SYSTEMATIC REVIEWS

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Efficacy and safety of low-dose minocycline for papulopustular rosacea: a systematic review and meta-analysis

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Abstract

DFD-29, a low-dose minocycline formulation (40 mg), demonstrated superior efficacy in the treatment of moderate-to-severe papulopustular rosacea compared with doxycycline at the same dosage and with placebo, as evidenced by Phase 3 clinical trials. The pooled analysis revealed an absolute difference of 18.0% to 28.3% in Investigator's Global Assessment (IGA) success rates and an additional reduction of 3.5 to 4.7 inflammatory lesions compared with doxycycline. Quantitative synthesis further demonstrated the superiority of DFD-29 over doxycycline, with an absolute risk difference of 23.9% (95% CI: 15.4%–32.4%; $p < 0.001$), and over placebo, with a difference of 33.4% (95% CI: 24.2%–42.7%; $p < 0.001$), indicating a consistent clinical benefit of the intervention. This therapeutic advantage is supported by the higher lipophilicity and potent anti-inflammatory activity of minocycline, while the safety profile remained favorable, with adverse event rates comparable to placebo and no effects associated with antimicrobial dosing. Plasma concentrations of DFD-29 consistently remained below the antimicrobial threshold, reinforcing its subinhibitory profile. Overall, DFD-29 appears to represent a superior and safe therapeutic option, positioning itself as a relevant alternative for the management of this condition.

KEYWORDS: Papulopustular Rosacea; DFD-29; Minocycline; Doxycycline; Tetracyclines.

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INTRODUCTION

Rosacea is a chronic inflammatory dermatosis characterized by recurrent episodes of centrofacial erythema, telangiectasia, papules, and pustules, with papulopustular rosacea (PPR) representing one of the most common clinical presentations and being associated with a substantial impact on patients' quality of life (Del Rosso & Thiboutot, 2019; van Zuuren et al., 2019; Schaller et al., 2022). In moderate-to-severe cases, systemic therapies from the tetracycline class administered at subantimicrobial doses are recommended, particularly modified-release doxycycline, which has historically been considered the main approved systemic option for this condition because of its anti-inflammatory effects and favorable safety profile (Del Rosso & Thiboutot, 2019; Schaller et al., 2022).

In parallel, minocycline has been used off-label in the management of rosacea and has more recently been investigated in low-dose and modified-release formulations, such as DFD-29, developed to enhance anti-inflammatory activity while reducing adverse events associated with antimicrobial doses (Tsianakas et al., 2021; Bhatia et al., 2025). Randomized clinical trials comparing DFD-29 with low-dose doxycycline and placebo evaluated clinically relevant outcomes, including global improvement assessed by the Investigator's Global Assessment (IGA) and reduction in inflammatory lesion counts, demonstrating promising and consistent findings across Phase II studies and confirmatory Phase III programs (Bhatia et al., 2025).

Despite these advances, integrative and quantitative syntheses systematically consolidating the available evidence regarding the efficacy and safety of DFD-29 compared with doxycycline and placebo remain limited. The absence of pooled estimates of clinical effect magnitude restricts a more comprehensive understanding of the therapeutic positioning of this

formulation in the management of moderate-to-severe papulopustular rosacea, representing a relevant scientific gap in the literature.

In this context, the aim of the present study was to conduct a systematic review with meta-analysis on the use of low-dose minocycline in adults with moderate-to-severe papulopustular rosacea, comparing it with low-dose doxycycline and placebo in order to evaluate clinical improvement, quantify the reduction in inflammatory lesions, assess IGA outcomes, and compare efficacy and safety across interventions.

METHODS

The present study was conducted with the aim of ensuring methodological transparency and reproducibility, using exclusively data derived from published studies and public records; therefore, ethics committee approval was not required. The study design was structured according to the PICOOT framework, considering adults with moderate-to-severe papulopustular rosacea as the target population, treated with low-dose minocycline (DFD-29, 40 mg), and compared with doxycycline 40 mg and placebo. Primary outcomes included success in the Investigator's Global Assessment (IGA) and reduction in inflammatory lesion counts, whereas secondary outcomes comprised adverse events, erythema, and quality of life. Randomized clinical trials were included without restrictions regarding year of publication.

The search strategy was conducted in the PubMed, Embase, and Cochrane databases using controlled descriptors and free-text terms related to the condition and interventions of interest, including "rosacea," "papulopustular rosacea," "minocycline," "DFD-29," "low dose," "subantimicrobial," "doxycycline," and "Oracea," combined using the Boolean operators

"OR" and "AND." The complete search strategy is described in Appendix A.

A total of 70 records were identified across the databases, of which 24 were duplicates, resulting in 46 articles eligible for screening. After title and abstract review, 37 studies were excluded for not meeting the inclusion criteria, leaving 9 articles for full-text assessment. Of these, 7 were excluded because they involved antimicrobial doses (>50 mg/day), lacked an appropriate comparator group, or did not provide specific data regarding papulopustular rosacea, resulting in two randomized clinical trials included in the final analysis.

The included studies corresponded to the Phase III trials MVOR-1 (NCT05296629) and MVOR-2 (NCT05343455), conducted by Bhatia et al. (2025), which evaluated the efficacy, safety, and tolerability of DFD-29 compared with doxycycline 40 mg and placebo in adults with moderate--to-severe papulopustular rosacea.

The methodological quality of the included studies was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, specifically developed for randomized clinical trials. The evaluated domains included the randomization process, deviations from intended interventions, incomplete outcome data, outcome measurement, and selection of reported results. Each domain was classified as low risk of bias, some concerns, or high risk of bias according to the criteria established by the instrument.

Given the substantial clinical and methodological similarity between the included studies, both derived from the same development program (MVOR-1 and MVOR-2), a quantitative synthesis of the data was performed through meta-analysis using a fixed-effect model and absolute risk difference as the effect measure for dichotomous outcomes. Heterogeneity between studies was assessed using the I^2 statistic and Cochran's Q test.

RESULTS

The final selection included two Phase III randomized clinical trials (MVOR-1 and MVOR-2), both conducted by Bhatia et al. (2025). The studies had a double-blind, multicenter design with a duration of 16 weeks and included adults with moderate-to-severe papulopustular rosacea, comparing DFD-29 (minocycline 40 mg) with doxycycline 40 mg and placebo.

The main methodological characteristics and findings of the included studies are summarized in Table 1. Overall, both trials demonstrated the superiority of DFD-29 over placebo and doxycycline in reducing inflammatory lesions and improving Investigator's Global Assessment (IGA) outcomes. Regarding safety, adverse event rates were comparable across groups, with a predominance of mild-to-moderate events, as detailed in Table 1.

A meta-analysis of the included studies was performed to evaluate the outcome of clinical success using a fixed-effect model and absolute risk difference as the effect measure.

In the comparison between DFD-29 and doxycycline, an absolute risk difference of 23.9% was observed (95% CI: 15.4%–32.4%; $p < 0.001$). Heterogeneity was low to moderate ($I^2 = 31.01\%$; $Q = 1.449$; $p = 0.229$), indicating consistency between studies (Figure 1).

In the comparison between DFD-29 and placebo, the meta-analysis demonstrated an absolute risk difference of 33.4% (95% CI: 24.2%–42.7%; $p < 0.001$). No heterogeneity was observed between studies ($I^2 = 0\%$; $Q = 0.000$; $p = 0.986$), indicating high consistency of the results (Figure 2).

Table 1. Methodological characteristics and main findings of the studies included in the systematic review with meta-analysis on the use of low-dose oral minocycline (DFD-29) for the treatment of papulopustular rosacea. The table presents the authors, trial registrations, study design, number of participants, presence of control and placebo groups, publication status of the results, and the main reported conclusions.

AUTHOR/ YEAR	STUDY TYPE	N TOTAL	PLACEBO/ CONTROL	EA DFD-29 (n, %)	EA DOXICICLINA (n, %	EA PLACEBO (n, %)	CONCLUSIONS
Bhatia et al., 2025	Phase 3 randomized, double-blind, multicenter clinical trial	323	Placebo/DFD-29 40 mg	32/121 (26.4%)	25/116 (21.6%)	27/76 (35.5%)	DFD-29 40 mg showed superior efficacy compared to placebo and doxycycline in reducing inflammatory lesions and improving IGA scores; adverse events were mild to moderate, with no severe cases reported.
Bhatia et al., 2025	Phase 3 randomized, double-blind, multicenter clinical trial	330	Placebo/DFD-29 40 mg	51/122 (41.8%)	40/121 (33.1%)	30/82 (36.6%)	Results were consistent with MVOR-1, confirming the efficacy and safety of DFD-29 40 mg in papulopustular rosacea.

Figure 1: Forest plot of the meta-analysis comparing DFD-29 and doxycycline for the clinical success outcome.

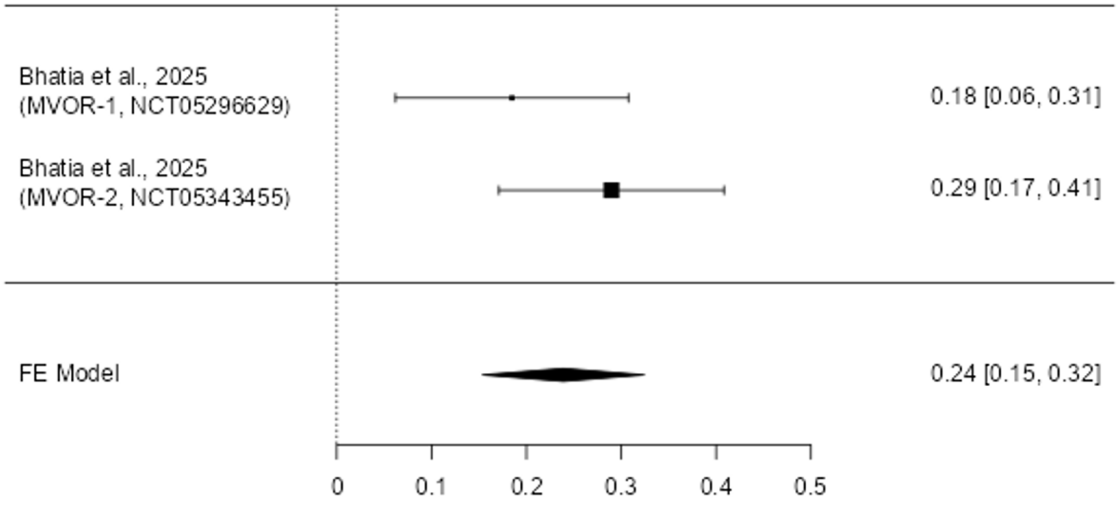
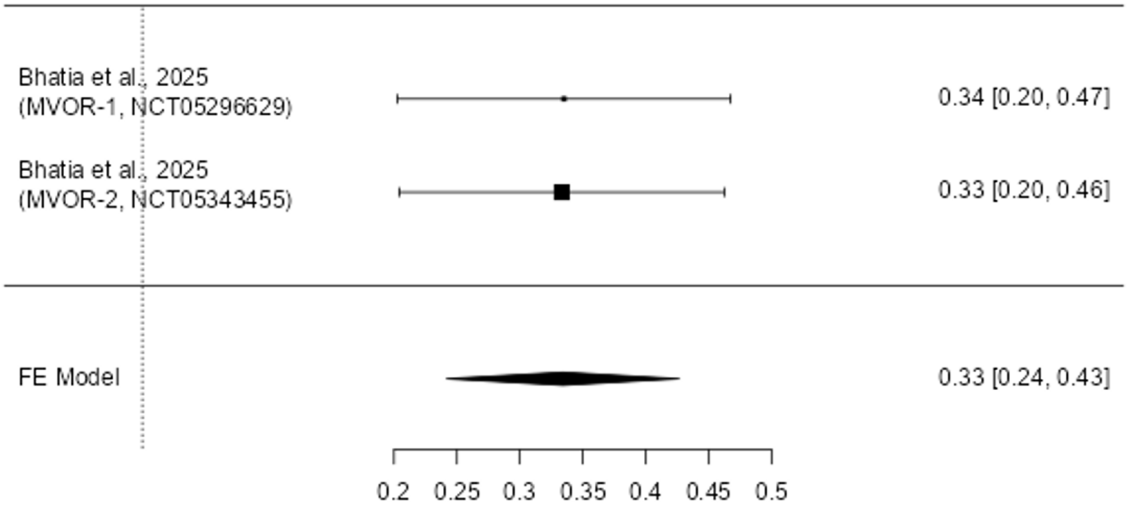


Figure 2: Forest plot of the meta-analysis comparing DFD-29 with placebo for the clinical success outcome.



RISK OF BIAS OF THE INCLUDED STUDIES

The risk of bias assessment indicated overall adequate methodological quality of the included trials (MVOR-1 and MVOR-2). Both studies showed low risk of bias in the domains of randomization, deviations from intended interventions, and outcome measurement, with adequate follow-up maintenance and use of standardized instruments such as the IGA. Losses to follow-up were low and similar between groups, suggesting no relevant impact of incomplete data. In addition, no evidence of selective outcome reporting was identified. Overall, the studies were classified as having low risk of bias.

DISCUSSION

The results of the present study demonstrate that DFD-29 is superior to doxycycline 40 mg and placebo in the treatment of moderate-to-severe papulopustular rosacea. This evidence is consistent with the findings of the phase 3 clinical trials MVOR-1 and MVOR-2 conducted by Bhatia et al.

(2025), which reported significant improvements in IGA success and reduction in inflammatory lesion count. The quantitative synthesis performed in this review further supports these findings, showing absolute risk differences of 23.9% compared with doxycycline and 33.4% compared with placebo, indicating a clinically relevant and consistent benefit of the intervention.

The findings of the meta-analysis expand the interpretation of the individual study results, demonstrating an absolute gain of approximately 24% in therapeutic success compared with doxycycline, corresponding to a number needed to treat of approximately four patients. In comparison with placebo, the magnitude of effect was even greater, with an absolute gain of approximately 33%, corresponding to a number needed to treat close to three patients. These results suggest consistency among the included studies and reinforce the robustness of the observed effect.

The randomized clinical trials MVOR-1 and MVOR-2 showed a consistent pattern of superiority of DFD-29 over doxycycline and placebo for the coprimary outcomes, including improvement in IGA and reduction of inflammatory lesions. The absolute differences observed across the individual studies corroborate the findings of the quantitative analysis, suggesting coherence among the available evidence. In addition, similar effect magnitudes had already been reported in previous studies involving subantimicrobial-dose tetracyclines, particularly doxycycline (Del Rosso et al., 2020; Fowler et al., 2017), helping to contextualize the therapeutic role of this drug class in rosacea management.

From a pharmacological perspective, two main mechanisms may explain the observed findings. The higher lipophilicity of minocycline favors tissue penetration and concentration within the sebaceous follicle, which may contribute to greater local effects compared with doxycycline (Sapadin and Fleischmajer, 2006). Furthermore, its more pronounced an-

ti-inflammatory activity, demonstrated by greater inhibition of neutrophil chemotaxis and reduction of pro-inflammatory cytokine release, may also be related to the clinical effect observed in the included studies (Skidmore et al., 2018).

The safety profile was favorable, with adverse event rates comparable among DFD-29, doxycycline, and placebo, as demonstrated in the phase 3 clinical trials evaluating this formulation (Bhatia et al., 2025). No adverse events typically associated with antimicrobial-dose minocycline formulations, such as cutaneous hyperpigmentation or significant vestibular symptoms, were observed, reinforcing the good tolerability of the low-dose formulation (Tsianakas et al., 2021; Del Rosso, 2020). In the context of long-term treatment, the maintenance of plasma concentrations below the antimicrobial threshold, combined with the absence of significant impact on the cutaneous and gastrointestinal microbiota, suggests lower potential for induction of bacterial resistance, an important aspect in the chronic management of rosacea (Schaller et al., 2022; Del Rosso et al., 2020).

Despite the demonstrated superiority of DFD-29 over doxycycline, its positioning in Brazilian clinical practice remains limited. Subantimicrobial-dose doxycycline remains the first-line systemic therapy due to its broad availability, lower cost, and incorporation into established clinical protocols. In contrast, DFD-29, as a newer modified-release minocycline formulation, is not yet widely available in the Brazilian market, which may limit its use in clinical practice. In addition, the potentially higher cost associated with newer pharmaceutical formulations may represent an additional barrier to its incorporation, particularly in resource-limited settings. Therefore, although DFD-29 represents a promising therapeutic alternative in terms of efficacy and safety, its clinical application should be interpreted considering issues of access, availability, and cost within the Brazilian context.

Among the limitations of this study, the small number of included trials (k=2) should be highlighted, which may limit the generalizability of the findings. Additionally, the underrepresentation of certain skin phototypes and the possible control of environmental factors in the included studies may have influenced the observed results. Although a fixed-effect model was adopted due to the similarity among the included studies, the limited number of available trials may restrict the identification of possible variations among estimates, and this aspect should be considered when interpreting the findings.

Despite these limitations, the consistency among the clinical findings, quantitative analysis, and observed pharmacological profile suggests that DFD-29 constitutes a relevant therapeutic alternative in the management of moderate-to-severe papulopustular rosacea.

CONCLUSIONS

Papulopustular rosacea is a chronic inflammatory condition that requires effective and safe therapeutic strategies for long-term management. The safety profile of DFD-29 was favorable throughout the evaluated period, with adverse event rates comparable to placebo and absence of the characteristic effects associated with antimicrobial-dose minocycline formulations. However, considering the chronic nature of the disease, these findings should be interpreted with caution, since the available data are limited to a 16-week follow-up period, highlighting the need for long-term safety evaluation. Collectively, these results suggest that DFD-29 represents a relevant therapeutic alternative in the management of moderate-to-severe papulopustular rosacea, particularly in patients with suboptimal response to doxycycline or those requiring prolonged therapy with minimization of antimicrobial resistance risks. Future investigations

should prioritize long-term studies (>16 weeks), evaluation in diverse populations, and cost-effectiveness analyses to further establish the role of this formulation within the therapeutic arsenal.

REFERENCES

TSIANAKAS, A.; PIEBER, T.; BALDWIN, H.; et al. Minocycline extended-release comparison with doxycycline for the treatment of rosacea: a randomized, head-to-head, clinical trial. **Journal of Clinical and Aesthetic Dermatology**, 14(12): 16–23, 2021. Accessed on: 27 set. 2025.

QPS. **Clinical Study Protocol DFD-29-CD-002 — 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**. 2018. Accessed on: 27 set. 2025.

EUROPEAN UNION CLINICAL TRIALS REGISTER. **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 (EudraCT 2016-003197-41)**. 2020. Accessed on: 27 set. 2025.

CLINICALTRIALS.GOV. **DFD-29 (Minocycline Hydrochloride) in Papulopustular Rosacea (MVOR-1) — NCT05296629; DFD-29 in Papulopustular Rosacea (MVOR-2) — NCT05343455**. 2025. Accessed on: 27 set. 2025.

[STUDY PROTOCOL]. **A multi-center, randomized, double-blind, parallel-group, controlled study of oral DFD-29 extended release capsules in papulopustular rosacea — Protocol synopsis / design highlights**. 2018. Accessed on: 27 set. 2025.

BHATIA, N.; DEL ROSSO, J.; STEIN GOLD, L.; et al. Efficacy, safety, and tolerability of oral DFD-29, a low-dose formulation of minocycline, in rosacea: two phase 3 randomized clinical trials. **JAMA Dermatology**, 161(5), 2025. DOI: 10.1001/jamadermatol.2024.6542. Accessed on: 27 set. 2025.

DEL ROSSO, J. Q.; THIBOUTOT, D. Status report on the management of rosacea: clinical considerations and future directions**. Journal of Clinical and Aesthetic Dermatology**, 12(3): 17–26, 2019. Accessed on: 27 set. 2025.

VAN ZUUREN, E. J.; FEDOROWICZ, Z.; CARTER, B.; VAN DER LINDEN, M. M. D.; CHARLAND, L. Interventions for rosacea. **Cochrane Database of Systematic Reviews**, 4(4): CD003262, 2019. Accessed on: 27 set. 2025.

DEL ROSSO, J. Q.; THIBOUTOT, D.; BALDWIN, H.; et al. Low-dose doxycycline and anti-inflammatory properties of tetracyclines in rosacea. **Cutis**, 105(2): 72–78, 2020. Accessed on: 27 set. 2025.

FOWLER, J. F. Jr.; JACKSON, J. M.; MOORE, A.; et al. Efficacy and safety of subantimicrobial dose doxycycline 40 mg in rosacea: results of two randomized controlled trials. **Journal of Drugs in Dermatology**, 16(6): 574–581, 2017. Accessed on: 27 set. 2025.

SAPADIN, A. N.; FLEISCHMAJER, R. Tetracyclines: nonantibiotic properties and their clinical implications. **Journal of the American Academy of Dermatology**, 54(2): 258–265, 2006. Accessed on: 27 set. 2025.

SKIDMORE, R.; KOVACH, R.; WALKER, C.; et al. Effects of subantimicrobial-dose doxycycline in the treatment of moderate rosacea. **British Journal of Dermatology**, 179(2): 420–426, 2018. Accessed on: 27 set. 2025.

DEL ROSSO, J. Q. Long-term safety and tolerability of subantimicrobial-dose doxycycline for the treatment of rosacea. Journal of Clinical and Aesthetic Dermatology, 13(5): 38–44, 2020. Accessed on: 27 set. 2025.

SCHALLER, M.; ALMEIDA, L. M.; BEWLEY, A.; et al. Recommendations for rosacea management: update from the Global ROSCO Consensus. **Journal of the European Academy of Dermatology and Venereology**, 36(9): 1365–1378, 2022. Accessed on: 27 set. 2025.

APPENDIX A – SEARCH STRATEGY

PubMed:

(Rosacea OR "Rosacea"[Mesh] OR "Papulopustular Rosacea" OR "Papulo-pustular Rosacea" OR PPR OR "Acne Rosacea") AND (Minocycline OR "Minocycline"[Mesh] OR "Low--Dose Minocycline" OR "Low Dose Minocycline" OR Minocin OR Solodyn OR Ximino) AND (Doxycycline OR "Doxycycline"[Mesh] OR "Low-Dose Doxycycline" OR "Low Dose Doxycycline" OR "Subantimicrobial Dose Doxycycline" OR "Sub-antimicrobial Dose Doxycycline" OR "Subantibiotic Dose Doxycycline" OR "Modified-Release Doxycycline" OR "Controlled-Release Doxycycline" OR "Doxycycline 40 mg" OR "40 mg Doxycycline" OR Oracea) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR clinical trials as topic[mesh:noexp] OR trial[ti] OR random*[tiab] OR placebo*[tiab])

Embase:

('rosacea'/exp OR rosacea OR 'papulopustular rosacea' OR 'papulo-pustular rosacea' OR PPR OR 'acne rosacea') AND ('minocycline'/exp OR minocycline OR 'low-dose minocycline' OR 'low dose minocycline' OR minocin OR solodyn OR ximino) AND ('doxycycline'/exp OR doxycycline OR 'low-dose doxycycline' OR 'low dose doxycycline' OR 'subantimicrobial dose doxycycline' OR 'sub-antimicrobial dose doxycycline' OR 'subantibiotic dose doxycycline' OR 'modified-release doxycycline' OR 'controlled-release doxycycline' OR 'doxycycline 40 mg' OR '40 mg doxycycline' OR oracea) AND ('controlled clinical trial'/exp OR random*:ti,ab OR placebo*:ti,ab OR trial:ti)

Cochrane Library:

(Rosacea OR "Papulopustular Rosacea" OR "Papulo-pustular Rosacea" OR PPR OR "Acne Rosacea") AND (Minocycline OR "Low-Dose Minocycline" OR "Low Dose Minocycline" OR Minocin OR Solodyn OR Ximino) AND (Doxycycline OR "Low-Dose Doxycycline" OR "Low Dose Doxycycline" OR "Subantimicrobial Dose Doxycycline" OR "Sub-antimicrobial Dose Doxycycline" OR "Subantibiotic Dose Doxycycline" OR "Modified-Release Doxycycline" OR "Controlled-Release Doxycycline" OR "Doxycycline 40 mg" OR "40 mg Doxycycline" OR Oracea)