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APPLICATION NUMBER:

50-805

MEDICAL REVIEW

CLINICAL REVIEW

Application Type NDA 505(b)(1)
Submission Number 50-805
Submission Code N000

Letter Date July 29, 2005
Stamp Date August 3, 2005
PDUFA Goal Date June 1, 2006

Reviewer Name Patricia Brown, MD
Review Completion Date May 26, 2006

Established Name Doxycycline
(Proposed) Trade Name (Oracea™)
Therapeutic Class Rosacea product
Applicant CollaGenex Pharmaceuticals

Priority Designation S

Formulation Capsule 40mg
Dosing Regimen Once Daily in morning
Indication — Inflammatory Lesions
(Papules and Pustules) of Rosacea
in Adult Patients
Intended Population Men and Women 18 years and
older

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1 EXECUTIVE SUMMARY

For this application, the sponsor has studied Oracea™ (doxycycline, USP) 40 mg capsules in four pharmacokinetic Phase 2 trials and 2 pivotal Phase 3 trials. Dose was selected by the sponsor to be putatively sub-antimicrobial and to be equivalent to Periostat®, a previously approved product held by the same sponsor. In comparison with other doxycycline products, no new safety issues were identified in clinical studies with Oracea™ (doxycycline, USP) 40 mg capsules. No deaths occurred in healthy patients during the development program. Serious adverse events were limited and appeared not related to study drug. The most common side effects attributable to study drug use were nasopharyngitis, diarrhea, hypertension, and sinusitis.

The sponsor's original proposed indication is to _____
_____ This has been since modified to treatment of only the inflammatory lesions (papules and pustules) of rosacea in adult patients. The sponsor has stated that at the systemic concentration provided by Oracea™, doxycycline is not effective as an antimicrobial agent and appears to exert its actions on inflammatory lesions of rosacea by mechanisms independent of antibacterial activity. The sponsor has not submitted data supporting this mechanism of action. Furthermore there are seen some possible indicators of antibacterial action in the form of an increase in diarrhea in the active treatment arms of the pivotal trials.

The change in total inflammatory lesion count from baseline to Week 16 was the primary endpoint specified in the protocols. Endpoints, however, were the subject of ongoing, repeated Agency comment during development of this drug product. The agency requested that a co-primary endpoint be a static Investigator Global Assessment that included clinical descriptors of rosacea.

Efficacy was evaluated in two randomized, placebo-controlled, multi-centered, double-blind Phase 3 trials. These trials extended for 16 weeks and involved 537 patients, 269 on Oracea™ doxycycline 40 mg capsules and 268 on placebo. At Week 16, patients in the Oracea™ doxycycline 40 mg capsule group were evaluated using co-primary endpoints of mean reduction in lesion counts and a dichotomized static Investigator's Global Assessment. Patients in the Oracea™ group exhibited a mean reduction in lesion count that exceeded that of the patients in the placebo group by 5.9 lesions in Study 301 and 5.2 lesions in Study 302. Using a static Investigator's Global Assessment score at Week 16 more patients in the Oracea™ group had improved into the lesser disease categories when compared to the placebo group in both Phase 3 studies. When success was dichotomized to Clear or Almost Clear (defined as 1 to 2 small papules or pustules), patients in the Oracea™ group exhibited success that exceeded that of patients in the placebo group by 11.3% in Study 301 and by 8.5% in Study 302.

The magnitude of the efficacy shown by the Oracea™ doxycycline product is clinically somewhat limited and modest for an oral medication. However, as compared with other products approved for rosacea, the efficacy demonstrated is in a similar range.

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While the sponsor did demonstrate efficacy in the co-primary endpoints, reduction in inflammatory lesion counts at Week 16 and in improvement in the sponsor defined IGA, these findings do not address the totality of the clinical signs of rosacea. In reference to erythema, this descriptor was removed from the Investigator's Global Assessment after the meeting of May 3, 2004. Using change from baseline in Clinician's Erythema Assessment Total Score, patients treated with Oracea™ (doxycycline, USP) 40 mg capsules did not demonstrate significant improvement in erythema when compared to those treated with placebo for the combined Studies 301 and 302.

It is the opinion of this reviewer that the endpoints as selected by the sponsor are not optimal; however, they are sufficient for approval. The efficacy demonstrated for this drug product is also sufficient for approval. This is stated in view of a relatively benign product safety profile and provided that labeling adequately informs the user/prescriber regarding what can be expected for benefit.

1.1 Recommendation on Regulatory Action

This reviewer recommends that Oracea™ (doxycycline, USP) 40 mg capsules be approved for treatment of only inflammatory lesions (papules and pustules) of rosacea in patients 18 years of age and older.

1.2 Recommendation on Post-Marketing Actions

1.2.1 Risk Management Activity

The standard risk management measures of prescription status, professional labeling and spontaneous adverse event reporting are sufficient risk management activities for this drug at this time.

1.2.2 Required Phase 4 Commitments

The required Phase 4 commitments will involve further safety evaluation of Oracea™ (doxycycline, USP) 40 mg capsules.

A) Conduct a properly designed human sperm motility and morphology study to evaluate the effects of long-term use of Oracea™ (doxycycline, USP) 40mg capsules on human sperm in male patients with rosacea.

The sponsor has agreed and will: 1) Submit study protocol September 2006. 2) Start study February 2007. 3) Submit study report June 2008.

B) Submission of carcinogenicity study protocol and dose finding data: June 2007. Carcinogenicity study start date: August 2007. Submission of final carcinogenicity study report: February 2010.

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The Sponsor agrees to this Phase 4 commitment as follows: 1) Submit carcinogenicity study protocol: June 2007. 2) Study start date: August 2007. 3) Final report submission: February 2010.

C) Conduct a study to examine longer term safety in at least 300 rosacea patients treated with Oracea™ (doxycycline, USP) 40mg capsules for at least 1 year. Study report submission within 2 years from date of approval.

The Sponsor contends that it has already fulfilled the requirements for study of long-term safety based on data from other studies extending as long as 12 to 18 months with another formulation of doxycycline.

Because this is a systemic drug and not topical, exposure is similar between Oracea™ and the other formulation of doxycycline. This response is acceptable.

D) A post-approval Medication Error Monitoring Program for the proprietary name, Oracea™. This program should consist of:

- 15-Day Reporting of all Medication Errors;
- Root Cause Analysis; and
- Trigger requiring a proprietary name change.

CollaGenex Pharmaceuticals agrees to a Medication Error Monitoring Program for the proprietary name, Oracea™, consisting of the above three components.

This Phase 4 commitment appears sufficient to address any concerns regarding the proprietary name, Oracea™, at this time.

1.2.3 Other Phase 4 Requests

No other phase 4 requests are made.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

TRADENAME (Oracea™) doxycycline 40mg capsules is an oral product intended for once daily administration for the treatment of inflammatory lesions in patients with rosacea. The sponsor has submitted a 505(b)(1) application. The sponsor has performed two pivotal Phase 3 trials, each having two arms and enrolling a total of 537 patients. Of these 269 were randomized to Oracea™ and 268 were randomized to placebo. The Phase 2 program included two pilot pharmacokinetic studies, a multiple-dose steady-state bioequivalence study comparing Oracea™ with Periostat®, and a food effect study. These studies enrolled a total of 94 patients, of these 47 were exposed to one daily dose of Oracea™ and 46 were exposed to Oracea™ once daily for a

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total of seven days. The safety database involves 362 patients exposed to Oracea™ in Phases 2 and 3. Oracea™ (doxycycline capsules) is not marketed in any country at this time.

1.3.2 Efficacy

Pivotal trials, COL-101-ROSE-301 and COL-101-ROSE-302, were nearly identical Phase 3, multi-center, randomized, placebo-controlled against the active drug, and double-blind. These trials were of adequate design and sufficiently powered to study the safety and efficacy of Oracea™ at a dose of 40mg once daily in patients 18 years and older.

In the pivotal trials COL-101-ROSE-301 (Study 301) and COL-101-ROSE-302 (Study 302) Oracea™ was statistically superior to placebo in producing a change from baseline in inflammatory lesion count at Week 16. For Study 301, ITT-LOCF population, the Week 16 changes from baseline lesion count were -11.8 and -5.9 for Oracea™ and placebo, respectively. For Study 302, ITT-LOCF population, the Week 16 changes from baseline lesion count were -9.5 and -4.3, respectively. These changes were statistically significant using an ANOVA model, $p \leq 0.0002$ and $p \leq 0.0001$ for studies 301 and 302.

The change in total inflammatory lesion count from baseline to Week 16 was the primary endpoint specified in the protocols; however, endpoints were the subject of ongoing, repeated Agency comment during development of this drug product. The agency had requested a co-primary endpoint to be a static Investigator Global Assessment that included clinical descriptors of rosacea.

As identified in the protocols a secondary endpoint was change from baseline in IGA at Week 16. This IGA largely reflects a grouping of lesion counts. The Division recommended dichotomizing this endpoint to define treatment responders as those having an IGA score of 0 (Clear) or 1 (Near Clear) at endpoint (Week 16). This endpoint, as dichotomized, was employed by the Division as a co-primary endpoint. The proportion of patients responding in the Oracea™ group was significantly greater than in the placebo group in both studies 301 and 302 ($p \leq 0.0361$ and $p \leq 0.0120$). More specifically, at Week 16, in Study 301, 30.7 % of the Oracea™ patients versus 19.4 % of the placebo patients were scored as successes on this endpoint. In Study 302, 14.8% of the Oracea™ patients versus 6.3% of the placebo patients were scored as successes on this endpoint.

Results for an erythema endpoint, change from baseline in the Clinician's Erythema Score, were only marginally clinically meaningful. Treatment differences were statistically significant in Study 301 ($p \leq 0.0164$) but not in Study 302 ($p \leq 0.4278$). For the combined studies, 301 and 302, treatment differences were not statistically significant ($p \leq 0.024$). Of note, erythema was removed from the Investigator's Global Assessment after the meeting of May 3, 2004. Attempting to provide a static overall IGA, the Clinical team defined a post hoc extended IGA that incorporated erythema. On this endpoint, there were no statistically significant treatment differences.

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Therefore, the sponsor has demonstrated efficacy of Oracea™ 40mg capsules for the treatment of only inflammatory lesions (papules and pustules) of rosacea in patients 18 years and older.

1.3.3 Safety

Six hundred thirty one patients were enrolled in the phase 2 and 3 studies. Of these 362 were exposed to Oracea™. In the phase 3 studies the mean exposure was 102 days with a median of 30 days. The 4 month safety update report was reviewed and did not reveal new safety issues.

No deaths in healthy patients have occurred during the clinical development program for Oracea™. In addition no deaths have occurred in healthy patients while participating in clinical studies with Periostat®, a related product. No serious adverse events (SAEs) occurred in the pivotal study COL-101-ROSE-301. During study COL-101-ROSE-302, five patients experienced serious adverse effects. Three patients in the Oracea™ treatment group experienced 8 SAEs which were not considered related to study drug.

Thirty two patients discontinued study drug due to AEs: 20/269 in the Oracea™ treatment group and 12/268 in the placebo group. Of the 20 patients in the Oracea™ treatment group who discontinued 13 were withdrawn due to AE's considered probably or possibly related to study medication. Four patients withdrew solely due to gastrointestinal disorders and four patients withdrew due to gastrointestinal disorders in addition to AE's in at least one other system organ class.

For the combined phase 3 studies, 55.4% of patients treated with Oracea™ and 45.5% of patients treated with placebo experienced adverse events. AE's reported by more than 1% of treated patients occurred at a higher rate in the Oracea™ than the placebo group, however between group differences were generally 4 or fewer patients. The largest between group differences were seen for diarrhea, hypertension, sinusitis, and upper respiratory tract infection. Diarrhea was noted in 12 patients in the Oracea™ group and 7 patients in the placebo group. Most of these AE's were considered possibly related to the study medication. (It is possible that the presence of an excess of diarrhea in the Oracea™ treatment group could suggest an antimicrobial effect.) However, an analysis was performed by the statistician of those AE's occurring in more than 1% of the Oracea™ subjects. Twenty five AEs were evaluated and only two showed statistical significance before adjusting for multiplicity and none after adjustment. It is noted that the studies are not powered to test for adverse events.

1.3.4 Dosing Regimen and Administration

Oracea™ capsules, 40 mg are intended for once daily oral administration. This is the dosage regimen studied in the Phase 2 pharmacokinetic studies and in the Phase 3 pivotal trials.

To select the optimal dose duration, and frequency of treatment, the Agency had recommended that Phase 2 dose-ranging studies be performed. The selection of the 40mg/day dose of Oracea™ was based on a previous study by the sponsor in which Periostat® tablets 20 mg twice

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daily given to patients with moderate rosacea over a 16 week period resulted in a significant reduction in the total inflammatory lesion count as compared with placebo.

Also pilot pharmacokinetic studies showed that plasma doxycycline concentrations with Oracea™ 40mg/day were maintained below the antimicrobial threshold, a plasma level (C_{max}) below 1.0 µg/mL. The sponsor states this antimicrobial threshold was defined based on previous experience with the approved drug Periostat®. A higher dose did not appear, according to the sponsor, to be necessary for efficacy and would expose patients to antimicrobial concentrations of doxycycline that might increase the risk of developing resistant organisms.

At steady state Oracea™ 40mg/day and Periostat® 20 mg twice a day have demonstrated similar drug exposure (AUC) in pharmacokinetic trials. According to the sponsor, this would indicate that the safety profile of Periostat® is similar to that of Oracea™. Since the safety profile of Periostat® has been shown to be similar to that of placebo, the sponsor asserts that there is no potential safety benefit expected with a lower dose of Oracea™.

1.3.5 Drug-Drug Interactions

The proposed labeling for Oracea™ will follow that of tetracycline class antibiotics.

1. Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.
2. Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline-class drugs in conjunction with penicillin.
3. The concurrent use of tetracycline and methoxyflurane has been reported to result in fatal renal toxicity.
4. Absorption of tetracyclines is impaired by bismuth subsalicylate, proton pump inhibitors, antacids containing aluminum, calcium or magnesium and iron-containing preparations.
5. Doxycycline may interfere with the effectiveness of low dose oral contraceptives. To avoid contraceptive failure, females are advised to use a second form of contraceptive during treatment with doxycycline.
6. There have been reports of pseudotumor cerebri (benign intracranial hypertension) associated with the concomitant use of isotretinoin and tetracyclines. Since both oral retinoids, including isotretinoin and acitretin, and the tetracyclines, primarily minocycline, can cause increased intracranial pressure, the concurrent use of an oral retinoid and a tetracycline should be avoided.

1.3.6 Special Populations

Oracea™ was studied in patients 18 years and older. This is appropriate for a disease that has its onset between the ages of 30 and 50 years. With respect to age, sex, and race the pivotal trial population studied was reflective of those most at risk for rosacea and not the U.S. population as

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a whole. Those studied on Oracea™ had a median age of 46.0 years, were predominantly female (69%), and were primarily Caucasian (90%).

In general Oracea™ was more effective than placebo across gender and age groups when analyzed for lesion counts and Week 16 IGA. In study 301 Oracea™ was more effective in males than females when the IGA is examined. This differential response was not seen in study 302. Few patients in these studies were non-Caucasian. While Oracea™ demonstrated efficacy in Caucasians it did not show superiority to placebo in non-Caucasians.

Pregnant and breast-feeding women were excluded from these studies. This is appropriate based on the teratogenic effects of tetracycline class antibiotics and which are given a Pregnancy Category D.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The sponsor, CollaGenex Pharmaceuticals Inc., has submitted a 505(b)(1) application for **TRADENAME** (Oracea™) doxycycline _____ 40mg an oral antibiotic rosacea product. The active ingredient, doxycycline monohydrate is synthetically derived from oxytetracycline. This new _____ dosage form consists of 2 types of beads that together provide a dose of 40mg of doxycycline over a 24 hour period. Oracea™ is intended to be taken once daily in the morning to _____ (≥ 18 years old) patients with rosacea. The sponsor claims that, at the systemic concentrations provided by Oracea™, doxycycline is not effective as an antimicrobial agent and appears to exert its beneficial actions on inflammatory lesions of rosacea by mechanisms independent of antimicrobial activity.

The sponsor has proposed the proprietary name Oracea _____. Consultation was obtained with the Division of Drug Medication Errors and Technical Support (DMETS) Office of Drug Safety. DMETS does not recommend the use of the proprietary name Oracea _____ due to its potential to look similar to Arava, Omacor, Ovace, and Orasone if the modifier _____ is omitted from the name. An additional product Orenzia*** (abatacept) was found to have look-alike and sound-alike potential with Oracea _____ also if the modifier _____ is omitted from the name.

2.2 Currently Available Treatment for Indications

Currently there are no oral medications indicated for the treatment of rosacea. However, in clinical practice tetracycline, doxycycline, and less commonly minocycline are employed to treat this condition.

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The only approved drugs listed in the electronic PDR for rosacea are all topical. They are as follows:

Finacea Gel, 15% - Azelaic Acid (Intendis)
Noritate Cream, 1% - Metronidazole (Dermik)

2.3 Availability of Proposed Active Ingredient in the United States

Doxycycline monohydrate was approved in the U.S. in 1967 under the trade name Vibramycin®. Doxycycline is currently an approved prescription drug for a number of antibacterial indications as well as adult periodontitis. Doxycycline is currently marketed by a number of sponsors in a variety of strengths, as tablets, capsules, powder for oral suspension, syrup, injection and as powder for injection. Doxycycline is available both as monohydrate and as hyclate. Generic formulations are also available.

Doxycycline is indicated for a wide variety of infections including; Rocky Mountain spotted fever, typhus fever, Mycoplasma pneumoniae, Chlamydia trachomatis, and Borrelia recurrentis, and tick fevers caused by Rickettsiae. Doxycycline is also indicated for gram-negative microorganisms including; Yersinia pestis, Francisella tularensis, Vibrio cholerae, Brucella species, and when bacteriologic testing indicates susceptibility; Escherichia coli, Shigella species, Haemophilus influenzae, and Klebsiella. Doxycycline is indicated in gram-positive susceptible organisms including Streptococcus pneumoniae and Bacillus anthracis. Doxycycline is indicated as an alternative drug in the treatment of microorganisms such as Neisseria gonorrhoeae, Treponema pallidum, Clostridium species and others. In severe acne, doxycycline may be useful adjunctive therapy.

The related product Periostat® (doxycycline hyclate) 20 mg was approved for marketing in the United States by CollaGenex Pharmaceuticals. The indication is for use as an adjunct to scaling and root planning to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis. The mechanism proposed is non-antimicrobial and involves inhibiting collagenase activity in gingival crevicular fluid of adult patients with periodontitis. Periostat® was marketed initially as the capsule formulation on September 30, 1998 (NDA 50-744) and became available by prescription in November 1998. The tablet formulation was approved for marketing on February 2, 2001 (NDA 50-783). Since April 2003, only the tablet formulation has been available.

2.4 Important Issues with Pharmacologically Related Products

The tetracycline class of antibiotics includes tetracycline, doxycycline, and minocycline. This class has been associated with a number of known safety concerns.

1) Doxycycline, like other tetracycline-class antibiotics, is a known teratogen and is considered Pregnancy Category D.

The use of drugs of the tetracycline class during tooth development (last half of pregnancy, infancy, and childhood up to the age of 8 years) may cause permanent discoloration of the teeth

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(yellow-gray-brown). This adverse reaction is more common during long-term use of the drug but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported.

All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in premature human infants given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued.

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can cause retardation of skeletal development on the developing fetus. Evidence of embryotoxicity has been noted in animals treated early in pregnancy.

2) Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range from mild to life-threatening. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associate colitis".

3) The anti-anabolic action of the tetracyclines may cause an increase in BUN. While this is not a problem in those with normal renal function, in patients with significantly impaired function, higher serum levels of tetracycline-class antibiotics may lead to azotemia, hyperphosphatemia, and acidosis. If renal impairment exists, even usual oral or parenteral doses may lead to excessive systemic accumulations of the drug and possible liver toxicity.

4) Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. This was not observed during the duration of the clinical studies with Oracea™.

5) As is the case with other antibiotic preparations, use of doxycycline may result in overgrowth of non-susceptible microorganisms, including fungi. The use of tetracyclines may increase the incidence of vaginal candidiasis.

6) Use of tetracyclines may result in the development of bacterial resistance to that class of drugs.

7) Tetracyclines have been associated with the development of autoimmune syndromes. Symptoms may be manifested by fever, rash, arthralgia, and malaise.

8) Tetracycline class antibiotics are known to cause hyperpigmentation. Tetracycline therapy may induce hyperpigmentation in many organs, including nails, bone, skin, eyes, thyroid, visceral tissue, oral cavity (teeth, mucosa, and alveolar bone), sclerae and heart valves. Skin and oral pigmentation has been reported to occur independently of time or amount of drug administration, whereas other pigmentation has been reported to occur upon prolonged administration. Skin pigmentation includes diffuse pigmentation as well as over sites of scars or injury.

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9) Bulging fontanels in infants and benign intracranial hypertension in adults have been reported in individuals receiving tetracyclines. These conditions disappeared when the drug was discontinued.

2.5 Pre-Submission Regulatory Activity

Pre-IND meeting held January 28, 2002:

a) The Sponsor planned to seek approval on the basis of two Phase 3 studies, one for each sub-type of acne (rosacea and _____ for their product, _____ mg. The sponsor was informed that; "Current evidence suggests that rosacea has a different pathogenesis than _____. Therefore, to support efficacy of doxycycline in both rosacea and _____ Sponsor should conduct two adequate, placebo-controlled trials for each indication."

b) The sponsor was further informed that regarding endpoints for rosacea:

"i. The Agency supports the following 2 primary endpoints: the Investigator's (Clinician's) Global Assessment and lesion counts. The Investigator's Global Assessment should be a static assessment at the efficacy endpoint and not a change from baseline. The Investigator's Global scale should be dichotomized a priori to success and failure. As presented in the briefing package, the Agency would support success as a score of "0" on the assessment scale.

If the Sponsor can be more precise in its description of the difference between score 1 and 2, and demonstrate that the level of disease in score 1 is such that treatment would not be necessary, then the Agency might consider adding category 1 to success." ...

"ii. There should be a statistically significant reduction in inflammatory lesions at endpoint. For approval, success must be demonstrated in both the Investigator's Global Assessment and in lesion counts.

iii. The Sponsor should be aware that if a reduction in erythema is sought as part of the indication, then this parameter should be incorporated into the Investigator's Global Assessment. Further, erythema should also be a separate assessment with static descriptors and not assessed as an improvement from baseline."

c) With respect to dose ranging, the Agency recommended that the Sponsor should ... "consider conducting Phase 2 dose ranging studies to determine the best dose, duration, and frequency of treatment for the indications under consideration."

Pre-IND/End of Phase 2 meeting held May 3, 2004:

This meeting addressed the Sponsor's COL-101 (doxycycline monohydrate) 40 mg _____ capsules. a) In regard to the Investigator's Global Assessment/Erythema Scale it was stated:

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“ii. ...The Agency recommends that the Clinician’s Global Severity Score be modified to include static clinical descriptors and categories (e.g., Clear, Almost Clear, Mild, Moderate, and Severe). The Clinician’s Global Severity Score appears to be similar to an Investigator’s Global Assessment (IGA) scale; however, as an IGA the Agency recommends use of clinical descriptors (e.g., papules, nodules, slight pinkness, fiery redness, telangiectasia, etc.) The Sponsor’s Clinician’s Global Severity Score includes an area specific ‘score’ which is not a clinical global assessment.”

b) The Sponsor proposed to remove erythema from the Clinician’s Global Severity Scale and evaluate erythema as a secondary variable since the Sponsor was not seeking the treatment of erythema as an indication. The Agency discussed this issue and addressed it in an addendum to the minutes of the May 3 meeting. In the addendum the Agency stated that: “Erythema may be evaluated separately as a secondary variable and not be included in the Clinician’s Global Severity Scale as proposed by the Sponsor. Erythema will be addressed as a secondary variable for labeling and erythema should not get worse.”

c) The Agency made the following comments regarding endpoints:

“i. The Agency recommends the following two primary efficacy endpoints for demonstrating efficacy in treatment of rosacea: 1) inflammatory lesion counts (papules, pustules, and nodules) and 2) the investigator’s static global assessment (IGA). Clinical signs (erythema and telangiectasia) should be incorporated into the static global assessment.

ii. As noted above, the Agency recommends that the IGA be a static scoring system. The IGA should be dichotomized a priori to success and failure.

iii. For approval, success must be demonstrated in both the IGA and in lesion counts. There should be a statistically significant reduction in inflammatory lesions at study endpoint.

iv. The Sponsor proposes a Clinician’s Erythema Score...which is obtained at endpoint as a sum obtained from evaluation of five facial areas (scale of 0 to 4). The Sponsor is reminded that if a reduction of erythema is sought as part of the indication, then this parameter should be incorporated into the IGA. Erythema should also be a separate assessment with static descriptors and not assessed as improvement from baseline. The erythema scale should also be dichotomized into success and failure a priori. Erythema will only be considered if the trial is a success regarding the IGA and lesion counts.”

d) Regarding dose ranging, the Agency stated that ...”additional information regarding dose and treatment efficacy and safety for rosacea could be useful (What is the differential effect between the 40 mg dose and other doses used historically? What effect do the different doses have on longevity of response after discontinuing medication? What effect do the different doses have on specific patient conditions, such as mild ocular symptoms associated with rosacea?).”

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From the meeting minutes: “The Sponsor is not planning to explore treatment at higher dose levels for this application because some efficacy has been demonstrated at the proposed level. After much discussion with the Agency regarding the effects of resistance at lower levels of exposure; the Sponsor offered to submit reference materials addressing the issue of development of microbial resistance at the proposed levels.”

e) Regarding safety and sample size, the Agency stated:

“Repeated intermittent use of this drug product can be expected; therefore, the Sponsor should refer to ICH-E1A Guideline for Industry (The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-Life Threatening Conditions) regarding the bare minimum sample size for patients on active drug in trials to demonstrate safety.”

IND Submission on 5/12/2004:

The sponsor planned to conduct two, randomized, double-blind, placebo-controlled, parallel-design clinical trials with use of doxycycline monohydrate 40 mg daily for 16 weeks. Approximately 264 patients (132 per treatment arm) were to be enrolled at eleven centers in order to have at least 222 patients (111 per treatment arm) in each clinical trial. Two apparently identical Phase 3 protocols (COL-101-ROSE-301 and COL-101-ROSE-302) were submitted for review.

Agency Comments for Sponsor on 9/27/2004:

Two apparently identical protocols (COL-101-ROSE-301 and COL-101-ROSE-302) were submitted for review. Comments were applicable to each protocol.

1. The Sponsor is reminded (as per the January 28, 2002 and May 3, 2004 Pre-IND/End of Phase 2 Meetings) that the Division recommends two primary efficacy endpoints to support the treatment of rosacea indication as follows:
 - a. Inflammatory lesion counts (papules, pustules, and nodules) and
 - b. The investigator's static global assessment (IGA). Clinical signs (erythema and telangiectasia) should be incorporated into the static global assessment.

The Agency recommends that the IGA be a static scoring system. The IGA should be dichotomized a priori to success and failure. For approval, success must be demonstrated in **both** the IGA and in lesion counts. There should be a statistically significant reduction in inflammatory lesions at study endpoint.

2. In the current submission, the IGA is listed as a secondary efficacy parameter; however as reiterated above, the Division recommends use of the IGA as a coprimary efficacy endpoint.
3. Telangiectasia should be included in the IGA since this clinical sign is an integral

descriptor of disease progression for rosacea. IGA of disease severity is intended to provide a morphological description of the patient's clinical condition at a discrete time point. As presented in the protocol, the sponsor's IGA only provides for lesion counts and should be modified to include telangiectasia as a descriptor. It should be noted that, erythema is being assessed separately and at the Sponsor's request the Agency has agreed that erythema will not be included as a descriptor in the IGA.

4. Perilesional erythema should not be included in assessment of nontransient erythema. As recommended by the Agency, nontransient erythema may be graded from 0 to 3 (e.g., absent, mild, moderate, or severe). However, the Sponsor is proposing a five point Clinician's Erythema Assessment Scale (Total Erythema Score) derived from the sum of all the Individual Erythema Scores. It is also recommended that in clinical studies, researchers may use instruments to objectively measure nontransient erythema. Erythema Reduction in papulopustular rosacea would not extrapolate to erythema of rosacea in the absence of papulopustular lesions.
5. Erythema will be assessed as a safety variable. At the May 3, 2004 Pre-IND/End of Phase 2 Meeting, the Sponsor stated that treatment of erythema will not be sought as a labeled indication and as stated above erythema will be assessed separately. The sponsor is reminded that if a reduction of erythema is sought as part of the indication, then this parameter should be incorporated into the IGA, and *a priori* be dichotomized into success and failure.
6. Post-treatment (e.g., 4 weeks, etc.) efficacy and safety evaluations are recommended for longevity of treatment effect. Longevity of effect is not needed for drug approval; however, would be useful for labeling based on the proposed anti-inflammatory mechanism of action.
7. The sponsor is reminded that adequate data are needed for review that substantiates the sponsor's claim that the proposed dose and formulation of doxycycline monohydrate to be used in planned studies will not adversely affect the microflora in a way that could potentially cause harmful effects to patients or cause increase bacterial resistance.
8. See Biostatistical comments ...for additional recommendations.

Pre-NDA Meeting held 3/30/2005:

The Sponsor referred to Question 3 of the March 1, 2005 briefing package (relating to endpoints): "Is the proposal regarding analysis of the IGA acceptable?"

Agency reply:

"1. No, analysis of the dichotomized IGA as a secondary variable is not acceptable. The Agency stands by the recommendation for use of co-primary efficacy endpoints for rosacea provided to the sponsor at the January 28, 2002, Pre-IND/End of Phase 2 meeting, May 3, 2004, End of Phase 2 Meeting, and protocol comments of September 27, 2004. As it is too late to

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modify the prespecified analysis plan, the Agency recommends the following analyses be submitted:

- a. Submit data analysis as pre-specified in your statistical analysis plan in your protocol.
 - b. Submit data analysis as was recommended by the Agency.
2. Two primary efficacy endpoints are needed for demonstrating efficacy in treatment of rosacea: a) inflammatory lesion counts (papules, pustules, and nodules) and b) the investigator's static global assessment (IGA). There should be a statistically significant reduction in inflammatory lesions at endpoint. For approval, success must be demonstrated in both the Investigator's Global Assessment and in lesion counts. Subjects enrolled with an IGA in the win category (i.e., clear or almost clear) should not be included in the analysis. It was discussed that erythema and telangiectasia are not included in the Investigator's global assessment scale, will be addressed as secondary variables, and should not get worse."

2.6 Other Relevant Background Information

This is a new formulation of doxycycline and is not approved in any country.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The active pharmaceutical ingredient of Oracea™ is doxycycline, USP. This is synthetically derived from oxytetracycline. Doxycycline, USP is a light yellow to pale yellow crystalline powder that dissolves in dilute solutions of alkali hydroxides and carbonates.

Oracea™ capsules are hard gelatin capsule shells filled with two types of doxycycline beads that together provide a dose of 40 mg of anhydrous doxycycline. This dose is contained 75% in immediate-release beads and 25% in delayed-release beads. Inert ingredients of the formulation are: hydroxypropyl methylcellulose, methacrylic acid copolymer, sugar spheres, talc, triethyl citrate, and ~~iron oxide red, iron oxide yellow, polyethylene glycol, Polysorbate 80, and titanium dioxide.~~ iron oxide red, iron oxide yellow, polyethylene glycol, Polysorbate 80, and titanium dioxide.)

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Table 1: Quantitative Composition as Weight Percentage of Components in IR Beads, DR Beads and Oracea™ and Function

Component	IR Beads	DR Beads	Oracea™	Function
Doxycycline, USP/NF	}	}		}
Hypromellose, USP/NF				
Methacrylic Acid Copolymer, USP/NF				
Triethyl Citrate, USP/NF				
Talc, USP/NF				

Sugar Spheres, _____ mesh, USP/NF				
Purified Water, USP/NF				
Hard Gelatin Capsule #2, Beige Opaque				
Total^a				

* Excluded from percent calculation

^a Total rounded to nearest whole number

† Removed during processing

Source: Sponsor's NDA submission, module 2, volume 1.1, pp. 6 and 8.

3.2 Animal Pharmacology/Toxicology

The sponsor did not perform new studies for this submission. The sponsor relied on published literature and previous FDA findings of safety for Periostat® (doxycycline hyclate 20 mg capsules) NDA 50-744. This NDA is held by CollaGenex, the same sponsor as the current NDA.

As indicated by the Pharm/Tox reviewer, examination of the literature and previous clinical experience with Periostat® and Vibramycin suggest that there are no safety pharmacology concerns associated with doxycycline.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Please see reviews associated with NDA 50-744.

The carcinogenicity of doxycycline was assessed by conducting a two-year bioassay in rats. The only statistically significant treatment-related observation in the study was an increased incidence of uterine polyps in females in the high-dose group (200mg/kg/day). The sponsor has committed to conduct a second carcinogenicity study in mice during Phase 4.

Two genetic toxicity tests were performed and found to be negative. These included an *in vitro* point mutation study with mammalian cells and an *in vivo* micronucleus assay conducted on CD-1 mice. Results from an *in vitro* assay with CHO cells for potential to cause chromosomal aberrations suggest that doxycycline is a weak clastogen.

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Doxycycline adversely affected fertility and reproductive performance of rats. The sponsor will be required to conduct a properly designed human spermatogenesis study to evaluate the effects of doxycycline on human spermatogenesis.

The use of drugs of the tetracycline class during tooth development (last half of pregnancy, infancy, and childhood up to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). The current label for Oracea™ has a Pregnancy Category of D.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sponsor's NDA submission was the primary source of clinical data used in this review.

4.2 Tables of Clinical Studies

Table 2: Description of Pharmacokinetic Studies of Oracea™

Study ID	No. of Centers	Design	Study Drugs & Treatment Duration	Study Objective	No. Patients Entered/ Completed	Gender, Median Age (Range)	Diagnosis/ Inclusion Criteria	Primary Endpoint(s)
PERIO-DOXYSR-103	Single center:	Randomized, open-label, 3-way crossover (7-day washout between periods)	Oracea™ 40 mg QD, Periostat® 20 mg BID, and Periostat® 40 mg QD Single dose	BA	18/17	9 M 9 F 32 years (22 to 45)	Healthy adult subjects	Extent (AUC _{0-t} , AUC _{0-∞}) and rate of absorption (C _{max}) of doxycycline
PERIO-DOXYSR-104	Single center:	Randomized, open-label, 2-way crossover (96-hour washout between periods)	Oracea™ 40 mg QD and Periostat® 20 mg BID 7 days	BA	14/13	7 M 7 F 27 years (19 to 44)	Healthy adult subjects	Comparison of PK with Oracea™ and Periostat®

Abbreviations: BA = bioavailability, BID = twice daily, F = female, M = male, PK = pharmacokinetics, QD = once daily

Source: Sponsor's NDA submission, module 2, volume 1.1, p. 231.

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Table 2: Description of Pharmacokinetic Studies of Oracea™ (continued)

Study ID	No. of Centers	Design	Study Drugs & Treatment Duration	Study Objective	No. Patients Entered/ Completed	Gender, Mean Age (Range)	Diagnosis / Inclusion Criteria	Primary Endpoint
COL-101-SDPK-105	Single center: []	Randomized, open-label, 2-way crossover (7-day washout between periods) Fasted Versus fed	Oracea™ 40 mg QD in fed versus fasted state Single dose	To evaluate effect of food on rate and extent of absorption	30/30	16 M 14 F 25 years (18 to 44)	Healthy adult subjects	Effects of food on C _{max} , AUC _{0-t} , and AUC _{0-∞} of doxycycline
COL-101-SSPK-106	Single center: []	Randomized, open-label, 2-way crossover (7-day washout between periods)	Oracea™ 40 mg QD and Periostat® 20 mg BID 7 days	To compare rate and extent of absorption at steady state	32/30	23 M 9 F 28 years (18 to 45)	Healthy adult subjects	C _{max} , C _{min} , and AUC _{ss} of doxycycline

Abbreviations: BID = twice daily, F = female, M = male, PK = pharmacokinetics, QD = once daily
 Source: Sponsor's NDA submission, module 2, volume 1.1, p. 232.

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Table 3: Description of Phase 3 Clinical Efficacy and Safety Studies of Oracea™

Study ID	No. of Centers	Design, Type of Control	Study Drugs & Treatment Duration	Study Objective	No. Patients Entered/ Completed by Group	Gender Median Age (Range) by Group	Diagnosis Inclusion Criteria	Primary Endpoint
COL-101-ROSE-301	14	Randomized, double-blind, parallel Placebo	Oracea™ 40 mg or Placebo QD for 16 weeks	Efficacy & safety	Oracea™: 127/101 Placebo: 124/103	Oracea™: 36 M 91 F 46 years (22 to 90) Placebo: 29 M 95 F 47 years (19 to 84)	Rosacea defined as 10 to 40 papules + pustules, ≤ 2 nodules, and IGA score of 2 to 4; moderate to severe erythema (≥ one area-specific score ≥ 2 and total score of 5 to 20 on CEA scale; telangiectasia	Change in total inflammatory lesion count (papules + pustules + nodules) from baseline to Week 16
COL-101-ROSE-302	14	Same as for 301	Same as for 301	Same as for 301	Oracea™: 142/115/84 ^a Placebo: 144/118/76 ^a	Oracea™: 48 M 94 F 46 years (20 to 80) Placebo: 49 M 95 F 47 years (19 to 82)	Same as for 301	Same as for 301

Abbreviations: CEA = Clinician's Erythema Assessment, F = female, IGA = Investigator's Global Assessment, M = male, QD = once daily.

^a Number enrolled in follow-up period.

Source: Sponsor's NDA submission, module 2, volume 1.1, p. 206.

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4.3 Review Strategy

The pivotal Phase 3 trials, COL-101-ROSE-301 (study 301) and COL-101-ROSE (study 302), were reviewed in detail with regard to both efficacy and safety. All of the studies including the four clinical pharmacodynamic studies (PERIO-DOXYSR-103, PERIO-DOXYSR-104, COL-101SDPK-105, COL-101-SSPK-106) were reviewed with regard to safety. The bulk of drug exposure, however, occurred in the Phase 3 studies, 301 and 302. The integrated safety analysis focuses on data from these studies.

4.4 Data Quality and Integrity

Review of the pivotal trial data by the biostatistician reviewer revealed a site, center # 200 in study 302 that had success rates somewhat higher, overall, than at other sites. The site name and address are Jorge L. Sanchez, MD, University of Puerto Rico, School of Medicine, P.O. Box 365067 San Juan, PR 00936-5067. A DSI consult with a request for clinical inspection was issued October 19, 2005. The report of the clinical inspection was signed May 17, 2006 by Roy Blay, Ph.D. The conclusion was as follows: "The inspection of Dr. Sanchez did not identify any significant observations that would adversely affect data acceptability. Overall, the data appear acceptable in support of the respective indication."

4.5 Compliance with Good Clinical Practices

The sponsor states that the studies were conducted in accordance with the ethical principles as described in the Declaration of Helsinki and with the standards of good clinical practice (GCP). The standards of Good Clinical Practice (GCP) include sections of U.S. Title 21 CFR governing the Protection of Human Subjects (21 CFR 50), Financial Disclosure by Clinical Investigators (21 CFR 54), Institutional Review Boards (21 CFR 56), Investigational New Drug Applications (21 CFR 312), and Applications for Food and Drug Administration Approval to Market a New Drug (21 CFR 314). Also included in GCP are International Conference on Harmonization (ICH) Guidelines. The sponsor also stated that informed consent was obtained from all patients in each of the six studies prior to any study procedures being performed.

4.6 Financial Disclosures

The sponsor has provided Forms FDA 3454, one covering the 14 clinical investigators in study COL-101-ROSE-301 and the other covering 13 of the 14 clinical investigators in study COL-101-ROSE-302. The sponsor certifies that these investigators did not have financial arrangements with the sponsor that would compromise the integrity of data submitted for NDA review. For the _____ the sponsor has provided form 3455 with financial disclosure information since that investigator has received payments of more than \$25,000 from the sponsor. The sponsor states that in order to minimize bias in study 302 it had been designed as a double-blinded, placebo controlled trial. Therefore neither the principal investigator nor study participants knew whether the

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administration of study medication was active or placebo. In addition this principal investigator only enrolled a total of 3 patients.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The pharmacokinetics of doxycycline following administration of single or multiple doses of Oracea™ 40 mg was evaluated in four studies. These were open-label, randomized cross-over studies performed in healthy male and female volunteers.

1. Study PERIO-DOXYSR-103 compared bioavailability after Oracea™, Periostat® 20 mg BID, and Periostat® 40 mg QD.
2. Study PERIO-DOXYSR-104 compared bioavailability on Days 1 and 7 between Oracea™ and Periostat® 20 mg BID.
3. Study COL-101-SDPK-105 evaluated the effect of food on bioavailability after Oracea™.
4. Study COL-101-SSPK-106 compared PK and bioequivalence between Oracea™ and Periostat™ 20 mg BID (fasted).

Single Dose Pharmacokinetics:

Studies 103, 104, and 105 showed comparable pharmacokinetics of doxycycline following single dose administration of Oracea™ as indicated by rate (C_{max}) and extent (AUC 0-24 or AUC 0-72) of absorption. The median T_{max} of doxycycline ranged from about 1 to 4 hours.

However, as compared with Periostat® BID, Oracea™ showed a higher rate and extent of absorption of doxycycline following single dose administration.

After a single dose of Oracea™ 40 mg capsules, the mean (SD) half life of doxycycline in healthy volunteers in studies 103 and 105 was respectively 15.1(5.49) and 21.2 (7.64) hours.

The effect of food on pharmacokinetics of a single dose of Oracea™ 40 mg capsules was studied in 30 healthy volunteers in study 105. This involved administration of Oracea™ in conjunction with a 1000 calorie, high-fat, high-protein meal that included dairy products and resulted in a decrease in the rate and extent of absorption (C_{max} and AUC) by about 45% and 22%, respectively compared to dosing under fasted conditions. There was a delay of about one hour for the mean T_{max} in the fed state compared with the fasted state. Because this decrease in systemic exposure can be clinically significant proposed labeling should recommend that if Oracea™ is taken close to meal times, it be taken at least one hour prior to or two hours after meals.

Multiple Dose Pharmacokinetics:

Studies 104 and 106 showed comparable pharmacokinetics of doxycycline following multiple dose administration of Oracea™ as indicated by rate (C_{max}) and extent (AUC 0-24 or AUC 0-

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72) of absorption. The median Tmax of doxycycline ranged from 0.5 to 4 hours and was comparable to that obtained following a single dose.

As compared in study 106 with Periostat® BID, Oracea™ was found to be equivalent in rate and extent of absorption following multiple dose administration for 7 days.

After multiple dosing for 7 days of Oracea™ 40 mg capsules, the mean (SD) half life of doxycycline in healthy volunteers was 23.2 (6.2) hours. This finding from study 106 is comparable to that following single dosing.

Distribution:

Doxycycline is greater than 90% bound to plasma proteins. This is the same as Periostat® product labeling and is based on published data summarized in NDA 50,744.

Metabolism:

No additional studies have been performed addressing metabolism. Major metabolites of doxycycline have not been identified as stated in approved Periostat® labeling (class labeling). However, enzyme inducers such as barbiturates, carbamazepine, and phenytoin decrease the half-life of doxycycline.

Excretion:

Doxycycline is excreted in the urine and feces as unchanged drug. In one study, reported by the sponsor, bioassay and reverse isotope dilution methods were used to analyze the recovery and form of metabolized doxycycline in the urine, feces, and bile. Approximately 25% of the radioactivity was recovered from urine and 75% from feces. Ninety percent of the original dose was recovered as undegraded doxycycline. In an another study it is reported that between 29% and 55.4% of an administered doxycycline dose can be accounted for in the urine 72 hours after dosing.

Gender:

In study 105, the pharmacokinetics of doxycycline following a single dose of Oracea™ were compared in 16 males and 14 females under fed and fasted conditions. While female subjects had a higher rate (Cmax) and (AUC) than male subjects, these differences were thought to be due to differences in body weight/lean body mass.

Gastric Insufficiency:

The sponsor reported an open-label crossover study in 24 healthy volunteer showing that the bioavailability of doxycycline monohydrate was reduced at high pH. The authors observed that in patients with high gastric pH this decreased absorption of doxycycline monohydrate may well have a clinical impact. The reduced bioavailability may be clinically significant in patients with gastrectomy, gastric bypass surgery, or who are otherwise deemed achlorhydric (e.g. due to frequent use of H2-blockers, proton pump inhibitors and antacids, as well as to physiologic achlorhydria.)

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Drug-Drug Interactions:

The proposed labeling for Oracea™ will follow that of tetracycline class antibiotics. The applicant included wording from the Periostat® label as well as a reference to proton pump inhibitors (bolded italics below). The latter was added based on the published study described under gastric insufficiency. See also Clinical Pharmacology and Biopharmaceutics review.

1. Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.
2. Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline-class drugs in conjunction with penicillin.
3. The concurrent use of tetracycline and methoxyflurane has been reported to result in fatal renal toxicity.
4. Absorption of tetracyclines is impaired by bismuth subsalicylate, proton pump inhibitors, antacids containing aluminum, calcium or magnesium and iron-containing preparations.
5. Doxycycline may interfere with the effectiveness of low dose oral contraceptives. To avoid contraceptive failure, females are advised to use a second form of contraceptive during treatment with doxycycline.
6. There have been reports of pseudotumor cerebri (benign intracranial hypertension) associated with the concomitant use of isotretinoin and tetracyclines. Since both oral retinoids, including isotretinoin and acitretin, and the tetracyclines, primarily minocycline, can cause increased intracranial pressure, the concurrent use of an oral retinoid and a tetracycline should be avoided.

5.2 Pharmacodynamics

The sponsor did not conduct pharmacodynamic studies for this application. A section of the proposed labeling follows.

MICROBIOLOGY

Doxycycline is a member of the tetracycline class of antibacterial drugs. The plasma concentrations of doxycycline achieved with TRADENAME during administration (see CLINICAL PHARMACOLOGY AND DOSAGE AND ADMINISTRATION) are less than the concentration required to treat bacterial diseases. *In vivo* microbiological studies utilizing a similar drug exposure for up to 18 months demonstrated no detectable long-term effects on bacterial flora of the oral cavity, skin, intestinal tract, and vagina.

TRADENAME should not be used for treating bacterial infections, providing antibacterial prophylaxis, or reducing the numbers or eliminating microorganisms associated with any bacterial disease.

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5.3 Exposure-Response Relationships

The sponsor did not conduct dose-response studies for this application.

At the systemic concentrations provided by Oracea™ doxycycline is not effective as an antimicrobial agent and, according to the sponsor, appears to exert its beneficial actions on inflammatory lesions of rosacea by mechanisms independent of antimicrobial activity. The sponsor states that inflammatory lesions of rosacea are thought to be products of a neutrophil mediated process. Activation of neutrophils is associated with several soluble mediators, including reactive oxygen species, interleukin-6 (IL-6), phospholipase A2, and nitric oxide. Doxycycline inhibits these mediators, down-regulating the pro-inflammatory response. The sponsor has not provided studies with the current application to support this proposed mechanism of action.

CollaGenex Pharmaceuticals, Inc previously developed an approved drug, Periostat®(doxycycline hyclate tablets) 20mg (NDA 50-783), for use twice daily as an adjunct to scaling and root planning to promote attachment level gain and to reduce pocket depth in patients with adult periodontitis. The goal of formulation development of Oracea™ was to achieve bioequivalence to Periostat® in terms of area under the concentration-by-time curve (AUC) while keeping the maximum plasma level (Cmax) below 1.0 µg/mL so as not to exceed the threshold for antimicrobial activity in vitro. The sponsor states this antimicrobial threshold was defined based on previous experience with the approved drug Periostat®. The sponsor proposes that a beneficial effect of this low concentration is reducing the risk of developing resistant microorganisms.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Rosacea is a common chronic skin disease of adults. An expert committee has stated that the diagnosis of rosacea requires the presence of one or more of the following signs and with a central facial distribution; flushing (transient erythema), nontransient erythema, papules and pustules, and telangiectasia.¹ With the exception of ocular rosacea this disorder does not present a serious threat to health although it can be disfiguring. Rosacea is common in the third and fourth decades of life and peaks between the ages of 40 and 50. Rosacea can occur in all skin types but is most common in fair-skinned individuals and is more common in women than men.² The cause of rosacea is still uncertain. Factors implicated in its pathogenesis include vasculature, climatic exposures, matrix degeneration, chemicals and ingested agents,

¹ Wilkin J, Dahl M, Detmar M, et al. Standard classification of rosacea: report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. *J Am Acad Dermatol* 2002; 46:584-7.

² Freedberg IM, Eisen, AZ, Wolf K, et al. *Fitzpatrick's Dermatology in General Medicine*, 5th Ed. © 1999, McGraw - Hill, New York, p 785.

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pilosebaceous unit abnormalities, and microbial organisms. Of these the most common theories center about abnormalities in cutaneous vascular homeostasis.¹

The disease has a variety of clinical manifestations with variable degrees of severity and has been grouped into subtypes including erythematotelangiectatic (vascular), papulopustular, phymatous (sebaceous), and ocular rosacea.² For the purposes of this application, the most germane subtypes are the erythematotelangiectatic and the papulopustular. The erythematotelangiectatic type is characterized by prolonged flushing with most intense color occurring in the central face. This form is often triggered by external stimuli and often accompanied by burning and stinging. Affected patients exhibit a lower threshold for irritation from topically applied substances. The papulopustular type is characterized by a marked red central portion of the face and accompanied by persistent inflammatory papules and pustules. Affected patients often have a history of flushing but it is milder than that experienced by patients with the erythematotelangiectatic type.¹

The sponsor's proposed indication is to _____
This has been since modified to treatment of only the inflammatory lesions (papules and pustules) of rosacea in adult patients.

6.1.1 Methods

The efficacy evaluation of Oracea™ Capsules will focus upon a detailed review of pivotal trials COL-101-ROSE-301 (study 301) and COL-101-ROSE-302 (study 302).

6.1.2 General Discussion of Endpoints

The stated objective, from study report text, of studies 301 and 302 was, "...to evaluate the safety and efficacy of COL-301 (doxycycline _____ capsules) 40 mg administered once daily for the treatment of rosacea compared with a placebo..."³ In the Summary of Clinical Efficacy this has been modified as follows, "...for _____, inflammatory lesions in patients with rosacea..."⁴

Thus the primary efficacy parameter, as used by the sponsor, was the change in total inflammatory lesion count from baseline to endpoint (Week 16). Total inflammatory lesion count was the sum of the papule count, the pustule count, and the nodule count.

Commonly employed endpoints found in applications for rosacea include percent reduction in inflammatory lesion counts and the percentage of patients reaching "clear" or "almost clear" in

¹ Crawford GH, Pelle MT, and James WD. Rosacea: I. Etiology, pathogenesis, and subtype classification. J Am Acad Dermatol 2004; 51(3):327-41.

² Crawford GH, Pelle MT, and James WD. Rosacea: I. Etiology, pathogenesis, and subtype classification. J Am Acad Dermatol 2004; 51(3):327-41.

³ Sponsor's NDA submission 50 – 805, module 5, vol. 1.9, p. 12 and vol. 1.32, p. 13.

⁴ Sponsor's NDA submission 50 – 805, module 2, vol. 1.1, p. 199.

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the static Investigator Global Assessment (IGA) at the end of the study. To be successful statistically significant efficacy should be demonstrated in the IGA as well as in lesion counts. The IGA should also include clinical descriptors such as papules, nodules, slight pinkness, fiery redness, and telangiectasia

6.1.3 Study Design

Pivotal Studies (COL-101-ROSE-301 and COL-101-ROSE-302):

Both Phase 3 safety and efficacy studies were identical in design except that COL-101-ROSE 302 (study 302) had a 4 week extension without treatment in order to assess longevity of treatment.

Pivotal Phase 3 Studies: Protocol Number COL-101-ROSE-301
 Protocol Number COL-101-ROSE-302

Title: “A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Clinical Trial to Determine the Effects of 40mg Doxycycline Monohydrate Modified Release Capsules (COL-101) Administered Once Daily Versus a Placebo Control Administered Once Daily for the Treatment of Rosacea”

Investigators (Study 301):

		Patients Randomized
Edward N. Kitces, MD, Richmond, VA	(center 0100)	3
Jorge L. Sanchez, MD, San Juan, Puerto Rico	(center 0200)	24
Hector Wiltz, MD, Miami, FL	(center 0300)	32
William Abramovits, MD, Dallas, TX	(center 0400)	13
Dennis Michael Hull, MD, Mt. Pleasant, SC	(center 0500)	23
T. Joseph Raoof, MD, Encino, CA	(center 0600)	24
Phoebe Rich, MD, Portland, OR	(center 0700)	30
Frank E. Schiavone, MD, Jacksonville, FL	(center 0800)	16
Marta I. Rendon, MD, Boca Raton, FL	(center 0900)	22
Daniel Fuller Smith, MD, Little Rock, AK	(center 1000)	19
Craig F. Teller, MD, Bellaire, TX	(center 1100)	22
John M. Humeniuk, MD, Greer, SC	(center 1200)	16
Robert Weiss, MD, Hunt Valley, MD	(center 1300)	4
J. John Goodman, MD, West Palm Beach, FL	(center 1400)	3

Investigators (Study 302):

		Patients Randomized
Robert W. Martin III, MD, Lafayette, IN	(center 0100)	46
Leonard J. Swinyer, MD, Salt Lake City, UT	(center 0200)	9

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Michael H. Gold, MD, Nashville, TN	(center 0300)	23
Peter A. Copperrider, MD, Kirkland, WA	(center 0400)	1
Mitchel P. Goldman, MD, La Jolla, CA	(center 0500)	19
Richard E. White, MD, Rock Hill, SC	(center 0600)	30
Helen M. Torok, MD, Medina, OH	(center 0700)	24
J. Mark Jackson, MD, Louisville, KY	(center 0800)	33
Robert A. Skrokov, MD, Bay Shore, NY	(center 0900)	14
James E. Turner, MD, Bartlett, TN	(center 1000)	14
Harry Sharata, MD, Madison, WI	(center 1100)	24
Frank Dunlap, MD, Tucson, AZ	(center 1200)	16
James Q. Del Rosso, DO, Las Vegas, NV	(center 1300)	3
Jo Lynne Herzog, MD, Birmingham, AL	(center 1400)	30

Objective: To evaluate the safety and efficacy of doxycycline monohydrate modified release capsules for the treatment of rosacea compared with a placebo. Of note, the final study report text read as follows...”for reducing inflammatory lesions in patients with rosacea.”¹

Institutional Review Board (for all investigators):

Independent Institutional Review Board, Inc.
6738 West Sunrise Blvd., Suite 102
Plantation, FL 33313
Chairman: Kim Lerner

Study Designs (301 and 302): These studies were outpatient, 14 center, randomized, double-blind, placebo-controlled, parallel-group trials.

Protocols:

Inclusion Criteria:

- 1) Healthy, post-pubescent males and females ≥ 18 years of age with rosacea, which was defined as 10 to 40 papules and pustules and ≤ 2 nodules plus a score of 2 to 4 on the Investigator’s Global Assessment (IGA, defined in Section 2.7.3.1.3)
- 2) Presence of moderate to severe erythema, defined as at least one area-specific score of ≥ 2 and a total score of 5 to 20 on the Clinician’s Erythema Assessment (CEA) scale (defined in Section 2.7.3.1.3)
- 3) Presence of telangiectasia
- 4) Female patients must have used one of the following methods of birth control throughout the study: intrauterine device (IUD); diaphragm with spermicide; condom with spermicide; oral, implantable, transdermal, or injectable contraceptive. If the patient was using an oral contraceptive, the patient must have used an additional barrier form of contraception. Patients could also participate if they were surgically sterilized, menopausal for a minimum of two years,

¹ Sponsor’s NDA submission 50 - 805, module 2, vol. 1.1, p. 199.

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in a monogamous relationship with a sterile partner, or signed an agreement stating that they would abstain from sexual intercourse during the course of the study.

- 5) Patients must have signed an informed consent form.
- 6) Female patients must have had a negative pregnancy test and have been non-lactating.

Exclusion Criteria:

- 1) Initiation of a hormonal method of contraception within 4 months of baseline, discontinuation during the course of study, or change in the product within 4 months of baseline or during the study
- 2) Use of topical acne treatments within 4 weeks of baseline
- 3) Use of systemic retinoids within 90 days of baseline
- 4) Use of topical or systemic antibiotics within 4 weeks of baseline
- 5) Use of an investigational drug with 90 days of baseline (for investigational topical or inhaled drugs the restriction was 4 weeks)
- 6) Pregnant women or women of childbearing potential who were not using an adequate form of birth control as described in the inclusion criteria;
- 7) Nursing women
- 8) Patients with a known hypersensitivity to tetracyclines
- 9) Patients on clinically significant concomitant drug therapy (see below);
- 10) Use of any acne treatment during the course of the study
- 11) Long-term use (> 14 days) of topical or systemic anti-inflammatories in the 4 weeks prior to baseline and during the study. Chronic use of aspirin at sub-analgesic doses (\leq 325 mg once daily) was acceptable for patients requiring platelet aggregation inhibition.
- 12) Use of topical or systemic corticosteroids 4 weeks prior to baseline and during the study;
- 13) Use of vasodilating agents 6 weeks prior to baseline or during the study.
- 14) Use of α -adrenergic receptor-blocking agents 6 weeks prior to baseline and during the study;
- 15) Patients with ocular rosacea and/or blepharitis/meibomianitis who required treatment by an ophthalmologist
- 16) Patients who had had surgeries that bypassed or excluded the duodenum
- 17) Patients who had been determined to be achlorhydric

Concomitant Medications:

The following medications were prohibited during the studies:

- 1) Chronic use (> 14 days) of sulfa drugs, erythromycin, cephalosporins, and quinolones;
- 2) Use of tetracycline antibiotics;
- 3) Use of any acne treatment during the course of the study, including spironolactone;
- 4) Chronic use (> 14 days) of nonsteroidal anti-inflammatory drugs (NSAIDs). Chronic use of aspirin at sub-analgesic doses (\leq 325 mg once daily) was allowed for patients requiring platelet aggregation inhibition;
- 5) Use of anti-microbial soaps;
- 6) Use of penicillin antibiotics (because the bacteriostatic action of doxycycline might have interfered with the bactericidal action of penicillin);
- 7) Use of sunscreens was to be recorded as a concomitant medication; and
- 8) Use of niacin at a dose of 500 mg or more per day.

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9) In addition, antacids and vitamins containing aluminum, calcium, or magnesium were allowed only if taken at least 1.5 hours before or 3.0 hours after the patient took the study medication. If taken sooner after the study medication, these agents might have impaired drug absorption.

Withdrawal Criteria:

- Protocol violation
- Patient request to withdraw
- Pregnancy
- A change in a patient's condition after entering the study, such that he/she no longer met inclusion or exclusion criteria
- Any patient who required use of an unacceptable concomitant medication
- In the Investigator's opinion, it was not in the patient's best interest to continue.

Blinding:

The investigators and patients were blinded to study medication. The active and placebo capsules were identical in size, shape and color. In addition, all employees of the sponsor and its affiliates who were involved data monitoring, data entry, or data analysis were blinded as well.

Study Procedures:

A complete medical history, lesion count (papules, pustules, and nodules), IGA (Investigator's Global Scale – see following), CEA Clinician's Erythema Assessment Scale – see following), and laboratory screening were performed by the Investigator for all patients entering the study. A series of full-face photographs was taken at the Baseline visit. Patients were randomized in a 1:1 ratio to Oracea™ 40 mg capsule or placebo following baseline evaluations. Patients were instructed to take one capsule orally each morning.

Patients returned to the clinic for evaluations at Weeks 3, 6, 12, 16 and 20 post-Baseline (20 - Study 302 only). At each visit, patients were evaluated for number and types of lesions, concomitant medication usage, AEs (adverse events), vital signs, height and weight. The IGA and CEA scale were performed at each visit. The results were recorded on the case report form (CRF). Female patients of childbearing potential were given a urine pregnancy test at Baseline and at the Week 16 visit. A series of full-face photographs was taken at baseline and at the Week 16 or exit visit.

Study 302 only: Treatment was completed at Week 16 and patients returned at Week 20 for follow-up clinical and safety evaluations. For the period between the Week 16 and Week 20 visits, patients were to refrain from taking the study drug or any systemic or topical rosacea or acne medication or any prohibited concomitant medication.

Patients were dispensed 100 capsules of study medication at Baseline and at Week 12. To determine drug accountability and compliance, patients returned the unused study medication at the Week 12 and Week 16 visits.

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Patients were cautioned about exposure to sunlight and were encouraged to apply sunscreen with a sun protection factor (SPF) value of at least 30, providing protection against both UVA and UVB light, whenever they went outdoors during daylight hours. Patients were to report any adverse events, including phototoxicity.

Table 4: Schedule of Efficacy and Safety Evaluations

Trial Period	Screening	Double-Blind				Follow-up
	Baseline Day 0	Week 3 Day 21 (±3 days)	Week 6 Day 42 (±3 days)	Week 12 Day 84 (±5 days)	Week 16a Day 112 (±5 days)	Study 302 only Week 20
Signed Informed Consent	X					X
Medical History	X					
Recorded Concomitant Medications	X	X	X	X	X	X
Clinical Laboratory Evaluation	X				X	
Full Face Photographs	X				X	
Vital Signs, Height, and Weight	X	X	X	X	X	X
Lesion Score, Investigator's Assessments (IGA/CEA)	X	X	X	X	X	X
Drug Dispensation	X			X		
Drug Accountability				X	X	
Recorded Adverse Events	X	X	X	X	X	X

^a Performed at the exit visit for patients who did not complete the study.

Source: Sponsor's NDA submission module 5, volume 1.32, pp. 20.

Efficacy Endpoints:

Primary Efficacy Parameter:

The primary efficacy parameter was the change in total inflammatory lesion count from baseline to endpoint (Week 16). Total inflammatory lesion count was the sum of the papule count, the pustule count, and the nodule count.

The Sponsor identified lesion count as the sole primary efficacy endpoint based on the proposed indication for Oracea™

Secondary Efficacy Parameters:

- 1) Change in the IGA score from baseline to endpoint (Week 16)

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- 2) Treatment responders at endpoint (Week 16), where response is defined as an IGA score of 0 (clear) or 1 (Near Clear), as well as a more restrictive definition of response as an IGA score of 0 (clear).
- 3) Change in CEA scale score from baseline to endpoint (Week 16)
- 4) Change in total inflammatory lesion count (papules + pustules + nodules) from baseline to Week 12.

Exploratory Analysis Parameters:

- 1) Change from baseline in total inflammatory lesion count at Weeks 3, 6, and 12.
- 2) Change in individual lesion counts (papules, pustules, and nodules) at Weeks 3, 6, 12, and 16.
- 3) Change from baseline in IGA score at Weeks 3, 6, and 12.
- 4) Change from baseline in CEA score at Weeks 3, 6, and 12.

Other Exploratory Parameters (Longevity of Treatment – Study 302 only):

The following parameters were exploratory to evaluate the maintenance of response of doxycycline : _____ 40 mg daily at 4 weeks after the end of treatment.

- 1) Change in total inflammatory lesion count from Week 16 to Week 20
- 2) Change in the CEA scale Score from Week 16 to Week 20
- 3) Change in the IGA score from Week 16 to Week 20

Table 5: Investigator’s Global Assessment (IGA)

Score/Grade	Definition	Guideline
(0) Clear	No signs or symptoms present	Skin is completely clear of inflammatory lesions
(1) Near Clear	One or two papules	1 or 2 small, non-inflammatory papules
(2) Mild	Some papules/pustules	3 to 10 papules/pustules
(3) Moderate	Moderate number of papules/pustules	11 to 19 papules/pustules
(4) Severe	Numerous papules/pustules; nodules	≥20 papules/pustules and nodules

Source: Sponsor’s NDA submission, module 2, vol. 1.1, p. 202.

Table 6: Clinician’s Erythema Assessment Scale (CEA)

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

Source: Sponsor’s NDA submission, module 2, vol. 1.1, p. 203.

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The CEA scale score was calculated as the sum of the erythema scores for the forehead, chin, nose, right cheek, and left cheek.

Safety Evaluations:

Safety evaluations assessed throughout the study included AEs, concomitant medication use, laboratory evaluations (hematology and chemistry evaluations, double-blind period only), and vital signs including weight. Due to reports of photosensitivity with doxycycline at higher, antimicrobial doses, the CEA scale was also used to determine that patients' erythema did not worsen during the course of treatment.

6.1.4 Efficacy Findings

Across both studies, 301 and 302, a total of 537 patients from 28 different investigative sites were enrolled and randomized to receive treatment with Oracea™ or placebo.

Table 7: Disposition of Study Subjects

Disposition	Study 301		Study 302		Combined Studies	
	Oracea™	Placebo	Oracea™	Placebo	Oracea™	Placebo
Number randomized	127	124	142	144	269	268
Number completed, n (%)	101 (79.5%)	103 (83.1%)	115 (81.0%)	118 (81.9%)	216 (80.3%)	221 (82.5%)
Number discontinued, n (%)	26 (20.5%)	21 (16.9%)	27 (19.0%)	26 (18.1%)	53 (19.7%)	47 (17.5%)
Reason discontinued, n (%)						
Treatment-emergent adverse event						
Illness not related to drug	10 (7.9%)	4 (3.2%)	9 (6.3%)	7 (4.9%)	19 (7.1%)	11 (4.1%)
Uncooperative	1 (0.8%)	1 (0.8%)	1 (0.7%)	0 (0.0%)	2 (0.7%)	1 (0.4%)
Protocol violation	5 (3.9%)	4 (3.2%)	2 (1.4%)	1 (0.7%)	7 (2.6%)	5 (1.9%)
Lost to follow-up	2 (1.6%)	2 (1.6%)	4 (2.8%)	5 (3.5%)	6 (2.2%)	7 (2.6%)
Treatment failure	4 (3.1%)	2 (1.6%)	5 (3.5%)	5 (3.5%)	9 (3.3%)	7 (2.6%)
Death	2 (1.6%)	2 (1.6%)	1 (0.7%)	4 (2.8%)	3 (1.1%)	6 (2.2%)
Other	0	0	0	0	0	0
	2 (1.6%)	6 (4.8%)	5 (3.5%)	4 (2.8%)	7 (2.6%)	10 (3.7%)

Source: Table 1.3 (Module 5: 301 – vol 1.9, p 72; 302 – vol 1.32, p 81; combined – vol 1.56, p 1)

Source: Sponsor's NDA submission, module 2, volume 1.1, p. 208.

In total, 269 patients were randomized to receive Oracea™ of whom 80.3% completed the study. A total of 268 patients were randomized to placebo of whom 82.5% completed the study. Patients discontinuing the study early included 19.7% in the Oracea™ group and 17.5% in the placebo group. The most frequent reason for early discontinuation was treatment-emergent adverse events, with a higher percentage reported in the Oracea™ (7.1%) than in the placebo group (4.1%). The next most frequent reason for early discontinuation was "other", with the

most commonly reported “other” reason being the patient withdrew consent or voluntarily withdrew from the study (12 patients).

Patient demographics are summarized in the following table.

Table 8: Patient Demographics (ITT Population)

Characteristic	Study 301		Study 302		Combined Studies	
	Oracea™ (n = 127)	Placebo (n = 124)	Oracea™ (n = 142)	Placebo (n = 144)	Oracea™ (n = 269)	Placebo (n = 268)
Age, years						
Mean (SD)	46.8 (13.17)	47.6 (11.50)	46.3 (12.66)	47.6 (13.34)	46.5 (12.88)	47.6 (12.50)
Median (range)	46.0 (22-90)	47.0 (19-84)	46.0 (20-80)	47.0 (19-82)	46.0 (20-90)	47.0 (19-84)
Age group, n (%)						
18 to 35 years	26 (20.5%)	16 (12.9%)	30 (21.1%)	27 (18.8%)	56 (20.8%)	43 (16.0%)
36 to 50 years	58 (45.7%)	60 (48.4%)	64 (45.1%)	57 (39.6%)	122 (45.4%)	117 (43.7%)
51 to 70 years	35 (27.6%)	44 (35.5%)	43 (30.3%)	52 (36.1%)	78 (29.0%)	96 (35.8%)
> 70 years	8 (6.3%)	4 (3.2%)	5 (3.5%)	8 (5.6%)	13 (4.8%)	12 (4.5%)
Gender, n (%)						
Male	36 (28.3%)	29 (23.4%)	48 (33.8%)	49 (34.0%)	84 (31.2%)	78 (29.1%)
Female	91 (71.7%)	95 (76.6%)	94 (66.2%)	95 (66.0%)	185 (68.8%)	190 (70.9%)
Race, n (%)						
Caucasian	108 (85.0%)	107 (86.3%)	135 (95.1%)	141 (97.9%)	243 (90.3%)	248 (92.5%)
Black	0	0	2 (1.4%)	0	2 (0.7%)	0
Asian	1 (0.8%)	0	1 (0.7%)	1 (0.7%)	2 (0.7%)	1 (0.4%)
Other ^a	18 (14.2%)	17 (13.7%)	4 (2.8%)	2 (1.4%)	22 (8.2%)	19 (7.1%)
Source: Table 2.1 (Module 5: 301 – vol 1.9, p 73; 302 – vol 1.32, p 83; combined – vol 1.56, p 2) a 301 Oracea™: 17 Hispanic, 1 Native American; 301 placebo: 15 Hispanic, 1 Spanish, 1 Latin 302 Oracea™: 2 Hispanic, 2 Native American; 302 placebo: 2 Hispanic						

Source: Sponsor’s NDA submission module 2, volume 1.1, Table 2.7.3-4, p. 209.

Reviewer comment: Within the phase 3 studies, treatment groups are similar with regard to age, sex, and race. Comparing study 301 with 302, demographic characteristics were similar. The age, sex and racial distribution reflect that of the disease.^{1,2}

¹ Freedberg IM, Eisen, AZ, Wolf K, et al. Fitzpatrick’s Dermatology in General Medicine, 5th Ed. © 1999, McGraw - Hill, New York, p 785.

² Powell FC. Rosacea. N Engl J Med. 2005; 352(8):793-803.

Baseline disease severity is outlined in the following table.

Table 9: Disease Characteristics at Baseline (ITT Population)

Characteristic	Study 301		Study 302		Combined Studies	
	Oracea™ (n = 127)	Placebo (n = 124)	Oracea™ (n = 142)	Placebo (n = 144)	Oracea™ (n = 269)	Placebo (n = 268)
Papule Count, n Mean (SD) Median (range) p-value ^a	15.2 (7.91) 13.0 (0-39)	16.4 (9.24) 15.0 (0-50)	17.4 (10.82) 15.0 (1-97)	17.8 (10.85) 16.0 (0-97)	16.3 (9.60) 14.0 (0-97)	17.1 (10.14) 15.0 (0-97)
	0.2674		0.7605		0.3552	
Pustule Count, n Mean (SD) Median (range) p-value ^a	4.1 (5.21) 2.0 (0-23)	3.7 (4.73) 2.0(0-22)	3.0 (4.52) 1.0 (0-27)	3.3 (6.00) 1.0 (0-47)	3.5 (4.88) 3.5 (5.45)	2.0 (0-27) 1.0 (0-47)
	0.5499		0.5955		0.9901	
Nodule Count, n Mean (SD) Median (range) p-value ^a	0.2 (0.57) 0.0 (0-2)	0.2 (0.49) 0.0 (0-2)	0.1 (0.47) 0.0 (0-4)	0.1 (0.47) 0.0 (0-3)	0.2 (0.52) 0.0(0-4)	0.2 (0.48) 0.0 (0-3)
	0.5303		0.7293		0.8081	
Total Infl. Lesions, n Mean (SD) Median (range) p-value ^a	19.5 (8.78) 17.0 (10-39)	20.3 (10.37) 17.0 (10-63)	20.5 (11.68) 17 (10-105)	21.2 (12.51) 18 (10-100)	20.0 (10.40) 17 (10-105)	20.8 (11.56) 17.5 (10-100)
	0.5165		0.6038		0.4160	
Investigator's Global Assessment (IGA), n (%) 0 – Clear 1 – Near Clear 2 – Mild 3 – Moderate 4 – Severe p-value ^a	0 0 8 (6.3%) 67 (52.8%) 52 (40.9%)	0 0 10 (8.1%) 65 (52.4%) 49 (39.5%)	0 0 17 (12.0%) 77 (54.2%) 48 (33.8%)	0 0 7 (4.9%) 80 (55.6%) 57 (39.6%)	0 0 25 (9.3%) 144 (53.5%) 100 (37.2%)	0 0 17 (6.3%) 145 (54.1%) 106 (39.6%)
	0.6759		0.0740		0.3097	
Clinician's Erythema Assessment (CEA) Total Score Mean (SD) Median (range) p-value ^a	9.7 (2.97) 9.0 (5-19)	9.5 (2.72) 9.0 (5-19)	9.5 (2.89) 9.0 (4-18)	9.1 (2.47) 9.0 (4-16)	9.6 (2.92) 9.0 (4-19)	9.3 (2.59) 9.0 (4-19)
	0.5777		0.2380		0.2141	

Source: Table 3.1 (Module 5: 301 – vol 1.9, p 75; 302 – vol 1.32, p 85; combined – vol 1.56, p 4)
 a P-values for testing the difference between treatment groups were calculated using the Cochran-Mantel-Haenszel test for discrete variables and a two-sample Students t-test for continuous variables.

Source: Sponsor's NDA submission, module 5, volume 1.1, p. 210.

Clinical findings at baseline were similar in studies 301 and 302 and between treatment groups as measured by the sponsor's chosen measures of number of papules, pustules, or nodules, total inflammatory lesion count, IGA score, and CEA score.

Reviewer's comments: Of note, the Placebo group in both studies 301 and 302 starts off with a slightly higher mean inflammatory lesion count. This has been noted by the statistician, Steven Thompson. He has stated that; "This is possibly an artifact of randomization, and differences

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remain statistically significant (in the ANOVA) even when one includes the baseline value as a covariate.” (Statistical Review, NDA 50-805, p. 16.)

The patient population that was excluded from the ITT population to produce the Per-Protocol population was similar for both studies 301 and 302. The nature of the protocol violations leading to patient exclusion was similar between studies 301 and 302 as well as between the Oracea™ (COL-101) and placebo treatment groups. See following tables.

Table 10: Patients Excluded from the Per-Protocol Analysis (Study 301)

Protocol Violation	COL-101 (N = 127) n (%)	Placebo (N = 124) n (%)	Total (N = 251) n (%)
Number of Patients Excluded from the Per-Protocol Analysis	30 (23.6%)	25 (20.2%)	55 (21.9%)
Compliance <80%	23 (18.1%)	14 (11.3%)	37 (14.7%)
Baseline Papules + Pustules <10 or >40	0	3 (2.4%)	3 (1.2%)
Clinically Significant Concomitant Medication Therapy	1 (0.8%)	0	1 (0.4%)
Use of Topical/Systemic Antibiotics Within 4 Weeks of Baseline	0	1 (0.8%)	1 (0.4%)
Use of Acne Treatment During Study	1 (0.8%)	0	1 (0.4%)
Use of Topical/Systemic Steroids 4 Weeks Prior to Baseline or During Study	0	2 (1.6%)	2 (0.8%)
Chronic Use of Antibiotics During Study	2 (1.6%)	0	2 (0.8%)
Tetracycline Use During Study	1 (0.8%)	0	1 (0.4%)
Chronic Use of NSAIDS During Study	2 (1.6%)	3 (2.4%)	5 (2.0%)
Long-Term Use of Anti-Inflammatories 4 Weeks Prior to Baseline or During Study	2 (1.6%)	3 (2.4%)	5 (2.0%)
Patient Determined to be Achlorhydric	1 (0.8%)	0	1 (0.4%)
Use of Proton Pump Inhibitors During Study	7 (5.5%)	11 (8.9%)	18 (7.2%)
Use of Sulfa Drugs During Study	3 (2.4%)	1 (0.8%)	4 (1.6%)

Note: Patients may have had more than one significant protocol violation/deviation. Percentages are based on the number of patients within each treatment group.

Data Source: Section 15, Table 4

Source: Sponsor’s NDA submission, module 5, volume 1.9, p. 31.

Table 11: Patients Excluded from the Per-Protocol Analysis (Study 302)

Protocol Violation	COL-101 (N = 142) n (%)	Placebo (N = 144) n (%)	Total (N = 286) n (%)
Number of Patients Excluded from the Per-Protocol Analysis	31 (21.8%)	33 (22.9%)	64 (22.4%)
Compliance <80%	12 (8.5%)	13 (9.0%)	25 (8.7%)
Baseline Papules + Pustules <10 or >40	6 (4.2%)	5 (3.5%)	11 (3.8%)
Baseline Nodules >2	1 (0.7%)	1 (0.7%)	2 (0.7%)
Baseline CEA score <5 or >20	2 (1.4%)	4 (2.8%)	6 (2.1%)
Use of Topical/Systemic Antibiotics Within 4 Weeks of Baseline	1 (0.7%)	1 (0.7%)	2 (0.7%)

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Use of Vasodilators 6 Weeks Prior to Baseline or During Study	1 (0.7%)	0	1 (0.3%)
Use of α -Adrenergic Receptor Blocking Agent 6 Weeks Prior to Baseline or During Study	1 (0.7%)	1 (0.7%)	2 (0.7%)
Chronic Use of Antibiotics During Study	0	1 (0.7%)	1 (0.3%)
Tetracycline Use During Study	2 (1.4%)	2 (1.4%)	4 (1.4%)
Chronic Use of NSAIDs During Study	6 (4.2%)	9 (6.3%)	15 (5.2%)
Long-Term Use of Anti-Inflammatories 4 Weeks Prior to Baseline or During Study	6 (4.2%)	10 (6.9%)	16 (5.6%)
Use of Proton Pump Inhibitors During Study	9 (6.3%)	11 (7.6%)	20 (7.0%)
Use of Rosacea Treatments 4 Weeks Prior to Baseline	1 (0.7%)	0	1 (0.3%)
Use of Sulfa Drugs During Study	0	1 (0.7%)	1 (0.3%)

Note: Patients may have had more than one significant protocol violation/deviation. Percentages are based on the number of patients within each treatment group. Data Source: Section 15, Table 4

Source: Sponsor's NDA submission, module 5, volume 1.32, p. 35.

Efficacy Endpoint Outcomes

Success Rate

The primary efficacy variable as proffered by the sponsor was change in total inflammatory lesion count from baseline to Week 16.

Table 12: Total Inflammatory Lesion Count: Baseline and Mean Change from Baseline at Week 16 (ITT Population), Sponsor's Analysis

Visit Statistics	Study 301		Study 302		Combined Studies	
	Oracea™ (n = 127)	Placebo (n = 124)	Oracea™ (n = 142)	Placebo (n = 144)	Oracea™ (n = 169)	Placebo (n = 268)
Baseline						
Mean (SD)	19.5 (8.78)	20.3 (10.37)	20.5 (11.68)	21.2 (12.51)	20 (10.40)	20.8 (11.56)
Median (range)	17.0 (10-39)	17.0 (10-63)	17.0 (10-105)	18.0 (10-100)	17.0 (10-105)	17.5 (10-100)
Week 16 ^a						
Mean (SD)	7.7 (7.96)	14.4 (16.42)	11.0 (11.29)	16.9 (14.69)	9.4 (9.98)	15.7 (15.54)
Median (range)	5.0 (0-38)	9.0 (0-111)	8.0 (0-135)	13.0 (1-78)	7.0 (0-105)	11.0 (0-111)
Change from Baseline to Week 16						
Mean (SD)	-11.8 (9.78)	-5.9 (13.91)	-9.5 (9.63)	-4.3 (11.57)	-10.6 (9.75)	-5.1 (12.71)
Median (range)	-10.0 (-38 to 11)	-8.0 (-46 to 89)	-8.0 (-41 to 28)	-6.0 (-34 to 38)	-9.0 (-41 to 28)	-7.0 (-46 to 89)
p-value ^b	< 0.001		< 0.001		< 0.001	

Source: Table 8.1.1 (Module 5: 301 – vol 1.9, p 118; 302 – vol 1.32, p 134; combined – vol 1.56, p 10) Total inflammatory lesion count included the number of papules, pustules, and nodules.
^a Week 16 was the last valid observation available on treatment.
^b P-value for treatment difference on change from baseline, using the Van Elteren test stratified by pooled center.

Source: Sponsor's NDA submission module 2, volume 1.1, p. 213

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According to the sponsor's analysis the mean difference, over placebo, favoring Oracea™ consists of a total of 5.9 lesions (study 301) and 5.2 lesions (study 302).

The FDA analysis follows.

Table 13: ROSE-301 (ITT-LOCF) Mean Change from Baseline in Lesion Count

Visit	Baseline	Week 3	Week 6	Week 12	Week 16
Change from Baseline					
Oracea (N=127)					
Mean	.	-6.54	-9.61	-10.80	-11.82
Std Dev	.	9.08	8.84	9.77	9.78
Placebo (N=124)					
Mean	.	-2.82	-3.96	-5.50	-5.94
Std Dev	.	10.79	9.87	11.95	13.91
p-value					
ANOVA	.	0.0048	<0.0001	0.0002	0.0003
van Elteren	.	0.0074	<0.0001	0.0001	0.0020
Total Lesions					
Oracea (N=127)					
Mean	19.54	13.01	9.94	8.75	7.72
Std Dev	8.78	9.95	8.73	8.54	7.96
Placebo (N=124)					
Mean	20.33	17.51	16.37	14.83	14.39
Std Dev	10.37	13.00	14.49	14.28	16.42
p-value					
ANOVA	0.4535	0.0011	<0.0001	0.0001	0.0001
van Elteren	0.7987	0.0027	0.0002	0.0050	0.0008

Source: Steve Thomson, Biostatistician, FDA, Statistical Review and Evaluation, NDA 50-805, p. 15.

Table 14: ROSE-302 (ITT-LOCF) Mean Change from Baseline in Lesion Count

Visit	Baseline	Week 3	Week 6	Week 12	Week 16	Week 20
Change from Baseline						
Oracea (N=142)						
Mean	.	-5.59	-7.22	-8.28	-9.48	-8.30
Std Dev	.	8.47	9.86	10.71	9.63	10.60
Placebo (N=144)						
Mean	.	-3.47	-3.65	-4.20	-4.31	-4.69
Std Dev	.	7.63	10.78	11.31	11.57	10.66
p-value						
ANOVA	.	0.0165	0.0005	<0.0001	<0.0001	0.0008
van Elteren	.	0.0051	<0.0001	<0.0001	0.0001	0.0022
Total Lesions						
Oracea (N=142)						
Mean	20.45	14.86	13.23	12.17	10.97	12.15
Std Dev	11.68	11.72	12.03	11.98	11.29	11.65
Placebo (N=144)						

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Mean	21.19	17.72	17.55	16.99	16.89	16.51
Std Dev	12.51	11.93	13.41	13.79	14.69	14.66
p-value						
ANOVA	0.5119	0.0202	0.0011	0.0004	<0.0001	0.0014
van Elteren	0.6562	0.0044	0.0002	<0.0001	<0.0001	0.0052

Source: Steve Thomson, Biostatistician, FDA, Statistical Review and Evaluation, NDA 50-805, p. 16.

The FDA analysis for this endpoint showed similar results, as shown in tables 13 and 14. The mean difference favoring Oracea consisting of a total of 5.88 lesions (study 301) and 5.17 lesions (study 302). Both studies show a statistically significant difference in reduction of total lesion count favoring Oracea™ over placebo. The results for the Per Protocol population were similar.

Investigator’s Global Assessment:

In pre-submission meetings the Agency had recommended that a static Investigator Global Assessment be a co-primary endpoint. The sponsor’s protocol specified that the change from baseline in the IGA be a secondary endpoint. The sponsor’s analysis follows.

Table 15: Investigator’s Global Assessment at Baseline and Change from Baseline at Week 16 (ITT Population), Sponsor’s Analysis

Visit Score	Study 301		Study 302		Combined Studies	
	Oracea™ (n = 127)	Placebo (n = 124)	Oracea™ (n = 142)	Placebo (n = 144)	Oracea™ (n = 269)	Placebo (n = 268)
Baseline, n (%)						
0 – Clear	0	0	0	0	0	0
1 – Near Clear	0	0	0	0	0	0
2 – Mild	8 (6.3%)	10 (8.1%)	17 (12.0%)	7 (4.9%)	25 (9.3%)	17 (6.3%)
3 – Moderate	67 (52.8%)	65 (52.4%)	77 (54.2%)	80 (55.6%)	144 (53.5%)	145 (54.1%)
4 – Severe	52 (40.9%)	49 (39.5%)	48 (33.8%)	57 (39.6%)	100 (37.2%)	106 (39.6%)
Change from Baseline to Week 16 ^a , n (%)						
-4	4 (3.1%)	2 (1.6%)	2 (1.4%)	0	6 (2.2%)	2 (0.7%)
-3	14 (11.0%)	9 (7.3%)	2 (1.4%)	1 (0.7%)	16 (5.9%)	10 (3.7%)
-2	40 (31.5%)	21 (16.9%)	28 (19.7%)	22 (15.3%)	68 (25.3%)	43 (16.0%)
-1	40 (31.5%)	40 (32.3%)	59 (41.5%)	45 (31.3%)	99 (36.8%)	85 (31.7%)
0	27 (21.3%)	45 (36.3%)	44 (31.0%)	62 (43.1%)	71 (26.4%)	107 (39.9%)
1	2 (1.6%)	7 (5.6%)	6 (4.2%)	14 (9.7%)	8 (3.0%)	21 (7.8%)
2	0	0	1 (0.7%)	0	1 (0.4%)	0
3	0	0	0	0	0	0
4	0	0	0	0	0	0
p-value ^b	< 0.001		0.004		< 0.001	

Source: Tables 3.1 and 11.1.1 (Module 5: 301 – vol 1.9, pp 76, 280; 302 – vol 1.32, pp 85, 320; combined – vol 1.56, pp 4, 93)
 a Week 16 was the last valid observation available on treatment.
 b P-value for treatment difference was based on a Cochran-Mantel-Haenszel Test stratified by pooled center.

Source: Sponsor’s NDA submission, module 2, volume 1.1, p. 215.

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In each study individually and in the combined studies there was an improvement in the Oracea™ group that was significantly greater than in the placebo group at week 16. In the Per Protocol population the results were similar for the combined studies ($p < 0.001$).

The second secondary efficacy parameter as identified in the protocol was treatment responders at endpoint (Week 16). If response is defined as an IGA score of 0 (clear) or 1 (Near Clear) the proportion of patients in the Oracea™ group responding was significantly greater than that in the placebo group in both study 301 and 302 ($p \leq 0.0361$ and $p \leq 0.0120$) and in the combined studies. If the definition of response used was an IGA score of 0 at Week 16, the treatment differences between the groups were not statistically significant in the individual studies or in the combined studies. For the Per Protocol Population the results were similar in the combined studies. Using the definition of responders having a score of 0 or 1 at Week 16 the difference was significant at $p = 0.005$. With definition restricted to a score of 0 there was no difference between the treatment groups.

**Table 16: Proportion of Treatment Responders (ITT Population)
 Sponsor's Analysis**

Characteristic	Study 301		Study 302		Combined Studies	
	Oracea™ (n = 127)	Placebo (n = 124)	Oracea™ (n = 142)	Placebo (n = 144)	Oracea™ (n = 269)	Placebo (n = 268)
Score of 0 or 1 at Week 16 ^a						
Yes	39 (30.7%)	24 (19.4%)	21 (14.8%)	9 (6.3%)	60 (22.3%)	33 (12.3%)
No	88 (69.3%)	100 (80.6%)	121 (85.2%)	135 (93.8%)	209 (77.7%)	235 (87.7%)
p-value ^b	0.036		0.012		0.001	
Score of 0 at Week 16 ^a						
Yes	12 (9.4%)	10 (8.1%)	2 (1.4%)	0	14 (5.2%)	10 (3.7%)
No	115 (90.6%)	114 (91.9%)	140 (98.6%)	144 (100.0%)	255 (94.8%)	258 (96.3%)
p-value ^b	0.718		0.134		0.423	
Source: Tables 10.1.1 and 10.2.1 (Module 5: 301 – vol 1.9, pp 254, 267; 302 – vol 1.32, pp 290, 305; combined – vol 1.56, pp 68, 80)						
a Week 16 was the last valid observation available on treatment.						
b P-value for treatment differences was based on a Cochran-Mantel-Haenszel test stratified by pooled center						

Source: Sponsor's NDA submission, module 2, vol. 1.1, p. 217.

As noted by the statistician, the IGA scores used by the sponsor represent grouped data values with different ranges of lesions for each level of the IGA. The computed differences in the IGA scores do not correspond to equal counts in the lesions. Thus the changes of value in the IGA do not correspond to equal magnitudes of changes in lesion count at different points in the IGA scale. In an effort to create a static overall IGA the Clinical team defined a post hoc extended

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IGA incorporating erythema. There were no statistically significant treatment differences on this endpoint. Please see Statistical Review and Evaluation.

To overcome potential problems with interpretation, the statistician performed an analysis based on mean IGA scores rather than on change from baseline. It was noted that this was a post hoc addition, not specified in the protocol. The FDA analysis follows.

Table 17: ROSE-301 (ITT-LOCF) Investigator's Global Assessment

Visit		Baseline	Week 3	Week 6	Week 12	Week 16
Oracea						
0. Clear	N	.	2	3	9	12
	%	.	1.6	2.4	7.1	9.4
1. Near Clear	N	.	4	20	18	27
	%	.	3.1	15.7	14.2	21.3
2. Mild	N	8	58	57	61	54
	%	6.3	45.7	44.9	48.0	42.5
3. Moderate	N	67	34	33	27	22
	%	52.8	26.8	26.0	21.3	17.3
4. Severe	N	52	29	14	12	12
	%	40.9	22.8	11.0	9.4	9.4
Placebo						
0. Clear	N	.	1	3	5	10
	%	.	0.8	2.4	4.0	8.1
1. Near Clear	N	.	2	6	14	14
	%	.	1.6	4.8	11.3	11.3
2. Mild	N	10	38	47	46	44
	%	8.1	30.6	37.9	37.1	35.5
3. Moderate	N	65	45	29	24	25
	%	52.4	36.3	23.4	19.4	20.2
4. Severe	N	49	38	39	35	31
	%	39.5	30.6	31.5	28.2	25.0
P-value						
Success (0,1)		.	0.3359	0.0079	0.2124	0.0361
Mean Score		0.7267	0.0086	<0.0001	0.0008	0.0014

Source: Steve Thomson, Biostatistician, FDA, Statistical Review and Evaluation, NDA 50-805, Addendum, p. 3.

With this analysis, differences using the mean scores were highly significant ($p \leq 0.0014$ and $P \leq 0.0001$ for studies 301 and 302, respectively).

Also showing on tables 17 and 18 is treatment responders at endpoint where response is defined as an IGA score of 0 (clear) or 1 (Near Clear). As noted with the sponsor's analysis, treatment differences were significant, ($p \leq 0.0361$ and $p \leq 0.0120$ for studies 301 and 302, respectively).

Using this static IGA score at Week 16 more patients in the Oracea™ group had improved into the lesser disease categories (dichotomization to no worse than Almost Clear defined as 1 to 2

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small papules or pustules) when compared to the placebo group in both pivotal studies (Study 301: Oracea™ 31% vs. placebo 19% and Study 302: Oracea™ 15% vs. placebo 6%).

When analyzing similar IGAs, as noted by the statistician, the Division has often recommended a dichotomization so that “success” is defined as “Clear” or “Near Clear” at study end with a change from baseline of a least two units. As explained by the statistician, for a score of “success” a subject with a baseline IGA of 3 or 4 would require an IGA of 0 or 1 at study endpoint, while a subject with a baseline IGA of 2 would require an endpoint IGA of 0. In study 301 with this definition, using LOCF in the ITT population at Week 16, there were 36 successes in the Oracea group versus 23 in the placebo group ($p \leq 0.0642$). In study 302, using LOCF in the ITT population at Week 16, there were 15 successes in the Oracea group versus 8 in the placebo group ($p \leq 0.1122$).

Table 18: ROSE-302 (ITT-LOCF) Investigator’s Global Assessment

	Visit	Week	Week	Week	Week	Week
	Baseline	3	6	12	16	20
Oracea						
0. Clear	N	.	.	3	2	6
	%	.	.	2.1	1.4	4.2
1. Near Clear	N	.	3	6	13	19
	%	.	2.1	4.2	9.2	13.4
2. Mild	N	17	59	69	64	65
	%	12.0	41.5	48.6	45.1	45.8
3. Moderate	N	77	54	46	42	37
	%	54.2	38.0	32.4	29.6	26.1
4. Severe	N	48	26	21	20	19
	%	33.8	18.3	14.8	14.1	13.4
Placebo						
0. Clear	N	.	.	2	2	3
	%	.	.	1.4	1.4	2.1
1. Near Clear	N	.	3	4	5	9
	%	.	2.1	2.8	3.5	6.3
2. Mild	N	7	41	44	42	49
	%	4.9	28.5	30.6	29.2	34.0
3. Moderate	N	80	56	48	55	47
	%	55.6	38.9	33.3	38.2	32.6
4. Severe	N	57	44	46	40	39
	%	39.6	30.6	31.9	27.8	27.1
P-value						
Success (0,1)	.	0.9974	0.9949	0.0285	0.0120	0.1227
Mean Score	0.0207	0.0035	0.0003	<0.0001	<0.0001	0.0027

Source: Steve Thomson, Biostatistician, FDA, Statistical Review and Evaluation, NDA 50-805, Addendum, p. 4.

Clinician’s Erythema Assessment:

The Clinician’s Erythema Score, change from baseline, was the third of four secondary efficacy parameters identified in the sponsor’s protocols.

Table 19: Clinician’s Erythema Assessment Total Score: Baseline and Mean Change from Baseline at Week 16 (ITT Population), Sponsor’s Analysis

Characteristic	Study 301		Study 302		Combined Studies	
	Oracea™ (n = 127)	Placebo (n = 124)	Oracea™ (n = 142)	Placebo (n = 144)	Oracea™ (n = 269)	Placebo (n = 268)
Baseline						
Mean (SD)	9.7 (2.97)	9.5 (2.72)	9.5 (2.89)	9.1 (2.47)	9.6 (2.92)	9.3 (2.59)
Median (range)	9.0 (5-19)	9.0 (5-19)	9.0 (4-18)	9.0 (4-16)	9.0 (4-19)	9.0 (4-19)
Week 16 ^a						
Mean (SD)	7.0 (3.69)	7.7 (3.53)	8.1 (3.16)	7.9 (3.26)	7.6 (3.46)	7.8 (3.38)
Median (range)	7.0 (0-18)	8.0 (1-19)	8.0 (0-18)	8.0 (0-19)	8.0 (0-18)	8.0 (0-19)
Change from Baseline to Week 16						
Mean (SD)	-2.7 (3.25)	-1.8 (2.89)	-1.4 (2.69)	-1.2 (3.02)	-2.0 (3.04)	-1.5 (2.97)
Median (range)	-3.0 (-10 to 5)	-1.0 (-10 to 5)	-1.0 (-10 to 6)	-1.0 (-9 to 9)	-2.0 (-10 to 6)	-1.0 (-10 to 9)
p-value ^b	0.017		0.428		0.024	

Source: Table 9.1 (Module 5: 301 – vol 1.9, p 224; 302 – vol 1.32, p 256; combined – vol 1.56, p 38)
 a Week 16 was the last valid observation available on treatment.
 b P-value for treatment difference on change from baseline, using an ANOVA model with treatment and pooled center as the main effects.

Source: Sponsor’s NDA submission, module 2, volume 1.1, p. 214.

For study 301, the Week 16 treatment difference in change from baseline for the CEA total score was significant, $p \leq 0.017$. For study 302, the Week 16 treatment difference in change from baseline for the CEA total score was not significant, $p \leq 0.428$. The FDA analysis found similar results with the Week 16 treatment difference in change from baseline for CEA score being statistically significant for study 301 ($p \leq 0.0164$) and not being statistically significant for study 302 ($p \leq 0.4278$).

The FDA also performed an analysis using the treatment difference in total erythema score at Week 16 and found that the difference between Oracea™ and placebo groups was not statistically significant in either study 301 ($p \leq 0.0847$) or study 302 ($p \leq 0.09735$).

A fourth secondary efficacy parameter identified in the protocols is change in total inflammatory lesion count from baseline to Week 12. The sponsor found a statistically significant greater reduction in the Oracea™ treatment group as compared with the placebo group. This was true

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for both study 301 ($p < 0.001$) and 302 ($p < 0.001$). The sponsor also reports similar results for the Per Protocol Population. The sponsor's results are shown in the following table.

Table 20: Total Inflammatory Lesions - Baseline and Mean Change from Baseline at Week 12 (ITT Population), Sponsor's Analysis

Characteristic	Study 301		Study 302		Combined Studies	
	Oracea™ (n = 127)	Placebo (n = 124)	Oracea™ (n = 142)	Placebo (n = 144)	Oracea™ (n = 269)	Placebo (n = 268)
Baseline						
Mean (SD)	19.5 (8.78)	20.3 (10.37)	20.5 (11.68)	21.2 (12.51)	20.0 (10.40)	20.8 (11.56)
Median (range)	17.0 (10-39)	17.0 (10-63)	17.0 (10-105)	18.0 (10-100)	17 (10-105)	17.5 (10100)
Week 12						
Mean (SD)	8.7 (8.54)	14.8 (14.28)	12.2 (11.98)	17.0 (13.79)	10.6 (10.61)	16.0 (14.03)
Median (range)	7.0 (0-51)	9.0 (0-64)	9.0 (0-105)	13.0 (0-78)	8.0 (0-105)	13.0 (0-78)
Change from Baseline to Week 12						
Mean (SD)	-10.8 (9.77)	-5.5 (11.95)	-8.3 (10.71)	-4.2 (11.31)	-9.5 (10.33)	-4.8 (11.61)
Median (range)	-10.0 (-38 to 12)	-7.0 (-52 to 42)	-8.0 (-34 to 39)	-4.0 (-43 to 64)	-9.0 (-38 to 39)	-5.0 (-52 to 64)
p-value ^a	< 0.001		< 0.001		< 0.001	
Source: Table 8.1.1 (Module 5: 301 – vol 1.9, p 118; 302 – vol 1.32, p 134; combined – vol 1.56, pp 10)						
Total inflammatory lesion count included the number of papules, pustules, and nodules.						
a P-value for treatment difference on change from baseline, using the Van Elteren test stratified by pooled center.						

Source: Sponsor's NDA submission module 2, volume 1.1, p. 218.

The FDA analysis for the Week 12 change from baseline in inflammatory lesions produced similar results with significant findings for both studies 301 and 302 at $p \leq 0.0002$ (ANOVA), $p \leq 0.0001$ (van Elteren). Please see tables 13 and 14 above.

Exploratory Analysis Parameters:

As listed in the protocols, an exploratory analysis parameter was change from baseline in total inflammatory lesion count at Weeks 3, 6, and 12. At weeks 3, 6 and 12 there was a significantly greater reduction in the Oracea™ treatment group than in the placebo group. This finding was true for each study individually and for the combined studies. See following table for weeks 3 and 6, preceding table for week 12. The FDA analysis is shown in tables 13 and 14 above. The findings with the van Elteren test are very similar.

Table 21: Total Inflammatory Lesions - Baseline and Mean Change from Baseline at Weeks 3 and 6 (ITT Population), Sponsor's Analysis

Characteristic	Study 301		Study 302		Combined Studies	
	Oracea™ (n = 127)	Placebo (n = 124)	Oracea™ (n = 142)	Placebo (n = 144)	Oracea™ (n = 269)	Placebo (n = 268)
Baseline						
Mean (SD)	19.5 (8.78)	20.3 (10.37)	20.5 (11.68)	21.2 (12.51)	20.0 (10.40)	20.8 (11.56)
Median (range)	17.0 (10-390)	17.0 (10-63)	17.0 (10-105)	18.0 (10-100)	17.0 (10-105)	17.5 (10100)
Week 3						
Mean (SD)	13.0 (9.95)	17.5 (13.00)	14.9 (11.72)	17.7 (11.93)	14.0 (10.94)	17.6 (12.41)
Median (range)	10.0 (0-47)	13.0 (0-80)	13.0 (1-105)	15.0 (2-78)	11.0 (0-105)	14.0 (0-80)
Change from Baseline to Week 3						
Mean (SD)	-6.5 (9.08)	-2.8 (10.79)	-5.6 (8.47)	-3.5 (7.63)	-6.0 (8.76)	-3.2 (9.21)
Median (range)	-6.0 (-38 to 29)	-3.0 (-29 to 63)	-5.0 (-34 to 28)	-3.0 (-34 to 20)	-6.0 (-38 to 29)	-3.0 (-34 to 63)
p-value ^a		0.005		0.005		< 0.001
Week 6						
Mean (SD)	9.9 (8.73)	16.4 (14.49)	13.2 (12.03)	17.5 (13.41)	11.7 (10.71)	17.0 (13.91)
Median (range)	7.0 (0-48)	12.0 (0-68)	10.0 (1-105)	13.5 (0-78)	9.0 (0-105)	13.0 (0-78)
Change from Baseline to Week 6						
Mean (SD)	-9.6 (8.84)	-4.0 (9.87)	-7.2 (9.86)	-3.6 (10.78)	-8.3 (9.45)	-3.8 (10.35)
Median (range)	-9.0 (-36 to 11)	-6.0 (-24 to 42)	-7.0 (-34 to 39)	-3.5 (-43 to 64)	-8.0 (-36 to 39)	-4.0 (-43 to 64)
p-value ^a		< 0.001		< 0.001		< 0.001

Source: Sponsor's NDA submission module 2, volume 1.1, p. 218.

A second exploratory analysis parameter listed in the protocol was change from baseline in individual lesion counts (papules, pustules, and nodules) at Weeks 3, 6, 12, and 16. This was not included in the combined analysis. For study 301, ITT population, significantly greater reductions from baseline were seen for the Oracea™ group as compared with the placebo group for papule counts at every visit and pustule counts at Weeks 3, 12, and 16. For study 302, ITT population, significantly greater reductions from baseline were seen for the Oracea™ group as compared with the placebo group for papule counts at Weeks 6, 12, and 16 and for pustule counts at Weeks 3, 6, and 16. The numbers of nodules in both studies were too small for analysis.

A third exploratory analysis parameter listed in the protocol was change from baseline in IGA at Weeks 3, 6, and 12. For this parameter a significantly greater improvement in the Oracea™ group versus the placebo group was seen in the combined analysis in the ITT population and the Per Protocol Populations, $p \leq 0.002$.

A fourth exploratory analysis parameter was change from baseline in CEA score at Weeks 3, 6, and 12. This was not significantly different between the Oracea™ and placebo groups in the

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combined analysis in the ITT and Per Protocol Populations. A mean reduction in score was noted in both treatment groups over time/visits.

Findings in Subpopulations:

Table 22: Total Inflammatory Lesion Count: Baseline and Mean Change from Baseline at Week 16 by Subgroup (Combined Analysis), Sponsor’s Analysis

Subgroup	Oracea™		Placebo		P-value ^b
	Baseline	Week 16 Change ^a	Baseline	Week 16 Change ^a	
Gender					
Male	20.4 (n= 84)	-11.7	19.5 (n= 78)	-3.7	< 0.001
Female	19.9 (n=185)	-10.1	21.3(n=190)	-5.6	0.002
Lesion counts > 20	30.2 (n=100)	-17.2	30.8(n=106)	-6.7	< 0.001
Age					
18 – 35	22.5 (n= 56)	-10.2	25.6 (n= 43)	-5.0	0.864
36 – 50	20.0 (n=122)	-9.9	21.1(n=117)	-5.7	0.006
51 – 70	18.8 (n= 78)	12.1	18.5 (n= 96)	-4.6	<0.001
> 70	16.5 (n= 13)	-9.8	18.7 (n= 12)	-2.7	0.311
Race ^c					
Caucasian	19.9 (n=243)	-10.5	20.8(n=248)	-4.6	< 0.001
Other	20.4 (n= 22)	-10.4	20.5(n= 19)	-10.5	0.641

Source: Tables 8.1.3 to 8.1.6 (Module 5: combined – vol. 1.56, pp 14-35)
 Total inflammatory lesion count included the number of papules, pustules, and nodules.
 a Week 16 was the last valid observation available on treatment.
 b P-value for treatment difference on change from baseline, using the Van Elteren test stratified by pooled center
 c Too few Black (n=2) and Asian (n=3) patients for analysis. “Other” included Hispanic (n=36), Native American (n=3), Spanish (n=1), and Latin (n=1)

Source: Sponsor’s NDA submission, module 2, volume 1.1, p. 222.

Gender:

When analyzed across gender, the Oracea™ treatment group showed greater improvement than the placebo treatment group for total inflammatory lesion count from baseline to Week 16, in the combined analysis. The FDA analysis provides similar results. When the parameter examined was relative success rate on the IGA (score of “0” or “1”) a statistically greater improvement was found in the Oracea™ group than in the placebo group for both genders, in the sponsor’s combined analysis (see table below). When broken down by study, in study 301 the relative treatment success rate was greater for men than women. In study 302 men and women had similar response rates. Both the FDA and sponsor analyses provided similar results.

Table 23: Proportion of Treatment Responders (IGA Score of 0 or 1) at Week 16^a by Subgroup (Combined Analysis), Sponsor’s Analysis

Subgroup	Oracea™	Placebo	P-value ^b
Gender			
Male	29.8% (25/ 84)	12.8% (10/ 78)	0.028
Female	18.9% (35/185)	12.1% (23/190)	0.042
Lesion counts > 20	14.0% (14/100)	4.7% (5/106)	0.021
Age			
18 – 35	12.5% (7/ 56)	11.6% (5/ 43)	0.802
36 – 50	18.0% (22/122)	11.1% (13/117)	0.092
51 – 70	33.3% (26/ 78)	13.5% (13/ 96)	0.003
> 70	38.5% (5/ 13)	16.7% (2/ 12)	0.705
Race ^c			
Caucasian	22.6% (55/243)	10.9% (27/248)	0.000
Other	18.2% (4/ 22)	31.6% (6/ 19)	0.353
Source: Tables 10.1.3 to 10.1.6 (Module 5: combined – vol. 1.56, pp 70-79)			
a Week 16 was the last valid observation available on treatment.			
b P-value for treatment difference was based on a Cochran-Mantel-Haenszel test stratified by pooled center			
c Too few Black (n=2) and Asian (n=3) patients for analysis. “Other” included Hispanic (n=36), Native American (n=3), Spanish (n=1), and Latin (n=1)			

Source: Sponsor’s NDA submission, module 2, volume 1.1, p.222.

Age:

When analyzed by age, the mean change in inflammatory lesion count, from baseline to Week 16, was similar across age groups, in the combined analysis. This was true in both sponsor and FDA analysis. The FDA analysis collapsed the age groups from 4 to 3 by combining over 70 with those 51 - 70. When the parameter is IGA success (score of “0” or “1”), the greatest success in the Oracea™ treatment group was noted in the 51 - 70 age group, sponsor’s analysis combined studies. When broken down by study, study 301 treatment success with Oracea was higher in the older age groups, 36 - 50, 51 - 70, >70 (sponsor), and 36 - 50, 51+ (FDA). In study 302, treatment success was greater in lowest and highest age groups, 18 - 35, 51 - 70, >70 (sponsor), and 19 - 35, 51+ (FDA). According to the statistician, Steve Thomson, these between study differences “...seem to be due to vagaries of studies where the results are not overwhelmingly strong.”

Baseline Lesion Counts:

When the change in total inflammatory lesions is stratified on magnitude of baseline lesion count, the treatment differences between Oracea™ and placebo are more marked when the baseline number of lesions is large. This was true in the sponsor’s and in the FDA analysis for the combined studies. When the parameter is IGA success (score of “0” or “1”), and baseline lesion counts are > 20 greater success is noted, combined studies, sponsor’s analysis. When broken down by study for both study 301 and 302, Week 16 IGA success is more marked when the number of lesions at baseline is > 20. This was true in both the sponsor’s and the FDA analysis.

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Race:

When the change in total inflammatory lesions is stratified on race, in the sponsor's analysis for the combined studies, statistically significant greater improvement at Week 16 is noted in the Oracea™ treatment group as compared with placebo, for Caucasians. Most of the patients in the study were Caucasian. Race was divided into only two groups, Caucasian and Other. For the purposes of the sponsor's analysis, "Other" included Hispanic (n=36), Native American (3), Spanish (1), and Latin (1). It appears that the Black (2) and Asian (3) patients were not included in the sponsor's analysis. For the FDA analysis the Black and Asian patients were included with "Other". In the FDA analysis, combined studies, the mean change from baseline at Week 16 showed a difference over placebo of -5.94 for Caucasians which mirrored that of the study as a whole. For the racial group "Other" treatment differences between Oracea™ and placebo were not observed in either the sponsor's or the FDA analysis.

For the parameter IGA success (score of "0" or "1") at Week 16, statistically greater success was shown for the Oracea™ group than placebo in Caucasian patients, sponsor's analysis, combined studies. The "Other" group did not show greater success for Oracea™ treatment as compared with placebo. As above, the sponsor's "Other" group included Hispanics, Native American, Spanish, and Latin. Black and Asian patients were not included. Examining the individual studies 301 and 302, treatment differences in the Week 16 IGA were noted in the Caucasian patients and not in the "Other" patients. This was true both in the sponsor's as well as the FDA analysis.

6.1.5 Clinical Microbiology

The sponsor has cross-referenced previous studies that evaluated Periostat® (doxycycline hyclate) 20 mg BID. The three microbiology studies cited by reference to NDA 50-744 include:

- a) Study 5732.11A: A 3 month, randomized, placebo-controlled clinical study to evaluate the microbial effects of five dose regimens of doxycycline hyclate on the oral cavity
- b) Study 5732.11 E&F: A 12 month, randomized, double-blind, placebo-controlled study to evaluate the microbial effects of 10 mg QD, 20 mg QD, and 20 mg BID of doxycycline hyclate on the oral cavity
- c) Study 5732.11 H: A 9 month, randomized, double-blind, placebo-controlled study to evaluate the microbial effects of 20 mg of doxycycline hyclate on the oral cavity.

According to the microbiology reviewer the object of this cross-referencing was to demonstrate that various regimen lengths and dose levels of doxycycline hyclate did not exert a discernable effect on the composition of the subgingival flora or on bacterial resistance.

For the Oracea™ (doxycycline) 40 mg capsule NDA 50 -805, the sponsor submitted two studies for review.

- a) Study 5732.11 J: A 9 month, randomized, double-blind, placebo-controlled study to evaluate the microbial effects of 20 mg BID of doxycycline hyclate on the intestinal and vaginal flora
- b) Study DERM-201: A 6 month, randomized, double-blind, placebo-controlled study to determine the microbial effects of 20 mg BID of doxycycline hyclate on the skin microflora

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In Study 5732.11 J 69 patients with periodontal disease (30-75 years of age) were randomized to receive drug or placebo control. The sponsor made an attempt to determine if sub-therapeutic doxycycline doses exerted any effect on intestinal flora that could be attributed to antimicrobial activity. The microbiology reviewer notes that the levels of doxycycline present in the intestine appeared lower than that required for stimulating any significant change in MIC. However, the reviewer also notes that longer treatment duration or results from a larger patient sample may show a trend towards the development of doxycycline resistance. The number of vaginal samples obtained that were adequate for evaluation was insufficient to draw significant conclusions. The microbiology reviewer notes that from the limited samples available low dose doxycycline did not appear to have an effect on vaginal candidiasis since yeast was recovered from only one subject.

Study DERM 201 involved 51 adults with moderate facial acne who were randomized to 20 mg BID of doxycycline hyclate or placebo for 6 months. The microbiology reviewer reports that treatment with low dose doxycycline had no effect on the composition of the normal skin flora. Treatment did not result in the emergence of organisms resistant to doxycycline or cross-resistant to other antimicrobial agents. The number of bacteria resistant to 4 µg/mL of doxycycline did not increase.

Agency Proposed Microbiology Section of the Label:

Doxycycline is a member of the tetracycline class of antibacterial drugs. The plasma concentrations of doxycycline achieved with this product during administration (see CLINICAL PHARMACOLOGY AND DOSAGE AND ADMINISTRATION) are less than the concentration required to treat bacterial diseases. *In vivo* microbiological studies utilizing a similar drug exposure for up to 18 months demonstrated no detectable long-term effects on bacterial flora of the oral cavity, skin, intestinal tract, and vagina.

TRADENAME should not be used for treating bacterial infections, providing antibacterial prophylaxis, or reducing or eliminating microorganisms associated with any bacterial disease.

Under PRECAUTIONS it is suggested that the following be added:

Bacterial resistance to the tetracyclines may develop in patients using TRADENAME; therefore the susceptibility of bacteria associated with infection should be determined before a tetracycline is used to treat infection. Because of the potential for tetracycline-resistant bacteria to develop during the use of TRADENAME, it should be used only as indicated.

6.1.6 Efficacy Conclusions

Pivotal trials, COL-101-ROSE-301 and COL-101-ROSE-302, were nearly identical Phase 3, multi-center, randomized, placebo-controlled against the active drug, and double-blinded. These trials were of adequate design and sufficiently powered to study the safety and efficacy of Oracea™ at a dose of 40mg once daily in patients 18 years and older.

In the pivotal trials COL-101-ROSE-301 (study 301) and COL-101-ROSE-302 (study 302) Oracea™ was statistically superior to placebo in producing a change from baseline in

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inflammatory lesion count at Week 16. For study 301, ITT-LOCF population, the Week 16 changes from baseline lesion count were -11.8 and -5.9 for Oracea™ and placebo, respectively. For study 302, ITT-LOCF population, the Week 16 changes from baseline lesion count were -9.5 and -4.3, respectively. These changes were statistically significant using an ANOVA model, $p \leq 0.0002$ and $p \leq 0.0001$ for studies 301 and 302.

The change in total inflammatory lesion count from baseline to Week 16 was the primary endpoint specified in the protocols; however, this was the subject of ongoing discussion during development of this drug product. The agency had requested a co-primary endpoint to be a static Investigator Global Assessment that included clinical descriptors of rosacea.

As identified in the protocols a secondary endpoint was change from baseline in IGA at Week 16. In the opinion of the Division, this IGA largely reflects a grouping of lesion counts. The Division also recommended dichotomizing this endpoint to define treatment responders as those having an IGA score of 0 (Clear) or 1 (Near Clear) at endpoint (Week 16). For the purpose of evaluating the Oracea™ drug product this was defined as a co-primary endpoint. The proportion of patients responding in the Oracea™ group was significantly greater than in the placebo group in both studies 301 and 302 ($p \leq 0.0361$ and $p \leq 0.0120$).

For the improvement of erythema as defined by the Clinician's Erythema Score (CEA) the Oracea™ drug product showed equivocal efficacy. For study 301, the Week 16 treatment difference in change from baseline for the CEA total score was significant, $p \leq 0.017$. For study 302, the Week 16 treatment difference in change from baseline for the CEA total score was not significant, $p \leq 0.428$. Similar results were found in both the sponsor and the FDA analysis. The FDA also performed an analysis using the treatment difference in total erythema score at Week 16 and found that the difference between Oracea™ and placebo groups was not statistically significant in either study 301 ($p \leq 0.0847$) or study 302 ($p \leq 0.09735$).

The sponsor has demonstrated efficacy of Oracea™ 40mg capsules for the treatment of only the papular and pustular components of rosacea in patients 18 years and older.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety review of Oracea™ Capsules will focus on adverse events and systemic safety (laboratory evaluation).

Deaths

No healthy subject or patient has died while participating in a clinical study with Oracea™ or Periostat®.

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Other Serious Adverse Events

No patients in study 302 experienced serious adverse events (SAEs).
 Five patients experienced 10 treatment emergent SAEs during study 301, including 3 patients in the Oracea™ treatment group (8 SAEs) and 2 patients in the placebo group (2 SAEs).

Table 24: Serious Adverse Events in Phase 3 Studies (ITT Population)

Treatment	Patient ^a	Sex/ Age ^b	MedDRA Preferred Term (Verbatim Term if Different)	Severity	Study Drug Relationship	Outcome
Oracea™	301-100-101	F/61	Uterine cancer	Mild	Not Related	Resolved
	301-600-601	F/51	Renal insufficiency (renal failure)	Severe	Not Related	Resolved
			Pulmonary embolism	Severe	Not Related	Resolved
			Respiratory arrest	Severe	Not Related	Resolved
			Deep vein thrombosis	Severe	Not Related	Resolved
			Large intestine perforation (perforated viscus of colon)	Moderate	Not Related	Resolved
			Hemoglobin decreased	Moderate	Not Related	Resolved
	301-1000-1008	M/74	Coronary artery disease	Mild	Not Related	Resolved
Placebo	301-1300-116	F/66	Pneumonia	Severe	Not Related	Resolved
	301-1400-917	F/51	Chest pain	Moderate	Not Related	Resolved

Source: Listing 10.3 (Module 5: combined - vol 1.57, p 239)
 a Shown as study-center-patient number
 b Age at baseline

Source: Sponsor's NDA submission, module 2, volume 1.1, p. 252.

No SAEs were reported in the pharmacokinetic studies; 103, 104, 105, and 106. As of June 30th, no SAEs had been reported in ongoing studies COL-101-ROSE-201, COL-101-ROSE-202, and COL-101-ACNE-201. Nine SAEs have been reported in study PERIO-DOXYMR-301 which also was ongoing at the time of submission of the original NDA. Please also see section 7.2.9 for further review of study PERIO-DOXYMR-301 from information submitted with the safety update. In study PERIO-DOXYMR-301, in the Oracea™ group 6 patients each experienced one SAE (testis cancer, viral infection, gastrointestinal ulcer, pleurisy, worsening of peripheral artery disease, basal cell carcinoma). None of these were considered treatment related. In the placebo group 3 patients each experienced one SAE (chest pain, arterial thrombosis limb, basal cell carcinoma).

Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Table 25: Disposition of Randomized Patients

Disposition	Study 301		Study 302		Combined Studies	
	Oracea™	Placebo	Oracea™	Placebo	Oracea™	Placebo
Number randomized	127	124	142	144	269	268
Number completed, n (%)	101 (79.5%)	103 (83.1%)	115 (81.0%)	118 (81.9%)	216 (80.3%)	221 (82.5%)
Number discontinued, n (%)	26 (20.5%)	21 (16.9%)	27 (19.0%)	26 (18.1%)	53 (19.7%)	47 (17.5%)
Reason discontinued, n (%)						
Treatment-emergent adverse event	10 (7.9%)	4 (3.2%)	9 (6.3%)	7 (4.9%)	19 (7.1%)	11 (4.1%)
Illness not related to drug	1 (0.8%)	1 (0.8%)	1 (0.7%)	0 (0.0%)	2 (0.7%)	1 (0.4%)
Uncooperative	5 (3.9%)	4 (3.2%)	2 (1.4%)	1 (0.7%)	7 (2.6%)	5 (1.9%)
Protocol violation	2 (1.6%)	2 (1.6%)	4 (2.8%)	5 (3.5%)	6 (2.2%)	7 (2.6%)
Lost to follow-up	4 (3.1%)	2 (1.6%)	5 (3.5%)	5 (3.5%)	9 (3.3%)	7 (2.6%)
Treatment failure	2 (1.6%)	2 (1.6%)	1 (0.7%)	4 (2.8%)	3 (1.1%)	6 (2.2%)
Death	0	0	0	0	0	0
Other	2 (1.6%)	6 (4.8%)	5 (3.5%)	4 (2.8%)	7 (2.6%)	10 (3.7%)

Source: Table 1.3 (Module 5: 301 – vol 1.9, p 72; 302 – vol 1.32, p 81; combined – vol 1.56, p 1)

Source: Sponsor's NDA submission, module 2, volume 1.1, p. 208.

The above table indicates that in the combined Phase 3 studies, 216 patients randomized to Oracea™ completed and 53 discontinued. In the placebo arms the total who completed was 221 with 47 discontinued.

For the pharmacokinetic studies:

- A) 103 – Eighteen subjects entered the study. One subject did not complete the study due to a positive alcohol screen, which was a protocol violation. Early termination procedures were performed with this subject.
- B) 104 – Fourteen subjects entered the study. One subject was withdrawn from the study by the PI for behavioral problems not related to study treatments.
- C) 105 – All thirty subjects completed the study.
- D) 106 – Thirty of thirty two subjects completed the study.
 One subject withdrew consent on Day 20, no other information provided.
 One subject withdrew consent on Day 4 due adverse events (AEs) that included nausea, headache, decreased appetite, and lower abdominal pain. All

of these AEs were judged by the investigator to be mild in severity and possibly related to study drug. This subject had received doxycycline as controlled-release 40 mg capsule from day1 through day 3.

Table 26: Summary of Adverse Events in Phase 3 Studies (ITT Population)

Characteristic	Study 301		Study 302		Combined Studies	
	Oracea™ (n = 127)	Placebo (n = 124)	Oracea™ (n = 142)	Placebo (n = 144)	Oracea™ (n = 269)	Placebo (n = 268)
No. of patients with AEs	56 (44.1%)	48 (38.7%)	93 (65.5%)	74 (51.4%)	149 (55.4%)	122 (45.5%)
No. of AEs	137	92	185	148	322	240
No. of patients with SAEs	3 (2.4%)	2 (1.6%)	0	0	3 (1.1%)	2 (0.7%)
No. of SAEs	8	2	0	0	8	2
Patients with AEs by severity						
Mild	24 (18.9%)	18 (14.5%)	34 (23.9%)	28 (19.4%)	58 (21.6%)	46 (17.2%)
Moderate	22 (17.3%)	24 (19.4%)	53 (37.3%)	43 (29.9%)	75 (27.9%)	67 (25.0%)
Severe	10 (7.9%)	6 (4.8%)	6 (4.2%)	3 (2.1%)	16 (5.9%)	9 (3.4%)
No. of patients who discontinued study drug due to AEs	10 (7.9%)	5 (4.0%)	10 (7.0%)	7 (4.9%)	20 (7.4%)	12 (4.5%)
No. of patients with treatment-related AEs						
Possible	25 (19.7%)	17 (13.7%)	31 (21.8%)	21 (14.6%)	56 (20.8%)	38 (14.2%)
Probable	20 (15.7%)	14 (11.3%)	22 (15.5%)	17 (11.8%)	42 (15.6%)	31 (11.6%)
	5 (3.9%)	3 (2.4%)	9 (6.3%)	4 (2.8%)	14 (5.2%)	7 (2.6%)

Source: Table 12.1 (Module 5: 301 – vol 1.10, p 2; 302 – vol 1.33, p 2) and Table 12.1.1 (Module 5: combined – vol 1.56, p 131)
 Abbreviations: AE = adverse event, SAE = serious adverse event

Source: Sponsor's NDA submission, module 2, volume 1.1, p. 238.

7.1.3.2 Adverse events associated with dropouts

Pivotal Studies:

Thirty two patients discontinued study drug due to AE's: 20/269 in the Oracea™ treatment group and 12/268 in the placebo group. Three patients in the Oracea™ treatment group were categorized as having serious adverse events (1. uterine cancer, 2. renal failure, pulmonary embolus, respiratory arrest, 3. deep venous thrombosis, perforated viscous of colon, decreased

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hemoglobin) that were felt by the investigator not to be related to study drug. One patient in the placebo group had a serious adverse event (pneumonia) not felt to be related to placebo.

Of the 20 patients in the Oracea™ treatment group who discontinued, 13 were withdrawn due to AEs considered probably or possibly related to study medication. The most frequently reported AEs leading to discontinuation in the Oracea™ treatment group were gastrointestinal disorders; 4 patients withdrew solely due to gastrointestinal disorders and 4 patients withdrew due to gastrointestinal disorders in addition to AEs in at least one other system organ class.

Of the 12 patients in the placebo group who discontinued, 8 were withdrawn due to AEs considered treatment-related. The most frequently reported AEs leading to discontinuation in the placebo group were also gastrointestinal disorders; 5 patients withdrew solely due to gastrointestinal disorders and 1 patient withdrew due to gastrointestinal disorders in addition to AEs in at least one other organ class.

In study 301, patient 220 (placebo) was considered to have discontinued due to “illness not related to study drug” according to the box checked on the End of Study page of the CRF; however, on the Adverse Event page of the CRF, an AE of rosacea (worsening rosacea) was recorded with an outcome of “study drug discontinued and patient withdrawn.” Therefore, this patient was not included in the number of patients discontinued due to AEs in summary tables of patient disposition.

In study 302, patient 610 in the COL-101 treatment group was also considered to have discontinued due to “illness not related to study drug” according to the box checked on the End of Study page of the CRF; however, on the Adverse Event page of the CRF, an AE of “HIV test positive” was recorded with an outcome of “study drug discontinued and patient withdrawn.” Therefore, this patient is not included in the 16 patients who discontinued due to AE’s, study 302.

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Table 27: Summary of DC of Study Drug due to AEs in Phase 3 Studies (ITT Pop.)

System Organ Class Preferred Term	Oracea™ (n = 269)	Placebo (n = 268)
No. of patients who discontinued (DC) due to AE	20 (7.4%)	12 (4.5%)
Cardiac Disorders		
Ventricular extrasystoles	1 (0.4%)	0
Ear and Labyrinth Disorders		
Ear congestion	1 (0.4%)	0
Vertigo	1 (0.4%)	0
Endocrine Disorders		
Hyperthyroidism	1 (0.4%)	0
Gastrointestinal Disorders		
Abdominal distention	1 (0.4%)	0
Abdominal pain	1 (0.4%)	0
Abdominal pain upper	1 (0.4%)	1 (0.4%)
Diarrhea	2 (0.7%)	2 (0.7%)
Dyspepsia	0	1 (0.4%)
Dysphagia	1 (0.4%)	0
Gastrointestinal discomfort	1 (0.4%)	0
Gastrointestinal pain	1 (0.4%)	0
Large intestine perforation	1 (0.4%)	0
Nausea	1 (0.4%)	4 (1.5%)
Stomach discomfort	0	1 (0.4%)
Vomiting	0	1 (0.4%)
Gen. Disorders & Admin. Site Conditions		
Malaise	1 (0.4%)	0
Infections & Infestations		
Cystitis	1 (0.4%)	1 (0.4%)
Fungal infection	1 (0.4%)	0
Furuncle	1 (0.4%)	0
Pneumonia	0	1 (0.4%)
Investigations		
Hemoglobin decreased	1 (0.4%)	0
HIV test positive	1 (0.4%)	0
Musculoskeletal & Connective Tissue Disorders		
Muscle cramp	0	1 (0.4%)
Neoplasms Benign, Malignant & Unspecified		
Renal neoplasm	0	1 (0.4%)
Uterine cancer	1 (0.4%)	0
Nervous System Disorders		
Dizziness	0	1 (0.4%)
Headache	1 (0.4%)	1 (0.4%)
Multiple sclerosis	0	1 (0.4%)
Petit mal epilepsy	1 (0.4%)	0
Psychiatric Disorders		
Anxiety	1 (0.4%)	0
Insomnia	1 (0.4%)	0

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Table 27 continued

System Organ Class Preferred Term	Oracea™ (n = 269)	Placebo (n = 268)
Renal & Urinary Disorders		
Renal insufficiency	1 (0.4%)	0
Repro. System & Breast Disorders		
Menstruation irregular	1 (0.4%)	0
Prostatitis	1 (0.4%)	0
Respiratory, Thoracic & Mediastinal Disorders		
Bronchospasm	1 (0.4%)	0
Dyspnea	1 (0.4%)	0
Pulmonary embolism	1 (0.4%)	0
Respiratory arrest	1 (0.4%)	0
Skin & Subcutaneous Tissue Disorders		
Face edema	1 (0.4%)	0
Rosacea	1 (0.4%)	1 (0.4%)
Skin reaction	1 (0.4%)	0
Vascular Disorders		
Deep vein thrombosis	1 (0.4%)	0
Source: Table 12.7 (Module 5: combined - vol 1.57, p 108)		

Source: Sponsor's NDA submission, module 2, volume 1.1, pp. 255-6.

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Table 28: Discontinuation Due to Adverse Events in Phase 3 Studies (ITT Population)

Treat-ment	Patient _a	Sex/ Age _b	MedDRA Preferred Term (Verbatim Term if Different)	Severity	Study Drug Relationship	Outcome
Oracea™	301-100-101	F/61	Uterine cancer	Mild	Not related	Resolved
	301-200-223	M/32	Abdominal distention (bloating)	Severe	Probably	Resolved
			Gastrointestinal discomfort (gastrointestinal upset)	Severe	Probably	Resolved
			Malaise	Severe	Probably	Resolved
	301-300-312	M/27	Abdominal pain	Mild	Possibly	Resolved
			Diarrhea	Mild	Possibly	Resolved
	301-300-317	F/45	Dyspnea (shortness of breath)	Mild	Probably	Resolved
	301-600-601	F/51	Renal insufficiency (renal failure)	Severe	Not Related	Resolved
			Pulmonary embolism	Severe	Not Related	Resolved
			Respiratory arrest	Severe	Not Related	Resolved
			Deep vein thrombosis	Severe	Not Related	Resolved
			Large intestine perforation (perforated viscus of colon)	Moderate	Not Related	Resolved
			Hemoglobin decreased	Moderate	Not Related	Resolved
	301-600-605	F/42	Rosacea (worsening of acne rosacea)	Severe	Not Related	Continues
	301-600-613	F/39	Nausea	Mild	Possibly	Resolved
			Menstruation irregular	Moderate	Not Related	Resolved
			Insomnia	Moderate	Possibly	Resolved
			Anxiety	Mild	Possibly	Resolved
	301-600-624	F/37	Abdominal pain upper (stomach aches)	Moderate	Probably	Resolved
	301-700-710	F/50	Gastrointestinal pain (intestinal cramping)	Moderate	Possibly	Resolved
	301-800-813	F/44	Diarrhea	Mild	Possibly	Resolved
	302-300-319	F/46	Skin reaction	Mild	Probably	Resolved
	302-600-610	F/25	HIV test positive	Mild	Not related	Continues
	302-700-718	M/61	Furuncle (boils neck, left temple)	Moderate	Probably	Continues
	302-700-722	M/53	Dysphagia (difficulty swallowing)	Mild	Probably	Continues
			Hyperthyroidism	Moderate	Not related	Continues
			Headache	Mild	Probably	Continues
	302-800-807	F/56	Bronchospasm (bronchial spasms)	Moderate	Probably	Resolved
			Face edema (facial edema)	Moderate	Probably	Resolved
	302-800-1019	F/49	Ear congestion (left ear congestion)	Moderate	Not related	Resolved
			Fungal infection (yeast infection)	Moderate	Probably	Continues

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**Table 28: Discontinuation Due to Adverse Events in Phase 3 Studies (ITT Population)
 continued**

Treat-ment	Patient ^a	Sex/ Age ^b	MedDRA Preferred Term (Verbatim Term if Different)	Severity	Study Drug Relationship	Outcome
	302-800-4059	F/44	Petit mal epilepsy Vertigo	Moderate Moderate	Not related Not related	Continues Continues
	302-900-905	F/43	Cystitis	Moderate	Not related	Continues
	302-1000-1006	M/32	Prostatitis	Moderate	Not related	Continues
	302-1400-921	F/33	Ventricular extrasystoles (premature ventricular contractions)	Mild	Possibly	Continues
Placebo	301-200-220	F/56	Rosacea (worsening [very severe] rosacea with +100 papules and pustules)	Severe	Not Related	Continues
	301-600-614	F/57	Nausea	Moderate	Probably	Resolved
	301-600-617	M/73	Abdominal pain upper (abdominal epigastric pain)	Moderate	Probably	Resolved
	301-700-708		Diarrhea Dyspepsia (heartburn) Stomach discomfort (upset stomach)	Moderate Severe Mild	Possibly Possibly Possibly	Resolved Resolved Resolved
	301-1300-116		Pneumonia	Severe	Not related	Resolved
	302-100-109	M/21	Nausea Muscle cramp (cramping in chest muscles) Dizziness	Moderate Moderate Moderate	Probably Probably Probably	Resolved Resolved Resolved
	302-300-303	M/48	Headache	Mild	Possibly	Resolved
	302-500-512	F/51	Renal neoplasm (renal tumor)	Moderate	Not related	Resolved
	302-700-713	F/58	Cystitis (bladder infection)	Moderate	Possibly	Continues
	302-800-1017	F/37	Nausea Vomiting	Moderate Moderate	Probably Probably	Resolved Resolved
	302-900-904	F/36	Multiple sclerosis (multiple sclerosis exacerbation)	Moderate	Not related	Resolved
	302-1100-405	F/66	Diarrhea Nausea	Moderate Moderate	Probably Probably	Resolved Resolved

Source: Listing 10.4 (Module 5: combined - vol 1.57, p 242)

^a Shown as study-center-patient number

^b Age at baseline

Source: Sponsor's NDA submission, module 2, volume 1.1, pp. 257-8.

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7.1.3.3 Other significant adverse events

Study 301:	study drug	action
Respiratory arrest 310-600-601: F/51, severe not related	Oracea	discontinued
Study 302:		
Petit mal epilepsy 302-800-4059: F/44, moderate not related	Oracea	discontinued
Multiple sclerosis, exacerbation 302-900-904: F/36, moderate not related	Placebo	discontinued

Reviewer comment: The narratives for the above cases have been evaluated by this reviewer. The designation of not related to study drug is found appropriate for all three cases.

7.1.4 Other Search Strategies

Table 29: No. of Patients with Severe Adverse Events in Phase 3 Studies Combined (ITT)

System Organ Class MedDRA Preferred Term	Oracea™ (n = 269)	Placebo (n = 268)
Gastrointestinal Disorders	4 (1.5%)	2 (0.7%)
Abdominal distension	1 (0.4%)	0
Abdominal pain	1 (0.4%)	0
Abdominal pain upper	1 (0.4%)	0
Diarrhea	0	1 (0.4%)
Dyspepsia	0	1 (0.4%)
Gastrointestinal discomfort	1 (0.4%)	0
Stomach discomfort	1 (0.4%)	0
General Disorders and Administration Site Conditions	2 (0.7%)	2 (0.7%)
Influenza like illness	1 (0.4%)	0
Malaise	1 (0.4%)	0
Pain	0	1 (0.4%)
Pyrexia	0	1 (0.4%)
Infections and Infestations	4 (1.5%)	2 (0.7%)
Bronchitis	0	1 (0.4%)
Influenza	1 (0.4%)	0
Kidney infection	1 (0.4%)	0
Pharyngitis streptococcal	1 (0.4%)	0
Pneumonia	0	1 (0.4%)
Upper respiratory tract infection	1 (0.4%)	0
Injury, Poisoning, and Procedural Complications	1 (0.4%)	1 (0.4%)
Laceration	1 (0.4%)	0
Muscle injury	0	1 (0.4%)
Investigations	1 (0.4%)	0
Weight increased	1 (0.4%)	0
Musculoskeletal and Connective Tissue Disorders	1 (0.4%)	1 (0.4%)
Back pain	1 (0.4%)	0
Muscle spasms	0	1 (0.4%)
Nervous System Disorders	0	2 (0.7%)
Headache	0	2 (0.7%)
Psychiatric Disorders	1 (0.4%)	0
Anxiety	1 (0.4%)	0

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System Organ Class MedDRA Preferred Term	Oracea™ (n = 269)	Placebo (n = 268)
Renal and Urinary Disorders	2 (0.7%)	0
Nephrolithiasis	1 (0.4%)	0
Renal insufficiency	1 (0.4%)	0
Renal tubular necrosis	1 (0.4%)	0
Reproductive System and Breast Disorders	1 (0.4%)	0
Menorrhagia	1 (0.4%)	0
Respiratory, Thoracic and Mediastinal Disorders	1 (0.4%)	0
Pulmonary embolism	1 (0.4%)	0
Respiratory arrest	1 (0.4%)	0
Skin and Subcutaneous Tissue Disorders	1 (0.4%)	2 (0.7%)
Rosacea	1 (0.4%)	1 (0.4%)
Seborrheic dermatitis	0	1 (0.4%)
Vascular Disorders	2 (0.7%)	0
Deep vein thrombosis	1 (0.4%)	0
Hypertension	1 (0.4%)	0

Source: Table 12.4 (Module 5: combined – vol. 1.57, p 39)

Source: Provided by sponsor at reviewer request, NDA 50-805.

Table 30: Severe Adverse Events - Active

STUDY	Patient ID	Event	Association	Action	
301	223	Bloating,	Probable	5	
		GI upset,	Probable	5	
		Malaise	Probable	5	
		520	Heavy menstrual bleeding	Not related	3
	601	Renal failure	Not related	3, 5	
		Pulmonary Embolus	Not related	3, 5	
		Respiratory arrest	Not related	4, 5	
		DVT	Not related	3, 5	
		605	Worsening of acne rosacea	Not related	5
	624	Weight gain	Possible	1	
		Stomach aches	Probable	1	
		702	URI	Not related	3
		710	Abdominal Pain	Possible	1
		723	Flu symptoms	Possible	3
	724	Stomach upset	Possible	1	
	3018	Flu-like symptoms	Not related	2	
302	513	Anxiety attack	Not related	4	
		Strep throat	Not related	3	
	4037	Hypertension	Not related	3	
	616	Kidney infection	Not related	3	
	905	Kidney stone	Not related	3, 4	
	1114	Multiple lacerations of finger	Not related	1, 3, 4	
	923	Back pain	Not related	3	

Table 30 cont'd: Severe Adverse Events - Placebo

Study	Patient ID	Event	Association	Action
301	208	Seborrheic dermatitis	Not related	3
	220	Worsening, very severe rosacea-100 papules	Not related	3
	708	Heart burn	Possible	5
	717	Headache	Not related	3
	720	Body aches Spasms in hip area Diarrhea Headaches	Possible Possible Possible Possible	2, 3 1 2 3
	116 center (1300)	Pneumonia	Not related	3, 5
302	116 center (100)	Torn muscle at calf	Not related	3
	4034	Bronchitis	Not related	3
	904	Pyrexia/ Intermittent fever due to Avonex	Not Related	1, 3

Source: Compiled by Reviewer from Sponsor's NDA submission, module 5: vol. 1.57, pp. 130 - 241.

Actions: 1 = no change in therapy
 2 = study drug interrupted
 3 = drug therapy required
 4 = non-drug therapy
 5 = study drug discontinued and patient withdrawn

Reviewer's comment: Examination of the serious adverse events reveals a mild preponderance of GI related complaints in the Oracea™ arms of the Phase 3 trials.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In the clinical studies (COL-101- ROSE 301 and 302) any adverse event including both observed and volunteered problems, complaints, or symptoms were to be recorded on the Adverse Event Case Report Form. At each study visit, patients were evaluated for concomitant medication usage and for adverse events and vital signs. Patients were encouraged to report any adverse events including phototoxicity.

In the clinical PK studies (PERIO-DOXYSR-103, PERIO-DOXYSR-104, COL-101-SDPK-105, COL-101-SSPK-106) all adverse events whether volunteered, elicited; or noted on physical examination were to be recorded from the first dose on Day 1 of period 1 until study completion.

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7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor's categorization of AE's and use of preferred terms appears reasonable.

7.1.5.3 Incidence of common adverse events

For the combined Phase 3 studies, 55.4% of patients treated with Oracea™ and 45.5% of patients treated with placebo experienced adverse events.

Table 31: Adverse Events Reported for More Than 1.0% of Patients Treated with Oracea™ in the Phase 3 Studies Combined by System Organ Class (ITT Population)

System Organ Class Preferred Term	Study 301		Study 302		Combined Studies	
	Oracea™ (n = 127)	Placebo (n = 124)	Oracea™ (n = 142)	Placebo (n = 144)	Oracea™ (n = 269)	Placebo (n = 268)
Gastrointestinal Disorders						
Abdominal distention	1 (0.8%)	0	2 (1.4%)	1 (0.7%)	3 (1.1%)	1 (0.4%)
Abdominal pain	2 (1.6%)	1 (0.8%)	1 (0.7%)	0	3 (1.1%)	1 (0.4%)
Abdominal pain upper	3 (2.4%)	1 (0.8%)	2 (1.4%)	0	5 (1.9%)	1 (0.4%)
Diarrhea	6 (4.7%)	4 (3.2%)	6 (4.2%)	3 (2.1%)	12 (4.5%)	7 (2.6%)
Dry mouth	1 (0.8%)	0	2 (1.4%)	0	3 (1.1%)	0
Nausea	2 (1.6%)	4 (3.2%)	3 (2.1%)	4 (2.8%)	5 (1.9%)	8 (3.0%)
Stomach discomfort	3 (2.4%)	1 (0.8%)	0	1 (0.7%)	3 (1.1%)	2 (0.7%)
General Disorders & Admin. Site Conditions						
Pain	1 (0.8%)	1 (0.8%)	3 (2.1%)	0	4 (1.5%)	1 (0.4%)
Infections & Infestations						
Fungal infection	3 (2.4%)	0	2 (1.4%)	1 (0.7%)	5 (1.9%)	1 (0.4%)
Influenza	2 (1.6%)	0	3 (2.1%)	3 (2.1%)	5 (1.9%)	3 (1.1%)
Nasopharyngitis	3 (2.4%)	2 (1.6%)	10 (7.0%)	7 (4.9%)	13 (4.8%)	9 (3.4%)
Sinusitis	2 (1.6%)	1 (0.8%)	5 (3.5%)	1 (0.7%)	7 (2.6%)	2 (0.7%)
Upper respiratory tract infection	5 (3.9%)	6 (4.8%)	4 (2.8%)	14 (9.7%)	9 (3.3%)	20 (7.5%)
Investigations						
ALT increased	1 (0.8%)	1 (0.8%)	3 (2.1%)	3 (2.1%)	4 (1.5%)	4 (1.5%)
AST increased	2 (1.6%)	1 (0.8%)	4 (2.8%)	1 (0.7%)	6 (2.2%)	2 (0.7%)
Blood glucose increased	2 (1.6%)	0	1 (0.7%)	0	3 (1.1%)	0
Blood LDH increased	1 (0.8%)	0	3 (2.1%)	1 (0.7%)	4 (1.5%)	1 (0.4%)
Blood pressure increased	2 (1.6%)	0	2 (1.4%)	1 (0.7%)	4 (1.5%)	1 (0.4%)
Musculoskeletal & Connective Tissue Dis.						
Back pain	1 (0.8%)	0	2 (1.4%)	0	3 (1.1%)	0
Nervous System Disorders						
Headache	4 (3.1%)	5 (4.0%)	8 (5.6%)	11 (7.6%)	12 (4.5%)	16 (6.0%)
Sinus headache	0	0	3 (2.1%)	0	3 (1.1%)	0
Psychiatric Disorders						
Anxiety	3 (2.4%)	0	1 (0.7%)	0	4 (1.5%)	0

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Respiratory, Thoracic, & Mediastinal Disorders						
Nasal congestion	0	1 (0.8%)	4 (2.8%)	1 (0.7%)	4 (1.5%)	2 (0.7%)
Pharyngolaryngeal pain	2 (1.6%)	0	1 (0.7%)	2 (1.4%)	3 (1.1%)	2 (0.7%)
Sinus congestion	2 (1.6%)	1 (0.8%)	1 (0.7%)	2 (1.4%)	3 (1.1%)	3 (1.1%)
Skin & Subcutaneous Tissue Disorders						
Dermatitis contact	2 (1.6%)	0	1 (0.7%)	1 (0.7%)	3 (1.1%)	1 (0.4%)
Pruritus	3 (2.4%)	2 (1.6%)	1 (0.7%)	2 (1.4%)	4 (1.5%)	4 (1.5%)
Vascular Disorders						
Hypertension	2 (1.6%)	1 (0.8%)	6 (4.2%)	1 (0.7%)	8 (3.0%)	2 (0.7%)

Source: Table 12.2 (Module 5: 301 – vol 1.10, p 3; 302 – vol 1.33, p 3) and Table 12.2.1 (Module 5: combined – vol 1.56, p 143)
 Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, LDH = lactate dehydrogenase

Source: Sponsor's NDA submission, module 2, volume 1.1, p. 240.

7.1.5.4 Common adverse event tables

Table 32: Adverse Events Reported for More Than 1.0% of Patients Treated with Oracea™ in the Phase 3 Studies Combined in Decreasing Order of Frequency (ITT Population)

Preferred Term	Study 301		Study 302		Combined Studies	
	Oracea™ (n = 127)	Placebo (n = 124)	Oracea™ (n = 142)	Placebo (n = 144)	Oracea™ (n = 269)	Placebo (n = 268)
Nasopharyngitis	3 (2.4%)	2 (1.6%)	10 (7.0%)	7 (4.9%)	13 (4.8%)	9 (3.4%)
Diarrhea	6 (4.7%)	4 (3.2%)	6 (4.2%)	3 (2.1%)	12 (4.5%)	7 (2.6%)
Headache	4 (3.1%)	5 (4.0%)	8 (5.6%)	11 (7.6%)	12 (4.5%)	16 (6.0%)
Upper respiratory tract infection	5 (3.9%)	6 (4.8%)	4 (2.8%)	14 (9.7%)	9 (3.3%)	20 (7.5%)
Hypertension	2 (1.6%)	1 (0.8%)	6 (4.2%)	1 (0.7%)	8 (3.0%)	2 (0.7%)
Sinusitis	2 (1.6%)	1 (0.8%)	5 (3.5%)	1 (0.7%)	7 (2.6%)	2 (0.7%)
AST increased	2 (1.6%)	1 (0.8%)	4 (2.8%)	1 (0.7%)	6 (2.2%)	2 (0.7%)
Abdominal pain upper	3 (2.4%)	1 (0.8%)	2 (1.4%)	0	5 (1.9%)	1 (0.4%)
Fungal infection	3 (2.4%)	0	2 (1.4%)	1 (0.7%)	5 (1.9%)	1 (0.4%)
Influenza	2 (1.6%)	0	3 (2.1%)	3 (2.1%)	5 (1.9%)	3 (1.1%)
Nausea	2 (1.6%)	4 (3.2%)	3 (2.1%)	4 (2.8%)	5 (1.9%)	8 (3.0%)
ALT increased	1 (0.8%)	1 (0.8%)	3 (2.1%)	3 (2.1%)	4 (1.5%)	4 (1.5%)

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Anxiety	3 (2.4%)	0	1 (0.7%)	0	4 (1.5%)	0
Blood LDH increased	1 (0.8%)	0	3 (2.1%)	1 (0.7%)	4 (1.5%)	1 (0.4%)
Blood pressure increased	2 (1.6%)	0	2 (1.4%)	1 (0.7%)	4 (1.5%)	1 (0.4%)
Nasal congestion	0	1 (0.8%)	4 (2.8%)	1 (0.7%)	4 (1.5%)	2 (0.7%)
Pain	1 (0.8%)	1 (0.8%)	3 (2.1%)	0	4 (1.5%)	1 (0.4%)
Pruritus	3 (2.4%)	2 (1.6%)	1 (0.7%)	2 (1.4%)	4 (1.5%)	4 (1.5%)
Abdominal distention	1 (0.8%)	0	2 (1.4%)	1 (0.7%)	3 (1.1%)	1 (0.4%)
Abdominal pain	2 (1.6%)	1 (0.8%)	1 (0.7%)	0	3 (1.1%)	1 (0.4%)
Back pain	1 (0.8%)	0	2 (1.4%)	0	3 (1.1%)	0
Blood glucose increased	2 (1.6%)	0	1 (0.7%)	0	3 (1.1%)	0
Dermatitis contact	2 (1.6%)	0	1 (0.7%)	1 (0.7%)	3 (1.1%)	1 (0.4%)
Dry mouth	1 (0.8%)	0	2 (1.4%)	0	3 (1.1%)	0
Pharyngolaryngeal pain	2 (1.6%)	0	1 (0.7%)	2 (1.4%)	3 (1.1%)	2 (0.7%)
Sinus congestion	2 (1.6%)	1 (0.8%)	1 (0.7%)	2 (1.4%)	3 (1.1%)	3 (1.1%)
Sinus headache	0	0	3 (2.1%)	0	3 (1.1%)	0
Stomach discomfort	3 (2.4%)	1 (0.8%)	0	1 (0.7%)	3 (1.1%)	2 (0.7%)

Source: Table 12.3 (Module 5: 301 – vol 1.10, p 11; 302 – vol 1.33, p 12) and Table 12.3.1 (Module 5: combined – vol 1.56, p 221)
 Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, LDH = lactate dehydrogenase

Source: Sponsor's NDA submission, module 2, volume 1.1, p. 239.

Regarding the AE's reported by more than 1% of patients treated with Oracea™, a higher percentage occurred in the Oracea™ group than the placebo group. The between group differences were generally four or fewer patients. The largest between group differences were seen for diarrhea, hypertension, sinusitis, and upper respiratory tract infection. Most AE's were rated as mild or moderate.

7.1.5.5 Identifying common and drug-related adverse events

Diarrhea was reported more frequently in the Oracea™ treatment group than in the Placebo group for both study 301 and 302. For the combined studies, diarrhea was noted in 12 patients (4.5%) in the Oracea™ group and in 7 patients (2.6%) in the placebo group. Most of these AE's were considered possibly related to the study medication. These events were all mild or moderate except for one severe case in the placebo group.

Reviewer's comment: The presence of the diarrhea may mean that, contrary to the sponsor's statement that at the systemic concentrations provided by Oracea™ doxycycline is not effective as an antimicrobial agent; the relative increase in diarrhea may indicate an antimicrobial effect on the intestinal flora.

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Hypertension was reported for 8 patients (3.0%) in the Oracea™ group and 2 patients (0.7%) in the placebo group. These events were all mild or moderate except for one severe case in the Oracea™ group. The events were considered by the investigator not related to study medicine. Sinusitis was reported for 7 patients (2.6%) in the Oracea™ group and 2 patients (0.7%) in the placebo group. The events were rated as mild to moderate and all were considered by the investigator to be not related to study medication.

Upper respiratory tract infection was reported for 20 patients (7.5%) in the placebo group and 9 patients (3.3%) in the Oracea™ group.

Reviewer's comment: It is possible this could be due to chance; however, the excess of upper respiratory infections in the placebo as compared with the Oracea™ arm suggests an antimicrobial effect.

Adverse events considered by the investigator to be treatment-related (including AEs considered possibly or probably related to study drug and events with missing relationship) for more than 1% of patients in the Oracea™ group were:

diarrhea (4.1%),
headache (2.2%),
upper abdominal pain (1.9%),
nausea (1.9%),
fungal infection (1.9%),
increased AST (1.5%),
and stomach discomfort (1.1%).

Treatment-related adverse events reported for more than 1% of patients in the placebo group were:

headache (4.1%),
nausea (3.0%),
diarrhea (1.5%),
vomiting (1.1%),
vaginal mycosis (1.1%),
and dizziness (1.1%)

Source: Sponsor's NDA submission, module 2, vol. 1.1, p. 243 (Compiled from Table 12.5, Module 5 – vol. 1.57, p 101).

Pharmacokinetic Studies:

In PERIO-DOXYSR-103, no AE was considered related to the study drug. All AE's were mild except joint sprain, rated as moderate.

In PERIO-DOXYSR-104, all AE's were mild except abdominal pain, loose stools, and urinary tract infection which were reported as moderate during treatment with Oracea™. Adverse events considered possibly related to study drug (Oracea™) were anorexia, constipation, hypotension, and abdominal pain. Adverse events considered possibly related to study drug (Periostat® BID) were abdominal pain, upper abdominal pain, dyspepsia, and headache.

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In Study COL-101-SDPK-105, one AE, dizziness, was considered possibly related to the study drug (Oracea™ Fasting). AE's were mild except for an occurrence of vasovagal syncope rated as moderate.

In study COL-101-SSPK-106, twenty eight AE's were considered possibly related to study drug (16 during Oracea™ treatment and 12 during Periostat® BID treatment). All AE's were mild except headache in two subjects and vomiting in one subject, which were rated as moderate. Among the 16 AE's considered possibly related to drug treatment with Oracea™ were headache (8), nausea (4), dry eye, eye redness, lower abdominal pain, and decreased appetite. Among the 12 AE's considered possibly related to drug treatment with Periostat® BID were nausea (3), abdominal pain (2), dry eye (2), loose stools, diarrhea, eye redness, vomiting, and headache.

Periostat® Clinical Studies

Capsule Formulation:

AE's of special interest for tetracycline class antibiotics include those related to the gastrointestinal system, skin, hypersensitivity reactions, and infection. There were reported no statistically significant differences in the frequency of these AE's and placebo groups (Source: Sponsor's NDA submission, module 2, vol. 1.1, table S, p. 280.).

Reviewer's comment: Of note, in the table there appears to be a trend to increasing numbers of gastrointestinal events with increasing Periostat® dose, 10mg, to 20mg, to 40mg QD.

Tablet Formulation:

In study DERM-301, the most frequently reported AE's were influenza in three patients in the Periostat® (n=26) group, headache in 3 patients in the placebo(n=25) group, and rash in 2 patients in the Periostat® group.

In study DERM-303, the most frequently reported AE's were headache (16.4% Periostat®, 9.0% placebo) and migraine (4.5% Periostat®, 0 placebo). The most frequently reported treatment related events were headache, migraine, and rash.

7.1.5.6 Additional analyses and explorations

Data for additional analyses was not submitted.

Less Common Adverse Events

Considering tetracycline drugs as a class and doxycycline more specifically, some categories of AE's are of particular interest. These include those related to the gastrointestinal system, skin, hypersensitivity reactions, and infection.

Gastrointestinal AEs occurred in a higher proportion of patients in the Oracea™ group than the placebo group (13.4% versus 8.6%). Photosensitivity was not reported, sunburn was reported for 2 patients in the Oracea™ group and 1 patient in the placebo group, and rash was reported for 2 patients in each treatment group. It should be noted that according to the protocols, patients were

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to be cautioned about exposure to sunlight and encouraged to apply sunscreen with an SPF value of 30 or more that provided protection against both UVA and UVB light whenever they went out of doors during daylight hours during the studies. No instances of hypersensitivity reactions were reported. Among infections, fungal infections and sinusitis were reported for somewhat higher percentages of patients in the Oracea™ group than in the placebo group (1.9% versus 0.4% and 2.6% versus 0.7%, respectively). No instances of vaginal candidiasis, vaginal mycosis, or vaginitis were reported in the Oracea™ group, while these AEs were reported for 5 patients in the placebo group.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Phase 3 Studies

Complete blood count (CBC) and chemistry panel tests (glucose, uric acid, calcium, sodium, potassium, chloride, alkaline phosphatase, total bilirubin, bicarbonate, creatinine, BUN, AST (SGOT), ALT(SGPT), LDH, total protein, albumin, and C-reactive protein were performed at Baseline and Week 16 or early exit visits.

Table 33: Number of Subjects Exposed to Study Drug with Laboratory Assessments

	COL-101-ROSE-301	COL-101-ROSE-302
Baseline	124	140
Follow-up*	104	128

*Follow-up for both studies was 16 weeks

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The pivotal trials COL-101-ROSE-301 (study 301) and ROSE-302 (study 302) were the only studies that were placebo-controlled and for which laboratory assessments were made.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

None were performed.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

For each study, laboratory data were summarized for each treatment group by visit and using shift tables from baseline to endpoint (last valid observation). There was no statistical analysis of treatment group differences.

There were no notable changes, according to the sponsor, for any laboratory parameter from baseline to endpoint in either treatment group for either study 301 or study 302. Of note, patients

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were not instructed to fast prior to having blood drawn for laboratory testing, which may have affected the outcome of some results such as glucose.

Study 301: (source - Sponsor's NDA submission module 5, vol. 1.9, pp. 54)

In the treatment group from baseline to endpoint, a decrease of $\geq 4\%$ in the percentage of patients with values within the normal range of test results was seen for glucose and for SGPT.

For glucose, the percentage of patients with values within the normal range decreased from 86% at baseline to 82% at endpoint. The percentage of patients with values above the normal range increased from 9% (11 patients) at baseline to 15% (16 patients) at endpoint. The percentage of patients with values below the normal range decreased from 6% (7 patients) at baseline to 3% (3 patients) at endpoint.

For SGPT, the percentage of patients with values within the normal range decreased from 87% at baseline to 82% at endpoint. The percentage of patients with values above the normal range increased from 13% (16 patients) at baseline to 18% (19 patients) at endpoint.

In the placebo group from baseline to endpoint, a decrease of $\geq 4\%$ in the percentage of patients with values within the normal range of test results were seen for glucose and hemoglobin.

For all other laboratory parameters, the change in percentage of patients with values within the normal range decreased by $\leq 3\%$ or increased in both treatment groups.

Study 302: (source – Sponsor's NDA submission module 5, vol. 1.32, pp. 60-61)

In the treatment group from baseline to endpoint, a decrease of $\geq 4\%$ in the percentage of patients with values within the normal range was seen for glucose and for SGOT.

For glucose the percentage of patients with values within the normal range decreased from 86% at baseline to 78% at endpoint. The percentage of patients with values above the normal range increased from 10% (14 patients) at baseline to 17% (22 patients) at endpoint. The percentage of patients (6 patients) with values below the normal range remained constant from baseline to endpoint.

For SGOT the percentage of patients with values within the normal range decreased from 92% at baseline to 88% at endpoint. The percentage of patients with values above the normal range increased from 8% (11 patients) at baseline to 12% (15 patients) at endpoint.

In the placebo group from baseline to endpoint, decreases of $\geq 4\%$ in the patients with values within the normal range of test results were seen for glucose, SGPT, absolute neutrophils, and alkaline phosphatase.

For all other laboratory parameters, the change in percentage of patients with values within the normal range decreased by $\leq 3\%$ or increased in both treatment groups.

Thirty patients (17 in the Oracea™ group and 13 in the placebo group) had laboratory test values at endpoint (last available on-treatment visit) that were considered by the investigator to be clinically significant laboratory abnormalities. In some cases, the clinically significant abnormal

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laboratory results at Week 16/endpoint followed results outside of the reference range at the baseline visit. For 18 of these patients (10 in the Oracea™ treatment group and 8 in the placebo group), abnormal laboratory test results were reported by the investigator as AEs. No patients discontinued study medication due to abnormal laboratory test results.

Table 34: Patients in Phase 3 Studies with Clinically Significant Laboratory Values at Endpoint

Study-Center-Patient (Sex/Age)	Test (Normal Range)	Visit: Value	AE (Y/N) Comments
Oracea™			
301-200-212 (F/44)	Glucose (3.9 – 6.4 mmol/L)	Baseline: 12.7 mmol/L (H; CS) Week 16/Endpoint: 11.3 mmol/L (H; CS)	No
	ALT (SGPT) (6 – 34 U/L)	Baseline: 71 U/L (H; CS) Week 16/Endpoint: 63 U/L (H; CS)	No
	AST (SGOT) (9 – 34 U/L)	Baseline: 55 U/L (H; CS) Week 16/Endpoint: 72 U/L (H; CS)	No
301-200-213 (F/38)	ALT (SGPT) (6 – 34 U/L)	Baseline: 32 U/L Week 16/Endpoint: 74 U/L (H; CS)	Yes; possibly related to study drug.
	AST (SGOT) (9 – 34 U/L)	Baseline: 23 U/L Week 16/Endpoint: 40 U/L (H; CS)	Yes; possibly related to study drug.
301-300-302 (F/33)	AST (SGOT) (9 – 34 U/L)	Baseline: 24 U/L Week 16/Endpoint: 67 U/L (H; CS)	Yes; probably related to study drug.
	LDH (53 – 234 U/L)	Baseline: 186 U/L Week 16/Endpoint: 253 U/L (H; CS)	Yes; probably related to study drug.
301-1100-1106 (F/49)	ALT (SGPT) (6 – 34 U/L)	Baseline: 48 U/L (H) Week 16/Endpoint: 96 U/L (H; CS)	Yes; not related to study drug
	AST (SGOT) (9 – 34 U/L)	Baseline: 50 U/L (H) Week 16/Endpoint: 119 U/L (H; CS)	
302-100-103 (F/54)	Glucose (3.9 – 6.4 mg/dL)	Baseline: 13.3 mg/dL (H) Baseline: 15.7 mg/dL (H; CS) Week 16/Endpoint: 15.8 mg/dL (H; CS)	No
302-1400-409 (F/42)	AST (SGOT) (9 – 34 U/L)	Baseline: 195 U/L (H; CS) Week 16/Endpoint: 315 U/L (H; CS)	Yes; possibly related to study drug
	ALT (SGPT) (6 – 34 U/L)	Baseline: 243 U/L (H; CS) Week 16/Endpoint: 260 U/L (H; CS)	Yes; possibly related to study drug
	LDH (53 – 234 U/L)	Baseline: 258 U/L (H) Week 16/Endpoint: 258 U/L (H; CS)	Yes; possibly related to study drug
302-600-612 (M/57)	Glucose (3.9 – 6.4 mg/dL)	Baseline: 6.2 mg/dL Week 16/Endpoint: 11.2 mg/dL (H; CS)	No
302-600-616 (F/56)	Glucose (3.9 – 6.4 mg/dL)	Baseline: 9.6 mg/dL (H; CS) Week 16/Endpoint: 8.8 mg/dL (H; CS)	No
	Potassium (3.4 – 5.4 mEq/L)	Baseline: 3.7 mEq/L Week 16/Endpoint: 2.9 mEq/L (L; CS)	No

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302-600-623 (F/43)	WBC Count (3.80 – 10.70 x 10 ³ /μL)	Baseline: 12.89 x 10 ³ /μL (H; CS) Week 16/Endpoint: 12.32 x 10 ³ /μL (H; CS)	No
	Neutrophils, absolute (1.96 – 7.23 x 10 ³ /μL)	Baseline: 10.45 x 10 ³ /μL (H; CS) Week 16/Endpoint: 9.43 x 10 ³ /μL (H; CS)	No

Study-Center-Patient (Sex/Age)	Test (Normal Range)	Visit: Value	AE (Y/N) Comments
302-700-705 (F/42)	Total Bilirubin (3 – 21 mg/dL)	Baseline: 22 mg/dL (H) Week 16: 32 mg/dL (H; CS) Week 16b: 24 mg/dL (H) Endpoint: 24 mg/dL (H)	No
	AST (SGOT) (9 – 34 U/L)	Baseline: 24 U/L Week 16: 50 U/L (H; CS) Week 16b: 36 U/L (H; CS) Endpoint: 36 U/L (H; CS)	No
	ALT (SGPT) (6 – 34 U/L)	Baseline: 33 U/L Week 16: 80 U/L (H; CS) Week 16b: 58 U/L (H; CS) Endpoint: 58 U/L (H; CS)	No
	Alkaline Phosphatase (31 – 106 U/L)	Baseline: 98 U/L Week 16: 130 U/L (H; CS) Week 16b: 117 U/L (H; CS) Endpoint: 117 U/L (H; CS)	No
302-700-719 (M/52)	Uric Acid (149 – 494 mg/dL)	Baseline: 523 mg/dL (H) Week 16/Endpoint: 535 mg/dL (H; CS)	No
	Glucose (3.9 – 6.4 mg/dL)	Baseline: 9.4 mg/dL (H) Week 16/Endpoint: 31.9 mg/dL (H; CS)	Yes (diabetes); not related to study drug
	ALT (SGPT) (6 – 43 U/L)	Baseline: 42 U/L Week 16/Endpoint: 45 U/L (H;CS)	No
302-800-807 (F/56)	Glucose (3.9 – 6.4 mg/dL)	Baseline: 12.2 mg/dL (H; CS) Week 16/Endpoint: 10.2 mg/dL (H; CS)	No
	CRP ≤0.287 mg/dL	Baseline: 15.900 mg/dL (H) Week 16/Endpoint: 14.200 mg/dL (H; CS)	No
302-900-902 (F/39)	Uric Acid (125 – 428 mg/dL)	Baseline: 369 mg/dL Week 16/Endpoint: 476 mg/dL (H; CS)	Yes; possibly related to study drug
302-1000-1004 (F/52)	Uric Acid (149 – 446 mg/dL)	Baseline: 494 mg/dL (H) Week 16/Endpoint: 619 mg/dL (H; CS)	Yes; not related to study drug
	ALT (SGPT) (6 – 34 U/L)	Baseline: 113 U/L (H; CS) Week 16/Endpoint: 119 U/L (H; CS)	Yes; not related to study drug
	AST (SGOT) (9 – 34 U/L)	Baseline: 83 U/L Week 16/Endpoint: 83 U/L (H; CS)	Yes; not related to study drug
	LDH (53 – 234 U/L)	Baseline: 277 U/L (H; CS) Week 16/Endpoint: 240 U/L (H;CS)	Yes; not related to study drug

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302-800-1020 (M/39)	AST (SGOT) (11 – 36 U/L)	Baseline: 23 U/L Week 16/Endpoint: 42 U/L (H; CS)	Yes; possibly related to study drug
302-100-4037 (M/80)	Hemoglobin (125 – 170 g/dL)	Baseline: 166 g/dL Week 16/Endpoint: 173 g/dL (H; CS)	Yes; not related to study drug

Study- Center- Patient (Sex/Age _a)	Test (Normal Range)	Visit: Value	AE (Y/N) Comments
	Hematocrit (0.37 – 0.51%)	Baseline: 0.53% (H) Week 16/Endpoint: 0.54% (H; CS)	Yes; not related to study drug
	Glucose (3.9 – 6.7 mg/dL)	Baseline: 6.4 mg/dL Week 16/Endpoint: 7.5 mg/dL (H; CS)	No
302-100-4041 (F/39)	Glucose (3.9 – 6.4 mg/dL)	Baseline: 4.1 mg/dL Week 16/Endpoint: 7.3 mg/dL (H; CS)	Yes; not related to study drug
	CRP ≤0.287 mg/dL	Baseline: 1.210 mg/dL Week 16/Endpoint: 4.240 mg/dL (H; CS)	Yes; not related to study drug
Placebo			
301-200-216 (F/39)	ALT (SGPT) (6 – 34 U/L)	Baseline: 33 U/L Week 16/Endpoint: 74 U/L (H; CS)	Yes; possibly related to study drug.
	AST (SGOT) (9 – 34 U/L)	Baseline: 28 U/L Week 16/Endpoint: 53 U/L (H; CS)	
301-800-815 (F/35)	Uric Acid (125 – 428 μmol/L)	Baseline: 375 μmol/L Week 16/Endpoint: 488 μmol/L (H; CS)	Yes; not related to study drug
	ALT (SGPT) (6 – 34 U/L)	Baseline: 47 U/L (H; CS) Week 16/Endpoint: 55 U/L (H; CS)	
	AST (SGOT) (9 – 34 U/L)	Baseline: 27 U/L Week 16/Endpoint: 38 U/L (H; CS)	
302-100-124 (F/38)	Atypical lymphocytes (N/A)	Baseline: No data available Week 16/Endpoint: 0 (H; CS)	Yes; not related to study drug
302-100-514 (M/40)	Uric Acid (125 – 488 mg/dL)	Baseline: 553 mg/dL (H; CS) Week 16/Endpoint: 613 mg/dL (H; CS)	Yes; not related to study drug
	AST (SGOT) (11 – 36 U/L)	Baseline: 41 U/L (H; CS) Week 16/Endpoint: 40 U/L (H; CS)	No
	ALT (SGPT) (6 – 43 U/L)	Baseline: 95 U/L (H; CS) Week 16/Endpoint: 81 U/L (H; CS)	No
302-100-518 (F/48)	ALT (SGPT) (6 – 34 U/L)	Baseline: 48 U/L (H;CS) Week 16/Endpoint: 44 U/L (H;CS)	Yes; not related to study drug
302-600-603 (F/42)	Glucose (3.9 – 6.4 mg/dL)	Baseline: 5.2 mg/dL Week 16/Endpoint: 7.5 mg/dL (H; CS)	No

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302-600-619 (F/52)	Glucose (3.9 – 6.4 mg/dL)	Baseline: 5.5 mg/dL Week 16/Endpoint: 6.8 mg/dL (H; CS)	No
302-600-624 (M/36)	Glucose (3.9 – 6.4 mg/dL)	Baseline: 8.7 mg/dL (H) Baseline: 7.2 mg/dl (H; CS) Baseline: 7.2 mg/dl (H; CS) Week 16/Endpoint: 7.2 mg/dL (H; CS)	No
	CRP ≤0.287 mg/dL	Baseline: 2.150 mg/dL Baseline: 2.370 mg/dL Week 16/Endpoint: 14.500 mg/dL (H; CS)	No

Study-Center-Patient (Sex/Age ^a)	Test (Normal Range)	Visit: Value	AE (Y/N) Comments
302-900-908 (F/33)	Alkaline Phosphatase (31 – 106 U/L)	Baseline: 148 U/L (H; CS) Baseline: 148 U/L (H; CS) Baseline: 119 U/L (H) Week 16/Endpoint: 134 U/L (H; CS)	No
302-900-909 (F/47)	Hemoglobin (116 – 164 g/dL)	Baseline: 91 g/dL (L; CS) Week 16/Endpoint: 113 g/dL (L; CS)	No
302-1100-1108 (M/80)	Hemoglobin (125 – 170 g/dL)	Baseline: 105 g/dL (L) Week 16/Endpoint: 93 g/dL (L; CS)	Yes (anemia); possibly related to study drug
	Hematocrit (0.37 – 0.51%)	Baseline: 0.35% (L) Week 16/Endpoint: 0.32% (L; CS)	
302-100-4044 (F/53)	ALT (SGPT) (6 – 34 U/L)	Baseline: 42 U/L (H; CS) Week 16/Endpoint: 36 U/L (H;CS)	Yes; not related to study drug
	LDH (53 – 234 U/L)	Baseline: 239 U/L (H; CS) Week 16/Endpoint: 273 U/L (H;CS)	Yes; not related to study drug
	CRP (≤0.287 mg/dL)	Baseline: 5.460 mg/dL (H; CS) Week 16/Endpoint: 4.000 mg/dL (H; CS)	Yes; not related to study drug
302-800-4058 (M/37)	ALT (SGPT) (6 – 43 U/L)	Baseline: 39 U/L Week 16: 54 U/L (H; CS) Week 16 ^b : 43 U/L Endpoint: 43 U/L	Yes; not related to study drug
	Platelets (140 – 400 x 10 ³ /μL)	Baseline: 281 x 10 ³ /μL Week 16: 112 x 10 ³ /μL (L; CS) Week 16 ^b /Endpoint: 217 x 10 ³ /μL	Yes; not related to study drug
^a Age at baseline ^b Unscheduled visit(s) L = Below normal range; H = Above normal range; CS = Value determined by the Investigator to be a clinically significant laboratory abnormality; EP = Endpoint; N/A = Not applicable Data Source: Module 5: 301 – vol 1.9, p 61; 302 – vol 1.32, p 69			

Source: Sponsor's NDA submission, module 2, volume 1.1, pp. 262-5.

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Reviewer comment: Note that, in the treatment group, most of the values that were reported as AEs consisted of liver function test abnormalities. However the total number of patients involved was low, only being 4.

Tetracyclines may cause an increase in BUN. That was not seen in the Phase 3 studies with Oracea™. In study 301 mean BUN was 5.49 mmol at baseline and 5.55 mmol at endpoint in the Oracea™ group; corresponding values in the placebo group were 5.18 and 5.26 mmol/L. In study 302 mean BUN was 5.09 mmol at baseline and 5.17 mmol at endpoint in the Oracea™ group; corresponding values in the placebo group were 5.41 and 5.30 mmol/L (Table 14.11, Module 5: 301 – vol. 1.10, p 99; 302 – vol. 1.33, p 117).

Other Oracea™ Studies

No clinically significant changes or findings were noted in clinical laboratory evaluations in studies 103, 104, 105, and 106.

Periostat® Clinical Studies

Studies with both capsule and table formulation reveal insignificant clinical laboratory safety signals.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

There were no marked outliers.

No patients discontinued study medication due to abnormal laboratory test results.

7.1.7.4 Additional analyses and explorations

No additional analyses were done.

7.1.7.5 Special assessments

No special assessments were performed.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs (systolic and diastolic blood pressure, pulse rate, respiration rate, weight and height) were measured at each scheduled visit in the Phase 3 studies, COL-ROSE-301 and 302.

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Vital signs (oral temperature, respiratory rate, and automated seated blood pressure and pulse) were obtained in the pharmacokinetic studies; 103, 104, 105, and 106 at screening, and at intervals variously including 12 hours, approximately 40 minutes prior to, and just prior to dosing and 3 hours, 12 hours, 24 hours, 36 hours, 48 hours, 60 hours and 72 hours post dosing.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Vital signs data from the pivotal trials, COL-101-ROSE 301 and 302 will be the principal subject of analysis below. Vital signs from the pharmacokinetic studies will be mentioned briefly.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 *Analyses focused on measures of central tendencies*

None were performed.

7.1.8.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

For each study descriptive statistics for baseline, analysis time point, and change from baseline were summarized. In addition, an endpoint was defined as the last valid observation for the ITT population. The last post-baseline observation was carried forward to the endpoint summary. There was no statistical analysis of treatment group differences.

There were only small mean changes from baseline and no apparent differences between the treatment groups in changes from baseline in vital signs and weight in either study 301 or 302.

Predefined criteria for changes of potential clinical importance were as follows:

<u>Variable</u>	<u>Criteria Values</u>
Systolic Blood Pressure	≥ 180 mmHg and an increase from baseline of ≥ 20 mmHg ≤ 90 mmHg and a decrease from baseline of ≥ 20 mmHg
Diastolic Blood Pressure	≥ 105 mmHg and an increase from baseline of ≥ 15 mmHg ≤ 50 mmHg and a decrease from baseline of ≥ 15 mmHg

Using the predefined criteria above, fourteen patients (6 in the Oracea™ group and 8 in the placebo group) had individual changes in blood pressure values that were considered clinically important. Except for one patient (4037) none of these clinically important changes in blood pressure were reported as Adverse Events.

Two patients in study 302 had individual changes in blood pressure values during the 4-week follow-up period that met the predefined criteria. Neither of the clinically important changes in blood pressure was reported as an AE.

Reviewer comment: The criteria for changes of clinical importance for the upper bounds of the systolic and diastolic blood pressure may be overly generous.

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Other Oracea™ Studies

No clinically significant changes or findings were noted in vital sign measurements or physical examinations in studies 103, 104, 105, and 106.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Patient 4037, in study 302 at center 100 and on Oracea™, had clinically important changes in blood pressure reported as an Adverse Event. This patient had an increase in systolic blood pressure from 150 mmHg at the Baseline Visit to 180 mmHg at the Week 3 Visit. Systolic blood pressure decreased to 120 mmHg at the Week 6 Visit, and increased to 182 mmHg at the Week 12 Visit. Systolic blood pressure was 170 mmHg and 120 mmHg at the Week 16/Endpoint and Week 20 Visits, respectively. Hypertension of severe intensity and considered not related to study medication was reported as an AE on Day 27 of the study. The hypertension was being treated, and was ongoing.

7.1.8.4 Additional analyses and explorations

None were performed.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECGs were not performed during any of the studies of Oracea™ (doxycycline capsules). Doxycycline is a member of the tetracycline class of antibiotics. As noted in the pharmacology/toxicology review, the literature and previous clinical experience with Periostat® and Vibramycin suggest that there is no safety pharmacology concern associated with doxycycline.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable because ECGs were not performed.

7.1.9.3 Standard analyses and explorations of ECG data

Not applicable because ECGs were not performed.

7.1.9.4 Additional analyses and explorations

Not applicable because ECGs were not performed.

7.1.10 Immunogenicity

Not applicable since the drug is not a therapeutic protein.

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7.1.11 Human Carcinogenicity

One case of uterine cancer was reported in study 301. The investigator considered this not related to study drug. The patient received the first dose of study drug on 08/04/04, developed uterine bleeding 09/26/04, and was diagnosed with a biopsy 09/28/04. The patient was then discontinued from the study.

No other tumors were reported for study 302 or for the pharmacokinetic studies 103, 104, 105, and 106. Of note these studies were generally of short duration; one was 20 weeks, another 16, and the others 23 days or less.

PERO-DOXYMR-301 was ongoing when the original NDA was submitted. This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the effect of Oracea™ once daily versus placebo, when administered in combination with scaling and root planning (SRP), on attachment level and pocket depth in patients with adult periodontitis. Patients received Oracea™ 40 mg or placebo once daily in conjunction with SRP for 9 months. The safety report dated 3/17/2006 indicated that in the treatment group (SRP + Oracea™, n=133) there was one case of testis cancer considered not related to the study drug. Also in the treatment group was a case of basal cell carcinoma and considered unrelated to study drug. In the placebo treatment group (SRP + Placebo, n=133) there was also a case of basal cell carcinoma.

7.1.12 Special Safety Studies

None were performed.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No instances of drug abuse were reported in pivotal study, 301 or 302. Tetracyclines as a class and doxycycline in particular are not known to be subject to drug abuse. There is no reason to expect a potential for drug abuse based on the pharmacologic properties of these drugs.

7.1.14 Human Reproduction and Pregnancy Data

A urine pregnancy test was obtained for women of childbearing potential at the pre-study screening visit and at the 16-week exit visit. No positive pregnancy tests were recorded in either study 301 or study 302.

No pregnancies have been reported during other clinical trials with Oracea™ or with Periostat® capsules or tablets. However, four pregnancies have been reported in post-marketing experience. Two of these involve healthy births with no complications. Another involves a birth, but no further information available. A fourth case involves a pregnancy with drug exposure in the first trimester. No follow-up information is available on this patient.

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The proposed labeling for Oracea™ is the same as that approved for Periostat® regarding pregnancy (Category D with a related warning). The proposed labeling is also the same as that approved for Periostat® regarding nursing mothers (use of Oracea™ contraindicated with a related warning).

7.1.15 Assessment of Effect on Growth

Not applicable because of short study duration.

7.1.16 Overdose Experience

No cases of overdose have been reported during clinical trials either with Oracea™ or with Periostat® (capsules or tablets).

Two cases of accidental overdose and one case of “antibiotic poisoning” have been reported in post-marketing experience. The accidental overdose cases involved one extra dose. In one case no complications were reported and in the other no further information was available.

The third case involved a sales representative who received a report from a dentist of “antibiotic poisoning” following treatment for 3 days with Periostat® 20 mg QD. The dentist said that the patient was not specific and did not describe his symptoms. No further information was available for this case.

7.1.17 Post-Marketing Experience

The related product Periostat® (doxycycline hyclate) 20 mg was approved for marketing in the United States as the capsule formulation on September 30, 1998 (NDA 50-744) and became available by prescription in November 1998. The tablet formulation was approved for marketing on February 2, 2001 (NDA 50-783). Since April 2003, only the tablet formulation has been available.

Since Periostat® became available in the United States, both the overall incidence of adverse drug reactions (ADRs) and the incidence of specific labeled ADRs, as reported through post-marketing surveillance, clinical studies, and in the scientific literature, have remained consistent with the current product labeling. Periodic safety update reports through 8/01/2005 have been examined. Current product labeling is as a tetracycline class antibiotic.

7.2 Adequacy of Patient Exposure and Safety Assessments

Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The clinical development program for Oracea™ included six clinical studies. These are described by the sponsor as, "...two pilot pharmacokinetic studies, a multiple-dose steady-state bioequivalence study comparing Oracea™ with Periostat®, a food-effect study, and two Phase 3 studies, COL-101-ROSE-301 and COL-101-ROSE-302..." All of these studies were conducted in the United States. (Sponsor's NDA submission module 2, vol. 1.1, p. 78)

Please see Section 4 (Data Sources, Review strategy and Data Integrity) for tables of clinical studies.

7.2.1.2 Demographics

Table 35: Summary of Demographics for Healthy Subjects in Phase 2 Studies

Characteristic	Study 103 (N = 18)	Study 104 (N = 14)	Study 105 (N = 30)	Study 106 (N = 32)
Age, years				
Mean (SD)	33 (7.8)	28 (8.3)	27 (6.8)	29 (8.4)
Median (range)	32 (22 to 45)	27 (19 to 44)	25 (18 to 44)	28 (18 to 45)
Gender				
Male	9 (50%)	7 (50%)	16 (53%)	23 (72%)
Female	9 (50%)	7 (50%)	14 (47%)	9 (28%)
Race				
Caucasian	16 (89%)	10 (71%)	22 (73%)	24 (75%)
Black	2 (11%)	1 (7%)	5 (17%)	4 (13%)
Asian	0	0	1 (3%)	1 (3%)
Other	0	3 (21%) ^a	2 (6%) ^b	3 (9%) ^c
Missing	0	0	0	0

Source: Study reports in Module 5

a One "mixed," one Black and Native American, and one Latino

b One Hispanic and one Hispanic/Korean

c Two Hispanic and one American Indian/Alaskan native

Source: Sponsor's NDA submission module 2, volume 1.1, Table 2.7.4-6, p. 237.

Reviewer comment: Demographics of healthy subjects in the Phase 2 studies revealed median ages of 25 to 32 years, a greater number of males than females (59% to 41%) and a majority of

Caucasians (77%). As compared with the phase 3 studies, (see table following) the median ages are lower, more males are present, and the Caucasian preponderance is not so marked in the Phase 2 studies.

Table 36: Summary of Demographics (ITT Population) Phase 3 Studies

Characteristic	Study 301		Study 302		Combined Studies	
	Oracea™ (n = 127)	Placebo (n = 124)	Oracea™ (n = 142)	Placebo (n = 144)	Oracea™ (n = 269)	Placebo (n = 268)
Age, years						
Mean (SD)	46.8 (13.17)	47.6 (11.50)	46.3 (12.66)	47.6 (13.34)	46.5 (12.88)	47.6 (12.50)
Median (range)	46.0 (22-90)	47.0 (19-84)	46.0 (20-80)	47.0 (19-82)	46.0 (20-90)	47.0 (19-84)
Age group, n (%)						
18 to 35 years	26 (20.5%)	16 (12.9%)	30 (21.1%)	27 (18.8%)	56 (20.8%)	43 (16.0%)
36 to 50 years	58 (45.7%)	60 (48.4%)	64 (45.1%)	57 (39.6%)	122 (45.4%)	117 (43.7%)
51 to 70 years	35 (27.6%)	44 (35.5%)	43 (30.3%)	52 (36.1%)	78 (29.0%)	96 (35.8%)
> 70 years	8 (6.3%)	4 (3.2%)	5 (3.5%)	8 (5.6%)	13 (4.8%)	12 (4.5%)
Gender, n (%)						
Male	36 (28.3%)	29 (23.4%)	48 (33.8%)	49 (34.0%)	84 (31.2%)	78 (29.1%)
Female	91 (71.7%)	95 (76.6%)	94 (66.2%)	95 (66.0%)	185 (68.8%)	190 (70.9%)
Race, n (%)						
Caucasian	108 (85.0%)	107 (86.3%)	135 (95.1%)	141 (97.9%)	243 (90.3%)	248 (92.5%)
Black	0	0	2 (1.4%)	0	2 (0.7%)	0
Asian	1 (0.8%)	0	1 (0.7%)	1 (0.7%)	2 (0.7%)	1 (0.4%)
Other ^a	18 (14.2%)	17 (13.7%)	4 (2.8%)	2 (1.4%)	22 (8.2%)	19 (7.1%)
Source: Table 2.1 (Module 5: 301 – vol 1.9, p 73; 302 – vol 1.32, p 83; combined – vol 1.56, p 2) ^a 301 Oracea™: 17 Hispanic, 1 Native American; 301 placebo: 15 Hispanic, 1 Spanish, 1 Latin 302 Oracea™: 2 Hispanic, 2 Native American; 302 placebo: 2 Hispanic						

Source: Sponsor's NDA submission module 2, volume 1.1, Table 2.7.3-4, p. 209.

Reviewer comment: Within the phase 3 studies the treatment groups are similar with regard to age, sex, and race. Comparing study 301 with 302, demographic characteristics were similar. The age, sex and racial distribution reflect that of the disease. Please also see section 6.1.4.

7.2.1.3 Extent of exposure (dose/duration)

Table 37: Oracea™ Exposure for Healthy Subjects in Phase 2 Studies (No. of Subjects)

	Study 103	Study 104	Study 105	Study 106
Oracea™ 40 mg single dose	17	NA	30 ^a	NA
Oracea™ 40 mg QD for 7 days	NA	14	NA	32 ^b
Source: Study reports, Module 5 Abbreviations: NA = not applicable, QD = once daily ^a Single dose in fed state and single dose in fasted state ^b One subject withdrew after 3 days of dosing.				

Source: Sponsor's NDA submission, module 2, volume 1.1, p. 236.

Table 38: Oracea™ Exposure for Patients in Phase 3 Studies (ITT Population)

Characteristic	Study 301		Study 302		Combined Studies	
	Oracea™ (n = 127)	Placebo (n = 124)	Oracea™ (n = 142)	Placebo (n = 144)	Oracea™ (n = 269)	Placebo (n = 268)
Exposure (days)						
N	121	119	137	140	258	259
Mean SD	103.1	106.9	101.2	106.9	102.1	106.9
Median	30.09	24.15	29.79	28.72	29.89	26.67
Range	113.0	113.0	112.0	113.0	112.0	113.0
	7 - 210	11 - 182	2 - 146	4 - 231	2 - 210	4 - 231
≤ 17 days	4 (3.1%)	1 (0.8%)	6 (4.2%)	3 (2.1%)	10 (3.7%)	4 (1.5%)
18 - 38 days	8 (6.3%)	4 (3.2%)	6 (4.2%)	4 (2.8%)	14 (5.2%)	8 (3.0%)
39 - 78 days	3 (2.4%)	6 (4.8%)	6 (4.2%)	7 (4.9%)	9 (3.3%)	13 (4.9%)
79 - 106 days	16 (12.6%)	5 (4.0%)	15 (10.6%)	7 (4.9%)	31 (11.5%)	12 (4.5%)
≥ 107 days	90 (70.9%)	103 (83.1%)	104 (73.2%)	119 (82.6%)	194 (72.1%)	222 (82.8%)
Unknown	6 (4.7%)	5 (4.0%)	5 (3.5%)	4 (2.8%)	11 (4.1%)	9 (3.4%)
Person-Days of Exposure	12,473	12,717	13,864	14,959	26,337	27,676

Source: Table 6.1 (Module 5: 301 – vol 1.9, p 111; 302 – vol 1.32, p 126; combined – vol 1.56, p 8)

Source: Sponsor's NDA submission, module 2, volume 1.1, p. 236.

All subjects who were enrolled and received at least one dose of Oracea™ were included in the safety analysis. In the Phase 3 studies, which had a 16-week treatment duration, 269 rosacea patients had a mean exposure to Oracea™ of 102 days (range 2 to 210 days) and the total person-days of exposure was 26,337 (see Table 2.7.4-4 above).

Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.1.4 Other studies

The primary studies used in the evaluation of safety were the six submitted to the NDA, the two phase 3 studies, 301 and 302, and the four pharmacokinetic studies, 103, 104, 105, and 106.

Also referred to, are the four ongoing studies with Oracea™: COL-101-ROSE-201, COL-101-ROSE-202, COL-101-ACNE-201, and PERIO-DOXYMR-301.

The following data for Periostat® (doxycycline hyclate) 20 mg are summarized as supportive safety information for Oracea™:

- A) Safety data from clinical trials with the capsule formulation, which were summarized in the NDA 50-744 safety summary and supported approval of that NDA
- B) Safety data from clinical trials with the tablet formulation (NDA 50-783)

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7.2.1.5 Post-marketing experience

Post-marketing experience with the capsule and tablet formulations:

The related product Periostat® (doxycycline hyclate) 20 mg was approved for marketing in the United States as the capsule formulation on September 30, 1998 (NDA 50-744) and became available by prescription in November 1998. The tablet formulation was approved for marketing on February 2, 2001 (NDA 50-783). Since April 2003, only the tablet formulation has been available. Periodic safety update reports through 8/01/2005 have been examined.

7.2.1.6 Literature

The sponsor has submitted literature regarding pharmacokinetics and bioavailability of doxycycline in humans, pathophysiology, classification, and treatment of rosacea, and safety considerations for tetracycline class antibiotics. Also submitted are a number of references related to the use and efficacy of sub-antimicrobial dose doxycycline. Of note, many of the latter report on research that was funded by the sponsor. The literature search is acceptable; however, a concern exists about bias in the references related to sub-antimicrobial dose doxycycline.

Adequacy of Overall Clinical Experience

In the Phase 3 studies, 269 rosacea patients had a mean exposure to Oracea™ of 102 days (range 2 to 210 days). The total person-days of exposure was 26,337. The median age was 46.0 years and is appropriate for a disease that has its onset between the ages of 30 and 50 years. While the racial makeup of the Phase 3 trials does not mirror that of the U.S. population, it does mirror those expected to be more at risk for rosacea, those with fairer skin.

The exposure in the four pharmacokinetic studies was much less, total person-days of exposure of 366. The median ages for the four studies were 32, 27, 25, and 28. The racial distribution more closely followed that of the general U.S. population. Since healthy volunteers were the subjects of these trials this is not unexpected.

The dose, Oracea™ 40 mg once daily, was determined based on a previous study by the sponsor in which Periostat® tablets 20mg twice daily were administered to patients with moderate rosacea. Over a 16 week period this resulted in a significant reduction in the total inflammatory lesion count compared with placebo (DERM-303 study report submitted to ). Pilot pharmacokinetic studies of Oracea™ showed plasma concentrations of doxycycline that are maintained below the antimicrobial threshold, a plasma level (C_{max}) below 1.0 µg/mL. The sponsor states this antimicrobial threshold was defined based on previous experience with the approved drug Periostat®. According to the sponsor a higher dose did not appear to be necessary for efficacy.

The safety profile for Periostat® has been shown to be similar to that of placebo. Since similar drug exposure was demonstrated at steady state with Oracea™ QD and Periostat® in pharmacokinetic trials, the safety profile of Periostat® is relevant to Oracea™. According to the

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sponsor, a lower dose Of Oracea™ would not be expected to garner any additional benefit with regard to safety or efficacy.

Reviewer comment: Whether the dose of Oracea™ 40mg once daily is optimal rests on whether this product truly operates by the proposed mechanism. The sub-antimicrobial mechanism of action as proposed may require further animal testing for support. Suggestions of GI toxicity in the side effects profile may indicate that it is not a truly sub-antimicrobial dose.

According to the sponsor, the 16-week treatment duration was chosen because longer treatment of patients with placebo was considered unethical. A protocol amendment extended the length of study 301 by 4 weeks without treatment in order to assess the longevity of treatment effects.

Reviewer comment: The sponsor may need to rely on the Agency's findings of safety for other doxycycline products in order to meet the requirements of ICH-E1A, clinical safety of drugs intended for long-term treatment of non-life threatening conditions.

The pivotal studies were multicenter, randomized, double-blind, placebo-controlled, parallel group trials. This design is acceptable to assess safety and efficacy.

The exclusion of pregnant women or women of childbearing potential who were not using an adequate form of birth control is acceptable as Oracea™ is classified as pregnancy category D in the proposed label.

Study patients who developed ocular rosacea that required treatment by an ophthalmologist or whose existing condition worsened during the course of the study and required referral to an ophthalmologist were to be withdrawn.

Reviewer comment: This exclusion may demonstrate that the utility of this drug is rather narrow.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

For this application the sponsor did not perform animal or *in vitro* testing but relied on the Agency's approval of NDA 50-744 (Periostat®). This data is owned by the sponsor. The pharmacology/toxicology reviewer found no nonclinical safety issues relevant to the clinical use of Oracea™. However, the sponsor has committed to conduct a 2-year carcinogenicity study with doxycycline monohydrate in mice.

7.2.5 Adequacy of Routine Clinical Testing

In the pivotal studies, 301 and 302, complete blood count (CBC) and chemistry panel tests (glucose, uric acid, calcium, sodium, potassium, chloride, alkaline phosphatase, total bilirubin, bicarbonate, creatinine, BUN, AST (SGOT), ALT(SGPT), LDH, total protein, albumin, and C-reactive protein) were performed at Baseline and Week 16 or early exit visits. According to existing labeling for Periostat®, the catabolic action of the tetracyclines may cause an increase in

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BUN. Also according to tetracycline class labeling, hemolytic anemia, thrombocytopenia, and eosinophilia have been reported. The sponsor's laboratory testing program was acceptable to detect these types of findings.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

For this application the sponsor did not perform metabolic, clearance or interaction workup. As noted by the pharmacology/toxicology reviewer, the pharmacokinetics of doxycycline has been thoroughly discussed in the scientific literature.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The sponsor encouraged patients to report any adverse events including phototoxicity.

The sponsor did not actively solicit for gastrointestinal or infectious adverse events. A number of these events were captured in the general screening for adverse events.

7.2.8 Assessment of Quality and Completeness of Data

Deficiencies in the quality or completeness of the safety data were not identified.

7.2.9 Additional Submissions, Including Safety Update

Additional submissions include a safety update report for Oracea™ dated March 17, 2006. This includes data from the clinical study PERIO-DOXYMR-301 which was ongoing when the original NDA was submitted.

The other element of the safety update report is post-marketing data for the approved product Periostat® (doxycycline hyclate) 20mg tablets. This is referenced in section 7.1.17 (Post-Marketing Experience) and will not be further referred to here.

Study PERIO-DOXYMR-301 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the effect of Oracea™ once daily versus placebo, when administered in combination with scaling and root planning (SRP), on attachment level and pocket depth in patients with adult periodontitis. Patients received Oracea™ 40 mg or placebo once daily in conjunction with SRP for 9 months. Patients were randomly assigned, 133 to receive SRP + Oracea™ and, 133 to receive SRP + placebo. The majority of patients completed the study, 110 (82.7%) in the Oracea™ group and 117 (88.0%) in the placebo group.

In the ITT population, age, sex, and racial distributions were similar between the treatment groups. The mean age was 48.5 years in the Oracea™ group and 49.9 years in the placebo

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group. In the Oracea™ and placebo groups the majority of the patients were Caucasian, 65.4% and 75.2% respectively. In both groups there was a higher proportion of female than male patients, 56.4% versus 43.6% in the Oracea™ group and 53.4% versus 46.6% in the placebo group. The mean length of exposure to study medication was similar between treatment groups, 252.7 days in the Oracea™ group and 256.8 days in the placebo group. The total person days of exposure were 31,846 for the Oracea™ group and 33,128 for the placebo group.

There were no deaths during this study. During the study nine patients (3.4%) experienced treatment-emergent Serious Adverse Events (SAEs). In the Oracea™ group 6 patients each experienced one SAE (testis cancer, viral infection, gastrointestinal ulcer, pleurisy, worsening of peripheral artery disease, basal cell carcinoma). None of these were considered treatment related. In the placebo group 3 patients each experienced one SAE (chest pain, arterial thrombosis limb, basal cell carcinoma).

Discontinuations due to adverse events included 7(5.3%) patients in the Oracea™ group and 5(3.8%) patients in the placebo group. In the Oracea™ group, among those 7 who discontinued, were 3 who were withdrawn due to AE's (nausea, constipation, and vomiting) considered possibly related to study medication. In the placebo group one patient withdrew due to an AE (back pain) considered possibly treatment related.

Considering adverse effects (AEs) overall, AEs were reported for 66.2% of patients treated with Oracea™ and 70.7% of patients treated with placebo. For those treated with Oracea™, the most frequently reported AEs were headache (13 patients, 9.8%), influenza (7 patients, 5.3%), and nasopharyngitis (7 patients, 5.3%). For the placebo group, the most commonly reported AEs were sensitivity of teeth (13 patients, 9.8%), headache (10 patients, 7.5%), and nasopharyngitis (10 patients, 7.5%).

The numbers of patients in either the Oracea™ or placebo groups with laboratory values out of the reference ranges were generally not remarkable. One exception was alkaline phosphatase wherein high values (6 Oracea™ and 1 placebo group patient) at screening were probably related to high values at the final visit. Another exception was glucose wherein 6 Oracea™ and 3 placebo group patients had high values at the last visit. Again for 2 of the Oracea™ and all 3 of the placebo group patients, this may have been related to high glucose values at screening. Additionally, glucose results may have been affected by the fact that patients were not instructed to fast prior to having blood drawn. No patients discontinued the study due to clinically significant laboratory test results.

Reviewer comment: The population of study PERIO-DOXYMR-301 is similar to that of the pivotal trials, 301 and 302. The exposure was somewhat longer in PERIO-DOXYMR-301 with a mean exposure to study drug of 252.7 days (total person days 31,846) as compared with 102.1 days (total person days 26,337) for the combined pivotal studies. The side effect profile for PERIO-DOXYMR-301 appears similar to that of the combined pivotal studies with a suggestion of a mild increase in gastrointestinal side effects.

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Microbiological monitoring was carried out on 87 subjects before initiation of treatment and after 9 months of treatment. According to the sponsor, the subjects randomized to Oracea™ presented with approximately an 8% greater load of doxycycline-resistant bacteria than the subjects randomized to placebo (12.69% and 3.95%, respectively). Over time, the treatment groups were equivalent in percentage change (5.09% and 5.38% respectively) and yielding final loads of 17.79% and 9.33% for the Oracea™ and the placebo groups. The sponsor concluded that Oracea™ treatment did not increase the total recoverable flora resistant to doxycycline.

Reviewer comment: The fact that the final load of doxycycline resistant bacteria is higher in the Oracea™ treatment group is explained by the sponsor as the result of the fact that subjects who were randomized to Oracea™ presented with higher a higher load initially. It is possible that other processes are occurring that would contradict the sponsor's conclusion that Oracea™ treatment did not increase the total load of recoverable flora resistant to doxycycline.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Adverse events for Oracea™ were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Common and drug related adverse events in the safety population of the pivotal studies, 301 and 302, follow in decreasing order of frequency:

- 1) The most common AEs were in the Infections and Investigations system organ class, Oracea™/Placebo = 14%/13%; upper respiratory tract infection, nasopharyngitis, and sinusitis were the most common among preferred terms.
- 2) The next class was the Gastrointestinal Disorders class, Oracea™/Placebo = 13%/7%; diarrhea and nausea were the most common among preferred terms.
- 3) The Investigations class showed Oracea™/Placebo = 7%/3%; ALT increased and AST increased were the most common among preferred terms.

The largest between treatment group differences were observed for the preferred terms, diarrhea, hypertension, and sinusitis, and upper respiratory tract infection. Please see further discussion of these in section 7.1.5.5.

For the purposes of this analysis the pharmacokinetic studies, 103, 104, 105, and 106 are less revealing as the comparison is Oracea™ to Periostat® (except 106 Oracea™ Fasting to Oracea™ Fed) and treatment times are short, one dose or 7 doses. Please see further discussion in section 7.1.5.5.

For study PERIO-DOXYMR-301, adverse events for Oracea™ were also coded using the Medical Dictionary for Regulatory Activities (MedDRA). Common and drug related adverse events in the safety population for this study follow in decreasing order of frequency:

- 1) Gastrointestinal Disorders system organ class, SRP + Oracea™/SRP + Placebo = 26.3%/33.1%; sensitivity of teeth, toothache, and gingival pain were the most common among preferred terms.

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2) Infections and Infestations system organ class, SRP + Oracea™/SRP + Placebo = 22.6%/29.3%; nasopharyngitis, tooth abscess, and influenza were the most common among preferred terms.

3) Nervous System Disorders system organ class, SRP + Oracea™/SRP + Placebo = 12.8%/9.0%; headache and dizziness were the common preferred terms.

In study PERI-DOXYMR-301, among those treated with Oracea™, the most frequently reported AEs were headache, influenza, and nasopharyngitis. For the placebo group, the most commonly reported AEs were sensitivity of teeth, headache, and nasopharyngitis. Please also see discussion above, section 7.2.9.

This analysis shows that drug related AEs were not a large or severe class. Noted principally in the pivotal studies, an increase in gastrointestinal side effects among those on Oracea™, is consistent with the known side effects of tetracycline class antibiotics.

7.4 General Methodology

Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Adverse event data from the two pivotal studies, 301 and 302, were pooled together. Both studies were identical in design except that 302 included a 4 week extension without treatment.

7.4.1.2 Combining data

The pooled studies were combined without weighting.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Not applicable as only one dose (Oracea™ capsule 40mg) was evaluated for this application.

7.4.2.2 Explorations for time dependency for adverse findings

In pivotal studies 301 and 302, twenty patients in the Oracea™ treatment group were withdrawn due to AEs. Thirteen of these patients were withdrawn due to AEs considered possibly or probably related to study medication. For twelve of these patients the timing of the AEs was consistent with study drug use. This group included 4 patients who withdrew solely due to

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gastrointestinal disorders and three who withdrew due to gastrointestinal disorders in addition to AEs in at least one other system organ class.

In the pharmacokinetic studies, only one patient, study 106, was discontinued due to AEs judged by the investigator to be related to study medication. The AEs included nausea, headache, decreased appetite, and lower abdominal pain. The timing appeared consistent with study drug use.

In study PERIO-DOXYMR, seven patients in the treatment group (Oracea™ + SRP) were withdrawn due to AEs. Three of these patients were withdrawn due to AEs (nausea, constipation, and vomiting) considered possibly related to study medication. Based on information available the timing of these AEs was consistent with study drug use.

7.4.2.3 Explorations for drug-demographic interactions

A subgroup analysis of adverse events by age, sex, race and gender was not performed for this NDA.

7.4.2.4 Explorations for drug-disease interactions

Not conducted for this NDA.

7.4.2.5 Explorations for drug-drug interactions

Not conducted for this NDA.

7.4.3 Causality Determination

The common drug related side effects were discussed in section 7.1.5.5 and include diarrhea, upper abdominal pain, fungal infection, increase AST, and stomach discomfort. Note that two additional common drug related side effects, headache and nausea, were seen in a higher percentage in the placebo group than in the Oracea™ treatment group. Most of these AEs are known AEs of tetracycline class antibiotics and therefore can be causally associated with Oracea™. In addition the time dependency of many adverse events, discussed in 7.4.2.2 above, strengthens the case for a finding of causality.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Oracea™ doxycycline 40 mg capsules are intended for once daily oral administration. This is the dosing regimen that was used in the Phase 2 and Phase 3 clinical studies. The selection of the 40mg/day dose of Oracea™ was based on a previous study by the sponsor in which Periostat® tablets 20 mg twice daily given to patients with moderate rosacea over a 16 week

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period resulted in a significant reduction in the total inflammatory lesion count as compared with placebo. Also pilot pharmacokinetic studies showed that plasma doxycycline concentrations with Oracea™ 40mg/day were maintained below the antimicrobial threshold.

The effect of food on pharmacokinetics of a single dose of Oracea™ 40 mg capsules was studied in 30 healthy volunteers in study 105. There was a delay of about one hour for the mean Tmax in the fed state compared with the fasted state. Because this decrease in systemic exposure can be clinically significant proposed labeling should recommend that if Oracea™ is taken close to meal times, it be taken at least one hour prior to or two hours after meals.

8.2 Drug-Drug Interactions

Studies of drug-drug interactions were not conducted for this NDA. Please see section 5, pharmacology, for discussion of labeled drug-drug interactions.

8.3 Special Populations

Oracea™ capsules were studied in patients aged 18 and greater since rosacea is uncommon in the pediatric age group.

In general Oracea™ was more effective than placebo across gender and age groups when analyzed for lesion counts and Week 16 IGA. In study 301 Oracea™ was more effective in males than females when the IGA is examined. This differential response was not seen in study 302. Few patients in these studies were non-Caucasian. While Oracea™ demonstrated efficacy in Caucasians it did not show superiority to placebo in non-Caucasians.

Pregnant and breast-feeding women were excluded from these studies. This is appropriate based on the teratogenic effects of tetracycline class antibiotics and which are given a Pregnancy Category D.

The bioavailability of doxycycline is reduced at high pH in a study in healthy volunteers. This reduced bioavailability may be clinically significant in patients with gastrectomy, gastric bypass surgery or who are otherwise deemed achlorhydric.

Studies have shown no significant difference in serum half-life of doxycycline in patients with normal and severely impaired renal function. Hemodialysis does not alter the serum half-life of doxycycline.

The anti-anabolic action of the tetracyclines may cause an increase in BUN. While this is not a problem in those with normal renal function, in patients with significantly impaired function, higher serum levels of tetracycline-class antibiotics may lead to azotemia, hyperphosphatemia, and acidosis. If renal impairment exists, even usual oral or parenteral doses may lead to excessive systemic accumulations of the drug and possible liver toxicity.

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Under such conditions, lower than usual total doses are indicated, and if therapy is prolonged, serum level determinations of the drug may be advisable.

8.4 Pediatrics

Oracea 40 mg doxycycline capsules are a new dosage form. A pediatric assessment is required per the Pediatric Research Equity Act (PREA). The sponsor requests a full waiver from the requirement to perform pediatric studies with the drug product for the claimed indication. This is in accord with 21 CFR § 314.55(2)(c)(ii) wherein the sponsor certifies that ...”Necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small or geographically dispersed; ...” Since rosacea is uncommon in patients less than 18 years of age it would be difficult to enroll patients in the pediatric age group. A pediatric waiver will be granted to the sponsor.

8.5 Advisory Committee Meeting

Not applicable. No Advisory Committee was convened in response to this application.

8.6 Literature Review

Literature would support the inclusion of additional clinical descriptors such as papules, nodules, slight pinkness, fiery redness, and telangiectasia in the Investigator Global Assessment. Rosacea as a disorder includes clinical findings beyond inflammatory lesions. Please also see section 6.1 (Indication) for further discussion of rosacea and references.

Commonly employed endpoints found in applications for rosacea include percent reduction in inflammatory lesion counts and the percentage of patients reaching “clear” or “almost clear” in the static Investigator Global Assessment (IGA) at the end of the study. To be successful statistically significant efficacy should be demonstrated in the IGA as well as in lesion counts.

8.7 Post-Marketing Risk Management Plan

The standard risk management measures of prescription status, professional labeling and spontaneous adverse event reporting are sufficient risk management activities for this drug at this time.

8.8 Other Relevant Materials

The sponsor has proposed the proprietary name Oracea — Consultation was obtained with the Division of Drug Medication Errors and Technical Support (DMETS) Office of Drug Safety. DMETS does not recommend the use of the proprietary name Oracea — due to its potential to look similar to Arava, Omacor, Ovace, and Orasone if the modifier — is omitted from the name. An additional product Orencia*** (abatacept) was found to have look-alike and sound-alike potential with Oracea — Also if the modifier — is omitted from the name.

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With respect to the proprietary name, Oracea™, DMETS is concerned about the introduction of a proprietary name for an extended-release formulation without the use of a modifier. DMETS acknowledges that the sponsor does not currently market an immediate-release formulation of doxycycline monohydrate. DMETS envisions errors and confusion if and when the sponsor decides to market an immediate-release formulation with a proprietary name.

DMETS notes that the sponsor proposes to use “doxycycline _____ capsules” as their established name. DMETS notes that _____ are not included in the established names of USP monographed products since they do not alter the interchangeability of the drug. The current monograph title for immediate-release doxycycline monohydrate is doxycycline capsules. Therefore DMETS requests that _____ be removed from the established name.

The Division of Drug Marketing, Advertising, and Communications (DDMAC) finds the name Oracea™ from a promotional perspective.

9 OVERALL ASSESSMENT

9.1 Conclusions

Oracea™ doxycycline 40 mg capsules are a rosacea product intended for once daily oral administration in patients 18 years and older.

In NDA 50-805, the sponsor demonstrated in two nearly identical Phase 3 trials that Oracea™ was statistically superior to placebo in producing a change from baseline in inflammatory lesion count at Week 16. As identified in the protocols a secondary endpoint was change from baseline in IGA at Week 16. The Division recommended dichotomizing this endpoint to define treatment responders as those having an IGA score of 0 (Clear) or 1 (Near Clear) at endpoint (Week 16). The proportion of patients responding in the Oracea™ group was significantly greater than in the placebo group in both study 301 and 302.

No deaths in healthy patients occurred during the development program for Oracea™ doxycycline 40 mg capsules. The most frequent adverse events related to study drug use were nasopharyngitis, diarrhea, headache, and upper respiratory tract infection. The side effects with the largest between group differences (Oracea™ versus placebo) were diarrhea, hypertension, and sinusitis. The between group differences seen in these instances, however, were not large. Pivotal trials, COL-101-ROSE-301 and COL-101-ROSE-302, were of adequate design and sufficiently powered to study the safety and efficacy of Oracea™ at a dose of 40mg once daily in patients 18 years and older.

The sponsor has demonstrated efficacy of Oracea™ 40 mg capsules for the treatment of only the papular and pustular components of rosacea in patients 18 years and older.

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9.2 Recommendation on Regulatory Action

This reviewer recommends that TRADENAME capsules be approved for treatment of only the papule and pustule component of rosacea in patients 18 years of age and older.

9.3 Recommendation on Post-Marketing Actions

9.3.1 Risk Management Activity

Prescription status, professional labeling, and spontaneous adverse event reporting are sufficient risk management activities for this drug product at this time.

9.3.2 Required Phase 4 Commitments

The required Phase 4 commitments will involve further safety evaluation of Oracea™ (doxycycline, USP) 40 mg capsules.

A) Conduct a properly designed human sperm motility and morphology study to evaluate the effects of long-term use of Oracea™ (doxycycline, USP) 40mg capsules on human sperm in male patients with rosacea.

The sponsor has agreed and will: 1) Submit study protocol September 2006. 2) Start study February 2007. 3) Submit study report June 2008.

B) Submission of carcinogenicity study protocol and dose finding data: June 2007. Carcinogenicity study start date: August 2007. Submission of final carcinogenicity study report: February 2010.

The Sponsor agrees to this Phase 4 commitment as follows: 1) Submit carcinogenicity study protocol: June 2007. 2) Study start date: August 2007. 3) Final report submission: February 2010.

C) Conduct a study to examine longer term safety in at least 300 rosacea patients treated with Oracea™ (doxycycline, USP) 40mg capsules for at least 1 year. Study report submission within 2 years from date of approval.

The Sponsor contends that it has already fulfilled the requirements for study of long-term safety based on data from other studies extending as long as 12 to 18 months with another formulation of doxycycline.

Because this is a systemic drug and not topical, exposure is similar between Oracea™ and the other formulation of doxycycline. This response is acceptable.

D) A post-approval Medication Error Monitoring Program for the proprietary name, Oracea™. This program should consist of:

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Patricia C. Brown, MD
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- 15-Day Reporting of all Medication Errors;
- Root Cause Analysis; and
- Trigger requiring a proprietary name change.

CollaGenex Pharmaceuticals agrees to a Medication Error Monitoring Program for the proprietary name, Oracea™, consisting of the above three components.

This Phase 4 commitment appears sufficient to address any concerns regarding the proprietary name, Oracea™, at this time.

9.3.3 Other Phase 4 Requests

No other phase 4 requests are made.

9.4 Labeling Review

Changes to the Oracea™ label supplied by the sponsor were based on evaluation of chemistry information, preclinical and clinical studies for the NDA, and DMETS/ODS review.

- 1) Replace (doxycycline _____ capsules) 40 mg with (doxycycline, USP) capsules 40 mg.
- 2) Modify Clinical Pharmacology section to delete mechanism of action.
- 3) Modify table of pharmacokinetic parameters to include standard deviations.
- 4) Modify Special Populations section on gender, relating to rate and extent of absorption.
- 5) Modify Clinical Studies section to reflect salient features of studies conducted. Include no effect on erythema as compared to placebo. All graphs were deleted.
- 6) Modify Indications and Usage section to reflect use of TRADENAME only for *treatment of the papule and pustule component of rosacea in adult patients*. No meaningful effect was demonstrated for generalized erythema (redness) of rosacea. This formulation of doxycycline has not been evaluated in the treatment or prevention of infections.
- 7) Update Warnings section to reflect teratogenic, gastrointestinal, metabolic effects, and photosensitivity.
- 8) Update Precautions section to include that safety beyond 9 months has not been established. Also include autoimmune syndromes, tissue hyperpigmentation, and the possibility of development of bacterial resistance to tetracyclines.
- 9) Modify Information for Patients so that it is contained in a discrete section and reflects safety and correct usage concerns.
- 10) Update Laboratory Tests section so that it reflects current labeling for tetracycline class antibiotics.
- 11) Update Drug Interactions to include effects on low dose oral contraceptives.
- 12) Update Adverse Reactions section so that in the table provided abdominal symptoms and signs are grouped.
- 13) Modify Dosage and Administration section to indicate that safety beyond 9 months has not been established.

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Patient Package Insert:

A Patient Package Insert (PPI) has been included and reviewed by the Division and appropriate Agency consultants. This insert is recommended to inform patients regarding safety concerns and the proper use of Oracea™ (doxycycline, USP) 40 mg capsules.

16 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

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/s/

Patricia Brown
5/26/2006 02:51:40 PM
MEDICAL OFFICER

Markham Luke
5/26/2006 04:34:07 PM
MEDICAL OFFICER
Please see Clinical Team Leader Secondary Review.

Stanka Kukich
5/26/2006 04:43:42 PM
MEDICAL OFFICER
Concur with the MO's recommendation that this application be
approved

evaluate erythema as a secondary endpoint. The description of efficacy was not sufficient to allow approval of this drug for the broader indication of rosacea. Additional descriptors to focus the indication to what was studied were needed. Thus, the INDICATIONS AND USAGE section of labeling now reads:

“TRADENAME is indicated for the treatment of only the inflammatory papules and pustules of rosacea in adult patients. No meaningful effect was demonstrated for generalized erythema (redness) of rosacea. TRADENAME has not been evaluated for the treatment of the erythematous, telangiectatic, or ocular components of rosacea. Efficacy of TRADENAME beyond 16 weeks and safety beyond 9 months have not been established.

This formulation of doxycycline has not been evaluated in the treatment or prevention of infections. TRADENAME should not be used for treating bacterial infections, providing antibacterial prophylaxis, or reducing the numbers or eliminating microorganisms associated with any bacterial disease.

To reduce the development of drug-resistant bacteria as well as to maintain the effectiveness of other antibacterial drugs, TRADENAME should be used only as indicated. “

In the future, the Investigator’s Global Assessment should be a comprehensive Global evaluation of the disease at hand, whether it be rosacea or acne. Lesion counts only evaluate a limited, albeit highly relevant, aspect of the disease.

In summary, the efficacy of TRADENAME is modest for an oral drug, with greater numbers of lesions cleared in patients with rosacea than seen with placebo and a greater number of subjects categorizable in the success category at the pre-chosen timepoint of evaluation. Please see biostatistics review by Steve Thomson.

Pharmacokinetics

Doxycycline is a long-acting tetracycline with a half-life of 14 to 22 hours. Doxycycline, unlike tetracycline and minocycline, is excreted primarily via the GI tract and while this drug may therefore be used in patients with renal compromise it is relatively contraindicated in patients with severe liver disease.

The applicant has attempted to differentiate its formulation from that of other formulations of doxycycline. However, as is pointed out by Abimbola Adebowale in the Biopharmaceutics review the mean plasma doxycycline concentration vs. time profile of TRADENAME Capsules is not very different from the immediate-release tablets.

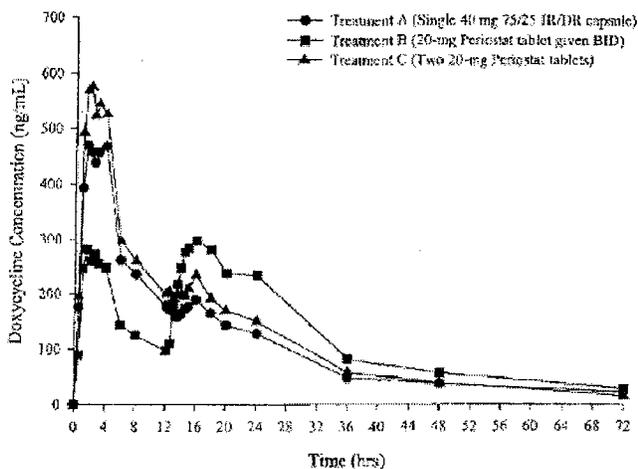


Figure 14.2.1-1. Mean Plasma Doxycycline Concentration versus Time Profile in the Normal Scale.

The applicant has requested a new dosage form name _____ for their product. This is not acceptable as was discussed and agreed upon in the Clinical Biopharmaceutics internal meeting on the 28th of April, 2006. Instead it was proposed that labeling incorporate description of the component immediate and delayed release beads.

Product Name

Please see review by the Division of Medication Errors and Technical Support, Office of Drug Safety. The applicant proposed name of ORACEA was determined via standard procedures implemented by ODS to have the likely possibility of being confused with other names. The applicant did not submit any other names upon request by the Agency until May 24, 2006. This delay did not allow sufficient time to review the new name proposed _____. The applicant offered to provide instead a mechanism for change of its product name should there be reported instances of name confusion. A decision has yet to be made, however, it is recommended by this reviewer that the guidance of the Division of Medication Errors and Technical Support be followed.

Summary

TRADENAME Capsules appears to be modestly effective in treating papules and pustules associated with rosacea. While the inflammatory lesions of rosacea are reduced in number, it has not been adequately demonstrated whether the anti-inflammatory effect is due to doxycycline or due to reducing inflammatory bacteria.

The Dermatology Clinical Team Leader agrees that TRADENAME (doxycycline) Capsules, 40 mg should be approvable for the indication "for the treatment of only the inflammatory papules and pustules of rosacea".

Markham C. Luke, M.D., Ph.D.
Lead Medical Officer, Dermatology

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this page is the manifestation of the electronic signature.**

/s/

Markham Luke

5/25/2006 03:15:07 PM

MEDICAL OFFICER

Clinical Team Leader Secondary Review for Doxycycline, 40 mg
for only inflammatory papules and pustules of rosacea.

Stanka Kukich

5/26/2006 03:44:26 PM

MEDICAL OFFICER

The applicant's proposed Phase IV Commitment, Medication Error Monitoring
Program, appears sufficient at this time to address
the Agency's concern regarding the proprietary name, Oracea.