5 PROTOCOL SYNOPSIS

TITLE	A Multi-Center, Randomized, Double-Blind, Parallel-Group, Controlled Study to Assess the Efficacy, Safety and Tolerability of Oral DFD-29 Extended Release Capsules for the Treatment of Inflammatory Lesions of Rosacea over 16 weeks
PHASE	2
CENTERS / COUNTRIES	At least 15 centers in Germany
INVESTIGATIONAL PRODUCT and DOSAGE FORMS	DFD-29 (minocycline HCl) Extended Release Capsules containing minocycline hydrochloride equivalent to 20 mg, and 40 mg of minocycline.
COMPARATIVE PRODUCT and DOSAGE FORMS	Placebo capsules Oraycea® modified release hard capsules containing 40 mg of anhydrous doxycycline
ROUTE OF ADMINISTRATION	Oral administration
OBJECTIVES	**Primary Objectives:** • To evaluate the efficacy of oral DFD-29 (minocycline HCl 40 mg capsules) in comparison to placebo in the treatment of inflammatory lesions of rosacea for 16 weeks • To evaluate the safety and tolerability of oral DFD-29 (minocycline HCl 40 mg capsules) in comparison to placebo in the treatment of inflammatory lesions of rosacea for 16 weeks. **Secondary Objectives:** • To evaluate the efficacy of oral DFD-29 (minocycline HCl 20 mg capsules) in comparison to placebo in the treatment of inflammatory lesions of rosacea for 16 weeks. • To evaluate the efficacy of the two dosage strengths of oral DFD-29 (minocycline HCl 20 mg and 40 mg capsules) in comparison to Oraycea® (doxycycline 40 mg capsules) in the treatment of inflammatory lesions of rosacea for 16 weeks. • To evaluate the safety and tolerability of oral DFD-29 (minocycline HCl 20 mg capsules) in comparison to placebo in the treatment of inflammatory lesions of rosacea for 16 weeks. • To evaluate the safety and tolerability of the two dosage strengths of oral DFD-29 (minocycline HCl 20 mg and 40 mg capsules) in comparison to Oraycea® (doxycycline 40 mg capsules) in the treatment of inflammatory lesions of rosacea for 16 weeks. • To evaluate the efficacy of oral DFD-29 (minocycline HCl 40 mg capsules) in comparison to oral DFD-29 (minocycline HCl 20 mg capsules) in the treatment of inflammatory lesions of rosacea for 16 weeks.

	• To evaluate the safety and tolerability of oral DFD-29 (minocycline HCl 40 mg capsules) in comparison to DFD-29 (minocycline HCl 20 mg capsules) in the treatment of inflammatory lesions of rosacea for 16 weeks.
DESIGN	This is a 16-week, multicenter, controlled, randomized, parallel group, double-blind study. Subjects, who are at least 18 years old, diagnosed with papulopustular rosacea will be randomized to 4 different treatment groups.
TREATMENTS	Each subject will be allocated to one of the following treatment groups, receiving 1 capsule once daily in the morning for 16 weeks: 1. DFD-29 (minocycline HCl) Extended Release Capsules (40 mg) 2. DFD-29 (minocycline HCl) Extended Release Capsules (20 mg) 3. Oraycea® (doxycycline) Modified Release Hard Capsules (40 mg) 4. Placebo Capsules
SUMMARY OF STUDY DESIGN	After assessing eligibility during an up to 28 days screening period, 200 subjects will be enrolled in the study (fifty subjects each in groups 1 to 4). Subject visits are scheduled at Screening, Baseline (Day 1), and Weeks 4, 8, 12 and 16. Clinical assessments of efficacy will be conducted based on Investigator's Global Assessment (IGA, modified scale without erythema), Clinician's Erythema Assessment (CEA), and on inflammatory lesion counts at Weeks 4, 8, 12 and 16 in comparison to Baseline. Additionally, high sensitivity C-reactive protein (hs-CRP) in the blood will be assessed at Baseline, and at Week 16 to explore any impact of the treatment on the inflammatory pathology. Laboratory assessments on blood (hematology and biochemistry) and urine (routine tests) will be conducted at Screening, Week 4 and Week 16 (End of the study) to assess for any changes in the safety parameters. Other safety assessments include vital signs, physical examination, urine pregnancy tests (only for females with child bearing potential), and collection of adverse event data. Impact of the treatment on the Quality of Life (QoL) of the subjects will be done using the rosacea specific tool RosaQoL at Baseline, and at Weeks 4, 8, 12 and 16.
STUDY POPULATION	Two hundred (200) male and female subjects with papulopustular rosacea will be enrolled to get 176 completed subjects (forty-four (44) completers each in groups 1 to 4).
INCLUSION CRITERIA	The criteria for inclusion are: 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, any gender or ethnicity (and of Fitzpatrick skin type I – III), must be in good general health as determined by the

	Investigator. 4. Subjects must have a clinical diagnosis of papulopustular rosacea, IGA grade 2 - 4. 5. Subjects must have 10 - 40 (both inclusive) inflammatory lesions (papules and pustules) of rosacea over the face. 6. Subjects must have not more than 2 nodules. 7. Subjects with moderate to severe erythema with a total score of 5 - 20 on the CEA scale. 8. Subjects must agree to only use the study products and to not use any other treatment for rosacea (prescription or Over The Counter (OTC)) during the course of the study. 9. Subjects must be free of any systemic or dermatologic disorder, which 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 must have a negative urine pregnancy test at the Screening and Baseline Visit. Sensitivity of such a test should at least be 25 mIU/mL or lower for 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 tubular occlusion† • vasectomy of sexual partner that was performed at least 90 days prior to Baseline, and has been medically assessed as successful† • 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. 12. Subjects must be in good general health as determined by the investigator and supported by the medical history and normal or not clinically significant abnormal vital signs (blood pressure and pulse). Subjects are eligible at screening if: a. Systolic BP ≤140 and ≥90 b. Diastolic BP ≤100 and ≥50 c. Pulse 50 – 100 bpm inclusive
EXCLUSION CRITERIA	Criteria for exclusion are: 1. Females who are pregnant or nursing or planning to become pregnant during the study. 2. Male whose female partner is planning to conceive a child. 3. Subjects who have been treated for rosacea within the 30 days prior to the Baseline Visit (e.g. metronidazole, azelaic acid, doxycycline or brimonidine). 4. Subjects who have been treated with systemic retinoids within 6 months prior to the Baseline visit. 5. Subjects who have participated in a trial involving any investigational product in the 90 days prior to the Baseline Visit. 6. Subjects with any disease or medical condition that would interfere with the study outcome or place the subject at undue risk. 7. Subjects who use or have used systemic steroids within the 30 days prior to the Baseline Visit or any other immunosuppressive medication. 8. Subjects who are on anti-coagulants or those who are likely to require anti-coagulants during the study period. 9. Subjects who have used methoxyflurane or other nephrotoxic drugs (as judged by the investigator) within the past 30 days. 10. Subjects with known hypersensitivity to minocycline or doxycycline or any component of the study products or against other kinds of tetracyclines.

11. Subjects with clinically significant abnormal laboratory test that, in the opinion of the investigator, would compromise the subject's safety or ability to participate in the trial.
12. Subjects who are unable to comply with study requirements.
13. History of organ transplant requiring immunosuppression, HIV, or other immune compromised state.
14. Subjects who in the opinion of the investigator or physician performing the initial examination, should not participate in the trial, e.g. due to probable noncompliance or inability to understand the trial and give adequately informed consent.
15. Subjects with close affiliation with the investigator (e.g. a close relative) or persons working at the respective trial sites or subjects who are an employee of the sponsor.
16. Subjects institutionalized because of legal or regulatory order.
17. History of drug or alcohol abuse in the last year.

CONCOMITANT MEDICATION

Product	**Washout period before Baseline**	**During Study**
Topical treatments on the face		
Benzoyl Peroxide (BPO)	14 days	Prohibited
Antibiotics (e.g. Macrolides, Clindamycin)	14 days	Prohibited
Anti-rosacea drugs (e.g. Metronidazole, azelaic acid, Brimonidine, Ivermectin)	30 days	Prohibited
Immunomodulators (including topical calcineurin inhibitors)	30 days	Prohibited
Corticosteroids	30 days	Prohibited
Retinoids	14 days	Prohibited
Astringents or abrasives (OTC scrubs, exfoliating cleansers and products containing salicylic acid and alcohol)	7 days	Prohibited
Anti-microbial soaps and face wash	Not applicable	Prohibited
Systemic Treatments		
Oral antibiotics (eg Minocycline, Doxycycline, Metronidazole or Macrolides)	30 days	Prohibited
Corticosteroids	30 days	Prohibited
Immunomodulators	30 days	Prohibited
Oral Ivermectin	30 days	Prohibited
Non-steroidal anti-inflammatory drugs (except aspirin at subanalgesic doses (i.e. <325 mg once daily) for subjects requiring platelet aggregation inhibition)	7 days	Chronic use of NSAIDs (>14 days) other than aspirin is prohibited
Niacin at doses >500 mg /day	7 days	Prohibited
Other systemic drugs used for	30 days	Prohibited

	treatment of rosacea | | | Barbiturates | 30 days | Prohibited Rifampicin | 30 days | Prohibited Carbamazepine | 30 days | Prohibited Phenytoin (Diphenylhydantoin) | 30 days | Prohibited Primidone | 30 days | Prohibited Cyclosporin | 30 days | Prohibited Methoxyflurane | 30 days | Prohibited
SAFETY / TOLERABILITY ENDPOINTS	The following parameters have been defined as parameters regarding safety and tolerability: • Change from Baseline to each scheduled time point up to EOS for vital signs. • Change from Screening up to EOS for physical examination. • Change from Screening up to EOS for clinical laboratory tests. • Treatment-emergent AEs up to EOS. • Treatment-emergent AEs leading to premature discontinuation of study drug. • Treatment-emergent SAEs up to EOS. For pre-existing conditions, any event that worsens during treatment will be considered treatment-emergent.
PRIMARY EFFICACY ENDPOINTS	**Co-Primary endpoints:** • Proportion of subjects with IGA (modified scale without erythema) 'treatment success' – Grade 0 or 1 at the end of study with at least 2 grade reduction from Baseline to Week 16. • Total inflammatory lesion count (sum of papules, pustules, and nodules) reduction from Baseline to Week 16.
SECONDARY EFFICACY ENDPOINTS	• Proportion of subjects with at least a 2 grade reduction in IGA (modified scale without erythema) score from Baseline to Week 16 • Median change in total RosaQoL score from Baseline to Week 16.
EXPLORATORY EFFICACY ENDPOINTS	• Proportion of subjects with IGA (modified scale without erythema) 'treatment success' from Baseline to Weeks 4, 8 and 12. • Total inflammatory lesion count (sum of papules, pustules, and nodules) reduction from Baseline to Weeks 4, 8 and 12. • Proportion of subjects with at least a 2 grade reduction in IGA (modified scale without erythema) score from Baseline to Week 4,8 and 12. • Median change in total RosaQoL score from Baseline to Weeks 4, 8 and 12. • Mean change in high sensitivity C-reactive protein (hs-CRP) levels from Baseline compared to Week 16. • Change in Telangiectasia score from Baseline compared to

	Week 16. • Proportion of subjects meeting CEA 'treatment success' criteria (i.e. a two grade improvement in the CEA scale) at Weeks 4, 8, 12 and 16
STATISTICAL METHODOLOGY	**Safety and tolerability** Safety and tolerability data will be listed individually and summarized using descriptive statistics and frequency tables. Change from Baseline will be analyzed for the following parameters: • Change from Baseline to each scheduled time point up to EOS for vital signs compared between DFD-29, Oraycea® and placebo. • Change from Screening up to EOS for physical examination compared between DFD-29, Oraycea®and placebo. • Change from Screening up to EOS for clinical laboratory tests compared between DFD-29, Oraycea® and placebo. • Treatment-emergent AEs up to EOS compared between DFD-29, Oraycea® and placebo. • Treatment-emergent AEs leading to premature discontinuation of study drug compared between DFD-29, Oraycea® and placebo. • Treatment-emergent SAEs up to EOS compared between DFD-29, Oraycea® and placebo. **Efficacy** For all endpoints, the comparison of oral DFD-29 (40 mg capsule) versus placebo will be the primary objective of the study. All other comparisons viz, between oral DFD-29 (20 mg capsule) and placebo, between oral DFD-29 (40 and 20 mg capsules) and Oraycea® and between oral DFD-29 40 mg capsules and DFD-29 20 mg capsules, will be treated as secondary. Co-Primary Endpoints • The proportion of subjects with IGA (modified scale without erythema) 'treatment success' – will be investigated with a Chi-square test. 'Treatment Success' is described as having at least 2 grade reduction from Baseline with grade 0 or 1 at Week 16. • The difference between the treatments in terms of the change from Baseline in the total inflammatory lesion count at Week 16 will be tested using MIXED Model, with the investigator as a random factor. Secondary Endpoints: • The proportion of subjects with at least a 2 grade reduction in IGA (modified scale without erythema) score from Baseline to Week 16, will be investigated with a Chi-square test.

	• Median change in total RosaQoL score from Baseline to Week 16 will be analyzed using ANOVA. Exploratory Endpoints: • Proportion of subjects with at least a two grade improvement of IGA (modified scale without erythema) grade from Baseline to Weeks 4, 8 and 12 will be investigated with a Chi-square test. • The difference between treatments in terms of the change from Baseline in the total inflammatory lesion count at Weeks 4, 8 and 12 will be tested using MIXED Model with the investigator as a random factor. • The proportion of subjects with at least a 2 grade reduction in IGA (modified scale without erythema) score from Baseline to Week 4, 8 and 12 will be investigated with a Chi-square test. • Median change in total RosaQoL score from Baseline to Weeks 4, 8 and 12 will be investigated using ANOVA. • The difference between treatments will be tested for the mean change in high sensitivity C-reactive protein (hs-CRP) levels from Baseline to Week 16 using ANOVA • Change in Telangiectasia score from Baseline to Week 16 will be investigated using ANOVA. • Proportion of subjects meeting CEA 'treatment success' criteria (i.e. a two grade improvement in the CEA scale) in the treatment groups at Weeks 4, 8, 12 and 16 will be investigated using ANOVA. Exploratory analyses for the following subgroups will be performed: • Male versus female. • Mild (score 2), moderate (score 3) and severe (score 4) IGA score. • Normal hs-CRP versus abnormal hs-CRP at Baseline.