Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

AusPAR Attachment 1

Extract from the Clinical Evaluation Report for Doxycycline monohydrate

Proprietary Product Name: Oracea

Sponsor: Galderma Australia Pty Ltd

Date of CER: 12 May 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
AAN	Australian approved name
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
CEA	Clinician's Erythema Assessment
CER	Clinical evaluation report
COPD	Chronic obstructive pulmonary disease
CSR	Clinical study report
GCP	Good clinical (research) practice
GGT	Gamma glutamyl transferase
HPLC	High performance liquid chromatography
IGA	Investigator's Global Assessment
ITT	Intention to treat
LC-MS/MS	Liquid chromatography–tandem mass spectrometry
LLQ	Lower limit of quantitation
LSM	Geometric least square mean
NA	Not applicable
PI	Product information
PK	Pharmacokinetic
PP	Per protocol
SAE	Serious adverse event
SOC	System organ class
SRP	Scaling and root planing
TIL	Total inflammatory lesions (papules + pustules + nodules)

1. Clinical rationale

The mode of action in rosacea is thought to be *via* properties of the drug other than its antimicrobial activity. Pre-clinical studies, and also some clinical pharmacodynamic results (*e.g.* Skidmore *et al.* 2003), suggest that the drug has effects in certain dermatologic conditions at concentrations generally below the antimicrobial level.

1.1. Guidance

TGA had advised as follows:

> "*TGA advises that the pharmacokinetic studies include comparisons with Periostat tablets. As this product is not registered in Australia, the sponsor is required to provide either a comparison with relevant Australian registered formulation, or a justification/comparative data etc for not doing so.*"

The sponsor's response was:

> *"The comparative PK studies with Periostat, PERIO-DOXYSR-103 (Mod 5, Vol 1), PERIODOXYSR-104 (Mod 5, Vol 3) & COL-101-SSPK-106 (Mod 5, Vol 4), submitted in Module 5.3.1.2 of the registration dossier are included in the dossier to demonstrate the PK parameters of doxycycline monohydrate (Oracea) which is the subject of this registration application.*
>
> *The dossier is not intended to be comparative and the studies are included as the available PK data for ORACEA. These PK studies in comparison with Periostat have been provided to show the bioequivalence with Oracea. Therefore, Galderma used the existing animal safety data performed with the product Periostat in this registration application.*
>
> *Oracea dossier is a stand-alone application with a full package of clinical data to demonstrate the safety & efficacy of a doxycycline product with a new indication."*

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The submission contained the following clinical information:

- Module 5
  - Five pharmacokinetic / bioavailability studies (nos. 110801, COL-101-SDPK-105, PERIO-DOXYSR-103, PERIO-DOXYSR-104 and COL-101-SSPK-106).
  - Five published clinical studies (in which the effect of chronic administration of low doses of doxycycline on antimicrobial resistance was examined: Thomas *et al.* (1998), Walker *et al.* (2000), Thomas *et al.* (2000), Skidmore *et al.* (2003) and Walker *et al.* (2005).
  - Three phase III, placebo-controlled studies in patients with rosacea: 2 with Oracea (COL-101-ROSE-301 and COL-101-ROSE-302) and 1 with a different product (DERM-303).

The level of detail provided in these study reports was as follows:

- 110801: A brief report only, lacking protocol and individual subject measurements. The document was not indexed, and referred extensively to documentation which was not presented. Th evaluator considered it unevaluable.

- COL-101-SDPK-105, PERIO-DOXYSR-103, PERIO-DOXYSR-104 and COL-101-SSPK-106: Full reports.
- Thomas et al. (1998), Walker et al. (2000), Thomas et al. (2000) and Walker et al. (2005): Brief published reports including data from apparently overlapping studies. I considered this material unevaluable.
- Skidmore et al. (2003): A brief published report.
- COL-101-ROSE-301 and COL-101-ROSE-302: Full reports.
- DERM-303: A brief report.

- Module 1
  - Application letter, application form, draft Australian PI and CMI, approved foreign PI; voluminous material relating to considerations by foreign regulatory authorities.
- Module 2
  - Clinical Overview, Clinical Summary.

Note. For brevity, study numbers will often be abbreviated to the last 3 digits.

2.2. Good clinical practice (GCP)

Routine GCP certification was presented for the following studies: COL-101-SDPK-105, PERIO-DOXYSR-103, PERIO-DOXYSR-104, COL-101-SSPK-106, COL-101-ROSE-301, COL-101-ROSE-302 and DERM-303.

GCP was not mentioned in any of the published reports, or in the report of Study 110801.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 1. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK - Single dose	110801	*
		COL-101-SDPK-105	
		PERIO-DOXYSR-103	*
	Multi-dose	PERIO-DOXYSR-104	*
		COL-101-SSPK-106	*
	Bioequivalence† - Single dose		
	Multi-dose		
	Food effect	COL-101-SDPK-105	*

* Indicates the primary aim of the study.
† Bioequivalence of different formulations.

Table 2 lists pharmacokinetic results that were excluded from consideration due to study deficiencies.

Table 2. Pharmacokinetic results excluded from consideration.

Study ID	Subtopic(s)	PK results excluded
110801	Absorption at different levels of the intestine.	All
PERIO-DOXYSR-104	Comparison of PK parameters for Oracea 40 mg/day and Periostat 20 mg bd.	C_{max} and T_{max} for Periostat on Day 1, and AUC_{0-24} for Periostat on Day 7.

3.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

3.2.1. Pharmacokinetics in healthy subjects

3.2.1.1. Absorption

In single-dose studies (103 and 105), under fasting conditions, Oracea mean C_{max} was 510-523 ng/mL; median T_{max} was 2-3 h, and mean $AUC_{0-\infty}$ was 7962-9227 h.ng/mL. The effect of food was to reduce rate and extent of absorption.

Both multiple-dose studies (104 and 106) were done under quasi-fasting conditions and compared Oracea 40 mg daily to an immediate-release US product (Periostat) 20 mg bd. In Study 104, the mean C_{max} measurements were comparable, as were the median T_{max} values. A valid comparison of AUC_{0-24} during chronic dosing was not available. In Study 106, the mean C_{max} measurements were comparable, as were the mean AUC_{SS} values.

In Study 103, in which Oracea 40 mg was compared to 40 mg of Periostat, mean C_{max} measurements.

[information redacted] raise the question of the extent to which Oracea is in fact a modified-release product.

3.3. Evaluator's overall conclusions on pharmacokinetics

The evaluator did not consider the values of C_{max} and T_{max} derived from the pharmacokinetic studies to be accurate, in view of the paucity of sampling points in the relevant time intervals.

The argument purporting to justify the introduction of a controlled-release doxycycline product for the treatment of rosacea is questionable. Even if the rationale described at section 2.2.1 above is accepted, the pharmacokinetic data from Study 103 suggest that if 40 mg daily of an immediate-release product is used, C_{max} values will generally remain below the target maximum of 1.0 µg/mL. The principle that the absorption characteristics of a pharmaceutical should not be unnecessarily complex relates to quality, as does the point in the next paragraph below.

It is questionable whether Oracea has meaningful controlled-release properties. Further study would be required, to elucidate differences from immediate-release products. Preferably, such comparisons should be with a product having the same active (doxycycline monohydrate).

3.3.1. Response to guidance

The evaluator accepted the sponsor's response, which points out that this is not an application for a generic (see *1.1 Guidance* above).

4. Pharmacodynamics

4.1. Studies providing pharmacodynamic data

Table 3 shows the studies relating to each pharmacodynamic topic and the location of each study summary. Note that none of these studies used Oracea.

Table 3. Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	Effect on subgingival microflora	Thomas *et al.* (1998) Walker *et al.* (2000) Thomas *et al.* (2000)	
	Effect on skin microflora	Skidmore *et al.* (2003)	
	Effect on intestinal and vaginal microflora	Walker *et al.* (2005)	

* Indicates the primary aim of the study.

Table 4 lists pharmacokinetic results that were excluded from consideration due to study or presentational deficiencies.

Table 4. Pharmacodynamic results excluded from consideration.

Study ID	Subtopic(s)	PD results excluded
Thomas *et al.* (1998)	Effect on subgingival microflora	All
Walker *et al.* (2000)	Effect on subgingival microflora	All
Thomas *et al.* (2000)	Effect on subgingival microflora	All
Walker *et al.* (2005)	Effect on intestinal and vaginal microflora	All

4.2. Summary of pharmacodynamics

The *Overview* explains that the pharmacodynamic studies presented (all in the form of published papers) are included in the dossier to provide information on whether there is likely to be a risk of resistance induction with Oracea. One of the studies presented (Skidmore at al. 2003) provides preliminary reassurance on this point.

4.3. Evaluator's overall conclusions on pharmacodynamics

All the pharmacodynamic studies presented were aimed at demonstrating the absence of certain unwanted effects, and thus were related to safety rather than efficacy. The sponsor sought to show that although doxycycline is a known broad-spectrum antibiotic, it lacks (at the dosage used for the claimed indication) a measurable effect in respect of

- antibacterial potency, and
- induction of resistance–specifically, in intestinal flora.

In view of the deficiencies noted at section 13 below, regarding the papers Thomas *et al.* (1998), Walker *et al.* (2000), Thomas *et al.* (2000), and Walker *et al.* (2005), the evaluator found it impossible to conduct a proper evaluation of these papers. If the sponsor believes the findings of the studies reported in these papers are important to the application, it should have provided separate, adequately detailed reports of the studies.

In addition to the confusion over the question of exactly which studies are covered by some of the papers presented, there is the question of the extent to which this small selection of published papers provides an objective and unbiased survey of the literature relevant to the antibacterial effect and extent of induction of resistance resulting from treatment with low dose doxycycline. This section of the dossier amounts to a literature-based submission, yet no attempt has been made to comply with the guidelines for such submissions. (See TGA 2003.)

Thus, in the evaluator's opinion, all that can be derived from the pharmacodynamic studies presented is the preliminary reassurance described at *Summary of Pharmacodynamics* above.

5. Dosage selection for the pivotal studies

The rationale for the dose used (Oracea 40 mg once daily) was:

- An expectation (based on previous studies) that it would produce plasma doxycycline levels not exceeding 1 µg/mL over the 24 hours in chronic treatment. This concentration was

considered to be below that required for an antimicrobial effect on many common micro-organisms.

- Study DERM-303, which demonstrated some efficacy in rosacea of doxycycline 20 mg (as hydrochloride) bd.

6. Clinical efficacy

6.1. Facial rosacea indication

6.1.1. Pivotal efficacy studies

Note that the term "pivotal" has been used when referring to studies 301 and 302 for convenience, because the studies are so designated by the sponsor. However, for the reason given under *Effect of food* below, the evaluator believed that the studies are in fact of little assistance to the application.

6.1.1.1. Studies Col-101-Rose-301 And Col-101-Rose-302

The designs of these two studies were identical except that a 4-week extension was added to study 302 to assess the longevity of the treatment effects. In that study, double-blind treatment ceased at 16 weeks, and in the period between Week 16 and Week 20 visits, patients were instructed to refrain from taking the study drug or any systemic or topical rosacea or acne medication or any prohibited Concomitant Medication.

6.1.1.1.1. Study design, objectives, locations and dates

This was a randomised, double-blind, parallell group study.

Objective: to evaluate the safety and efficacy of doxycycline 40 mg (as monohydrate) controlled-release capsules administered once daily for the treatment of rosacea compared to placebo.

Study COL-101-ROSE-301 was conducted at 14 centres in USA, 22 June 2004 - 1 April 2005.

Study COL-101-ROSE-302 was conducted at 14 other centres in USA, 24 June 2004 - 4 April 2005.

6.1.1.1.2. Inclusion and exclusion criteria

Inclusion criteria included:

- Healthy males and females ≥ 18 years of age with rosacea.
- Presence of 10 - 40 papules and pustules and ≤ 2 nodules, plus a score of 2 - 4 on the IGA scale (see Table 5).

Table 5. Investigator's Global Assessment (Only one score may be checked)

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	3-10 papules/pustules
	(3) Moderate	Moderate number of papules/pustules	11-19 papules/pustules
	(4) Severe	Numerous papules/pustules; nodules	≥ 20 papules/pustules and nodules

- Presence of moderate to severe erythema (ie at least one area-specific score of ≥ 2 and a total score of 5 - 20 on the CEA scale).

Table 6 A and B. Clinician's erythema assessment scale

A. Erythema definition

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

Table 6B. Erythema score

- Check one box for each area of the face based upon the definitions given above
- Enter the Erythema Score for each area of the face
- Sum all of the individual Erythema Scores to obtain the Total Erythema Score

	Forehead	Chin	Nose	Right Cheek	Left Cheek
	❑ none (0)	❑ none (0)	❑ none (0)	❑ none (0)	❑ none (0)
	❑ mild (1)	❑ mild (1)	❑ mild (1)	❑ mild (1)	❑ mild (1)
	❑ moderate (2)	❑ moderate (2)	❑ moderate (2)	❑ moderate (2)	❑ moderate (2)
	❑ significant (3)	❑ significant (3)	❑ significant (3)	❑ significant (3)	❑ significant (3)
	❑ severe (4)	❑ severe (4)	❑ severe (4)	❑ severe (4)	❑ severe (4)
Erythema Score					

- Presence of telangiectasia.

Exclusion criteria included:

- Initiation of a hormonal method of contraception within 4 months of baseline, discontinuation during the course of study, or change in the product used within 4 months of baseline or during the study.
- Use of topical acne treatments within 4 weeks of baseline.
- Use of systemic retinoids within 90 days of baseline.
- Use of topical or systemic antibiotics within 4 weeks of baseline.
- Long-term use (>14 days) of topical or systemic NSAIDs in the 4 weeks prior to baseline or during the study. Chronic use of aspirin at sub-analgesic doses (≤ 325 mg/day) could be used by those patients requiring platelet aggregation inhibition.
- Use of topical or systemic corticosteroids 4 weeks prior to baseline or during the study.

6.1.1.1.3. Study treatments

- Oracea 40 mg or placebo each morning for 16 weeks.

The protocols did not stipulate whether medication was to be taken fasted or with food. (301 Protocol, page 6: "T*he patient will be instructed to take one capsule every morning*.")

The following medications were prohibited during the study:

- Chronic use (>14 days) of sulfa drugs, erythromycin, cephalosporins, and quinolones.
- Tetracycline or penicillin antibiotics.
- Any acne treatment, including spironolactone.
- Antimicrobial soaps.
- Niacin at a dose of 500 mg or more per day.

Use of sunscreens was to be recorded as concomitant medication.

6.1.1.1.4. Efficacy variables and outcomes

The main efficacy variables were:

- Total inflammatory lesion count (papules + pustules + nodules)
- CEA score
- IGA score

The primary efficacy outcome was the difference between Oracea and placebo in the change in total inflammatory lesion count from baseline to endpoint (Week 16), based on the last observation carried forward.

Other efficacy outcomes included:

- Change in the Clinician's Erythema Assessment Scale score from baseline to endpoint (Week 16).
- Change in the Investigator's Global Assessment (IGA) score from baseline to endpoint (Week 16).
- 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).
- Change in total inflammatory lesion count from baseline to Week 12.

6.1.1.1.5. Sample size

Based on previous studies, it was anticipated that active treatment would result in a mean change from baseline of -7.0 in total lesion count and placebo would result in a mean change of -3.5 with a common standard deviation of 8.0. 111 patients per treatment group would be sufficient to ensure a power of 90% in correctly concluding superiority of the Oracea capsules over placebo at the two-sided $\alpha = 0.05$ level of significance. To ensure a power of 85%, a total of 95 patients in each treatment group would be sufficient. Plan was to have approximately 132 patients in each arm.

6.1.1.1.6. Randomisation and blinding methods

A single list of randomisation codes was used across all centres. Blinding was achieved by the use of placebo with similar appearance to active.

6.1.1.1.7. Statistical methods

Planned primary analysis was as follows (301 *Protocol*, page 14):

Total lesion count will be summarised for each treatment group and at each visit using mean, standard deviation, median, minimum, and maximum. The comparison between the two treatments will be based on the difference for each patient between the endpoint visit and the baseline visit. ANOVA will be performed to test the null hypothesis of no treatment effect. The dependent variable will be the difference between the endpoint value and the baseline value. Treatment group and study centre will be the main effects in the model. This analysis will be performed on the ITT and PP populations. Efficacy will be declared if the treatment effect p-value for the ITT population is no greater than 0.05 and is favourable to Oracea.

6.1.1.1.8. Participant flow

This is shown below.

According to 301 *CSR* Table 1.1 and 302 *CSR* Table 1.1, all screened patients were randomised.

Figure 1. Study 301 Participant flow

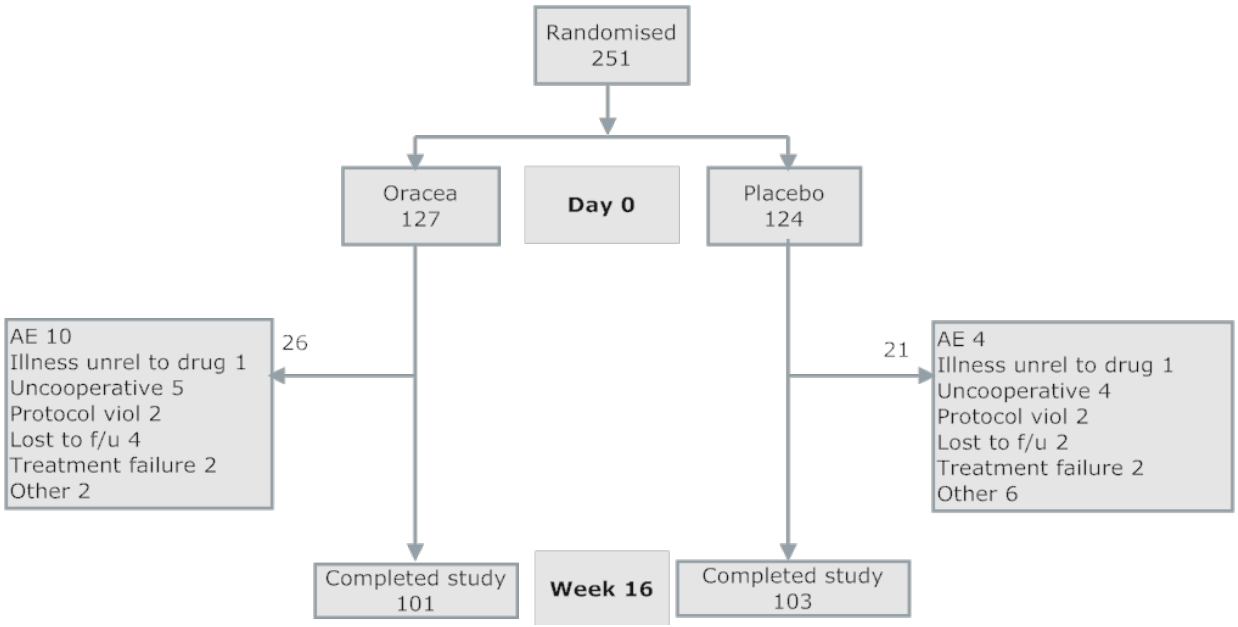
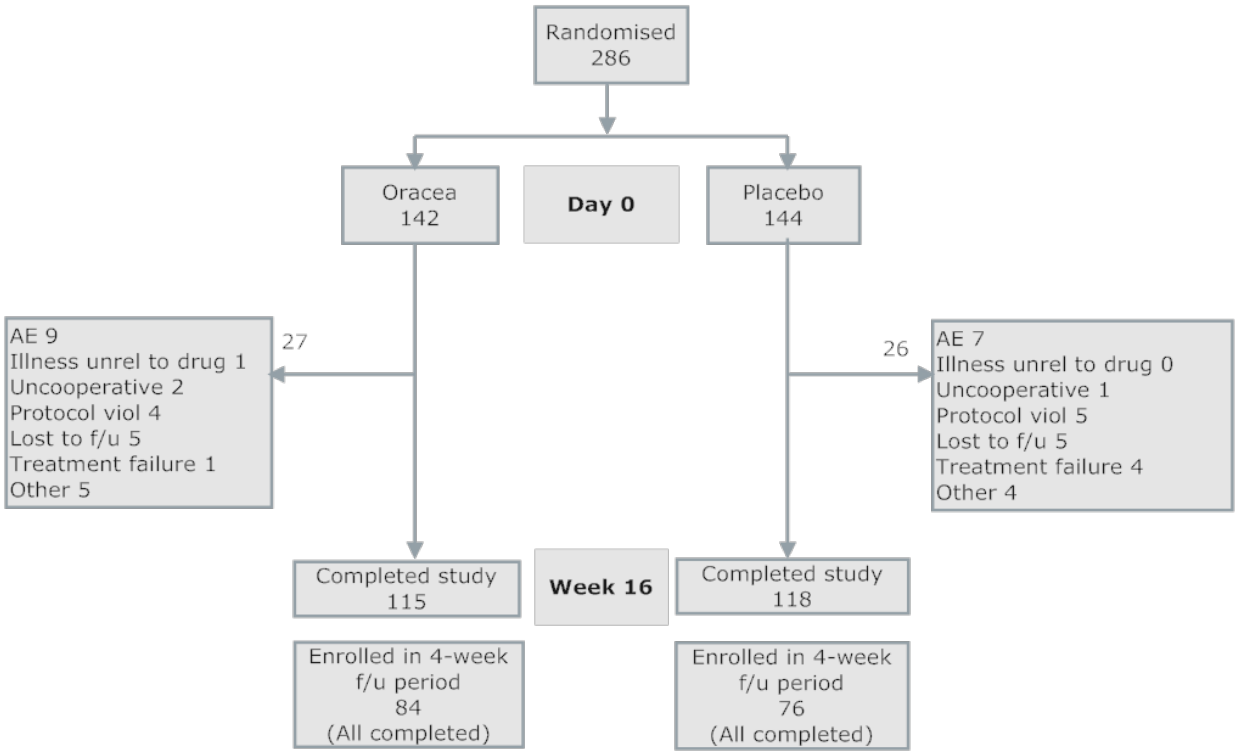


Figure 2. Study 302 Participant flow



6.1.1.1.9. Baseline data

The principal demographic and baseline clinical characteristics are tabulated below. Almost all patients were Caucasian.

Table 7. Study 301

Characteristic	Oracea (N=127)	Placebo (N=124)	Total (N=251)
Age Mean Years(sd)	46.8 (13.2)	47.6 (11.5)	47.2 (12.4)
Age Median Years (Range)	46.0 (22-90)	47.0 (19-84)	47.0 (19-90)
Male	36	29	65
Female	91	95	186
Papule count, mean (sd)	15.2 (7.9)	16.4 (9.2)	15.8 (8.6)
Pustule count, mean (sd)	4.1 (5.2)	3.7 (4.7)	3.9 (5.0)
Nodule count, mean (sd)	0.2 (0.6)	0.2 (0.5)	0.2 (0.5)
TIL, mean (sd)	19.5 (8.8)	20.3 (10.4)	19.9 (9.6)
IGA 0 (Clear)	0	0	0
1 (Near clear)	0	0	0
2 (Mild)	8	10	18
3 (Moderate)	67	65	132
4 (Severe)	52	49	101
CEA, mean (sd)	9.7 (3.0)	9.5 (2.7)	9.6 (2.8)

Table 8. Study 302

Characteristic	Oracea (N=142)	Placebo (N=144)	Total (N=286)
Age Mean Years (sd)	46.3 (12.7)	47.6 (13.3)	47.0 (13.0)
Age Median Years (Range)	46.0 (20-80)	47.0 (19-82)	46.0 (19-82)
Male	48	49	97
Female	94	95	189
Papule count, mean (sd)	17.4 (10.8)	17.8 (10.8)	17.6 (10.8)
Pustule count, mean (sd)	3.0 (4.5)	3.3 (6.0)	3.1 (5.3)
Nodule count, mean (sd)	0.1 (0.5)	0.1 (0.5)	0.1 (0.5)
TIL, mean (sd)	20.5 (11.7)	21.2 (12.5)	20.8 (12.1)
IGA 0 (Clear)	0	0	0
1 (Near clear)	0	0	0
2 (Mild)	17	7	24
3 (Moderate)	77	80	157
4 (Severe)	48	57	105
CEA, mean (sd)	9.5 (2.9)	9.1 (2.5)	9.3 (2.7)

6.1.1.1.10. Results for the primary efficacy outcome

Table 9. Study 301

Total inflammatory lesions – ITT population		Oracea (N=127)	Placebo (N=124)	p-value
Baseline	**Mean (sd)**	19.5 (8.8)	20.3 (10.4)	
	Median (Range)	17.0 (10-39)	17.0 (10-63)	
Week 16	**Mean (sd)**	7.7 (8.0)	14.4 (16)	
	Median (Range)	5.0 (0-38)	9.0 (0-111)	
Change from baseline to Week 16, mean (sd)		-11.8 (9.8)	-5.9 (14)	< 0.001[1]

[1] Van Elteren test stratified by centre

In the PP population, the mean change from baseline in total inflammatory lesions showed a statistically significant reduction in the Oracea treatment group compared to the placebo group at Week 16 (p=0.004).

Table 10. Study 302

Total inflammatory lesions – ITT population		Oracea (N=142)	Placebo (N=144)	p-value
Baseline	**Mean (sd)**	20.5 (11.7)	21.2 (12.5)	
	Median (Range)	17.0 (10-105)	18.0 (10-100)	
Week 16	**Mean (sd)**	11.0 (11.3)	16.9 (14.7)	
	Median (Range)	8.0 (0-105)	13.0 (1-78)	
Change from baseline to Week 16, mean (sd)		-9.5 (9.6)	-4.3 (11.6)	< 0.001[1]

[1] Van Elteren test stratified by centre

In the PP population, the mean change from baseline in total inflammatory lesions showed a statistically significant reduction in the Oracea treatment group compared to the placebo group at Week 16 ($p < 0.001$).

6.1.1.1.11. Results for other efficacy outcomes

Table 11. Study 301

Clinician's Erythema Assessment – ITT population[2]		Oracea (N=127)	Placebo (N=124)	p-value
Baseline	**Mean (sd)**	9.7 (3.0)	9.5 (2.7)	
	Median (Range)	9.0 (5-19)	9.0 (5-19)	
Week 16	**Mean (sd)**	7.0 (3.7)	7.7 (3.5)	
	Median (Range)	7.0 (0-18)	8.0 (1-19)	
Change from baseline to Week 16, mean (sd)		-2.7 (3.2)	-1.8 (2.9)	0.017[1]

[1] ANOVA model, with treatment and pooled centre as main effects
[2] For the PP population, outcome was also significant (p=0.005)

Table 12. Investigator's Global Assessment – ITT population

Investigator's Global Assessment – ITT population[2]		Oracea (N=127)	Placebo (N=124)	p-value
Change from Baseline at Week 16	**-4**	4 (3.1%)	2 (1.6%)	<0.001[1]
	-3	14 (11.0%)	9 (7.3%)	
	-2	40 (31.5%)	21 (16.9%)	
	-1	40 (31.5%)	40 (32.3%)	
	0	27 (21.3%)	45 (36.3%)	
	1	2 (1.6%)	7 (5.6%)	
	2	0	0	
	3	0	0	
	4	0	0	

[1] Based on a Cochran-Mantel-Haenszel Test stratified by pooled centre
[2] For the PP population, outcome was also significant (p=0.005)

Table 13. Proportion of treatment responders – ITT population

Proportion of treatment responders – ITT population[2]	Oracea (N=127)	Placebo (N=124)	p-value[1]
IGA score 0 or 1 at Week 16			
Yes	39 (30.7%)	24 (19.4%)	0.036
No	88 (69.3%)	100 (80.6%)	
IGA score 0 at Week 16			
Yes	12 (9.4%)	10 (8.1%)	0.718
No	115 (90.6%)	114 (91.9%)	

[1] Based on a Cochran-Mantel-Haenszel Test stratified by pooled centre
[2] For the PP population, no significant differences were observed, using either definition

Figure 3. Change from Baseline in Total Inflammatory Lesions – ITT Population

(Similar results were found in the PP population.)

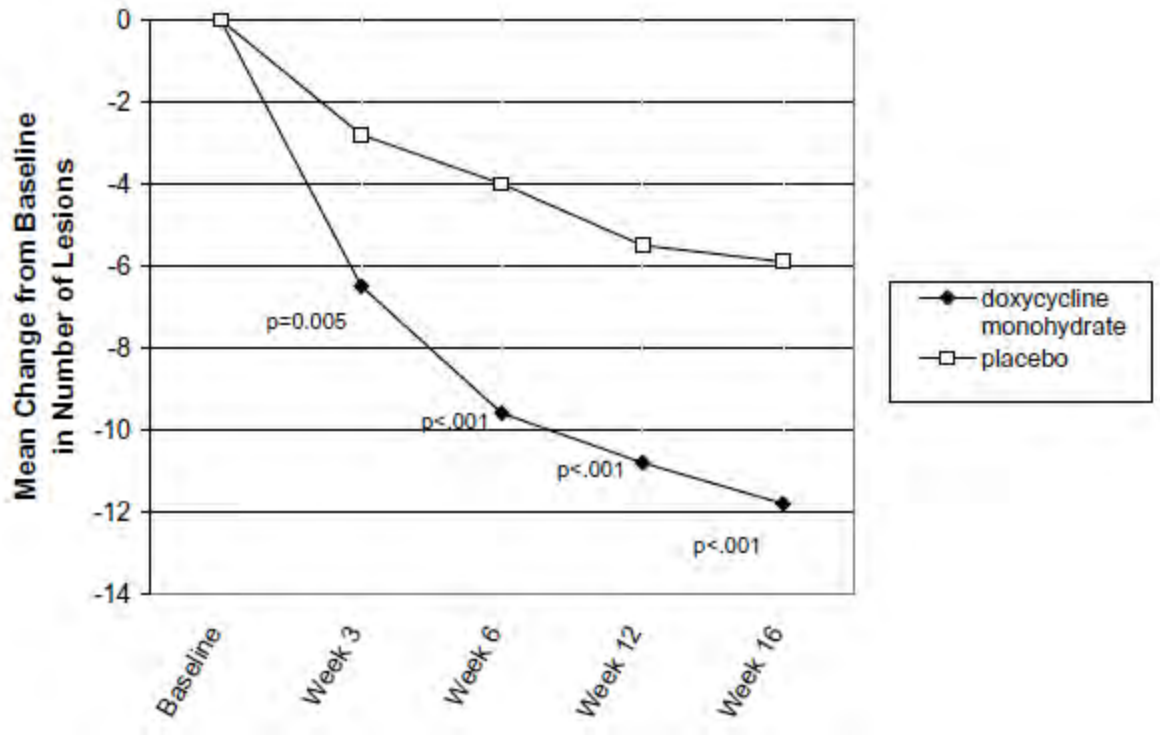


Table 14. Clinician's Erythema assessment. Study 302

Clinician's Erythema Assessment – ITT population[2]		Oracea (N=142)	Placebo (N=144)	p-value
Baseline	**Mean (sd)**	9.5 (2.9)	9.1 (2.5)	
	Median (Range)	9.0 (4-18)	9.0 (4-16)	
Week 16	**Mean (sd)**	8.1 (3.2)	7.9 (3.3)	
	Median (Range)	8.0 (1-18)	8.0 (0-19)	
Change from baseline to Week 16, mean (sd)		-1.4 (2.7)	-1.2 (3.0)	NS[1]

[1] ANOVA model, with treatment and pooled centre as main effects

[2] For the PP population, outcome was also not significant

Table 15. Investigator's Global Assessment – ITT population

Investigator's Global Assessment – ITT population[2]	Oracea (N=142)	Placebo (N=144)	p-value
Change from Baseline at Week 16 -4	2 (1.4%)	0	<0.004[1]
-3	2 (1.4%)	1 (0.7%)	
-2	28 (19.7%)	22 (15.3%)	
-1	59 (41.5%)	45 (31.3%)	
0	44 (31.0%)	62 (43.1%)	
1	6 (4.2%)	14 (9.7%)	
2	1 (0.7%)	0	
3	0	0	
4	0	0	

[1] Based on a Cochran-Mantel-Haenszel Test stratified by pooled centre
[2] For the PP population, outcome was also significant (p=0.011)

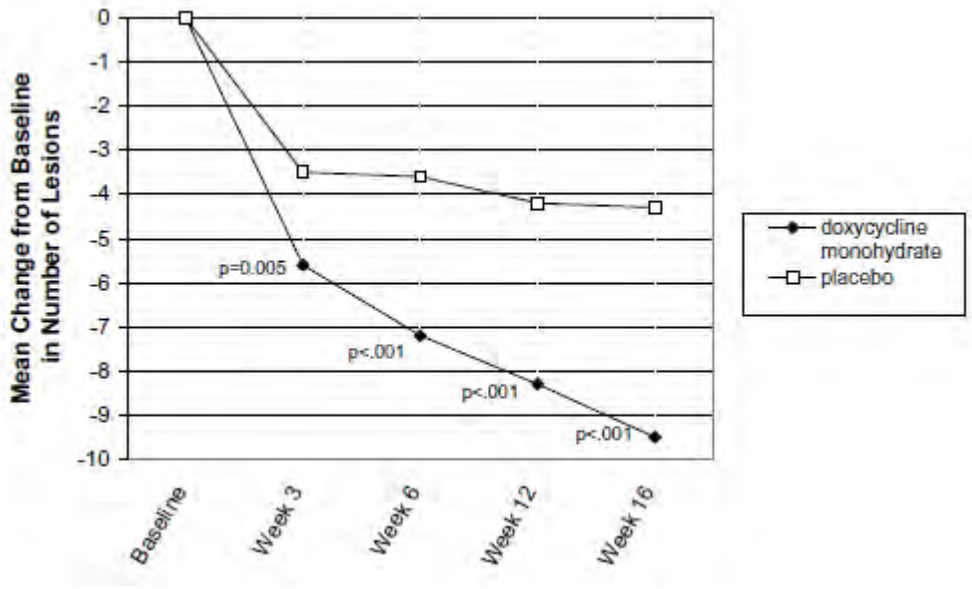
Table 16. Proportion of treatment responders – ITT population

Proportion of treatment responders – ITT population[2]	Oracea (N=142)	Placebo (N=144)	p-value[1]
IGA score 0 or 1 at Week 16			
Yes	21 (14.8%)	9 (6.3%)	0.012
No	121 (85.2%)	135 (93.8%)	
IGA score 0 at Week 16			
Yes	2 (1.4%)	0	0.134
No	140 (98.6%)	144 (100.0%)	

[1] Based on a Cochran-Mantel-Haenszel Test stratified by pooled centre
[2] For the PP population, a significant difference was observed (p=0.007) only for the first definition (*ie*, score 0 or 1).

Figure 4. Change from Baseline in Total Inflammatory Lesions – ITT Population

(Similar results were found in the PP population.)



6.1.1.1.12. Results for longevity of treatment effect (Study 302 only)

Patients who received Oracea during the Treatment Period (to Week 16) and enrolled in the 4-Week Follow-Up Period maintained a treatment benefit at Week 20 when compared to patients who had received placebo during the Treatment Period. The mean lesion count at Week 20 was 10.3 for the Oracea group and 15.3 for the placebo group, a mean treatment difference of 5 lesions.

6.1.2. Other efficacy studies

6.1.2.1. Study DERM-303

This was a randomised, double-blind, placebo-controlled, parallel-group study of doxycycline hydrochloride 20 mg (Periostat) tablets taken bd for 16 weeks by patients with rosacea. Inclusion and exclusion criteria were similar to those used in the pivotal studies. 134 patients were randomised (67 Periostat, 67 placebo). Baseline demographics are tabulated below.

Table 17. Baseline demographics

Characteristic	Periostat (N=67)	Placebo (N=67)	Total (N=134)
Age Years Mean (Range)	44.5 (25-65)	48.9 (26-81)	46.7 (25-81)
Male	13	27	40
Female	54	40	94

Analyses of the 2 designated primary efficacy variables are tabulated below.

Table 18. Primary efficacy variables

Parameter – ITT population	Periostat (N=67)	Placebo (N=67)	p-value
Total inflammatory lesions[1]			
Baseline, N	67	67	
Mean (sd)	18.7 (6.8)	17.4 (7.1)	
Endpoint (Week 16), N	61	66	
Mean (sd)	11.7 (10.2)	13.7 (9.6)	
Change from baseline to Week 16, mean (sd)	-6.7 (8.9)	-3.8 (8.2)	< 0.009[2]

Table 19. CEA Total score

CEA, Total score			
Baseline, N	67	67	
Mean (sd)	8.8 (2.6)	8.4 (2.5)	
Endpoint (Week 16), N	61	66	
Mean (sd)	5.9 (2.7)	6.4 (2.4)	
Change from baseline to Week 16, mean (sd)	-3.0 (3.1)	-2.0 (2.8)	NS[3]

[1] For this criterion (but not for CEA) the outcome was also significant for the PP population (p=0.035)
[2] Van Elteren test stratified by centre
[3] ANCOVA model with treatment as the main effect with centre as the covariate

Evaluator's comments

This was a study done with a different product, but expected to achieve similar plasma concentrations of doxycycline during a 24-hour period. A small beneficial effect was shown. In terms of efficacy, this study adds nothing to the 2 pivotal studies.

6.2. Analyses performed across trials (pooled analyses and meta-analyses)

The evaluator believed nothing was to be gained from pooled efficacy analysis of the pivotal studies.

6.3. Evaluator's conclusions on clinical efficacy

The aetiology of rosacea is not known, and the mode of action of doxycycline in this condition is uncertain. The sponsor suggests – largely on the basis of published pre-clinical studies – that low dose doxycycline has an anti-inflammatory effect, at dosage below that required for a significant antimicrobial effect. This is a matter for the pre-clinical evaluator, or for possible future clinical studies, preferably in conditions of known aetiology in which microorganisms are not thought to play any role. The evaluator did not consider that approval of the present application need depend upon elucidation of the mode of action.

6.3.1. Major problems

6.3.1.1. Modified-release property

A fundamental problem with the present application is lack of evidence that the modified-release property of Oracea is necessary to its use in rosacea. See *Evaluator's Overall Conclusions on Pharmacokinetics* above. The relevant guideline (EMEA 2000) states, at section 2.1:

> "*The development of a prolonged or delayed release formulation has to be based on a well-defined clinical need and on an integration of physiological, pharmacodynamic and pharmacokinetic considerations*."

Speculation about the mode of action, or about a possible advantage over immediate release preparations regarding resident microflora, cannot in my opinion take the place of clinical testing, aimed at establishing whether Oracea has any efficacy or safety advantage over a once daily dose of an immediate release preparation.

6.3.1.2. Effect of food

An unusual feature of this application is that the main efficacy and safety studies have been done with a modified-release preparation. Although those studies have demonstrated some efficacy and provided safety data, we do not know (because the study protocols were silent on the matter) exactly how the patients were treated: *ie*, with Oracea taken in fasting conditions, or Oracea taken with food. This point is important, because food has been shown (in Study 105) to have a significant effect on absorption – particularly on C_{max} – and the fundamental rationale for the product's development (see discussions above) relates particularly to the C_{max} which it produces. In the evaluator's opinion therefore, Studies 301 and 302 contribute no valid efficacy data to the application. The sponsor argues (Module 2, section 2.5, page 18):

> "*In the single-dose food-effect study involving healthy volunteers … concomitant administration of Oracea with a 1000 calorie, high-fat, high protein meal that included dairy products resulted in a decrease in peak plasma levels of 43.4% and a decrease in overall doxycycline exposure of 20.3% compared to fasted conditions. Thus, the decrease in overall exposure to doxycycline following a high-fat meal (arguably the worst case situation) was modest and is smaller than the variability between the genders observed in the same study …. Patients in the Phase 3 clinical studies were advised to take Oracea capsules once daily in the morning, with no specific instruction with respect to ingestion before or after food. In view of the limited effect of food on doxycycline bioavailability from Oracea and in view of the efficacy observed in Phase 3 studies where timing of dose in relation to meals was not restricted, it is considered that Oracea may be administered with or without food in clinical practice.*"

The evaluator rejects every part of this argument. The decrease in overall exposure resulting from food is significant, and the decrease in peak level is substantial. The sponsor has implied elsewhere that the latter is of particular relevance in the present application. The argument in the last sentence lacks logic: The fact that some efficacy was demonstrated in a trial with unrestricted dosing conditions leaves open the possibility that efficacy or safety might have been different in patients who dosed (say) 2 hours before breakfast, compared to efficacy or safety in patients who dosed after breakfast. (The data on "responders", see *Pivotal Efficacy Studies* above, are also relevant to this point.)

6.3.1.3. Dose-finding

As no dose-finding studies were presented, it is not known whether the dosage proposed is optimal.

6.3.2. Other problems

As rosacea is a clinical diagnosis, some patients with other diagnoses may have been enrolled in the clinical trials. The exclusion criterion relating to topical corticosteroid use would have

excluded patients with steroid-induced acne, and the requirement for telangiectasia would have reduced the risk of including adult-onset acne patients in the studies. However, the possibility exists that some of the responses in the pivotal studies may have been in patients who in fact suffered from adult-onset acne rather than rosacea.

From the outcome of the pivotal studies, the benefit of Oracea treatment in rosacea appears to be modest, and confined to certain aspects of the condition. Erythema is a principal feature, but benefit was not consistent across the studies. Telangiectasia is often a prominent aspect of rosacea, and presence of this feature was an inclusion criterion in the pivotal studies. However, telangiectasia was not considered in any of the efficacy measures (presumably because it was thought unlikely to respond).

As symptoms in rosacea are principally concerned with its appearance, it would have been of interest to include patient self-assessments in the pivotal studies. This is particularly relevant in the present application, where one of the principal features of the condition is regarded as refractory to the treatment studied (see previous paragraph).

There were no studies comparing Oracea with any other active treatment – such as topical metronidazole or azelaic acid. Studies with active comparators are of particular interest where the first phase 3 studies show only a small benefit.

7. Clinical safety

7.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs) were assessed by open-ended questioning at each study visit (Weeks 3, 6, 12 and 16).
- Routine haematology and clinical chemistry laboratory tests at baseline and study end (Week 16).

Dose-response and non-pivotal efficacy studies

Safety data from Study DERM-303 not included, as Oracea was not administered in that study.

Clinical pharmacology studies

Of the clinical pharmacology studies presented, only the following used Oracea: COL-101-SDPK-105, PERIO-DOXYSR-103, PERIO-DOXYSR-104 and COL-101-SSPK-106. AEs, vital signs, haematology and clinical chemistry were recorded in these studies, all of which enrolled participants who were not in the target population and who received Oracea for periods of a week or less.

7.2. Pivotal studies that assessed safety as a primary outcome

None presented.

7.3. Patient exposure

Table 20. Exposure to Oracea and comparators in clinical studies. Numbers of subjects.

Study type	Controlled studies			Uncontrolled studies	Total Oracea
	Oracea	Placebo	Periostat	Oracea	
Clinical pharmacology[1]	93	0	63	0	93
Phase III					
Pivotal	269	268		0	269
Other	0	67	67	0	0
TOTAL	362	335	130	0	362

[1] Studies COL-101-SDPK-105, PERIO-DOXYSR-103, PERIO-DOXYSR-104 and COL-101-SSPK-106.

Table 21. Exposure to Oracea in clinical studies according to dose and duration.

Study type	Proposed dose range			
	≥ 3 mo.	≥ 6 mo.	≥ 12 mo.	Any duration
Clinical pharmacology	0	0	0	93
Phase III				
Placebo-controlled	269	0	0	269
Active-controlled	0	0	0	0
Uncontrolled	0	0	0	0
TOTAL	269	0	0	362

7.4. Adverse events

7.4.1. All adverse events (irrespective of relationship to study treatment)

Table 22. Adverse events reported for > 1% of patients treated with Oracea in the pivotal studies combined in decreasing order of overall frequency (ITT population). Table continued across 2 pages.

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%)
Diarrhoea	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%)
URTI	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 ↑	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 ↑	1(0.8%)	1(0.8%)	3(2.1%)	3(2.1%)	4(1.5%)	4(1.5%)
Anxiety	3(2.4%)	0	1(0.7%)	0	4(1.5%)	0
Blood LDH ↑	1(0.8%)	0	3(2.1%)	1(0.7%)	4(1.5%)	1(0.4%)
Blood pressure ↑	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 distension	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 ↑	2(1.6%)	0	1(0.7%)	0	3(1.1%)	0

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)
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
Pharyngo-laryngeal 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%)	00	1(0.7%)	3(1.1%)	2(0.7%)

Table 23. Adverse events reported for > 1% of patients treated with Oracea in the Phase 3 studies combined by SOC (ITT population). Table continued across 2 pages.

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 distension	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%)
Diarrhoea	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 & administration 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%)

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)
URTI	5(3.9%)	6(4.8%)	4(2.8%)	14(9.7%)	9(3.3%)	20(7.5%)
Investigations						
ALT ↑	1(0.8%)	1(0.8%)	3(2.1 %)	3(2.1 %)	4(1.5%)	4(1.5%)
AST ↑	2(1.6%)	1(0.8%)	4(2.8%)	1(0.7%)	6(2.2%)	2(0.7%)
Blood glucose ↑	2(1.6%)	0	1(0.7%)	0	3(1.1 %)	0
Blood LDH ↑	1(0.8%)	0	3(2.1 %)	1(0.7%)	4(1.5%)	1(0.4%)
Blood pressure ↑	2(1.6%)	0	2(1.4%)	1(0.7%)	4(1.5%)	1(0.4%)
Musculoskeletal & connective tissue diseases						
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
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%)

7.4.2. Treatment-related adverse events (adverse drug reactions)

7.4.2.1. Pivotal studies

The number of patients experiencing AEs classified as treatment-related (either "possible" or "probable") in the combined pivotal studies (301 and 302) is shown below.

Table 24. Number of patients experiencing AEs classified as treatment-related. Studies 301 and 302

Number of patients	Oracea (N = 269)	Placebo (N = 268)
Reporting treatment-related AEs	56 (20.8%)	38 (14.2%)
Classified possible	42 (15.6%)	31 (11.6%)
Classified probable	14 (5.2%)	7 (2.6%)

Numbers of patients experiencing AEs classified as treatment-related (either "possible" or "probable") in the combined pivotal studies (301 & 302) is shown below (extracted from Module 5, section 5.3.5.3 Table 12.5). SOC data are comprehensive, but only Preferred Terms reported by > 1% in either treatment group are included.

Table 25. Numbers of patients experiencing AEs classified as treatment-related (either "possible" or "probable") in the combined pivotal studies (301 and 302) By System Organ Class (SOC). Table continued across 2 pages.

SOC Preferred Term	Oracea (N = 269)	Placebo (N = 268)
	n (%)	n (%)
Any such AE	56 (20.8)	38 (14.2)
Blood and lymphatic system disorders	0	1 (0.4)
Cardiac disorders	1 (0.4)	1 (0.4)
Ear and labyrinth disorders	1 (0.4)	1 (0.4)
Eye disorders	1 (0.4)	0
Gastrointestinal disorders	28 (10.4)	18 (6.7)
Abdo pain upper	5 (1.9)	1 (0.4)
Diarrhoea	11 (4.1)	4 (1.5)
Nausea	5 (1.9)	8 (3.0)
Stomach discomfort	3 (1.1)	2 (0.7)
Vomiting	1 (0.4)	3 (1.1)

SOC Preferred Term	**Oracea (N = 269)**	**Placebo (N = 268)**
	n (%)	**n (%)**
General disorders and admin site cond	3 (1.1)	1 (0.4)
Infections and infestations	10 (3.7)	7 (2.6)
Fungal infection	5 (1.9)	1 (0.4)
Vaginal mycosis	0	3 (1.1)
Injury, poisoning, procedural comp	2 (0.7)	2 (0.7)
Investigations	7 (2.6)	2 (0.7)
AST ↑	4 (1.5)	0
Metabolism and nutrition disorders	1 (0.4)	0
Musculoskeletal and connective tissue	1 (0.4)	2 (0.7)
Nervous system disorders	10 (3.7)	14 (5.2)
Dizziness	1 (0.4)	3 (1.1)
Headache	6 (2.2)	11 (4.1)
Renal and urinary disorders	1 (0.4)	0
Reproductive system and breast	1 (0.4)	0
Respiratory, thoracic and mediastinal	4 (1.5)	1 (0.4)
Skin and subcutaneous tissue	8 (3.0)	2 (0.7)

7.4.3. Deaths and other serious adverse events (SAE)

No deaths occurred during any of the studies. In the combined pivotal studies, 3 patients on Oracea reported 8 SAEs (coronary artery disease, large intestine perforation, haemoglobin decrease (↓) uterine cancer, renal insufficiency, pulmonary embolism, respiratory arrest, DVT), and 2 patients on placebo reported 2 SAEs (chest pain, pneumonia).

7.4.4. Discontinuation due to adverse events

In the 2 pivotal studies, 20 (7.4%) patients on Oracea and 12 (4.5%) patients on placebo discontinued due to AEs. Those withdrawing due to AEs at least one of which was classified as treatment-related are listed below, with those AEs which were classified as treatment-related.

Table 26. Treatment-related AEs leading to discontinuation.

Oracea (13 patients)	Placebo (7 patients)
abdo distension, gastrointestinal discomfort, malaise abdo pain, diarrhoea abdo pain upper anxiety, insomnia, nausea bronchospasm, face oedema diarrhoea dysphagia, headache dyspnoea fungal infection furuncle gastrointestinal pain skin reaction ventricular extrasystoles	abdo pain upper cystitis diarrhoea, nausea headache muscle cramp, dizziness, nausea nausea nausea, vomiting

7.5. Laboratory tests

7.5.1. Pivotal studies

There were no notable changes from baseline to endpoint in either treatment group for any laboratory parameter.

Clinically significant laboratory values at endpoint visit, when reported as AEs and classified as treatment-related (possible or probable) are listed below.

Table 27. Clinically significant laboratory values at endpoint visit, when reported as AEs and classified as treatment-related (possible or probable)

Oracea		Placebo	
Abnormality	**Comment**	**Abnormality**	**Comment**
AST↑, ALT↑		AST↑, ALT↑	
AST↑, LDH↑		Hb↓, Hct↓	
AST↑, ALT↑, LDH↑	Also ↑ at baseline		
glucose↑	Also ↑ at baseline		
Uric acid↑			
AST↑			

7.6. Postmarketing experience

Safety Summary Reports for Periostat, covering the period 1 January 1999 to 1 February 2005, were included in the dossier, as was a *NDA 50-805 Safety Update Report* for Oracea, dated 17 March 2006 (covering the period 2 February to 1 May 2005), which did not relate to post-marketing experience. The evaluator considered these reports irrelevant.

Also included was *Periodic Safety Update Report No. 1 for Doxycycline Products*, dated 27 July 2009 (covering the period 25 April 2008 to 31 May 2009). [information redacted]. In a table headed "All Medically Confirmed Reactions", the following reports related to cases in which it was stated that the patient had been treated with Oracea or "doxycycline capsules 40 mg daily":

Table 28. All Medically Confirmed Reactions

Description of AE	Comment
hearing loss	
ocular hyperaemia	Onset after few days treatment. Positive rechallenge
dyspepsia	Resolved 2 days after stopping Oracea
pseudomembranous colitis recurrence	Clostridium difficile cultured from stool
onychomycosis	
UTI	Treating physician believed unrelated to Oracea
Clostridium difficile colitis	
rectal injury	
arthralgia	
myalgia	Onset about 3 weeks after starting Oracea
headache	
benign intracranial hypertension	Onset about 19 weeks after starting Oracea
headache	
migraine	Patient on multiple drugs
confusional state	Onset day after starting Oracea.
dyspnoea	
rash	Onset 4 hours after starting Oracea.

7.7. Specific safety issues of regulatory importance

The principal safety issue relates to the question of whether long-term exposure to low dosage doxycycline might have an effect on resident microflora – such as induction of resistance, or increase in the risk of opportunistic infection such as yeasts.

See discussions above.

7.8. Other safety issues

Not applicable.

7.9. Evaluator's overall conclusions on clinical safety

The safety data from studies 301 and 302 are of only ancillary value, for the reason given under *Effect of food* above.

The safety data from the pivotal studies suggest that use of Oracea is associated with gastrointestinal AEs, and that the possibility of an effect on BP should be kept under review, but do not raise any major concern. Also, safety should be considered in the context of the long history of doxycycline use at dosages of 100 mg daily, often for months at a time (as an anti-malarial) – a fact which provides useful general safety reassurance.

Studies like that of Skidmore *et al.* (2003) can provide some reassurance in relation to the point described at section 8.7 above. But

- the concept of attempting to identify a particular plasma concentration of an antibiotic, below which micro-organisms, **wherever they occur in the body**, are not expected to be affected, is in the evaluator's opinion fundamentally flawed; and
- any study which focuses on examination of the microflora in small patient groups leaves open the possibility that some unrecognised or unstudied microorganism may be affected by prolonged treatment with low-dose doxycycline, with adverse results for the patient.

In principle, this aspect of safety should involve use of the actual product proposed for registration. Ultimately, Phase III clinical studies of adequate size and duration must be relied upon for safety reassurance – including reassurance on the question of possible effects of low dose doxycycline on microflora. Thus, the evaluator doubted that there is much to gain from the submission of further studies of the kind considered at *Pharmacodynamics* above. The question of co-morbidities which may require periodic antibiotic treatment should also be given some consideration. For example, COPD affects > 1 million Australians, and for initial treatment of exacerbations therapeutic guidelines recommend amoxycillin or doxycycline (Therapeutic Guidelines Limited, 2010). It would be of interest to study whether exacerbations in these patients are more difficult to treat if they have been taking long-term low-dose doxycycline for rosacea.

The guideline on population exposure appropriate for the assessment of clinical safety for medicines intended for long-term treatment of non-life-threatening conditions (EU, 1998) recommends 300-600 patients over 6 months, with perhaps 100 patients exposed for 1 year. In the evaluator's opinion, in view of the point made in the first paragraph in this section, further Phase III trials need to include at least 300 patients studied over 6 months, with specific attention being given to problems which may result from an effect on resident microflora.

8. First round benefit-risk assessment

8.1. Preliminary assessment of benefits

In view of the flaws in the pivotal studies, the evaluator believed no valid efficacy data survive, and no benefits have been proven.

In case the vealuator's opinion in the paragraph above is not accepted, note that the benefits of the treatment proposed are modest, have not been subjected to patient self-assessment, and

have not been compared to those which are offered by other treatment (see *Evaluator's Conclusions on Clinical Efficacy* above).

8.2. Preliminary assessment of risks

The evaluator believed that safety has not been adequately studied (see *Evaluator's Conclusions on Clinical Safety* above).

8.3. Preliminary assessment of benefit-risk balance

In view of the discussions of *Benefits* and *Risks* above, the evaluator believed that the benefit-risk balance is unfavourable. Also, the evaluator would observe that proper assessment of the benefit-risk balance requires dose-finding studies, which have not been done.

8.4. First round recommendation regarding authorisation

The evaluator recommended refusal, on the grounds of

- inadequate evidence of quality; and
- an unfavourable benefit-risk balance.

9. Clinical questions

The evaluator believed there was no point in pursuing this application further unless the sponsor can produce an argument which rescues the pivotal studies. If the sponsor does achieve this, then the sponsor might be invited

- to address the problem raised under *Modified-release property*; and
- to respond to the question of whether Oracea has meaningful modified-release properties.

10. References

10.1. Published papers presented for evaluation

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10.2. Other references

European Agency for the Evaluation of Medical Products (EMEA). 1999. *Note for Guidance on Modified Release Oral and Transdermal Dosage Forms: Section II (Pharmacokinetic and Clinical Evaluation).* Document CPMP/EWP/280/96.

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European Union (EU). 1998. The extent of population exposure to assess clinical safety for medicines intended for long-term treatment of non-life-threatening conditions. *Rules* 3(c) - 3cc5a, pages 121-125.

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