1 TITLE PAGE

Title:	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
Protocol No.:	DFD-29-CD-005
Acronym:	MVOR-2
EudraCT No.:	2021-005382-40
Co-Sponsors:	Dr. Reddy's Laboratories Ltd., 8-2-337, Road No. 3 Banjara Hills, Hyderabad Telangana 500034, India Phone: +91-40-4900 2900 Journey Medical Corporation 9237 E. Via De Ventura Blvd., Suite 105 Scottsdale, AZ 85258, USA Phone: +1 480-434-6675
Phase:	3
Protocol Version:	3.0
Amendment No.:	02
Current Protocol Version Date:	01 November 2022
Previous Versions of the Protocol:	Version 1.0 dated 22 December 2021 Version 2.0 dated 04 July 2022

2 SPONSOR/CRO SIGNATURE PAGE

PROTOCOL NUMBER: DFD-29-CD-005

PROTOCOL VERSION: 3.0

AMENDMENT NO.: 02

PROTOCOL DATE: 01 November 2022

PROTOCOL TITLE: 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

Signatures of the following individuals indicate that all agree this version is final.

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

Date

DocuSigned by:
Srinivas Sidgiddi
8E2E89622B4B495...

09-Nov-2022 | 6:27 AM PST

Srinivas Sidgiddi, M.D.
Vice President
Clinical Development & Medical Affairs
Journey Medical Corporation

Date

DocuSigned by:
Debra Dow
9886BBF4D34944E...

03-Nov-2022 | 6:21 PM IST

Debra A. Dow, PharmD
Vice President, Scientific Affairs
Symbio, LLC

Date

3 SYNOPSIS AND STUDY FLOW CHART

3.1 Synopsis

Title of Study: 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

Name of Sponsor: Dr. Reddy's Laboratories Ltd., India

Name of Finished Product: DFD-29 Extended Release Capsules

Name of Active Ingredient: Minocycline HCl

Objectives

Primary: To evaluate the safety, efficacy, and tolerability of oral DFD-29 (Minocycline HCl Extended Release Capsules), 40 mg (hereafter referred to as DFD-29) compared to placebo in the treatment of papulopustular rosacea for 16 weeks

Secondary: To evaluate the safety, efficacy, and tolerability of 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

Study Design: This is a 16-week, multicenter, randomized, parallel-group, double-blind, controlled study. After assessing eligibility during a screening period of up to 30 days, approximately 320 subjects at least 18 years old who are diagnosed with moderate to severe papulopustular rosacea will be randomized in a 3:3:2 ratio to DFD-29 (40 mg), Doxycycline capsules 40 mg, or Placebo once daily for 16 weeks.

Subject visits are scheduled at Screening, Baseline (Day 1), and Weeks 2, 4, 8, 12, and 16.

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.

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) to assess for any changes in the safety parameters. Other safety assessments include vital signs, physical examination, urine pregnancy tests (for females of childbearing potential), and collection of AE data.

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

Number of Study Centers: Approximately 29 study centers in the United States (US) and Europe (Poland and Germany) to enroll a total of approximately 320 subjects. There will be approximately 15 study centers in the US, 4 in Poland, and 10 in Germany.

Duration of Participation: Each subject will participate in the study for approximately 20 weeks from the time the subject signs the informed consent form (ICF) through the final contact. The screening period is up to 30 days and duration of treatment is 16 weeks.

Duration of Study: The study will require approximately 10 months from the beginning to the end of the study (first subject signing the ICF to last contact with last subject).

Key Inclusion/Exclusion Criteria: Male and female subjects at least 18 years of age in good general health with a clinical diagnosis of papulopustular rosacea, IGA grade 3 (moderate) or grade 4 (severe) at Baseline will be selected to participate in the study. Subjects must have 15 to 60 (both inclusive) inflammatory lesions (papules and pustules) of rosacea over the face and not more than 2 nodules or cysts at Baseline.

Investigational Product, Dose, Route of Administration, and Regimen:

To maintain the double-blind design, all 3 study medications will be over-encapsulated with the original capsules enclosed within a second, larger (size 0) capsule shell.

Investigational product: DFD-29 (Minocycline Hydrochloride Extended-Release Capsules), 40 mg (Dr. Reddy's Laboratories, Ltd.)

Active control: Doxycycline Capsules 40 mg [*an authorized generic of Oracea® in the United States* (marketed by Prasco Laboratories, Mason OH 45040 USA)]

Placebo: Capsules matching DFD-29 with same excipients but without minocycline HCl (Dr. Reddy's Laboratories Ltd.)

The study medication will be taken at a fixed time of the day once a day for 16 consecutive weeks. The preferred time of administration will be in the morning, after an overnight fast.

Statistical Methods:

Analysis Populations:

- Intent-to-treat (ITT) population includes all randomized subjects (i.e., assigned to a treatment group). The ITT population will be the primary population for the efficacy analysis.
- Safety population includes subjects who received at least one dose of study medication and had at least one safety assessment post-Baseline. The safety population will be used for analysis of tolerability and safety variables.
- Per-protocol population (PP) comprises all subjects who did not violate the protocol in a way that might affect the evaluation of the effect of the study medication on the primary endpoint (without major protocol violations or deviations). Key protocol deviation categories that would influence the decision to include a subject in the PP population at time of final review before study database lock will be pre-specified in the Statistical Analysis Plan (SAP).

Sample Size: The sample size was calculated based on results of a Phase 2 study with orally administered DFD-29 (40 mg) in the treatment of inflammatory lesions of papulopustular rosacea. Based on the sample size calculations and an assumed dropout rate of 20%, the final planned sample size is 120 subjects each in the DFD-29 and Doxycycline capsules 40 mg groups and 80 subjects in the placebo group for a total of 320 subjects. This sample size will provide adequate power to assess the superiority of DFD-29 against both placebo and Doxycycline capsules 40 mg in terms of efficacy on both co-primary endpoints.

Safety/Tolerability Endpoints:

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

- Change from Baseline to each scheduled time point up to End of Study (EOS) for vital signs, physical examination and clinical laboratory tests. The clinical laboratory tests obtained at screening visit will be defined as baseline assessments.
- Treatment-emergent AEs up to EOS.
- Treatment-emergent AEs leading to premature discontinuation of study drug.
- Treatment-emergent SAEs up to EOS.

For pre-existing conditions, any event that worsens during treatment will be considered treatment emergent.

Efficacy Endpoints:

Co-Primary Efficacy Endpoints:

- Proportion of subjects with IGA (modified scale without erythema) 'treatment success' – Grade 0 or 1 at Week 16 with at least 2 grade reduction from Baseline to Week 16, in the DFD-29 group compared to Placebo
- Total inflammatory lesion count (sum of papules, pustules, and nodules) reduction from Baseline to Week 16, in the DFD-29 group compared to Placebo

Secondary Efficacy Endpoints:

- Percentage Change in Total inflammatory lesion count (sum of papules, pustules, and nodules) from Baseline to Week 16, in the DFD-29 group compared to Placebo
- Proportion of subjects with IGA treatment success at week 16 in the DFD-29 group compared to Doxycycline capsules 40 mg.
- Total inflammatory lesion count reduction from Baseline to week 16 in the DFD-29 group compared to Doxycycline capsules 40 mg.
- Percentage Change in Total inflammatory lesion count (sum of papules, pustules, and nodules) from Baseline to Week 16, in the DFD-29 group compared to Doxycycline capsules 40 mg.
- Proportion of subjects with at least 2-grade reduction in CEA score from Baseline to Week 16 in the DFD-29 group compared to Placebo.

Exploratory Efficacy Endpoints:

All the following endpoints for DFD-29 will be compared against Placebo and Doxycycline capsules 40 mg

- Proportion of subjects with IGA 'treatment success' from Baseline to Weeks 2, 4, 8 and 12.
- Total inflammatory lesion count (sum of papules, pustules, and nodules) reduction from Baseline to Weeks 2, 4, 8 and 12.
- Percentage Change in Total inflammatory lesion count (sum of papules, pustules, and nodules) from Baseline to Weeks 2, 4, 8 and 12.
- Proportion of subjects with at least 2-grade reduction in IGA score from Baseline to Weeks 2, 4, 8 12 and 16.
- Change in RosaQoL score from Baseline to Weeks 2, 4, 8, 12 and 16.
- Change in DLQI score from Baseline to Weeks 2, 4, 8, 12 and 16.

- Proportion of subjects with at least 2-grade improvement in the CEA score at Weeks 2, 4, 8, 12 (and 16, in case of DFD-29 vs Doxycycline capsules 40 mg comparison).

Safety and Tolerability Analysis

Safety and tolerability data will be listed individually and summarized using descriptive statistics and frequency tables.

Efficacy Analysis

Co-Primary Endpoints:

- The proportion of subjects with IGA treatment success (DFD-29 versus placebo) will be investigated with a Cochran-Mantel-Haenszel (CMH) test for general association adjusted for site. Treatment success is defined as having at least a 2-grade reduction from Baseline with Grade 0 or 1 at Week 16.
- The difference between the treatments (DFD-29 versus placebo) in terms of the change from Baseline in the total inflammatory lesion count at Week 16 will be tested using an Analysis of Covariance (ANCOVA) model with treatment and site included in the model as fixed effects, and Baseline total inflammatory lesion count as a covariate.

Secondary Endpoints:

- Percentage Change in Total inflammatory lesion count (sum of papules, pustules, and nodules) from Baseline to Week 16, in the DFD-29 group compared to Placebo will be tested using an ANCOVA model with treatment and site included as fixed effects, and Baseline total inflammatory lesion count as a covariate.
- Proportion of subjects with IGA treatment success (DFD-29 versus Doxycycline capsules 40 mg) at Week 16 will be investigated with a CMH test for general association adjusted for site.
- The difference between treatments (DFD-29 versus Doxycycline capsules 40 mg) in change from Baseline in the total inflammatory lesion count at Week 16 will be tested using an ANCOVA model with treatment and site included as fixed effects, and Baseline total inflammatory lesion count as a covariate.
- Percentage Change in Total inflammatory lesion count (sum of papules, pustules, and nodules) from Baseline to Week 16, in the DFD-29 group compared to Doxycycline capsules 40 mg group will be tested using an ANCOVA model with treatment and site included as fixed effects, and Baseline total inflammatory lesion count as a covariate.
- Proportion of subjects with at least a 2-grade reduction in CEA score from Baseline to Week 16 will be investigated with a CMH test for general association adjusted for site (DFD-29 versus placebo).

Exploratory Endpoints:

All the following endpoints for DFD-29 will be compared against Placebo and Doxycycline capsules 40 mg

- Proportion of subjects with IGA treatment success from Baseline to Weeks 2, 4, 8 and 12 will be investigated with a CMH test for general association adjusted for site. Treatment success is defined as having at least a 2-grade reduction from Baseline with Grade 0 or 1.
- The difference between treatments in terms of the change from Baseline in the total inflammatory lesion count at Weeks 2, 4, 8 and 12 will be tested using mixed model repeated measures (MMRM) with treatment, site, visit, and treatment-by-visit interaction included in the model as fixed effects, Baseline total inflammatory lesion count as a covariate, and the subjects as a random factor
- Percentage Change in Total inflammatory lesion count (sum of papules, pustules, and nodules) from Baseline to Weeks 2, 4, 8 and 12 will be tested using MMRM with treatment, site, visit, and treatment-by-visit interaction included in the model as fixed effects, Baseline total inflammatory lesion count as a covariate, and the subjects as a random factor
- The proportion of subjects with at least 2-grade reduction in IGA score from Baseline to Weeks 2, 4, 8, 12 and 16 will be investigated with a CMH test for general association adjusted for site.
- Change in total RosaQoL score from Baseline to Weeks 2, 4, 8, 12 and 16 will be investigated using MMRM with treatment, site, visit, and treatment-by-visit interaction included in the model as fixed effects, Baseline RosaQoL as a covariate, and the subjects as a random factor.
- Change in DLQI score from Baseline to Weeks 2, 4, 8, 12 and 16 will be investigated using MMRM with treatment, site, visit, and treatment-by-visit interaction included in the model as fixed effects, Baseline DLQI as a covariate, and the subjects as a random factor.
- Proportion of subjects with at least a 2-grade improvement in the CEA score from Baseline to Weeks 2, 4, 8, 12 (and 16, in case of DFD-29 vs Doxycycline capsules 40 mg comparison) will be investigated with a CMH test for general association adjusted for site.

Exploratory analyses for the following subgroups will be performed with respect to the primary endpoints:

- Males versus females.
- Baseline Moderate (IGA 3) versus severe (IGA 4).
- Baseline Inflammatory lesion count below versus above Median count.
- Fitzpatrick skin types I-III versus IV-VI

Interim Analysis: No formal interim analysis is planned.

3.2 Study Flow Chart

	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[d]	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[d]	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

4 TABLE OF CONTENTS

4.1 List of Tables

5 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
AE	Adverse event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of variance
CEA	Clinician's Erythema Assessment
CFR	Code of Federal Regulations
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel test
COVID-19	Coronavirus disease 2019
CRA	Clinical Research Associate
CRO	Contract research organization
CRP	C-reactive Protein
DFD-29	Minocycline HCl (formulated as Extended Release capsules)
DLQI	Dermatology Life Quality Index
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End of study
ET	Early Termination
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HCl	Hydrochloride
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonization
IGA	Investigator's Global Assessment modified scale without erythema
ITT	Intention to treat
IRB	Institutional review board
IEC	Independent Ethics Committee
IUD	Intrauterine device
IWRS	Interactive web response system
MedDRA	Medical Dictionary for Regulatory Affairs
MI	Multiple imputation
MMRM	Mixed model repeated measures
MVOR-2	Minocycline Versus Oracea in Rosacea – Study 2

Term	Definition
OTC	Over the counter
PI	Principal Investigator
PP	Per protocol
PT	Preferred term
QoL	Quality of life
RosaQoL	Rosacea Quality of Life
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Suspected adverse reaction
SOC	System organ class
TEAE	Treatment-emergent adverse event
US	United States
UV	Ultraviolet

6 INTRODUCTION

6.1 Background

Rosacea is a chronic relapsing inflammatory cutaneous disorder, primarily of the convexities of the central face (cheeks, chin, nose, and central forehead). The main clinical forms of the disease are erythematotelangiectatic rosacea (subtype 1), papulopustular rosacea (subtype 2), phymatous rosacea (subtype 3), and ocular rosacea (subtype 4) [25]. In addition to the classification system, the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea devised a standard method for assessing gradations of the severity of rosacea [26]. This standard grading system is essential to perform research, analyze results, and compare data; provides a common reference for diagnosis, treatment, and assessment of results in clinical practice; and is the basis for the Investigator's Global Assessment in rosacea.

The accurate incidence of rosacea is not known but it is estimated by the National Rosacea Society of the US that 16 million Americans suffer from the signs and symptoms of rosacea, and millions more may be in temporary remission [17]. An earlier preliminary study conducted in the US in 2993 women aged between 10 and 70 years found a prevalence rate for rosacea of 16% in Caucasian women and an overall rosacea incidence of nearly 10% in the total population including Hispanics, African-Americans, Asians, and Indians [23]. A recent epidemiological study estimated an overall incidence for diagnosed rosacea of 1.65 per 1000 person-years in the United Kingdom [18]. In 3052 and 3013 subjects aged between 18 and 65 years drawn from the general populations of Germany and Russia, respectively, the prevalence of rosacea was found to be 12.3% (95% confidence interval [CI], 10.2-14.4) in Germany and 5.0% (95% CI, 2.8-7.2) in Russia [21]. In a Swedish study in a non-selected population of 809 office employees (454 women and 309 men), 81 people were diagnosed as having rosacea giving a prevalence of 10% (women 14%, men 5%) [2]. In a cross-sectional study of 348 subjects randomly selected from a working population ≥ 30 years of age in Estonia, 78 (22%) had one or more primary features of rosacea [1]. Rosacea is a chronic skin condition that disproportionately affects fair-skinned persons of European and Celtic origin.

The pathogenesis of rosacea is poorly understood. Contributing factors may include immune and inflammatory abnormalities, vascular alterations, neurogenic dysregulation, presence of cutaneous microorganisms, ultraviolet (UV) damage, and skin barrier dysfunction [10, 14, 20, 24, 27]. Clinical features and trigger factors of rosacea indicate a complex dysregulation of inflammatory, vascular, and neuronal systems at an early stage. Elevated levels of antimicrobial peptides (cathelicidins), processing enzymes (epidermal serine protease kallikrein 5), proinflammatory cytokines, and toll-like receptors (TLR) seem to play a role in maintaining chronic inflammation in rosacea, which may induce modification of dermal structures mediated by vascular changes and collagen degeneration. Complex vascular mechanisms contribute to local vasodilation, angiogenesis, and tissue fibrosis in rosacea. The involvement of the nervous system is supported by the fact that symptoms of rosacea are triggered when subjects are under emotional stress.

Consistent with its immuno-inflammatory and neurovascular pathophysiology, rosacea was found to be associated with several autoimmune diseases [8], with cardiovascular disease risk factors and cardiovascular diseases [7, 15], with migraine [19], and with a 2- to 5-fold increased risk of depression and anxiety disorders [9, 13]. In addition, almost half of the rosacea subjects report a significant impairment in their quality of life [3, 21]. Taking into consideration these findings and that about 50% of the subjects receive no rosacea care, effective treatment might contribute not

only to symptomatic relief, but also to reduce cardiovascular risk and to improve the emotional health and the quality of life of subjects with rosacea.

Oral tetracyclines, especially doxycycline and minocycline, have been a cornerstone of systemic treatment in rosacea. Independently of their antibacterial properties, tetracyclines at low doses exert anti-inflammatory effects, decrease matrix metalloproteinase activity involved in kallikrein activation, act as oxygen scavengers, and improve epidermal barrier function. All of these biological activities could contribute to the effectiveness of low-dose tetracyclines in rosacea treatment. The use of tetracyclines was also found to be associated with a decreased incidence of vascular disease in veterans with rosacea [6].

Details about specific benefits and risks for subjects participating in this study may be found in the accompanying consent documents for this study.

The study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

6.2 Rationale for the Study and Study Design

6.2.1 Study Rationale

This is a Phase 3 multicenter, randomized, double-blind, parallel-group, active and placebo-controlled study to assess the efficacy, safety and tolerability of oral DFD-29 (Minocycline Hydrochloride Extended Release Capsules), 40 mg (hereafter referred to as DFD-29) for the treatment of papulopustular rosacea over 16 weeks.

Papulopustular rosacea is the second most common form of the disease and represents a more inflammatory subtype. Papulopustular rosacea is characterized by persistent central facial erythema with transient papules or pustules or both in a central facial distribution, but it can also present with telangiectasias (usually masked by its typical manifestations) and can occur concomitantly with acne vulgaris [25, 27]. Although multiple therapeutic options are available for the treatment of papulopustular rosacea, the most widely used systemic agents are oral tetracycline derivatives, particularly doxycycline and minocycline.

The main concern with the long-term use of tetracyclines in rosacea has been antibacterial resistance. However, the recent findings that tetracyclines exert anti-inflammatory effects and seem to be effective in papulopustular rosacea at low sub-antimicrobial doses opens new options for its clinical use in this indication that warrant further investigation [10, 11, 12, 22]. Doxycycline and minocycline show a variety of biological actions independent of their antibiotic activity, including scavenging of oxygen radicals, anti-inflammatory and anti-apoptotic actions, and inhibition of proteolysis, angiogenesis, and tumor growth. Tetracyclines may reduce the inflammation associated with rosacea by downregulating proinflammatory cytokines and inhibiting matrix metalloproteinases involved in kallikrein activation [10, 11, 12].

Minocycline modulates glutamate-induced excitotoxicity and has anti-apoptotic, antioxidant, anti-inflammatory, and neuroprotective effects that proved beneficial in experimental models of various diseases with an inflammatory basis, including dermatological, autoimmune, vascular, psychiatric, and neurological conditions, for which it has been postulated as an adjunctive therapy [4, 11, 12]. The lack of photosensitivity represents a potential advantage of minocycline for the treatment of papulopustular rosacea because doxycycline exhibits a dose-related phototoxicity [5]. Minocycline demonstrated benefit in the treatment of inflammatory lesions in subjects with rosacea [16, 22] and proved remarkably effective in decreasing serum C-reactive protein (CRP)

levels in other conditions [18]. However, the dose-related efficacy of minocycline at sub-antimicrobial doses in improving the clinical symptoms and reducing serum CRP in papulopustular rosacea has not been investigated.

Dr. Reddy's completed a Phase 2 study in November 2018, which evaluated the efficacy, safety, and tolerability of DFD-29 for the treatment of papulopustular rosacea over 16 weeks, in Germany. This study demonstrated a significantly greater efficacy with DFD-29 (40 mg and 20 mg) compared to placebo, and with DFD 29 (40 mg) compared to Oraycea® (Doxycycline Capsules 40 mg) (EU product). Based on the assessment of clinical and laboratory adverse events (AEs) as well as all other safety parameters, DFD-29 developed by Dr. Reddy´s Laboratories Ltd. was safe and well tolerated.

This Phase 3 study is intended to provide efficacy data across a larger study population with approximately 29 study centers in the US and Europe (Poland and Germany). There will be approximately 15 study centers in the US, 4 in Poland, and 10 in Germany.

6.2.2 Dose Selection

The proposed dose strength of DFD-29 to be evaluated in this study is 40 mg. The safety, efficacy, and tolerability of DFD-29 at doses of 20 mg and 40 mg were evaluated in the Phase 2 study referenced above. Based on the assessment on the clinical and laboratory AEs as well as other safety parameters, DFD-29 (40 mg) demonstrated no significant safety or tolerability issues and therefore is considered to be safe and well tolerated when used in subjects with rosacea. Minocycline, along with doxycycline and tetracycline, has found a place in dermatologists' therapeutic armamentarium for treatment of inflammatory lesions (papules and pustules) in subjects with moderate to severe rosacea; however, only a sub-antimicrobial dose of doxycycline has been approved in the US for this indication.

The selection of DFD-29 doses lower than the approved minocycline dose is based on the lower protein binding and higher lipophilicity of minocycline compared to doxycycline, which is expected to lead to higher tissue penetration and exposures of minocycline than those achieved with the 40 mg oral dose of doxycycline used for rosacea. Assuming comparable anti-inflammatory effects, similar or higher exposure of minocycline achieved using the proposed DFD-29 doses is postulated to translate into efficacy that is better than that seen with doxycycline 40 mg.

7 STUDY OBJECTIVES

7.1 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

7.2 Secondary Objectives

To evaluate the safety, efficacy, and tolerability of oral DFD-29 compared to Doxycycline capsules 40 mg in the treatment of papulopustular rosacea for 16 weeks

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design

This is a 16-week, multicenter, randomized, parallel-group, double-blind, controlled study. After assessing eligibility during a screening period of up to 30 days, approximately 320 subjects at least

18 years old who are diagnosed with moderate to severe papulopustular rosacea will be randomized to one of the following treatment groups:

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

** An authorized generic of Oracea (Doxycycline capsules 40 mg) in the United States (marketed by – Prasco Laboratories, Mason OH 45040 USA) will be used as the active comparator product.*

Subject visits are scheduled at Screening, Baseline (Day 1), and Weeks 2, 4, 8, 12, and 16. 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.

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) to assess for any changes in the safety parameters. Other safety assessments include vital signs, physical examination, urine pregnancy tests (for females of childbearing potential), and collection of AE data.

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

The study design is appropriate for the indication studied. Validated methods of data collection, analysis, and evaluation will be used for the study.

8.2 Beginning and End of Study

A subject is considered to be enrolled in the study when he/she has provided written informed consent and has been randomized to study medication.

A subject is considered to have completed the study after he/she has completed Visit 7 (Week 16).

A subject is considered to have discontinued after he/she has withdrawn consent or has been discontinued under the conditions specified in Section 8.3.3.

A subject is considered to have been lost to follow-up if he/she cannot be contacted by the investigator. The investigator will document efforts to attempt to reach the subject twice by telephone and will send a certified letter before considering the subject lost to follow-up. The end of participation for a subject lost to follow-up is documented as the delivery/return date of the certified letter.

Each subject will be monitored for the occurrence of AEs, including serious adverse events (SAEs), starting immediately after the subject has signed the informed consent form (ICF). Each subject will be followed for safety monitoring until he/she is discharged from the study. Follow-up procedures related to pregnancy, AEs, or SAEs may continue beyond the end of the study.

Each subject will participate in the study for approximately 20 weeks from the time he/she signs the ICF through the final contact. After a screening phase of approximately 30 days, each subject will apply assigned treatment for 16 weeks.

It is anticipated that the duration of this study will be 10 months.

8.3 Study Population

Approximately 320 healthy males and females, at least 18 years of age and with a diagnosis of papulopustular rosacea (IGA grade 3[moderate] or grade 4 [severe]) will be selected to participate in the study.

8.3.1 Inclusion Criteria

Subjects **must** meet all of the following criteria to be eligible for the study:

1. Subjects must be able to understand the requirements of the study and be willing to give written informed consent.
2. Male and female subjects aged 18 years and above.
3. Subjects must be in good general health as determined by the investigator and supported by the medical history.
4. Subjects must have a clinical diagnosis of papulopustular rosacea with IGA grade 3 (moderate) or IGA grade 4 (severe) at Baseline.
5. Subjects must have 15 to 60 (both inclusive) inflammatory lesions (papules and pustules) of rosacea over the face at Baseline.
6. Subjects must have not more than 2 nodules or cysts at Baseline.
7. Subjects must agree to only use the study medication and to not use any other treatment for rosacea (prescription or over-the-counter [OTC]) during the course of the study.
8. Subjects must be willing to minimize or not significantly change external factors that might trigger rosacea flare-ups (such as spicy food, thermally hot foods, soups and drinks, hot environments, prolonged sun exposure, strong winds, alcoholic beverages, etc.) throughout the study.
9. Subjects must be free of any systemic or dermatologic disorder that, in the opinion of the investigator, will interfere with the study results, and especially free of any skin diseases (for example peri-oral dermatitis, facial keratosis pilaris, seborrheic dermatitis, and acne vulgaris) that may confound the evaluation of rosacea.
10. Females of childbearing potential must have a negative urine pregnancy test at the Screening and Baseline Visits. Sensitivity of such a test should at least be 25 mIU/mL or lower for human chorionic gonadotropin (hCG).
11. Females must either be postmenopausal with no menses for at least 12 months or surgically sterile (hysterectomy or tubal ligation) or agree to use a highly effective method of contraception with a pearl index of <1% up to 1 month after last dose. Contraception methods with low user dependency should preferably be used, in particular when contraception is introduced as a result of participation in this clinical study.

'Highly effective' methods of birth control include:

- combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation*:
  - oral
  - intravaginal
  - transdermal
- progesterone-only hormonal contraception associated with inhibition of ovulation*:
  - oral
  - injectable
  - implantable†
- intra-uterine device (IUD) †
- intra-uterine hormone releasing system (IUS) †
- bilateral tubal occlusion†
- vasectomy of sexual partner that was performed at least 90 days prior to Baseline, and has been medically assessed as successful†
- total (as opposed to periodic or cyclic) sexual abstinence
  - Note: Sexually inactive female subjects may be enrolled at the investigator's discretion provided that they are counseled to refrain from heterosexual intercourse for the duration of the study and for one month after the last dose, and understand the possible risks involved in getting pregnant during the study.

* Hormonal methods: If on hormonal contraceptives, must have been on the same hormonal contraceptive product for 3 months (90 days) prior to Baseline and continued on the same method and dose throughout the duration of the study. If subject had used hormonal birth control and had stopped, this should have occurred more than 6 months prior to Baseline. Female subjects on low dose oral contraceptives (containing ≤35 µg of ethinyl estradiol or equivalent dose of other estrogens) must use a second form of contraceptive during the study.

† Contraception methods that are considered to have low user dependency.

8.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. Female subjects who are pregnant or nursing or planning to become pregnant during the study.
2. Male subjects whose female partner is planning to conceive a child.
3. Clinically significant abnormal laboratory test results that, in the opinion of the investigator, would compromise the subject's safety or ability to participate in the trial.

4. History of organ transplant requiring immunosuppression, HIV, or other immune compromised state.
5. History of lupus-like syndrome, autoimmune hepatitis, vasculitis, or serum sickness.
6. Use of any treatment listed in Table 8.1 more recently than the indicated washout period prior to Baseline (Visit 2/Day 1).

Table 8.1 Prohibited Topical Drugs, Systemic Drugs, and Other Treatments

Product	Washout period before Baseline
Corticosteroids	30 days
Retinoids (e.g., tretinoin, adapalene, retinol, tazarotene) and other cosmetic retinoids)	30 days
Immunomodulators (including topical calcineurin inhibitors [e.g. Protopic® (tacrolimus) ointment])	30 days
Anti-inflammatory agents or topical non-steroidal anti-inflammatory drugs (NSAID)	14 days
Topical antimycotics	14 days
Benzoyl peroxide, Sodium Sulfacetamide 10%, Sulfur 5%	14 days
Topical antibiotics (e.g., Zilxi® (minocycline) topical foam, macrolides, clindamycin)	14 days
Any anti-rosacea topical treatments (e.g., metronidazole, azelaic acid, brimonidine, ivermectin, oxymetazoline)	14 days
Medicated cleansers (e.g., benzoyl peroxide, salicylic acid, sulfur or triclosan)	7 days
Astringents or abrasives (OTC scrubs, exfoliating cleansers and products containing salicylic acid and alcohol)	7 days
Anti-microbial soaps and face wash	Not applicable (use should be discontinued at baseline)
Oral Retinoids [e.g., Accutane®] or therapeutic vitamin A supplements of >10,000 units per day	180 days
Radiation therapy and/or anti-neoplastic agents	90 days
Beta-blockers – use must remain constant during the study	Initiation of therapy or change of dose within 90 days
Hormonal treatment (oral, implant, topical contraceptives and androgens) – use must remain constant during the study	Initiation of therapy or change of dose within 90 days
Vitamin D supplements of > 4,000 units/day or >100 mcg (daily multivitamins with Vitamin D not exceeding more than 4,000 IU/day are allowed) A constant stable prescribed weekly dose is allowed and subjects should remain on this dose during the study	30 days

Product	Washout period before Baseline
Oral antibiotics known to impact rosacea (e.g., tetracyclines, minocycline, doxycycline, metronidazole, or macrolides) Short-term treatment of all other antibiotics (not affecting rosacea) for ≤14 days is acceptable	30 days
Corticosteroids – Intranasal and inhaled corticosteroids are allowed and may be used throughout the study if at a stable dose.	30 days
Immunosuppressive agents or Immunomodulators	30 days
Oral ivermectin	30 days
Spironolactone	30 days
Anticoagulants Subjects on anticoagulant therapy who are eligible will require consultation with their physician for review and downward adjustment of their dosage, if necessary. Documentation from their treating physician is required prior to randomization. After any dose adjustment, use must remain on this dose for at least 30 days prior to randomization	Initiation of therapy or change of dose within 30 days
Other systemic drugs used for treatment of rosacea	30 days
Barbiturates	30 days
Rifampicin	30 days
Carbamazepine	30 days
Phenytoin (diphenylhydantoin)	30 days
Primidone	30 days
Cyclosporin	30 days
Methoxyflurane or other nephrotoxic drugs	30 days
Nonsteroidal anti-inflammatory drugs (NSAIDs) (except aspirin at subanalgesic doses < 325 mg once daily for subjects requiring platelet aggregation inhibition) Chronic use of NSAIDs (> 14 days) other than low-dose aspirin is prohibited.	7 days
Niacin at doses > 500 mg /day	7 days

Product	Washout period before Baseline
Use on the face of the following: Cryodestruction or chemodestruction Dermabrasion Photodynamic therapy Acne Surgery Intralesional steroids Laser resurfacing or electrodessication X-ray therapy Laser: Non-ablative lasers, Vascular (Pulse dye lasers 585 and 596 nm) lasers, multichromatic lasers, long-pulsed Nd-YAG laser Intense pulse light (IPL) or pulse light laser Electrocautery or electrocoagulation CO_2 laser, Fractioned lasers, or loop electrosurgery Facial peels or other facial cosmetic surgery (e.g. Thermage, etc.)	30 days
Use of tanning booths, sun lamps, or excessive UV radiation (e.g. phototherapy, daily extended exposure or occupational exposure to the sun), sunbathing or excessive exposure to sun	7 days

7. Need or intent to use any treatment listed in **Table** 8.1 during the current study.
8. History of allergy or known sensitivity to minocycline, doxycycline, other tetracyclines, or any component of the study medication.
9. Consumption of excessive alcohol, abuse of drugs, or a condition that could compromise the subject's ability to comply with study requirements and/or have drug or alcohol addiction requiring treatment in the past 12 months.
10. Any clinically significant condition or situation other than the condition being studied that, in the opinion of the investigator, would interfere with the study evaluations or optimal participation in the study.
11. Use of any investigational drugs within 90 days prior to Baseline (Visit 2/Day 1).
12. Participation in any other clinical study within 90 days prior to Baseline.
13. Previous participation in this study.
14. Subjects institutionalized due to legal or regulatory disorder
15. Employees of the research center or Investigator.
16. Family members of employees of the research center of Investigator

8.3.3 Subject Discontinuation Criteria

A subject may discontinue from the study at any time for any reason.

A subject will be discontinued from the study if his/her safety or well-being is determined to be at risk. Discontinuation will be made at the discretion of the investigator or at the subject's request.

A subject must be discontinued from the study and study medication for any of the following reasons:

- The subject or legal representative withdraws consent
- The subject becomes pregnant
- The subject's medication code is unblinded
- There is a significant protocol violation or non-compliance with the protocol

A subject may be discontinued from the study for any of the following reasons:

- AE, including intercurrent illness, for which the subject desires to discontinue treatment or the investigator determines that it is in the subject's best interest to be discontinued
- Condition worsens and requires alternative or supplemental therapy for treatment of rosacea during the study
- Noncompliant use of the study medication
- Lost to follow-up
- Investigator discretion

Discontinuation is permanent; after a subject has been discontinued, he/she will not be allowed to enroll again.

If a subject is discontinued from the study for any reason, the Visit 7 (EOS or early termination) procedures should be completed and any outstanding data and study medication should be collected. Data, including the date and primary reason for discontinuation, must be documented on the EOS electronic case report form (eCRF) and source document.

If a subject discontinues the study at any time due to an AE, the reason for discontinuation, the nature of the AE, and its clinical course must be fully documented. The investigator must strive to follow the subject until the AE has resolved, become clinically insignificant, is stabilized, or the subject is lost to follow-up. For any SAE, follow procedures provided in Section 8.9.6.

Subjects with protocol deviations should not be withdrawn automatically unless there is a safety concern. The protocol deviation should be recorded in the subject's case record form and included in the study report. Other than safety reasons, any decision by the Investigator to discontinue a subject from the study for reasons of violation of inclusion/exclusion criteria or protocol deviations should be discussed with the CRO/Sponsor medical monitor, as far as possible, prior to discontinuing the subject.

As far as possible, investigators must advise subjects to refrain from consuming the prohibited medication (as specified in **Table 8.1.**). In case a subject consumes a prohibited concomitant medication or needs to take one, a joint decision will be taken by the CRO medical monitor and Sponsor medical monitor on whether or not the subject should continue in the study or be withdrawn, depending upon the potential for harmful drug-drug interaction and influence on study efficacy assessments. The investigator must communicate information about the drug taken/required by subject, including its generic name, dose and duration of treatment and reason

for subject taking/being advised to take the drug, as soon as it comes to his/her knowledge, to CRO Project Manager. The CRO Project Manager in turn should forward the information to CRO and Sponsor medical monitors for a decision on continuation of the subject to be taken.

Subjects who experience an AE resulting in or requiring discontinuation of study product use should be encouraged to be followed up in the study until the AE is resolved or stabilized.

Subjects whose treatment randomization is unblinded by the study site should stop the study treatment immediately and be withdrawn from the study after follow-up.

If a female subject becomes pregnant during the study, the study product will be discontinued immediately, and she will be followed through the pregnancy and delivery. Details of the pregnancy, delivery and health of the infant should be recorded on the Pregnancy Report Form and the sponsor should be notified immediately.

If the sponsor terminates or suspends the study, the investigator or his/her designee should promptly inform the IRB/IEC (and/or regulatory authorities where required) of a temporary halt including the reason for such an action.

8.3.4 Replacement of Subjects

A subject who discontinues from the study after having received at least one dose of study medication will not be replaced.

8.4 Treatments

The investigator will take responsibility for and will take all steps to maintain appropriate records and ensure appropriate supply, handling, storage, distribution, and use of study materials in accordance with the protocol and any applicable laws and regulations.

8.4.1 Dosage and Formulations

The DFD-29, Placebo, and Doxycycline capsules 40 mg will be provided by Dr. Reddy's Laboratories Ltd. To maintain the double-blind design, all 3 study medications will be over-encapsulated with the original capsules enclosed within a second, larger (size 0) capsule shell.

Table 8.2: Identity of Test

	Test treatment
Name:	DFD-29 (Minocycline HCl Extended Release Capsules)
Active ingredient:	Minocycline HCl
Formulation:	Extended Release Capsules
Dose strength:	40 mg minocycline
Dose:	1 capsule
Posology:	Once daily, in the morning
Mode of administration:	Oral administration with approx. 240 mL water
Administration condition:	Fasting state preferred, but not mandatory

	Test treatment
Duration of administration:	16 weeks
Batch number & Expiry date:	Will be given in the Trial Master File (TMF) ***.

*** The documentation allowing traceability will be provided in the TMF.

Table 8.3: Identity of Placebo

	Placebo treatment
Name:	Placebo for DFD-29
Active ingredient:	Not applicable
Formulation:	Capsules
Dose strength:	Not applicable
Dose:	1 capsule
Posology:	Once daily, in the morning
Mode of administration:	Oral administration with approx. 240 mL water
Administration condition:	Fasting state preferred, but not mandatory
Duration of administration:	16 weeks
Batch number & Expiry date:	Will be given in the TMF ***.

*** The documentation allowing traceability will be provided in the TMF.

Table 8.4: Identity of Doxycycline capsules 40 mg

	Doxycycline capsules 40 mg treatment
Name:	Doxycycline capsules 40 mg
Active ingredient:	Doxycycline anhydrous
Formulation:	Capsule with 30 mg immediate release and 10 mg delayed release beads
Dose strength:	40 mg doxycycline
Dose:	1 capsule
Posology:	Once daily, in the morning
Mode of administration:	Oral administration with approx. 240 mL water
Administration condition:	Fasting state preferred, but not mandatory
Duration of administration:	16 weeks
Batch number & Expiry date:	Will be given in the TMF ***.

*** The documentation allowing traceability will be provided in the TMF.

8.4.2 Method of Treatment Assignment, Randomization, and/or Stratification

Upon screening, the subject will be assigned a unique 7-digit subject number preceded by the letter "S", where the first 4 digits are the site number and the last 3 digits will be a subject number that increments sequentially at the site (i.e., S1001-001, S1001-002). At the Baseline Visit (Visit 2/Day 1), subjects eligible for participation will retain the same subject number without the letter "S" preceding it (i.e., 1001-001, 1001-002). All subjects will retain this subject number for the remainder of the study. Each subject will be dispensed a total of 4 bottles and will be randomly assigned a unique bottle number at each visit study medication is dispensed (Visit 2/Day 1, Visit 4/Day 29, Visit 5/Day 57 and Visit 6/Day 85), using the Interactive Web Response System (IWRS).

Subjects who satisfy all of the inclusion and none of the exclusion criteria will be randomized in a 3:3:2 ratio to the DFD-29, Doxycycline capsules 40 mg, or Placebo group, respectively.

Randomization will be stratified by site. Stratification will be managed via the IWRS.

8.4.3 Selection and Timing of Dose for Each Subject

The study medication will be taken at a fixed time of the day once a day for 16 consecutive weeks. The preferred time of administration will be in the morning, after an overnight fast. One capsule of the assigned study medication will be swallowed with 240 mL (1 glass) of still water on an empty stomach.

Substances that can potentially interfere with absorption of minocycline like antacids, multivitamins, or other products containing aluminum, magnesium and calcium, oral iron preparations, bismuth subsalicylate, and milk and other dairy products should be avoided from 1.5 hours before to 3.0 hours after intake of study medication.

The dosage regimen in this study is that approved for Doxycycline capsules 40 mg [28].

8.4.4 Blinding of Study Medication

A double-blind technique will be used. DFD-29, its matching placebo, and Doxycycline capsules 40 mg are indistinguishable after over-encapsulation. 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.

See Section 8.9.7.4 for a description of the method of unblinding a subject during the study if such action is warranted.

8.4.5 Method of Packaging, Labeling, Storage, and Dispensing

Study medications will be supplied in high-density polyethylene (HDPE) bottles containing 35 capsules each. Bottles will be individually labeled and packaged so that neither the subject nor the investigator can identify the treatment.

Each subject will be dispensed a total of 4 bottles and will be randomly assigned a unique bottle number at each visit study medication is dispensed (Visit 2/Day 1, Visit 4/Day 29, Visit 5/Day 57 and Visit 6/Day 85), using the IWRS.

At the Visit 2/Day 1, each subject enrolled will receive 1 bottle of study medication. At Visits 4/Day 29, 5/Day 57, and 6/Day 85, the study medication will be collected, and 1 new bottle of

study medication will be dispensed. Study medication will be collected and re-dispensed at Visit 3/Day 14.

A label with a tear-off portion will be attached to each bottle. The tear-off section of the label will be attached to the Study Medication Dispensing Log when a new bottle is dispensed. To nullify any remaining differences in product packaging and to maintain double-blinding, the investigator/sub-investigator performing the study clinical assessments will not be involved with the dispensing or return of study medication.

At the minimum, the following information will be stated on the labels:

- Study number (DFD-29-CD-005)
- EudraCT Number (Europe only)
- Visit No.
- Bottle number
- Subject number and initials (US only)
- Amount (35 capsules of either DFD-29 40 mg / Placebo / Doxycycline capsules 40 mg)
- Batch Number and Expiry Date (Europe only)
- Name of Investigator (Europe only)
- Sponsor's Name and Address
- CRO's Name and Address
- Route of administration (e.g., oral)
- Directions for use
- Storage conditions
- "For clinical trial use only" or similar cautionary statement
- "Keep out of reach of children" or similar cautionary statement

All study medication will be stored at controlled room temperature 68° - 77°F (20° - 25°C) with excursions permitted between 59° - 86°F (15° - 30°C), in a climate-controlled, limited access area.

The investigator agrees to store and dispense the study medication only at the site(s) listed on Form FDA 1572 (or investigator agreement/statement). The investigator, sub-investigator(s), or qualified designees also agree that the study medication will be dispensed only to subjects who have provided written informed consent and have met all entry criteria. Clinical supplies may not be used for any purpose other than as stated in the protocol.

See the Study Flow Chart in Section 3.2 for a schedule of when clinical supplies are to be dispensed to the subjects.

8.4.6 Replacement of Study Medication

If replacement bottles are needed for subjects for any reason, this will be done through IWRS. The study site should contact the CRO to provide information regarding replacement bottles for documentation purposes.

8.4.7 Study Medication Accountability

Subjects will be instructed to return all used and partially used study medication at all protocol-specified visits for study medication inventory and assessment of subject compliance.

All IP receipts at the site will be confirmed via IWRS and final IP reconciliation and returns will be conducted via IWRS, at study end. The dispensing and return of study medication for subjects

will be recorded on the study medication dispensing log. The subject number/initials and the initials and date of the person dispensing and receiving the returned medication will be documented on this form.

Inventory records must be readily available for inspection by the study monitor and/or auditor, and open to inspection by regulatory authorities at any time.

8.4.8 Prior and Concomitant Medications

All medications and other treatments taken by the subject within 30 days before signing the ICF and during the study are to be recorded on the eCRF using their generic name, if known, with the corresponding indication. The medications to be recorded include prescription and OTC medications and dietary supplements. All medications taken on a regular basis, including vitamins, aspirin, and acetaminophen, should be recorded prior to first use of the study medication.

The use of any concomitant medication must relate to the subject's documented medical history, prophylaxis, or an AE.

8.4.8.1 Medications, Supplements, and Other Substances Prohibited Before Study Entry and During the Study

The medications prohibited prior to Baseline are listed in Table 8.1 in the exclusion criteria.

The medications and therapies listed in Table 8.1 are the treatments that subjects must not take during the study, from Visit 2 through Visit 7 (EOS or early termination).

Substances which can potentially interfere with absorption of minocycline like antacids, multivitamins or other products containing aluminum, magnesium and calcium, oral iron preparations, bismuth subsalicylate and milk and other dairy products should be avoided from 1.5 hours before to 3.0 hours after intake of study drug.

Anti-microbial soaps and face wash are not allowed during the study.

In case a subject consumes a prohibited concomitant medication or needs to take one, a joint decision will be taken by the CRO medical monitor and Sponsor medical monitor on whether or not the subject should continue in the study or be withdrawn, depending upon the potential for harmful drug-drug interaction and influence on study efficacy assessments.

8.4.8.2 Other Restrictions

8.4.8.2.1 Sun Exposure

Excessive sun exposure and/or UV radiation should be avoided, and protective measures should be taken.

8.4.8.2.2 Contraceptives

Special attention has to be paid to female subjects taking low dose oral contraceptives (35 micrograms of ethinyl estradiol or equivalent dose of other estrogens) as their effectiveness may be affected by the use of DFD-29. To avoid contraceptive failure, female subjects who are taking low dose oral contraceptives have to use a second acceptable form of contraceptive from Screening up to 1 month after last dose.

Note: 'Acceptable' methods of contraception include double barrier methods (e.g. a combination of male condom with either, cap, diaphragm or sponge with spermicide) in addition to the "highly effective birth control methods that are described in Section 8.3.1, inclusion criterion 1011.

Please refer to inclusion criterion 10 (Section 8.3.1) for further details on contraception for females.

8.4.8.3 Concomitant Medications, Supplements, and Other Substances Allowed During the Study

Medications necessary for the health and well-being of the subject are permitted. The use of any medication that could affect the course of rosacea is prohibited during the entire study period. Subjects should be instructed to refrain from making any significant change in the use of consumer products (including facial cleanser, make-up, bland non-medicated emollients or moisturizers, etc.) during the course of the study.

Multivitamins and acetaminophen for pain relief may be used as needed throughout the study.

8.4.9 Assessment of Compliance

At all protocol-specified visits, the investigator or qualified designee will record whether treatment had been taken per protocol in the preceding interval. If not, the date(s) and reason for each dosing noncompliance must be recorded.

Compliance will be determined from the diary card, on which the subject will be instructed to record all doses taken or missed. The number of doses will be totaled by the study coordinator or designee and recorded on the diary card and on the compliance page of the eCRF. The total number of doses taken and/or missed will be determined based upon the first dose taken through and including the last dose taken. The first and last dates of treatment should be recorded in the eCRF. The total of taken and missed doses should also be recorded. By definition, there are no missed doses before the first date of treatment or after the last date of treatment. Subjects will be considered compliant if they administer at least 80% and no more than 120% of doses. Subjects who miss 7 or more consecutive doses of study medication will be considered noncompliant and must be withdrawn from the study by the investigator in agreement with the CRO/Sponsor medical monitor.

8.5 Study Schedule

The visit-by-visit schedule of study activities is provided in the Study Flow Chart in Section 3.2. The timing of each visit is relative to Day 1.

All visits should be performed within the windows specified on the Study Flow Chart. Every attempt should be made to have each subject attend each visit as scheduled. If a subject is unable to attend a visit within the specified window, however, the visit should be scheduled as closely as possible to the applicable window.

8.6 Study Procedures

The Study Flow Chart in Section 3.2 summarizes the study procedures to be performed at each visit. Individual study procedures are described below.

All clinical assessments (IGA, CEA, and total inflammatory lesion count) must be conducted by qualified investigators listed on the Form FDA 1572 (who have been delegated these tasks by the

principal investigator (PI). The PI may delegate this task to physicians, physician assistants, or nurse practitioners who have documented training and past experience conducting the assessment.

To minimize variability of evaluations, the same investigator/sub-investigator should perform these assessments for any given subject and anticipate evaluating the subject at each visit, to the extent possible.

8.6.1 Study Initiation

The investigational staff may not enroll any subjects prior to completion of an initiation visit. This visit will include, but is not limited to, an inventory of study supplies (if present) and a detailed review of the protocol, eCRFs, investigator's brochure, and the investigator's responsibilities as outlined on Form FDA 1572 / investigator commitments in an equivalent of Form 1572 (EU sites only).

8.6.2 Written Informed Consent

The study personnel will review the ICF with each subject and give the subject an opportunity to have all questions answered before proceeding. A copy of the signed ICF will be given to every subject and the original will be maintained with the subject's records.

8.6.3 Significant Medical History/Demographic Information

Significant medical history and demographic information will be obtained at Visit 1 (Screening). The medical history will include a complete review of all current diseases and their respective durations and treatments. Demographic information will include date of birth, sex, race, ethnicity, and Fitzpatrick skin type.

For inclusion in the study subjects must have a clinical diagnosis of papulopustular rosacea, IGA grade 3 (moderate) or IGA grade 4 (severe).

Medical history will be reviewed/updated at Visit 2 (Baseline).

8.6.4 Physical Examination (Including Vital Signs)

A complete physical examination will be performed and height, weight, and vital signs recorded at Screening to determine that the subject is healthy enough to participate in the study. Weight will also be measured at Visit 2 (Baseline). Physical examination and weight will also be performed at Visit 7 (EOS or early termination).

Blood pressure (measured after at least 5 minutes in a sitting position) and pulse rate will be measured at every study visit, as part of Vital Signs Assessment.

8.6.5 Prior Medication Review

Prior medications (prescription, OTC, and dietary supplements), including the necessary washout times, will be reviewed with the subject. A record of prior medication taken or used by the subject within 30 days before signing the ICF will be obtained. Prior medication will be reviewed/updated at Visit 2 (Baseline).

8.6.6 Laboratory Assessments

Laboratory tests for hematology, blood chemistry, and urinalysis are specified in Table 8.5. Blood samples for laboratory tests are to be taken prior to administration of study medication. Blood (hematology and chemistry) and urine samples will be collected at Visit 1 (Screening) and Visit 7

(EOS or early termination). Serology for anti-HIV I, anti-HIV 2, HBsAG, and anti-HCV antibodies will only be performed at screening.

The samples will be sent to the central laboratory for analysis. Details regarding overall blood volume collected, sample handling, processing and shipment will be provided in a separate laboratory manual.

Any other investigation (including anti-nuclear antibody and hepatic transaminases for suspected drug-induced lupus or auto-immune hepatitis in symptomatic subjects) will have to be symptom-driven or on investigator judgment on a case to case basis.

Additional safety samples may be taken at investigator discretion in consultation with the Sponsor.

Table 8.5: Laboratory Tests

Hematology	Chemistry	Urinalysis	Others
Complete Blood Count (CBC) including differential count	Glucose Uric acid Calcium Sodium Potassium Chloride Alkaline phosphatase Total bilirubin Direct bilirubin Creatinine BUN AST (SGOT) ALT(SGPT) LDH Total protein Albumin	Urobilinogen Nitrites pH Glucose Protein Blood Ketones Pregnancy[a]	Serology (for anti-HIV I, anti-HIV 2, HBsAG, and anti-HCV antibodies)[b] ANA (Anti-nuclear-Ab) AST/ALT/GGT (hepatic-transaminases)[c]

[a] Only required for women of childbearing potential
[b] Will only be done at screening for eligibility
[c] Will be done on a case to case basis based on Investigator judgement or symptom-driven

8.6.7 Urine Pregnancy Test and Acceptable Contraceptive Methods

Women of childbearing potential, in addition to having a negative urine pregnancy test at Visit 1 (Screening) and Baseline, prior to randomization, must be willing to use an acceptable form of birth control during the study.

'Highly effective' methods of birth control include

- combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation*:
  - oral
  - intravaginal
  - transdermal
- progesterone-only hormonal contraception associated with inhibition of ovulation*:

- oral
- injectable
- implantable†

- intra-uterine device (IUD) †
- intra-uterine hormone releasing system (IUS) †
- bilateral tubal occlusion†
- vasectomy of sexual partner that was performed at least 90 days prior to Baseline, and has been medically assessed as successful†
- total (as opposed to periodic or cyclic) sexual abstinence
  - Note: Sexually inactive female subjects may be enrolled at the investigator's discretion provided that they are counseled to refrain from heterosexual intercourse for the duration of the study and for one month after the last dose, and understand the possible risks involved in getting pregnant during the study.

* Hormonal methods: If on hormonal contraceptives, must have been on the same hormonal contraceptive product for 3 months (90 days) prior to Baseline and continued on same method and dose throughout the duration of the study. If subject had used hormonal birth control and had stopped, this should have occurred more than 6 months prior to Baseline. Female subjects on low dose oral contraceptives (containing ≤35 µg of ethinyl estradiol or equivalent dose of other estrogens) must use a second form of contraceptive during the study.

† Contraception methods that are considered to have low user dependency.

A urine pregnancy test will be performed for women of child-bearing potential at every study visit from Screening up to Week 16 (or at early termination if previous pregnancy testing was performed more than 28 days prior).

8.6.8 Investigator's Global Assessment (IGA)

The IGA (Appendix 15.1) is carried out by visual inspection by the investigator or delegated sub-investigator at every study visit from Screening through Week 16 (EOS or early termination). If possible, the same study staff member should perform the assessment on an individual subject at all visits.

8.6.9 Clinician's Erythema Assessment (CEA)

The CEA (Appendix 15.2) is carried out by visual inspection by the investigator or delegated sub-investigator at every study visit from Screening through Week 16 (EOS or early termination). The erythema assessment will be carried out separately at 5 locations on the face: forehead, nose, chin, right cheek, and left cheek. A ≥ 2-grade reduction from Baseline to Week 16 will be assessed on the most severe CEA score/s out of the 5 locations on the face. If more than one location have the most severe scores, then the ≥ 2-grade reduction has to be on the average scores for those locations at Week 16 (for e.g. if the baseline CEA scores for the right and left cheeks are 3, the nose is 1 and the forehead and chin are 0 each, the baseline average score is equal to 3 for the right and left cheeks, then the average of the scores for the two cheeks at Week 16 has to be '1' or below, to be considered as at least a 2-grade reduction on the CEA). Subjects 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.

8.6.10 Total Inflammatory Lesion Count

The total inflammatory lesion count is carried out by visual inspection by the investigator or delegated and trained study staff at every study visit from Screening through Week 16 (EOS or early termination). Inflammatory lesions will be recorded on a diagram of a human face (Appendix 15.3) divided in 4 quadrants. If possible, the same study staff member should perform the assessment on an individual subject at all visits.

8.6.11 Rosacea Quality of Life (RosaQoL)

The RosaQoL assessment (Appendix 15.4) will be carried out by asking questions as per the validated RosaQoL questionnaire instrument at every study visit from Baseline through Week 16 (EOS or early termination). Subjects will rate 21 questions on a 5-grade scale and their perception of the impact that rosacea has on various dimensions influencing their quality of life. Calculation of the score will be described in the SAP.

8.6.12 Dermatology Life Quality Index (DLQI)

The DLQI questionnaire (Appendix 15.5) will be carried out at every study visit from Baseline through Week 16 (EOS or early termination).

The DLQI questionnaire consists of 10 questions covering the following topics: symptoms, embarrassment, shopping and home care, clothes, social and leisure, sport, work or study, close relationships, sexuality and treatment. Each question refers to the impact of the skin disease on the subject's life.

Each question is scored from 0 to 3 and totaled, giving a possible score range from 0 (meaning no impact of skin disease on quality of life) to 30 (meaning maximum impact on quality of life).

8.6.13 Review Inclusion/Exclusion Criteria

The inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the study.

8.6.14 Study Medication Dispensing and Collection

An independent drug dispenser, not involved in the clinical evaluations, will dispense study medication to qualified subjects and keep accurate accountability of all study medication. Study medication will be dispensed at Visits 2, 4, 5, and 6 and bottles will be collected at Visits 3, 4, 5, 6, and 7 to assess compliance and drug accountability. Study medication will be collected and re-dispensed at Visit 3.

8.6.15 Subject Instruction, Diary Card, and Compliance

Subjects will be instructed on the correct use of study medication at the study site during Visit 2 (Baseline). Subjects will be instructed to take study medication at a fixed time of the day once a day for 16 consecutive weeks. The preferred time of administration will be in the morning, after an overnight fast. One capsule of the assigned study medication will be swallowed with 240 mL (1 glass) of still water on an empty stomach. Additional instructions will be reviewed with each subject.

A diary card will be dispensed to each enrolled subject at Visit 2 (Baseline). The subject will be instructed to complete the diary card to record each dose or missed dose of study medication. At subsequent visits, study personnel will review and collect the diary card, and dispense a new diary card and re-review subject instructions.

8.6.16 Adverse Events and Serious Adverse Events Assessment

See Section 8.9 for instructions on the assessment and reporting of AEs and SAEs and Section 8.9.6 for instructions on reporting SAEs to the sponsor or designee.

8.6.17 Concomitant Medication Review

Medications, including prescription, OTC, and dietary supplements (other than study medication) taken and other treatments used by the subject during the study will be reviewed at each study visit.

8.6.18 Study Medication Accountability

Adherence to study medications will be assessed by the study diary review, pill count and subject questioning at all visits during the treatment period. The investigator or other designated study personnel will note in the source documents and appropriate eCRF page whether the subject took study medication per protocol in the preceding interval.

Subjects will be instructed to return all used and partially used bottles of study medication at Visits 3, 4, 5, 6, and 7 for study medication inventory and assessment of subject compliance. The site staff will count and record the number of remaining capsules in each returned bottle.

All IP receipts at the site will be confirmed via IWRS and final IP reconciliation and returns will be conducted via IWRS, at study end. The dispensing and return of study medication for subjects will be recorded on the study medication dispensing log. The subject number/initials and the initials and date of the person dispensing and receiving the returned medication will be documented on this form.

Inventory records must be readily available for inspection by the study monitor and/or auditor, and open to inspection by regulatory authorities at any time.

8.7 Visit-Specific Procedures

The following sections outline the procedures required at each visit.

8.7.1 Visit 1/Day -30 to -3: Screening

1. Obtain written informed consent (Section 8.6.2)
2. Obtain medical history and demographic information (Section 8.6.3)
3. Perform physical examination, including height, weight, and vital signs (blood pressure and pulse rate) (Section 8.6.4)
4. Obtain/record prior medications (Section 8.6.5)
5. Collect blood and urine for laboratory assessments (Section 8.6.6)
6. Perform urine pregnancy test for all women of childbearing potential (Section 8.6.7)
7. Perform IGA (Section 8.6.8)
8. Perform CEA (Section 8.6.9)

9. Perform lesion count (Section 8.6.10)
10. Evaluate inclusion/exclusion criteria (Section 8.6.13)
11. Schedule next visit
12. Complete eCRFs (Section 11.2.1)

8.7.2 Visit 2/Day -1: Baseline

1. Update medical history (Section 8.6.3)
2. Measure weight and vital signs (blood pressure and pulse rate) (Section 8.6.4)
3. Update prior medications (Section 8.6.5)
4. Perform urine pregnancy test for all women of childbearing potential (Section 8.6.7)
5. Perform IGA (Section 8.6.8)
6. Perform CEA (Section 8.6.9)
7. Perform lesion count (Section 8.6.10)
8. Perform RosaQoL (Section 8.6.11)
9. Perform DLQI (Section 8.6.12)
10. Evaluate inclusion/exclusion criteria (Section 8.6.13)
11. Randomization (Section 8.4.2)
12. Dispense study medication and record study medication accountability (Sections 8.6.14 and 8.6.18)
13. Instruct subjects on proper study medication administration (Section 8.6.15)
14. Assess AEs (Section 8.6.16)
15. Dispense diary card and review instructions (Section 8.6.15)
16. Schedule next visit
17. Complete eCRFs (Section 11.2.1)

8.7.3 Visit 3/Day 14 (± 3 days), Visit 4/Day 29 (± 3 days), Visit 5/Day 57 (± 5 days), and Visit 6, Day 85 (± 5 days)

1. Measure vital signs (blood pressure and pulse rate) (Section 8.6.4)
2. Concomitant medications (Section 8.6.17)
3. Perform urine pregnancy test for all women of childbearing potential (Section 8.6.7)
4. Perform IGA (Section 8.6.8)
5. Perform CEA (Section 8.6.9)
6. Perform lesion count (Section 8.6.10)
7. Perform RosaQoL (Section 8.6.11)
8. Perform DLQI (Section 8.6.12)

9. Collect and dispense study medication, record study medication accountability, and assess compliance (Sections 8.6.14 and 8.6.18). Study medication will be collected and re-dispensed at Visit 3/Day 14.
10. Assess AEs (Section 8.6.16)
11. Collect and dispense diary card and review instructions (Section 8.6.15)
12. Schedule next visit
13. Complete eCRFs (Section 11.2.1)

8.7.4 Visit 7/Day 113 (± 5 days): End of Study or Early Termination

1. Perform physical examination, including weight, and vital signs (blood pressure and pulse rate) (Section 8.6.4)
2. Concomitant medications (Section 8.6.17)
3. Collect blood and urine for laboratory assessments (Section 8.6.6)
4. Perform urine pregnancy test for all women of childbearing potential (Section 8.6.7)
5. Perform IGA (Section 8.6.8)
6. Perform CEA (Section 8.6.9)
7. Perform lesion count (Section 8.6.10)
8. Perform RosaQoL (Section 8.6.11)
9. Perform DLQI (Section 8.6.12)
10. Collect study medication, record study medication accountability, and assess compliance (Sections 8.6.14 and 8.6.18)
11. Assess AEs (Section 8.6.16)
12. Collect diary card (Section 8.6.15)
13. Complete eCRFs (Section 11.2.1)

8.7.5 COVID-19 Considerations

As a consequence to the COVID-19 pandemic that had a worldwide impact, including cases in North America and Europe, control measures in place in different regions may impact the ability to adhere to some of the study procedures described in this protocol. Due to challenges that include, but are not limited to, subject preferences, site closures, travel restrictions, and quarantines, some modifications to study conduct during the COVID-19 pandemic may be necessary to ensure study continuity. The following are allowable, as necessary, modifications to study conduct during the COVID-19 pandemic.

- At Screening, if a potential subject is known to be infected with COVID-19, the subject should not be enrolled in the study.
- Prior to a study visit at the site, the subject may be contacted and screened for potential exposure or infection to COVID-19 per site, local or federal requirements. If the subject is suspected to be exposed or infected with COVID-19, the on-site visit should either be re-scheduled or a virtual visit may be performed instead, as applicable.

- In the event that a subject cannot attend their regularly scheduled study visits in person due to COVID-19 due to quarantine, state COVID rules, etc. necessitating a limit on in-person contact, the Investigator may perform safety and certain efficacy assessments by phone or video (see below). The Investigator may use the technology platform that is currently available to them. Suggested platforms include Apple FaceTime, Zoom for Healthcare, Facebook Messenger video chat, Microsoft Teams, Google Hangouts video, Skype, or any other platform, which is suitable from a technology and data protection perspective, as determined by the site.
    - Screening, Baseline and Week 16/ End of Study/ Early Termination visits must be conducted in-person. The efficacy assessments of Total Inflammatory Lesion count, IGA grading, and CEA grading as well as the Quality of Life assessment of DLQI scoring at Baseline and Weeks 16 visits must be performed in-person.
    - Visits at Weeks 2, 4, 8 and 12 may be conducted in-person or as virtually (using suitable technology platform).
- Source documentation should note that the visit was performed virtually (not face-to-face). If certain study procedures or assessments cannot be completed per the schedule of events, the reason for the missed assessment must be noted in the source documentation (e.g., COVID-19), captured in the protocol deviations documentation, and reported to the IRB/IEC, as applicable.

A detailed assessment of COVID-19 related risk and mitigation measures will be documented in the appropriate study plans.

8.8 Efficacy Assessments

8.8.1 Co-Primary Efficacy Endpoints

- Proportion of subjects with IGA (modified scale without erythema) "treatment success" – Grade 0 or 1 at Week 16 with at least a 2-grade reduction from Baseline to Week 16, in the DFD-29 group compared to placebo.
- Total inflammatory lesion count (sum of papules, pustules, and nodules) reduction from Baseline to Week 16, in the DFD-29 group compared to placebo.

8.8.2 Secondary Efficacy Endpoints

- Percentage Change in Total inflammatory lesion count (sum of papules, pustules, and nodules) from Baseline to Week 16, in the DFD-29 group compared to Placebo.
- Proportion of subjects with IGA treatment success at Week 16 in the DFD-29 group compared to Doxycycline capsules 40 mg.
- Total inflammatory lesion count reduction from Baseline to Week 16 in the DFD-29 group compared to Doxycycline capsules 40 mg.
- Percentage Change in Total inflammatory lesion count (sum of papules, pustules, and nodules) from Baseline to Week 16, in the DFD-29 group compared to Doxycycline capsules 40 mg.
- Proportion of subjects with at least a 2-grade reduction in CEA score from Baseline to Week 16 in the DFD-29 group compared to placebo.

8.8.3 Exploratory Efficacy Endpoints

All of the following endpoints for DFD-29 will be compared against Placebo and Doxycycline capsules 40 mg:

- Proportion of subjects with IGA treatment success from Baseline to Weeks 2, 4, 8, and 12.
- Total inflammatory lesion count (sum of papules, pustules, and nodules) reduction from Baseline to Weeks 2, 4, 8, and 12.
- Percentage Change in Total inflammatory lesion count (sum of papules, pustules, and nodules) from Baseline to Weeks 2, 4, 8 and 12 .
- Proportion of subjects with at least a 2-grade reduction in IGA score from Baseline to Weeks 2, 4, 8, 12 and 16.
- Change in RosaQoL score from Baseline to Weeks 2, 4, 8, 12 and 16.
- Change in DLQI score from Baseline to Weeks 2, 4, 8, 12and 16, .
- Proportion of subjects with at least a 2-grade improvement in the CEA score at Weeks 2, 4, 8, 12 (and 16, in case of DFD-29 vs Doxycycline capsules 40 mg comparison).

8.9 Assessment of Safety

8.9.1 Safety Endpoints

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

- Change from Baseline for vital signs and clinical laboratory tests. The clinical laboratory tests obtained at screening visit will be defined as baseline assessments.
- Treatment-emergent AEs.
- Treatment-emergent AEs leading to premature discontinuation of study medication.
- Treatment-emergent SAEs.

8.9.2 Definitions of Terms

8.9.2.1 Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a drug, without any judgment about causality.

A treatment-emergent AE (TEAE) is any AE temporally associated with the use of a study drug, whether or not considered related to the study drug.

AEs will be collected by spontaneous reports from subjects, either verbal or recorded in the subject's diary, by directed question of subjects, and by observation. All AEs from the time of signing of the ICF up to the EOS visit will be recorded.

Adverse events include:

- Exacerbation of a pre-existing disease.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.

- Disease or medical condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at Baseline that worsen following the start of the study.
- Events considered by the investigator to be related to study-mandated procedures.
- Abnormal assessments, e.g., vital signs or physical examination findings, must be reported as AEs if they represent a clinically significant finding that was not present at Baseline or worsened during the course of the study.
- Laboratory test abnormalities must be reported as AEs if they represent a clinically significant finding, symptomatic or not, which was not present at Baseline or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study drug.

Adverse events do not include:

- Medical or surgical procedure, e.g., surgery, endoscopy, tooth extraction, transfusion. However, the event leading to the procedure is an AE. If this event is serious, the procedure must be described in the SAE narrative.
- Pre-existing disease or medical condition that does not worsen.

For the purpose of this study, worsening of rosacea is not to be recorded as an AE unless it results in discontinuation of the subject from the study or the use of further treatment for rosacea.

8.9.2.2 Suspected Adverse Reaction

A suspected adverse reaction (SAR) is defined as any AE for which there is reasonable possibility that the drug caused the AE.

8.9.2.3 Unexpected Adverse Event

An AE or SAR is considered unexpected if it is not listed in the Investigator Brochure or is not listed at the specificity or severity that has been observed or, if an Investigator Brochure is not required or available, is not consistent with the risk information described elsewhere (for example, approved prescribing information).

8.9.2.4 Serious Adverse Event

An SAE is defined as any AE or SAR that, in the view of the investigator or sponsor, results in any of the following outcomes:

- Death
- Life-threatening AE (Note: the term "life-threatening" as used here refers to an event that in the view of the investigator or sponsor places the subject at immediate risk of death at the time of the event; it does not include an AE or SAE that, had it occurred in a more severe form, might have caused death
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- Congenital anomaly/birth defect
- Any "other" important medical event. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The following are not considered an SAE:

- Treatment on an emergency or outpatient basis for an event not fulfilling the definition of seriousness given above and not resulting in hospitalization.
- The following reasons for hospitalizations are not considered AEs, and therefore not SAEs:
    - Hospitalizations for cosmetic elective surgery, social and/or convenience reasons.
    - Standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a subject with stable angina pectoris.
    - Elective treatment of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for chemotherapy for cancer, elective hip replacement for arthritis

8.9.2.5 Planned Hospitalization

A hospitalization planned by the subject prior to signing the ICF is considered a therapeutic intervention and not the result of a new SAE and should be recorded as medical history. If the planned hospitalization or procedure occurs as planned, the record in the subject's medical history is considered complete. However, if the event/condition worsens during the study, it must be reported as an AE.

8.9.2.6 Pregnancy

Pregnancies occurring after the first dose of study medication require immediate reporting and discontinuation of the study medication. They must be reported within 24 hours after the investigator has become aware of the pregnancy. The subject should immediately be withdrawn from the study and early termination study procedures must be performed.

A pregnancy report will be completed and sent by email to Dr. Reddy's Laboratories Ltd, Clinical Pharmacovigilance, the Sponsor medical monitor, and the CRO medical monitor within 24 hours of becoming aware of the pregnancy. The expected date of delivery or expected date of the end of the pregnancy should be included in this information. The investigator is instructed to contact the subject every 3 months until the end of her pregnancy and report the outcome to the sponsor. The investigator is instructed to contact the subject for 8 weeks after delivery for follow up on infant.

The investigator will collect follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant that must also be reported to the Dr. Reddy's Laboratories Ltd, Clinical Pharmacovigilance, the Sponsor medical monitor, and the CRO medical monitor. Upon awareness of the outcome of the pregnancy, the PI or designee must forward a follow-up

Pregnancy Report with any relevant information to Dr. Reddy's Laboratories Ltd, Clinical Pharmacovigilance, the Sponsor medical monitor, and the CRO medical monitor.

If the outcome of the pregnancy meets the criteria for immediate classification of an SAE (e.g., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the investigator will report the event by emailing a completed SAE report form to Dr. Reddy's Laboratories Ltd, Clinical Pharmacovigilance, the Sponsor medical monitor, and the CRO medical monitor within 24 hours of being notified of the pregnancy report.

Details of the pregnancy, delivery and health of the infant should be recorded on the Pregnancy Report Form.

The following outcomes of pregnancy fall under the criteria for serious adverse events and should be reported as such: delivery complications prolonging hospitalization, spontaneous abortion, stillbirth, death of newborn baby, congenital anomaly, and anomaly in a miscarried/stillborn fetus

8.9.3 Monitoring Adverse Events and Laboratory Evaluations

Each subject will be monitored for the occurrence of AEs, including SAEs, immediately after the subject has signed the ICF. Each subject will be followed for safety monitoring until discharged from the study. Follow-up procedures related to pregnancy or AEs or SAEs may continue beyond the end of the study.

Subjects will be questioned and/or examined by the investigator or a qualified designee for occurrence of AEs throughout the study. The presence or absence of specific AEs should not be elicited from subjects. Subjects having AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by the investigator.

AEs, actions taken as a result of AEs, and follow-up results must be recorded in the eCRF, as well as in the subject's source documentation. Follow-up laboratory results should be filed with the subject's source documentation.

For all AEs that require the subject to be discontinued from the study and SAEs, relevant clinical assessments and laboratory tests will be repeated as clinically appropriate until final resolution or stabilization of the event(s).

All laboratory assessments will be performed centrally at a certified laboratory selected by the sponsor. The clinical laboratory values will be reported to the investigator by the laboratory and the Investigator will review them for significance and consideration as an AE.

8.9.4 Assessment of Adverse Events

8.9.4.1 Assessment of Severity

Severity of AEs will be graded according to the following definitions:

Mild: Event may be noticeable to subject; does not influence daily activities; usually does not require intervention.

Moderate: Event may make subject uncomfortable; performance of daily activities may be influenced; intervention may be needed.

Severe: Event may cause noticeable discomfort; usually interferes with daily activities; subject may not be able to continue in the study; treatment or intervention is usually needed.

8.9.4.2 Assessment of Causality

AEs should be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to the study drug and reported as either definite, probable, possible, not related, as defined below:

- Not Related: The event is clearly due to extraneous causes (e.g., diseases, environment, etc.) or the event is most probably produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant therapy and does not follow a known response pattern to the study product.
- Possibly Related: The event is temporally related to study product use but can be explained by another etiology. Information on the effect of study product withdrawal may be lacking.
- Probably Related: The event is temporally related to study product use and is consistent with known effects of the study product and/or improves upon withdrawal of the study product.
- Definitely Related: The event follows a reasonable temporal sequence from the time of study product administration and/or follows a known response pattern to the study product and could not have been produced by other factors such as the subject´s clinical state, therapeutic intervention, or concomitant therapy, and either occurs immediately following study product administration or improves on stopping the product, or there is a positive reaction at the application site

8.9.5 Reference Safety Information for Assessing Expectedness of Adverse Events

The reference safety information for assessing the expectedness of an AE for the study medication in this study is the most recent Investigator's Brochure.

8.9.5.1 Known Potential Toxicities of Investigational Product

Refer to the Investigator's Brochure OR package insert for additional information on AEs related to toxicities observed to date.

8.9.6 Reporting Safety Observations

All SAEs must be reported by the investigator to Dr. Reddy's Laboratories Ltd, Clinical Pharmacovigilance, the Sponsor medical monitor, and the CRO medical monitor within 24 hours of the investigator's knowledge of the event.

All SAEs must be recorded on SAE forms, irrespective of the study drug received by the subject, whether or not this event is considered by the investigator to be related to study drug.

These SAE forms must be sent via E-mail to Dr. Reddy's Laboratories Ltd, Clinical Pharmacovigilance, the Sponsor medical monitor, and the CRO medical monitor. The investigator must assess the relationship to study drug.

All AEs, regardless of the relationship to study drug, will be recorded in the subject source record and eCRF. Standard medical terminology should be used when describing AEs. The anatomical location of the AEs must be specified where applicable.

Whenever possible a diagnosis should be made and recorded on the eCRF rather than listing signs and symptoms. Intermittent AEs can be recorded once

The following information should be recorded on the eCRF:

- Description
- Onset date
- Resolution date or date of death
- Severity of the event (see Intensity for details)
- Study drug use continued or not
- Outcome of the event (resolved, unknown, death)
- Relationship to study drug (see Relationship to Study drug (Causality) for details)
- Rationale from PI on causality assessment
- Indication of whether the event is serious (see Seriousness for details)
- Actions taken including treatment with concomitant medication

When reporting an SAE, the Investigator/designee must complete the SAE reporting form and mention Investigator's name/designee's name, email ID, the telephone number where they can be reached, and the protocol number and title as well as the information in the above paragraph.

Contact details are provided below:

Dr. Reddy's Laboratories Ltd, Pharmacovigilance:

Pharmacovigilance GPVC

Email: pharmacovigilance@drreddys.com.

Dr. Reddy's Laboratories Ltd, Medical Monitor:

Srinivas Shenoy B., MD

Director, Clinical Development

Cell number: +91-9833974488

E-mail: srinivasshenoyb@drreddys.com

Symbio (CRO) Medical Monitor:

Evyan Cord-Cruz, MD

Director, Medical Affairs

Tel No: 516-982-0677 (cell)/ 631-403-5126 (direct)

E-mail: ecruz@symbioresearch.com

In addition, the Sponsor (or Sponsor's designated agent) will evaluate the expectedness according to the reference document/the IB.

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed in the SAE.

Serious adverse event reporting will extend from signing of informed consent until End of Study Visit /Early Termination visit.

An SAE which occurs before administration of study drug (e.g. during screening/as a result of screening) will not be considered for expedited reporting to the FDA/local EU regulatory authorities but will be entered in the subject's source records and the eCRF

If the subject took one or more suspect medicinal product(s) other than the study drug, the relevant manufacturer(s) of this medicinal product(s), will be informed about the SAE by the sponsor.

Preliminary reports will be followed by detailed descriptions that should include copies of hospital case reports, autopsy reports, hospital discharge summaries and other documents when requested and applicable. Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it. The Sponsor's Pharmacovigilance department may contact the investigator to obtain further information.

Suspected (considered related to the study drug) and Unexpected (not previously described in the reference safety document), Serious Adverse Reactions (SUSARs) will be expedited by the sponsor's Pharmacovigilance department to Health Authorities. The CRO will report to the EC/IRBs as applicable. All SAEs judged to be SUSARs and reportable will be unblinded. SUSAR related unblinding will be performed by the Sponsor's Pharmacovigilance department as outlined within the Safety Management Plan.

The Sponsor must notify the FDA/local EU regulatory authorities of any SAE observed during conduct of the study, which is serious and unexpected and for which there is a reasonable possibility that it has caused the SAE, for which there is basis to believe there is a causal relationship between the drug and the occurrence of the adverse event, as soon as possible but in no case later than 15 calendar days after becoming aware of its occurrence through an IND Safety Report to the FDA (21 CFR 320.31(d)(3)) or within the timelines required by local regulations .

If the AE is fatal or life-threatening, and with reasonable possibility of its being related to the study drug, the Sponsor must also notify the FDA/ local EU regulatory authorities as soon as possible, but in no case later than 7 calendar days after becoming aware of its occurrence to the FDA as per regulatory guidelines (21 CFR 320.31(d)(3)) or within the timelines required by local regulations.

Unblinding Instructions:

Breaking the blind

The blind should ordinarily be broken for all SAE IND safety reports submitted to FDA/local EU regulatory authorities.

The unblinding procedures and follow-up will be performed in accordance with the protocol and the Sponsor's SOPs.

All SAEs observed in the investigational drug group, if considered drug related (Suspected Adverse Reaction) will be reported to FDA/ local EU regulatory authorities as an unblinded IND Safety Report,

If the blind is broken and a subject with an adverse event was receiving placebo, the event should not be reported in an IND safety report because there is not a reasonable possibility that the drug caused the adverse event.

The blind should not be broken at the study site level except in a medical emergency (where knowledge of the study drug received would affect the treatment of the emergency) or regulatory requirement (e.g., for SAEs or death).

For medical emergency, the blind must only be broken following discussion on a case-by-case basis, at the discretion of the Investigator/treating physician/sponsor.

If the blind is broken, the date, time, and reason must be recorded in the subject's source record, eCRF, and any associated AE report.

If an Investigator, site personnel performing assessments, or subject, is unblinded, the unblinding incident and unblinded subject must be listed as a major protocol deviation.

A subject for whom the blind is broken will discontinue study product and be scheduled for a safety follow up visit and then discontinued from the study. The subject will be encouraged to stay in the study until the AE is resolved or stabilized.

For regulatory requirement, reporting of SAEs not previously unblinded at the site level, the blind will be broken by Pharmacovigilance reporting team for all SAEs observed in any treatment arm. All other individuals, including primary investigators, will receive notification of the SAE in the form of a blinded report unless the SAE was previously unblinded at the site level due to a medical emergency.

Laboratory and Vital Signs Variables

Vital signs and laboratory abnormalities should be reported as an AE if they are considered to be clinically significant, as per Investigator's judgment. If an abnormal laboratory value is associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated abnormal laboratory result should be considered additional information.

Subjects who have had an SAE must be followed clinically until the event has resolved, become clinically insignificant, has stabilized, or the subject is lost to follow-up. The investigator must provide a written follow-up report as soon as possible when any additional information is received.

New SAEs occurring at any time after the 30-day follow-up period after study drug discontinuation (whichever comes first) may be reported to Dr. Reddy's Laboratories Ltd, Clinical Pharmacovigilance within 24 hours of the investigator's knowledge of the event, if felt appropriate by the investigators.

Such information will only be entered into the drug safety database and hence will not affect study closure.

8.9.7 Discontinuation, Treatment Interruption, and Unblinding of Blinded Treatment Due to Safety Observations

8.9.7.1 Discontinuation

See Section 8.3.3 for the criteria for discontinuing a subject. If a subject is discontinued early from the study, the activities specified for Visit 7 on the Study Flow Chart (Section 3.2) should be completed if possible.

8.9.7.2 Treatment Interruption

A subject may have the study medication temporarily interrupted for any of the following reasons:

- An AE
- A diagnostic or therapeutic procedure
- An abnormal assessment (e.g., vital signs or laboratory abnormalities)
- Administrative reasons, in particular withdrawal of the subject's consent, or subject becomes uncooperative.

The reason for study drug interruption or premature discontinuation must be documented in the eCRF and the Sponsor must be informed. If the reason for discontinuation from study drug is an abnormal result on a laboratory test or vital sign this information will be recorded as an AE in the eCRF. The subject will remain under the supervision of the investigator until satisfactory health has returned.

8.9.7.3 Modification of Dose of Study Medication

The dose of study medication to any subject may not be modified. If necessary, a subject must be discontinued for the reasons described in Section 8.3.3.

8.9.7.4 Unblinding Treatment for a Subject During the Study

IWRS will be used for emergency unblinding. The identity of the study drug may be revealed only if the subject experiences a medical emergency whose management would benefit by the knowledge of the treatment assignment. Subjects who have been unblinded by the study site must be discontinued from the study.

The occurrence of any unblinding during the study must be clearly justified and explained by the investigator. Before unblinding, every attempt must be made by the investigator to discuss the intended code break with the Sponsor Medical Monitor. In all cases, the Sponsor must be informed as soon as possible before or after the code break.

8.10 Criteria for Early Termination of the Study

There are no prespecified criteria for terminating the study early.

Further recruitment in the study or at (a) particular site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems, or the number of discontinuations for administrative reasons is too high.

9 STATISTICAL METHODS

Prior to the database lock, a detailed, finalized Statistical Analysis Plan (SAP) will be completed and placed on file. The Statistical Analysis Plan will contain a more comprehensive explanation than that provided here of the methodology used in the statistical analyses, as well as the rules and data handling conventions used to perform the analyses and the procedure used to account for missing data. In case of any conflicting /discrepant information pertaining to statistical analysis between the methodology specified hereunder and in the final SAP, the information in the final SAP will supersede the protocol.

9.1 Statistical Analysis Plan

A statistical analysis plan (SAP) will be written and finalized before the study closure, i.e., database closure and unblinding of the randomization code of the study. The SAP will provide full

details of the analyses, level of significance to be used, the data displays and the algorithms to be used for data derivations.

9.2 Analysis Populations

Three populations are defined for the analyses:

- Intent-to-treat (ITT) population: This analysis population includes all randomized subjects (i.e., assigned to a treatment group). The ITT population will be the primary population for the efficacy analysis.
- Safety population: This analysis population includes subjects who received at least one dose of study medication and had at least one safety assessment post-Baseline. The safety population will be used for analysis of tolerability and safety variables.
- Per-protocol population (PP): 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 medication on the primary endpoint (without major protocol violations or deviations). Key protocol deviation categories that would influence the decision to include a subject in the PP population at the time of final review before study database lock will be pre-specified in the Statistical Analysis Plan (SAP).

9.3 General Considerations

9.3.1 Handling of Missing Data

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 the numerator or denominator unless otherwise specified.

For the ITT analysis of the total inflammatory lesion count, IGA, CEA, and DLQI efficacy data, in case of missing measurements at Week 16, multiple imputation (MI) will be used to impute the missing values.

9.4 Demographics, Medical History, Baseline Characteristics, and Concomitant Medications

The statistical significance of any treatment group difference in the distribution of categorical variables such as gender will be tested using Cochran–Mantel–Haenszel (CMH) test for general association adjusted for site. Continuous variables, such as age, will be analyzed using a 2-way analysis of variance (ANOVA) model with site and treatment as a fixed effect.

Summary statistics (mean, median, standard deviation, min, max, number of available observations) will be provided for continuous demographic variables (e.g., age, height, weight). Individual subject listings of demographic data will be provided.

Qualitative demographic characteristics (gender, race) will be summarized by counts and percentages. Medical history will be summarized by system organ class (SOC) and preferred term (PT). Other Baseline subject characteristics (e.g., physical examination clinical findings, and inclusion/exclusion checklist) will only be listed.

Distributions of these parameters will be compared between the treatment groups only descriptively. No statistical inference will be performed.

9.5 Exposure to Study Drug and Treatment Compliance

A listing with information about the drug administration will be provided. Summaries of study drug exposure and compliance will be provided.

9.6 Efficacy Evaluations

For all endpoints, the comparison of DFD-29 versus placebo will be the primary objective of the study. Comparison between oral DFD-29 and Doxycycline capsules 40 mg will be treated as secondary. The ITT will be used to perform all efficacy analyses. The analyses of the co-primary endpoints will also be performed on the PP population.

To maintain the study-wise Type I error rate of 0.05, the multiplicity issue of testing DFD-29 against placebo and against Doxycycline capsules 40 mg for multiple primary and secondary endpoints will be addressed through a fixed-sequence method described in the SAP, according to a defined sequence for the primary and secondary endpoints.

9.6.1 Co-Primary Endpoints

- The proportion of subjects with IGA treatment success (DFD-29 versus placebo) will be investigated with a CMH test for general association adjusted for site. Treatment success is defined as having at least a 2-grade reduction from Baseline with Grade 0 or 1 at Week 16.
- The difference between the treatments (DFD-29 versus placebo) in terms of the change from Baseline in the total inflammatory lesion count at Week 16 will be tested using an Analysis of Covariance (ANCOVA) model with treatment and site included in the model as fixed effects, and Baseline total inflammatory lesion count as a covariate.

9.6.2 Secondary Endpoints

- Percentage Change in Total inflammatory lesion count (sum of papules, pustules, and nodules) from Baseline to Week 16, in the DFD-29 group compared to Placebo will be tested using an ANCOVA model with treatment and site included as fixed effects, and Baseline total inflammatory lesion count as a covariate.
- Proportion of subjects with IGA treatment success (DFD-29 versus Doxycycline capsules 40 mg) at Week 16 will be investigated with a CMH test for general association adjusted for site.
- The difference between treatments (DFD-29 versus Doxycycline capsules 40 mg) in change from Baseline in the total inflammatory lesion count at Week 16 will be tested using an ANCOVA model with treatment and site included in the model as fixed effects, and Baseline total inflammatory lesion count as a covariate.
- Percentage Change in Total inflammatory lesion count (sum of papules, pustules, and nodules) from Baseline to Week 16, in the DFD-29 group compared to Doxycycline capsules 40 mg group will be tested using an ANCOVA model with treatment and site included as fixed effects, and Baseline total inflammatory lesion count as a covariate.
- Proportion of subjects with at least a 2-grade reduction in CEA score from Baseline to Week 16 will be investigated with a CMH test for general association adjusted for site (DFD-29 versus placebo).

9.6.3 Interim Analysis

No formal interim analysis is planned.

9.7 Safety Analyses

Definitions of the safety and tolerability parameters are described in Section 8.9.1.

The safety population set is used to perform all safety analyses.

The medical history is coded using the most recent Medical Dictionary for Regulatory Activities (MedDRA) version 24.1.

All AEs and SAEs are coded using the most recent MedDRA version 24.1.

The treatment-emergent AEs are tabulated by system organ class (SOC), and individual preferred terms within each SOC by treatment group. The number and percentage of subjects who experienced AEs coded with the same preferred term and SOC will be summarized by treatment group (in descending order according to the incidence in the investigational study drug group). AEs will also be tabulated by severity and by relationship to study drug. Summary tables will be accompanied by individual subject listings broken down by treatment group, including pre-dose events.

SAEs, AEs leading to premature discontinuation of study drug, and AEs of special interest each will be listed and summarized similarly to AEs.

Reasons for death will only be listed.

Reasons for premature discontinuation of study drug will be listed and summarized by frequency tables.

Individual subject listings of vital signs data, physical examination, and laboratory measurements will be provided.

Observed values and changes from Baseline in vital sign measurements and laboratory measurements will be summarized at each time point using mean, median, standard deviation, minimum, maximum, number of available observations.

Standard numeric laboratory parameters are presented in the units supplied. If needed, a conversion will be made to standard units.

Concomitant medications will be classified according to the World Health Organization (WHO) Drug Dictionary and will be presented in data listings.

9.8 Other Analyses

9.8.1 Exploratory Analyses

Exploratory data-driven analyses may be performed with the caveat that any statistical inference will not have any confirmatory value. All of the following will be compared for DFD-29 versus placebo and Doxycycline capsules 40 mg.

- Proportion of subjects with IGA treatment success from Baseline to Weeks 2, 4, 8, and 12 will be investigated with a CMH test for general association adjusted for site. Treatment success is defined as having at least a 2-grade reduction from Baseline with Grade 0 or 1.

- The difference between treatments in terms of the change from Baseline in the total inflammatory lesion count at Weeks 2, 4, 8, and 12 will be tested using mixed model repeated measures (MMRM) with treatment, site, visit, and treatment-by-visit interaction included in the model as fixed effects, Baseline total inflammatory lesion count as a covariate, and the subjects as a random factor.
- Percentage Change in Total inflammatory lesion count (sum of papules, pustules, and nodules) from Baseline to Weeks 2, 4, 8 and 12 will be tested using MMRM with treatment, site, visit, and treatment-by-visit interaction included in the model as fixed effects, Baseline total inflammatory lesion count as a covariate, and the subjects as a random factor
- The proportion of subjects with at least a 2-grade reduction in IGA score from Baseline to Weeks 2, 4, 8, 12, and 16 will be investigated with a CMH test for general association adjusted for site.
- Change in total RosaQoL score from Baseline to Weeks 2, 4, 8, 12 and 16 will be investigated using MMRM with treatment, site, visit, and treatment-by-visit interaction included in the model as fixed effects, Baseline RosaQoL as a covariate, and the subjects as a random factor.
- Change in DLQI score from Baseline to Weeks 2, 4, 8, 12 and 16 will be investigated using MMRM with treatment, site, visit, and treatment-by-visit interaction included in the model as fixed effects, Baseline DLQI as a covariate, and the subjects as a random factor.
- Proportion of subjects with at least a 2-grade improvement in the CEA score at Weeks 2, 4, 8, 12 (and 16, in case of DFD-29 vs Doxycycline capsules 40 mg comparison) will be investigated with a CMH test for general association adjusted for site.

Exploratory analyses for the following subgroups will be performed for the primary endpoints:

- Males versus females
- Baseline rosacea severity:moderate (IGA 3) versus severe (IGA 4)
- Baseline total inflammatory lesion count below versus above the median count
- Fitzpatrick skin types I-III versus IV-VI

9.9 Sample Size Determination

The sample size for this study was calculated on the basis of the results obtained from the preceding Phase 2 study with orally administered DFD-29 (40 mg) in the treatment of inflammatory lesions of papulopustular rosacea.

Assuming a difference in treatment means of 8.5 lesions between the DFD-29 and placebo groups, and a common standard deviation of 16.3 for the endpoint of inflammatory lesion count reduction, the sample size required is calculated to be 100 DFD-29 subjects and 65 placebo subjects to achieve 90% power, with a two-sided alpha of 0.05, for a 3:2 randomization ratio.

Assuming the proportion of IGA treatment success will be 0.60 in the DFD-29 group and 0.15 in the placebo group, the sample size of 100 DFD-29 subjects and 65 placebo subjects will provide greater than 99% power to detect a statistically significant difference in these proportion at alpha=0.05 (two-sided), for a 3:2 randomization ratio.

For the comparisons of DFD-29 to Doxycycline capsules 40 mg assuming a difference in treatment means of 7.5 lesions and the common standard deviation of 16.3 for the endpoint of inflammatory lesion count reduction, the sample size required is calculated to be 101 subjects in each treatment group to achieve 90% power, with a two-sided alpha of 0.05. In addition, the sample size of 100 subjects per group will yield greater than 90% power to detect a difference in the assumed proportion of IGA success of 0.60 in the DFD-29 group 0.35 in the Doxycycline capsules 40 mg group, using a two-sided alpha of 0.05.

Based on these sample size calculations and an assumed dropout rate of 20%, the final sample size will be 120 subjects each in the DFD-29 and Doxycycline capsules 40 mg groups and 80 subjects in the placebo group for a total of 320 subjects. This sample size will provide adequate power to assess the superiority of DFD-29 against both placebo and Doxycycline capsules 40 mg in terms of efficacy on both co-primary endpoints.

Efforts will be made to minimize the dropout rate and to ensure proper follow-up of subjects.

10 ETHICS

10.1 Informed Consent

The principles of informed consent, according to local regulations and International Council for Harmonization (ICH) guidelines on GCP, will be followed. A copy of the proposed ICF must be submitted with the protocol to the IRB/IEC for approval.

The informed consent process must be conducted and the ICF must be signed before each subject undergoes any Visit 1 procedures that are performed solely for the purpose of determining eligibility for the study, in compliance with local regulations. Each subject's signed ICF must be kept on file by the investigator for inspection by regulatory authorities at any time. A copy of the signed ICF will be given to the subject. A notation will be made in the subject's medical record indicating the date informed consent was obtained.

10.2 Institutional Review Board (IRB) / Independent Ethics Committee (IEC)

The study protocol and ICF must be approved in writing by an appropriate IRB/IEC as defined by FDA/local EU regulatory authority prior to enrollment of any study subjects.

Any changes to the protocol or a change of investigator approved by the sponsor must also be approved by the site's IRB/IEC and documentation of that approval provided to the sponsor or designee. Records of the IRB/IEC review and approval of all documents pertaining to this study must be kept on file by the investigator and are subject to inspection by regulatory authorities during or after completion of the study. SAEs must also be reported to the IRB/IEC as needed by local regulations.

Periodic status reports must be submitted to the IRB/IEC at least annually, as well as notification of completion of the study and a final report at study completion or termination.

The investigator will ensure that an IRB/IEC that complies with the local regulatory requirements will be responsible for the initial and continuing review and approval of the study.

10.3 Subject Confidentiality

All subject data will be identified only by a subject identification number and subject initials. However, in compliance with federal guidelines regarding the monitoring of clinical studies and in fulfillment of his/her obligations to the sponsor, the investigator must permit the study monitor,

sponsor representative or auditor, and/or FDA representative or other regulatory authority to review the portion of the subject's medical record that is directly related to the study. This shall include all study-relevant documentation including medical history to verify eligibility, admission/discharge summaries for hospital stays occurring while the subject is enrolled in the study, and autopsy reports if a death occurs during the study.

As part of the required content of informed consent, each subject must be informed that his or her medical chart may be reviewed by the sponsor, the sponsor's authorized representatives, FDA or other regulatory authority. If access to the medical record requires a separate waiver or authorization, it is the investigator's responsibility to obtain such permission from the subject in writing before the subject is entered into the study.

10.4 Study Registration

The study will be registered by the sponsor on an appropriate free public web site such as clinicaltrials.gov, which is a service of the United States National Institutes of Health. Additionally the study has been registered in the EU Clinical Trials Register (clinicaltrialsregister.eu) under the corresponding Eudra CT number 2021-005382-40.

11 DATA HANDLING AND RECORDKEEPING

11.1 Site Regulatory Documents Required for Initiation

The sponsor or designee will receive the following documents prior to the initiation of the study:

- Completed, signed Form FDA 1572 / investigator commitments in an equivalent of Form 1572 (EU sites only)
- Current curricula vitae, signed and dated, for the principal investigator (PI) and co-investigators named on Form FDA 1572 / investigator commitments in an equivalent of Form 1572 (EU sites only)
- Current license(s) of the PI and co-investigators named on Form FDA 1572 / investigator commitments in an equivalent of Form 1572 (EU sites only)
- Documentation of IRB/IEC approval of the study protocol, investigator, and ICF
- Current IRB/IEC membership list as applicable
- A copy of the protocol signature page signed by the PI
- Original Non-disclosure Agreements for the PI and co-investigators named on Form FDA 1572/ investigator commitments in an equivalent of Form 1572 (EU sites only)
- Debarment Certification for the PI and co-investigators named on Form FDA 1572 (US sites only)
- Financial Disclosure Statement for all individuals named on Form FDA 1572/ investigator commitments in an equivalent of Form 1572 (EU sites only)

11.2 Maintenance and Retention of Records

The study will be conducted according to GCP as outlined in ICH guidelines by the FDA as well as any applicable local EU regulatory authorities. It is the responsibility of the investigator to maintain a comprehensive and centralized filing system of all relevant documentation. Investigators will be instructed to retain all study records required by the sponsor and the

regulations in a secure and safe facility with limited access. Regulations require retention for a period of at least 2 years after marketing approval and notification from the sponsor. These regulatory documents should be retained for a longer period if required by local regulatory authorities.

These records include documents pertaining to the receipt and return of drug supplies, IRB/IEC, informed consent, source documents, and final signed eCRFs. No documents shall be transferred from the site or destroyed without first notifying the sponsor.

11.2.1 Electronic Case Report Forms (eCRFs)

Database set-up will be performed by Symbio (CRO) in collaboration with the electronic data capture (EDC) vendor, using an appropriate fully validated, 21 CFR Part 11 as well as any other applicable local regulations compliant EDC system. eCRFs will be provided to each site via a secured web link. All applicable study data collected on each subject will be recorded by approved site personnel into the eCRF. Only authorized site personnel will be able to enter/modify/correct data to the eCRF.

Approved staff at CRO will verify all data entered into eCRFs for completeness and accuracy with reference to the source documents and records and will issue manual data queries to correct missing data or discrepancies found against the source within the EDC system.

Data validation will consist of automated and manual edit checks that are created directly into EDC. Automated edit checks will be executed on all data points defined and documented by the study team and data management. Study metrics will be reported from the EDC system.

After all data have been verified by approved staff at CRO, an Investigator or Sub-Investigator (listed on Form FDA 1572 / investigator commitments in an equivalent of Form 1572 (EU sites only)) is required to review and approve all eCRFs prior to database lock and breaking of the blind.

After database lock, each site will be provided with a transportable media that will include the eCRF data from their site for local archival purposes.

Quality assurance verification via a 10% database audit of eCRF data will be conducted before the treatment assignment codes are released.

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

Source documents such as the clinic chart are to be maintained separately from the eCRF to allow data verification. Because of the potential for errors, inaccuracies, and illegibility in transcribing data onto eCRFs, originals of laboratory and other test results must be kept on file with the subject's eCRF. eCRFs, source documents, and copies of test results must be available at all times for inspection by the study monitor. The following should also be available for review:

- Subject Screening Log, which should reflect the reason any subject screened for the study was found to be ineligible
- Delegation of Authority Log, which will list all site personnel with their responsibilities as delegated by the PI and their signatures. This log will be maintained at the site throughout the study

- Monitoring Log, which will list the date and purpose of all monitoring visits by the sponsor or designee
- Enrollment Log, which will list subject initials and start and end dates for all enrolled subjects
- Drug Inventory/Packing Slip, which will list the total amount of drug shipped to the site and received and signed for by the investigator
- Study Medication Dispensing Log, which will list the total amount of study medication dispensed to and returned by each subject
- ICF which must be available for each subject and be verified for proper documentation
- All correspondence

11.2.2 Primary Source Documents

The investigator must maintain primary source documents supporting significant data for each subject's medical notes. These documents, which are considered "source data," should include documentation of:

- Demographic information
- Evidence supporting the diagnosis/condition for which the subject is being studied
- General information supporting the subject's participation in the study
- General history and physical findings
- Hospitalization or Emergency Room records (if applicable)
- Each study visit by date, including any relevant findings/notes by the investigator(s), occurrence (or lack) of AEs, and changes in medication usage, including the date the study medication was started and stopped
- Any additional visits during the study
- Any relevant telephone conversations with the subject regarding the study or possible AEs
- An original, signed ICF for study participation

The investigator must also retain all subject-specific printouts/reports of tests and procedures performed as a requirement of the study. During monitoring visits the monitor will validate eCRF entries against these sources of data.

11.3 Study Monitoring

Symbio (CRO) will be responsible for monitoring the study according to GCP and applicable regulations. The study will be monitored by a Clinical Research Associate (CRA) in compliance with GCP, ICH guidelines, and applicable regulations. The investigator will be visited by a CRA prior to the study and at regular intervals during the course of the study. These visits are to verify adherence to the protocol. The CRA will review the ICFs and verify eCRF entries by comparing them with the source documents (hospital/clinic/office records) that will be made available for this purpose. The CRA will review the maintenance of regulatory documentation and drug accountability (to the bottle level). The monitor will review the progress of the study with the

investigator and other site personnel on a regular basis. At the end of the study, a closeout monitoring visit will be performed. Monitoring visits will be arranged with site personnel in advance at a mutually acceptable time. Sufficient time must be allowed by the site personnel for the monitoring of eCRFs and relevant source documents. The coordinator and/or investigator should be available to answer questions or resolve data clarifications. Adequate time and space for these visits should be made available by the investigator and study staff.

11.4 Audits and Inspections

During the course of the study and/or after it has been completed, 1 or more sites may be audited by authorized representatives of the sponsor. The purpose of the audit is to determine whether or not the study is being conducted and monitored in compliance with recognized GCP/ICH guidelines and regulations.

Additionally, the study may be inspected by regulatory authorities. These inspections may take place at any time during or after completion of the study and are based on local regulations.

11.5 Modifications to the Protocol

The procedures defined in the protocol and eCRFs will be carefully reviewed to ensure that all parties involved with the study fully understand the protocol. To ensure the validity of the data, no deviations from the protocol (with minimal exceptions) may be made unless the issue is broad enough to warrant revision of the protocol. Such revisions must be submitted to and have documented approval from the sponsor and IRB/IEC prior to implementation. The only circumstance in which an amendment may be initiated without prior IRB/IEC approval is to eliminate an apparent immediate hazard to a subject or subjects. In such a case, however, the investigator must notify the sponsor immediately and the IRB/IEC within 5 working days after implementation.

11.6 Completion of the Study

The investigator is required to forward eCRFs and all other relevant data and records to CRO. The investigator will complete and report (submission of eCRFs) his/her study in satisfactory compliance with the protocol as soon as possible after the completion of the study.

The investigator must submit a final report to the IRB/IEC and the sponsor within 1 month of study completion or early termination.

12 CONFIDENTIALITY, USE OF INFORMATION, AND PUBLICATION

All information related to this study that is supplied by the sponsor and not previously published is considered confidential information. This information includes but is not limited to data, materials (protocol, eCRFs), equipment, experience (whether of a scientific, technical, engineering, operational, or commercial nature), designs, specifications, know-how, product uses, processes, formulae, costs, financial data, marketing plans and direct selling systems, customer lists, and technical and commercial information relating to customers or business projections used by the sponsor in its business. Any data, inventions, or discoveries collected or developed as a result of this study are considered confidential. This confidential information shall remain the sole property of the sponsor, shall not be disclosed to any unauthorized person or used in any unauthorized manner without written consent of the sponsor, and shall not be used except in the performance of the study.

The information developed during the course of this study is also considered confidential and will be used by the sponsor in the development of the study medication. The information may be disclosed as deemed necessary by the sponsor. To allow the use of the information derived from this study, the investigator is obliged to provide the sponsor with complete test results and all data developed in the study. The information obtained during this study may be made available to other investigators who are conducting similar studies.

The investigator shall not make any publication related to this study without the express written permission of the sponsor. If the investigator wants to publish or present the results of this study, he or she agrees to provide the sponsor with an abstract, manuscript, and/or presentation for review 60 days prior to submission for publication or presentation. The sponsor retains the right to delete confidential information and to object to suggested publication/presentation and/or its timing (at the sponsor's sole discretion).

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14 INVESTIGATOR AGREEMENT

Protocol Number: **DFD-29-CD-005**

Protocol Title: **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**

I have carefully read and understand the foregoing protocol and agree that it contains all the necessary information for conducting this study safely. I will conduct this study in strict accordance with this protocol, ICH guidelines for Good Clinical Practice, the Code of Federal Regulations/local clinical trial regulations, the local data protection regulations (HIPAA, GDPR), and any other applicable local regulatory guidelines. I will attempt to complete the study within the time designated. I will ensure that the rights, safety, and welfare of subjects under my care are protected. I will ensure control of the drugs under investigation in this study. I will provide copies of the protocol and all other study-related information supplied by the sponsor to all personnel responsible to me who participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the drug and conduct of the study. I agree to keep records on all subject information (case report forms, shipment and drug return forms, and all other information collected during the study) and drug disposition in accordance with applicable regulations. I will not enroll any subjects into this protocol until IRB/IEC approval and sponsor approval are obtained.

_____

Investigator Name (Print)

_____ _____

Investigator Signature Date

15 APPENDICES

15.1 IGA Scale

Score	Definition
0 = Clear	No signs or symptoms present
1 = Near clear	Rare papules
2 = Mild	Some papules and pustules with no plaques
3 = Moderate	Several small/large papules and pustules, with no plaques
4 = Severe	Numerous small/large papules and pustules, with or without plaques and nodules

15.2 CEA Scale

Score	**Definition**
0 = None	No redness present
1 = Mild	Slight pinkness
2 = Moderate	Definite redness
3 = Significant	Marked erythema
4 = Severe	Fiery redness

Tan J, Liu H, Leyden JJ, Leoni MJ. Reliability of clinician erythema assessment grading scale. J Am Acad Dermatol. 2014;71(4):760-3.

15.3 Diagram of the Face

Each pustule to be marked by "X" at its approximate location.

Each papule to be marked by "□" at its approximate location.

Each nodule/cyst to be marked by "O" at its approximate location

15.4 Example of the Rosacea Quality of Life Instrument

PATIENT (NAME OR NUMBER) **DATE**

	Never	Rarely	Sometimes	Often	All the time
1. I worry that my rosacea may be serious	☐1	☐2	☐3	☐4	☐5
2. My rosacea burns or stings	☐1	☐2	☐3	☐4	☐5
3. I worry about getting scars from my rosacea	☐1	☐2	☐3	☐4	☐5
4. I worry that my rosacea may get worse	☐1	☐2	☐3	☐4	☐5
5. I worry about side effects from rosacea medications	☐1	☐2	☐3	☐4	☐5
6. My rosacea is irritated	☐1	☐2	☐3	☐4	☐5
7. I am embarrassed by my rosacea	☐1	☐2	☐3	☐4	☐5
8. I am frustrated by my rosacea	☐1	☐2	☐3	☐4	☐5
9. My rosacea makes my skin sensitive	☐1	☐2	☐3	☐4	☐5
10. I am annoyed by my rosacea	☐1	☐2	☐3	☐4	☐5

	Never	Rarely	Sometimes	Often	All the time
11. I am bothered by the appearance of my skin (redness, blotchiness)	☐1	☐2	☐3	☐4	☐5
12. My rosacea makes me feel self-conscious	☐1	☐2	☐3	☐4	☐5
13. I try to cover up my rosacea (with make-up)	☐1	☐2	☐3	☐4	☐5
14. I am bothered by persistence/reoccurrence of my rosacea	☐1	☐2	☐3	☐4	☐5
15. I avoid certain foods or drinks because of my rosacea	☐1	☐2	☐3	☐4	☐5
16. My skin feels bumpy (uneven, not smooth, irregular)	☐1	☐2	☐3	☐4	☐5
17. My skin flushes	☐1	☐2	☐3	☐4	☐5
18. My skin gets irritated easily (cosmetics, aftershaves, cleansers)	☐1	☐2	☐3	☐4	☐5
19. My eyes bother me (feels dry or gritty)	☐1	☐2	☐3	☐4	☐5
20. I think about my rosacea	☐1	☐2	☐3	☐4	☐5
21. I avoid certain environments (heat, humidity, cold) because of my rosacea	☐1	☐2	☐3	☐4	☐5

15.5 Example of the Dermatology Life Quality Index

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date:
Name: Score: ☐
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	☐ ☐	Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

Please check you have answered EVERY question. Thank you.