseline in Total Inflammatory Lesion Count at Week 16 Visit	Intent-to-Treat	16.2.6.2
14.2.1.2.3	Sensitivity (Excluding Site Outliers) Analysis of the Co-Primary Efficacy Endpoint: Proportion of Subjects with IGA Treatment Success at Week 16 Visit	Intent-to-Treat (Note: Performed only if site outliers are identified)	16.2.6.1

Table Number	Title	Population(s)	Listing Reference
14.2.1.2.4	Sensitivity (Excluding Site Outliers) Analysis of the Co-Primary Efficacy Endpoint: Change from Baseline in Total Inflammatory Lesion Count at Week 16 Visit	Intent-to-Treat (Note: Performed only if site outliers are identified)	16.2.6.2
14.2.1.3.1	Investigator's Global Assessment by Visit	Intent-to-Treat	16.2.6.1
14.2.1.3.2	Investigator's Global Assessment by Visit	Per-Protocol	16.2.6.1
14.2.1.3.3	Total Inflammatory Lesion Count by Visit	Intent-to-Treat	16.2.6.2
14.2.1.3.4	Total Inflammatory Lesion Count by Visit	Per-Protocol	16.2.6.2
14.2.2.1.1	Analyses of Secondary Efficacy Endpoint: Percentage Change from Baseline in Total Inflammatory Lesion Count at Week 16 Visit	Intent-to-Treat and Per-Protocol (Note: DFD-29 to Placebo Comparison)	16.2.6.2
14.2.2.1.2	Analysis of the Secondary Efficacy Endpoint: Proportion of Subjects with IGA Treatment Success at Week 16 Visit	Intent-to-Treat and Per-Protocol	16.2.6.1
14.2.2.1.3	Analysis of the Secondary Efficacy Endpoint: Change from Baseline in Total Inflammatory Lesion Count at Week 16 Visit	Intent-to-Treat and Per-Protocol	16.2.6.1
14.2.2.1.4	Analyses of Secondary Efficacy Endpoint: Percentage Change from Baseline in Total Inflammatory Lesion Count at Week 16 Visit	Intent-to-Treat and Per-Protocol (Note: DFD-29 to Doxycycline Comparison)	16.2.6.2
14.2.2.1.5	Analysis of the Secondary Efficacy Endpoint: Proportion of Subjects with at Least a Two-Grade Reduction from Baseline in Clinician's Erythema Assessment Score at Week 16 Visit	Intent-to-Treat and Per-Protocol	16.2.6.4
14.2.2.2.1	Sensitivity (Tipping Point and LOCF) Analyses of Secondary Efficacy Endpoint: Percentage Change from Baseline in Total Inflammatory Lesion Count at Week 16 Visit	Intent-to-Treat	16.2.6.2
14.2.2.2.2	Sensitivity (Tipping Point and LOCF) Analyses of the Secondary Efficacy Endpoint: Proportion of Subjects with IGA Treatment Success at Week 16 Visit	Intent-to-Treat	16.2.6.1
14.2.2.2.3	Sensitivity (Tipping Point and LOCF) Analyses of the Secondary Efficacy Endpoint: Change from Baseline in Total Inflammatory Lesion Count at Week 16 Visit	Intent-to-Treat	16.2.6.2

Table Number	Title	Population(s)	Listing Reference
14.2.2.2.4	Sensitivity (Tipping Point and LOCF) Analyses of the Secondary Efficacy Endpoint: Proportion of Subjects with at Least a Two-Grade Reduction from Baseline in Clinician's Erythema Assessment Score at Week 16	Intent-to-Treat	16.2.6.4
14.2.2.3.1.1	Total Inflammatory Lesion Count by Visit (Note: % change from Baseline)	Intent-to-Treat	16.2.6.2
14.2.2.3.1.2	Total Inflammatory Lesion Count by Visit (Note: % change from Baseline)	Per-Protocol	16.2.6.2
14.2.2.3.2.1	Clinician's Erythema Assessment by Visit	Intent-to-Treat	16.2.6.4
14.2.2.3.2.2	Clinician's Erythema Assessment by Visit	Per-Protocol	16.2.6.4
14.2.3.1.1	Analysis of the Exploratory Efficacy Endpoint: Proportion of Subjects with IGA Treatment Success at Week 2, 4, 8, and 12 Visits	Intent-to-Treat (Note: DFD-29 to Placebo Comparison)	16.2.6.1
14.2.3.1.2	Analysis of the Exploratory Efficacy Endpoint: Proportion of Subjects with IGA Treatment Success at Week 2, 4, 8, and 12 Visits	Intent-to-Treat (Note: DFD-29 to Doxycycline Comparison)	16.2.6.1
14.2.3.2.1	Analysis of the Exploratory Efficacy Endpoint: Change from Baseline in Total Inflammatory Lesion Count at Week 2, 4, 8, and 12 Visits	Intent-to-Treat (Note: DFD-29 to Placebo Comparison)	16.2.6.2
14.2.3.2.2	Analysis of the Exploratory Efficacy Endpoint: Change from Baseline in Total Inflammatory Lesion Count at Week 2, 4, 8, and 12 Visits	Intent-to-Treat (Note: DFD-29 to Doxycycline Comparison)	16.2.6.2
14.2.3.3.1	Analysis of the Exploratory Efficacy Endpoint: Percentage Change from Baseline in Total Inflammatory Lesion Count at Week 2, 4, 8, and 12 Visits	Intent-to-Treat (Note: DFD-29 to Placebo Comparison)	16.2.6.2
14.2.3.3.2	Analysis of the Exploratory Efficacy Endpoint: Percentage Change from Baseline in Total Inflammatory Lesion Count at Week 2, 4, 8, and 12 Visits	Intent-to-Treat (Note: DFD-29 to Doxycycline Comparison)	16.2.6.2
14.2.3.4.1	Analysis of the Exploratory Efficacy Endpoint: Proportion of Subjects with at Least a Two-Grade Reduction in Investigator's Global Assessment scores at Week 2, 4, 8, 12, and 16 Visits	Intent-to-Treat (Note: DFD-29 to Placebo Comparison)	16.2.6.1

Table Number	Title	Population(s)	Listing Reference
14.2.3.4.2	Analysis of the Exploratory Efficacy Endpoint: Proportion of Subjects with at Least a Two-Grade Reduction in Investigator's Global Assessment scores at Week 2, 4, 8, 12, and 16 Visits	Intent-to-Treat (Note: DFD-29 to Doxycycline Comparison)	16.2.6.1
14.2.3.5.1.1	Analysis of the Exploratory Efficacy Endpoint: Change from Baseline in Rosacea Quality of Life Score at Week 2, 4, 8, 12, and 16 Visits	Intent-to-Treat (Note: DFD-29 to Placebo Comparison)	16.2.6.5
14.2.3.5.1.2	Analysis of the Exploratory Efficacy Endpoint: Change from Baseline in Rosacea Quality of Life Score at Week 2, 4, 8, 12, and 16 Visits	Intent-to-Treat (Note: DFD-29 to Doxycycline Comparison)	16.2.6.5
14.2.3.5.2	Rosacea Quality of Life Instrument by Visit	Intent-to-Treat	16.2.6.5
14.2.3.6.1.1	Analysis of the Exploratory Efficacy Endpoint: Change from Baseline in Dermatology Life Quality Index Score at Week 2, 4, 8, 12, and 16 Visits	Intent-to-Treat (Note: DFD-29 to Placebo Comparison)	16.2.6.3
14.2.3.6.1.2	Analysis of the Exploratory Efficacy Endpoint: Change from Baseline in Dermatology Life Quality Index Score at Week 2, 4, 8, 12, and 16 Visits	Intent-to-Treat (Note: DFD-29 to Doxycycline Comparison)	16.2.6.3
14.2.3.6.2	Dermatology Life Quality Index by Visit	Intent-to-Treat	16.2.6.3
14.2.3.7.1	Analysis of the Exploratory Efficacy Endpoint: Proportion of Subjects with at Least a Two-Grade Reduction in Clinician's Erythema Assessment at Week 2, 4, 8, and 12 Visits	Intent-to-Treat (Note: DFD-29 to Placebo Comparison)	16.2.6.4
14.2.3.7.2	Analysis of the Exploratory Efficacy Endpoint: Proportion of Subjects with at Least a Two-Grade Reduction in Clinician's Erythema Assessment at Week 2, 4, 8, 12, and 16 Visits	Intent-to-Treat (Note: DFD-29 to Doxycycline Comparison)	16.2.6.4
14.2.3.8	Summary of Subgroups for Co-Primary Endpoint: Proportion of Subjects with IGA Treatment Success at Week 16 Visit	Intent-to-Treat	16.2.6.1
14.2.3.9	Summary of Subgroups for Co-Primary Endpoint: Change from Baseline in Total Inflammatory Lesion Count at Week 16 Visit	Intent-to-Treat	16.2.6.2
Safety			
14.3.1	Treatment Exposure and Compliance	Safety	16.2.5.2

Table Number	Title	Population(s)	Listing Reference
14.3.2.1	Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class and Preferred Term	Safety	16.2.7.1
14.3.2.2	Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	16.2.7.1
14.3.2.3	Treatment-Emergent Adverse Events (TEAEs) that Led to Treatment Interruption or Discontinuation by MedDRA System Organ Class and Preferred Term	Safety	16.2.7.1
14.3.2.4	Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term and Severity	Safety	16.2.7.1
14.3.2.5	Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term and Relationship to Study Drug	Safety	16.2.7.1
14.3.3.1	Summary of Systolic Blood Pressure by Visit	Safety	16.2.8.2
14.3.3.2	Summary of Diastolic Blood Pressure by Visit	Safety	16.2.8.2
14.3.3.3	Summary of Pulse Rate by Visit	Safety	16.2.8.2
14.3.3.4	Summary of Body Weight by Visit	Safety	16.2.4.3
14.3.4.1	Summary of Hematology by Visit	Safety	16.2.8.4
14.3.4.2	Summary of Chemistry by Visit	Safety	16.2.8.5
14.3.4.3	Summary of Urinalysis by Visit	Safety	16.2.8.6
14.3.4.4	Summary of Hepatic Transaminases	Safety	16.2.8.9
14.3.5	Summary of Abnormal Physical Examination by Visit	Safety	16.2.4.3
14.3.6	Summary of Concomitant Medications	Safety	16.2.9.1

*Mock shells provided as an attachment.

6.3.2 Summary Listings*

Listing Number	Title
16.2.1.1	Subject Status
16.2.1.2	End of Study
16.2.1.3	Date of Visits
16.2.1.4.1	Subject Eligibility (Randomized Subjects)
16.2.1.4.2	Description of Inclusion Criteria
16.2.1.4.3	Description of Exclusion Criteria
16.2.2.1	Protocol Violations (PV) and Protocol Deviations (PD)
16.2.2.2	Comments
16.2.3	Exclusions from Efficacy Analyses
16.2.4.1	Demographics and Fitzpatrick Skin Type
16.2.4.2	Medical History
16.2.4.3	Physical Examination
16.2.5.1	Subject Study Treatment and Diary Dispensing
16.2.5.2	Treatment Record
16.2.6.1	Investigator's Global Assessment (IGA) of Disease Severity
16.2.6.2	Total Inflammatory Lesion Count
16.2.6.3	Dermatology Life Quality Index (DLQI)
16.2.6.4	Clinician's Erythema Assessment
16.2.6.5	Rosacea Quality of Life Assessment
16.2.7.1	Adverse Events
16.2.7.2	Adverse Events Leading to Study Drug Withdrawn or Temporarily Stopped
16.2.7.3	Serious Adverse Events
16.2.7.4	Predose Adverse Events
16.2.8.1	Deaths
16.2.8.2	Vital Signs
16.2.8.3	Urine Pregnancy Test (Female Subjects Only)
16.2.8.4	Hematology
16.2.8.5	Chemistry
16.2.8.6	Urinalysis
16.2.8.7	Serology
16.2.8.8	Anti-Nuclear-Ab
16.2.8.9	Hepatic-Transaminases
16.2.9.1	Prior or Concomitant Medications
16.2.9.2	Subject Eligibility (Screen Failure Subjects)
16.2.9.3	COVID-19 Impact

*Mock shells provided as an attachment