CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-808

MEDICAL REVIEW

CLINICAL REVIEW

Application Type: NDA 505(b)(1)
Submission Number: 50-808
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Reviewer Name: Bindi Nikhar, MD
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Established Name: Minocycline Hydrochloride
(Proposed) Trade Name: Solodyn™
Therapeutic Class: Antimicrobial
Applicant: Medicis Pharmaceutical Corporation

Priority Designation: S

Formulation: Modified Release
Dosing Regimen: Once a day
Indication: Treatment of inflammatory lesions of moderate-severe acne vulgaris
Intended Population: Patients 12 years and older

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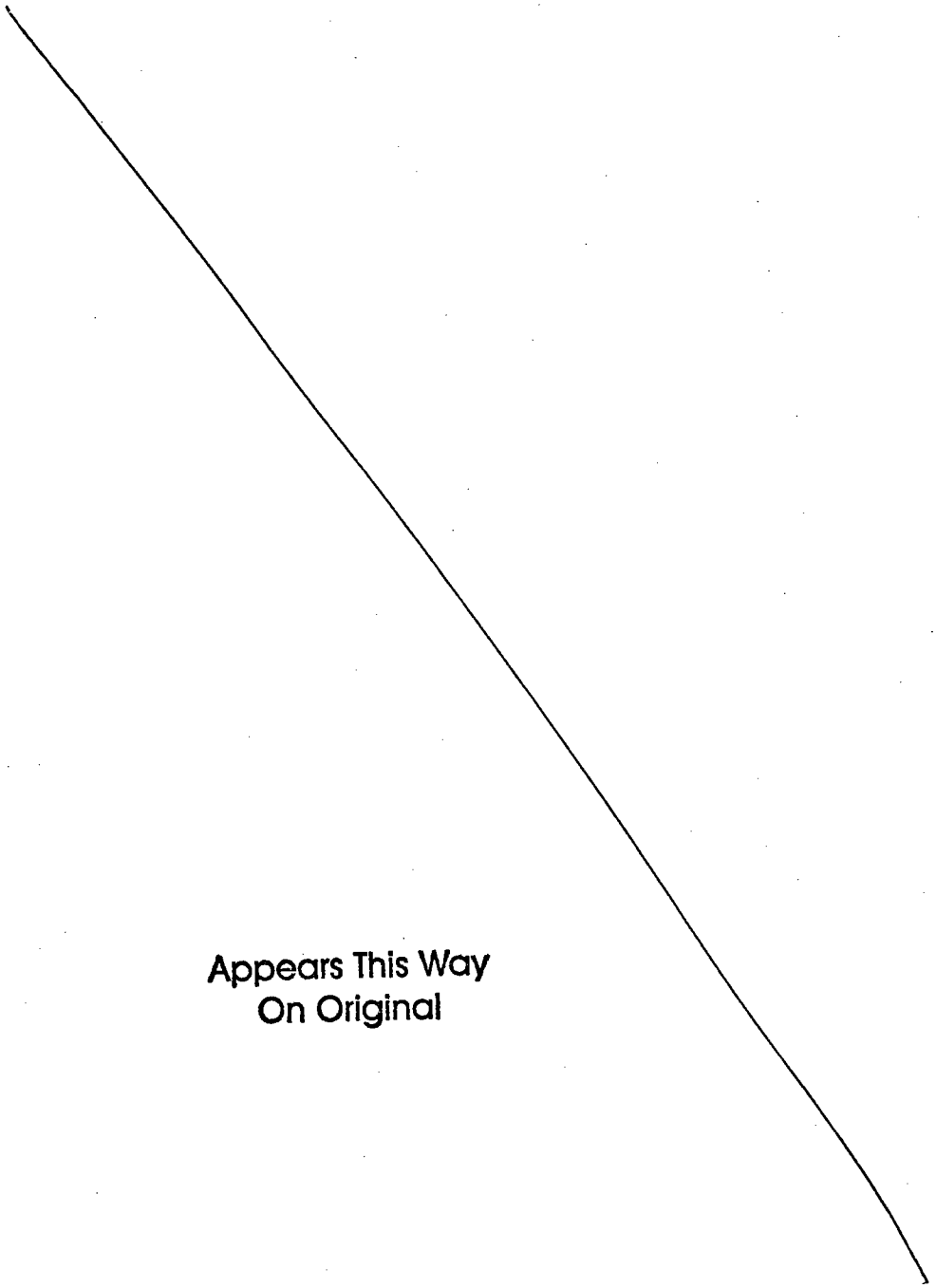

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The sponsor, Medicis Pharmaceutical Corporation has submitted a 505(b)(1) marketing application for Solodyn tablets, which is an extended-release formulation of minocycline. The indication sought by the sponsor is the once a day treatment of inflammatory lesions associated with moderate-severe acne vulgaris in patients 12 years of age and older. Upon review, the indication will be 'the once a day treatment of only inflammatory lesions of non-nodular, moderate-severe acne vulgaris in patients 12 years of age and older'. Based upon adequate demonstration of safety and efficacy, this application should be approved.

Minocycline is a semi-synthetic, second-generation tetracycline that has been used for many years, primarily as an antibiotic. Currently marketed immediate-release formulations of minocycline are indicated as adjunctive therapy for severe acne. In clinical practice minocycline is generally used to treat inflammatory lesions of acne vulgaris, often in combination with topical agents to treat non-inflammatory lesions.

Solodyn was originally conceived as an extended-release formulation that would help prevent the vestibular adverse effects that may be associated with the rapid absorption of immediate-release minocycline products. However, pharmacokinetic testing for Solodyn revealed its absorption profile was not vastly different from the immediate-release formulation. Solodyn has not been compared to the immediate-release formulation of minocycline in safety and efficacy clinical trials.

Efficacy analysis for Solodyn has been derived from two Phase 3, twelve-week, pivotal efficacy and safety studies in patients ≥12 years conducted by the sponsor in the US, while the integrated safety analysis is based on all clinical studies conducted for evaluation of Solodyn. Patients with ≥ 25 and ≤ 75 inflammatory facial lesions and with < 2 nodules/cysts were included in pivotal studies.

In two clinical studies, Solodyn was able to meet the co-primary efficacy endpoints:
1) Mean percent change in inflammatory lesion counts from baseline to 12 weeks *and*
2) Percentage of subjects with an Evaluator's Global Severity Assessment of clear or almost clear at 12 weeks

Results of these twelve-week studies showed Solodyn to be safe and effective in the treatment of only inflammatory lesions of non-nodular, moderate-severe acne vulgaris. Solodyn did not demonstrate any effect on non-inflammatory lesions (benefit or worsening).

Minocyline, like other tetracyclines, is known to have certain adverse effects that may preclude its use beyond 12 weeks. These include hypersensitivity, hepatotoxicity, autoimmunity syndromes (lupus-like syndrome, vasculitis, and hepatitis), thyroid gland dysfunction,

pseudotumor cerebri and hyperpigmentation of various tissues. Other possible adverse effects include deleterious effects on human spermatogenesis and effects on growth in pediatric age groups. The human spermatogenesis study conducted by the sponsor was found to be inadequate and will need to be repeated. In general, these adverse effects are expected to occur over long-term therapy with minocycline, although there are some adverse effects that are not necessarily dose or duration limited.

Currently, the safety of Solodyn has not been established beyond 12 weeks of use. A 2-year open-label safety study that is ongoing will attempt to elucidate long-term safety given that acne vulgaris is a chronic indication that is commonly seen in teenagers; a pediatric growth study is included as part of this study.

In conclusion, an Approval action is recommended for Solodyn for the once a day treatment of only non-nodular, moderate-severe inflammatory lesions of acne vulgaris in patients 12 years of age and older.

1.2 Recommendation on Post-marketing Actions

1.2.1 Risk Management Activity

No risk management activity for Solodyn is planned at this time.

1.2.2 Required Phase 4 Commitments

Post-marketing commitments include:
Clinical:
1) Submit results of ongoing 2-year, open-label safety study (MP-0104-07) which includes a growth assessment of a subset of pediatric subjects within 3 months of study completion.

2) Conduct an appropriately designed human spermatogenesis study to evaluate effects of minocycline on male spermatogenesis within 3 months of drug approval and submit results to agency within 3 months after study completion. This study should be appropriately representative of US demographics and should include a racially diverse population.

Non-Clinical:
1) Submit protocols for non-clinical rat and mice carcinogenicity studies within 3 months of drug approval and submit results within 3 months after study completion.

1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The sponsor has submitted an NDA application for oral Solodyn™ (minocycline extended-release) tablets as a 505(b)(1) application. Minocycline is a semi-synthetic, second-generation tetracycline that is more lipophilic than first-generation tetracyclines. Currently marketed immediate-release formulations of minocycline have been approved as adjunctive therapy for severe acne. Solodyn is not bioequivalent to the currently approved formulations of minocycline.

Solodyn was originally conceived as an extended-release (ER) formulation that would help prevent vestibular adverse effects that may be associated with the rapid absorption of immediate-release minocycline products. However, pharmacokinetic testing revealed that the absorption profile of Solodyn is not vastly different from the immediate-release products. The sponsor was asked to compare the new extended-release formulation of minocycline to the immediate-release formulation for safety and efficacy purposes, but this was not done.

The dose of 1 mg/kg for Solodyn was chosen based on a Phase 2, twelve week, dose-ranging study that assessed safety and efficacy of minocycline ER formulation at 1 mg/kg, 2 mg/kg and 3 mg/kg in subjects with moderate-severe acne vulgaris. No trends for efficacy were observed at doses higher than 1 mg/kg and the incidence of adverse events appeared to be increase with higher doses.

The efficacy of Solodyn was tested in the treatment of inflammatory lesions of non-nodular, moderate to severe acne vulgaris in two pivotal clinical trials, MP-0104-04 and MP-0105-05. Effect of Solodyn on non-inflammatory lesions was also tested as part of the clinical program.

The integrated safety analysis was based on an overall combined review of safety results obtained from pharmacokinetic (PK), pharmacodynamic (PD), dose-ranging and clinical studies conducted as part of the drug development program.

1.3.2 Efficacy

Both pivotal studies MP-0104-04 and MP-0104-05 were nearly identical Phase 3, multi-center, randomized, double-blind, active and placebo-controlled studies designed to evaluate the safety and efficacy of minocycline ER formulation (Solodyn) at 1 mg/kg in the treatment of inflammatory lesions of non-nodular, moderate-severe acne vulgaris in subjects 12 years of age and older. In Phase 3 studies, a total of 924 subjects were included in the ITT population, out of which, 615 subjects received minocycline 1 mg/kg and 309 subjects received placebo. All investigative centers were in the United States.

Minocycline was considered to be superior to placebo if both primary efficacy endpoints were statistically significantly in favor of minocycline compared to placebo.

Primary efficacy endpoints in the ITT population were:

1) Percent change from baseline to day 84 (end-of-treatment) in inflammatory lesion counts *and*
2) Proportion of subjects who achieved success defined as a score of 0 (clear) or 1 (almost clear) on the dichotomized Evaluator's Global Severity assessment (EGSA) scale (inflammatory lesion counts only) at day 84.

Based on a protocol amendment, an EGSA that included non-inflammatory lesions was added to the study and was included as a secondary efficacy endpoint. This was added to confirm that the action of minocycline on inflammatory lesions did not result in a secondary exacerbation of the non-inflammatory process.

Secondary efficacy endpoints in the ITT population were:
1) Percent change in non-inflammatory lesions
2) Two grade reduction on the EGSA *and*
3) Success (clear or almost clear) on a second global assessment that took into account both inflammatory and non-inflammatory lesions

Study MP-0104-04 results
Minocycline demonstrated superiority over placebo in the two primary efficacy endpoints in the ITT population:
- Mean percent reduction from baseline in inflammatory lesion counts at day 84, minocycline/placebo = 43.1%/31.7% (p=0.001) *and*
- Dichotomized analysis (success = clear/almost clear) of the Evaluator's Global Severity Assessment scale at day 84, minocycline/placebo = 17.3%/7.9% (p=0.006).

Study MP-0104-05,
Minocycline demonstrated superiority over placebo in the two primary efficacy endpoints in the ITT population:
- Mean percent reduction from baseline in inflammatory lesion counts at day 84, minocycline/placebo = 45.8%/30.8% ($p < 0.001$) and
- Dichotomized analysis (success = clear/almost clear) of the Evaluator's Global Severity Assessment scale at day 84, minocycline/placebo = 15.9%/9.5% ($p = 0.018$).

Results in the ITT population were supported by those in the PP population in both studies.

Efficacy analysis conclusions:
Results from both 12-week pivotal studies MLP-0104-04 and MP-0104-05 indicated that Solodyn™ (minocycline HCl) extended release tablets were statistically superior to placebo for the two primary efficacy endpoints. Solodyn tablets were shown to be effective in the treatment of only inflammatory lesions of non-nodular, moderate-severe facial acne vulgaris in subjects' ≥ 12 years of age.

No claims for efficacy should be made for non-facial areas, since they were not included in the efficacy analysis. Solodyn did not demonstrate any effect on non-inflammatory lesions (benefit or worsening).

Subgroup analyses revealed success rates to be generally higher in females and in ≥ 18 years age groups and success rates were much lower in patients with more severe disease at baseline, i.e. those with EGSA scores ≥ 4 in both studies. Success rates were in general higher in White subjects compared to Non-White subjects; however, both pivotal clinical studies did not include adequate Asian/Pacific Islander or American Indian/Alaskan subjects.

1.3.3 Safety

Safety was determined from an integrated analysis of all clinical studies performed during the Solodyn drug development program. These included the PK/PD studies as well as the Phase 2 dose-ranging study MP-0104-01 and the two pivotal safety and efficacy studies MP-0104-04 and MP-0104-05. The number of subjects across the Phase 2 dose-ranging study and the Phase 3 pivotal safety and efficacy studies who received minocycline 1 mg/kg for 12 weeks was 674 compared to 364 on placebo.

Safety analysis for Phase 2 and 3 studies was conducted based on adverse events noted during clinical trails and lab monitoring (complete blood counts, comprehensive metabolic profile, liver function tests, thyroid function tests, anti-nuclear antibody and Urinanalysis).

No deaths were reported in any of the clinical studies conducted for Solodyn extended-release tablets. Across Phase 2 (dose ranging) and Phase 3 (pivotal safety and efficacy) studies, 379 (56%) of subjects on minocycline (M) 1 mg/kg and 197 (54%) on placebo (P) reported treatment-emergent AEs in the 12 week period. Most commonly reported AEs in the minocycline/placebo groups included headache 23%/23%, nausea 10%/11%, fatigue 9%/7%, dizziness 9%/5%, diarrhea 5%/6%, gastrointestinal pain 5%/7%, upper abdominal pain 3%/4%, and pruritus 5%/4%. Other relevant AEs in the M/P groups included mood alteration 3%/3%, vomiting 2%/3%, urticaria 2%/0.3%, tinnitus 1.5%/1.4% and vertigo 1.2%/0.8%.

Vestibular and skin-related AEs such as urticaria and pruritus were higher in the minocycline group compared to the placebo group. Drug-related AEs for minocycline were highest in the nervous system disorders class (headache and dizziness), followed by general disorders (fatigue and malaise) and skin and subcutaneous tissue disorders (pruritus and urticaria).

Severe treatment-emergent AEs were reported by 20 (3%) of subjects in the minocycline group and 7 (2%) in the placebo group. In the minocycline/placebo groups, these included gastrointestinal pain 2/0, vomiting 1/0, aggravated acne 1/0, rash 1/0, sunburn 1/0, urticaria 1/0 and pruritus 1/0.

Out of the 4 serious AEs reported, only 1 was considered possibly related to minocycline; this involved a case of neck pain, hypoaesthesia and paraesthesia that occurred after strenuous yard work and led to hospitalization.

Limited spermatogenesis study results showed that minocycline may have a deleterious effect on male spermatogenesis. Protocol design for these studies was inadequate and the sponsor will have to repeat these studies.

Lab changes – In the 12 week studies, most frequent changes in labs in the minocycline versus placebo group were in liver function tests (slight elevations of ALT and AST); there were also slight elevations in the incidence of ANA and TSH values. None of the patients exhibited clinically relevant signs and symptoms and most AEs resolved.

Safety analysis conclusions:
Commonly occurring treatment-emergent AEs in at least 1% of the population in the minocycline group included headache, dizziness, nausea and fatigue. Severe treatment-related AEs (GI and skin related AEs) were higher in the minocycline compared to the placebo groups. Vestibular AEs were in general higher in the minocycline group compared to placebo. Overall, most AEs noted in 12 week studies were in keeping with labeled AEs of minocycline.

Given that acne vulgaris is a chronic indication, to assess long-term safety the sponsor is conducting a 2 year open-label safety study where subjects will receive 12-week courses of minocyline as needed; this will include a growth study in pediatric subjects to evaluate effects of minocyline deposition in epiphyseal growth plates. Effects on minocycline on male spermatogenesis need to be evaluated by conducting well-controlled studies.

Safety concerns that are known to occur with tetracycline class of antibiotics and minocycline in particular include:

- Hepatotoxicity
- Autoimmunity syndromes such as lupus-like reactions, autoimmune hepatitis, vasculitis, etc.
- Hypersensitivity reactions
- Hyperpigmentation of various tissues
- Thyroid gland dysfunction. Few cases of papillary thyroid cancer have been reported in the minocycline-induced 'black thyroid' setting.
- Central nervous system AEs such as pseudotumor cerebri

1.3.4 Dosing Regimen and Administration

Solodyn tablets are intended for once a day oral dosing at 1 mg/kg without a loading dose; there are three strengths of tablets 45 mg, 90 mg and 135 mg. The dose was chosen based on dose-ranging conducted by the sponsor, where no trends for efficacy were seen at higher doses and adverse effects in general appeared to be greater at higher doses.

1.3.5 Drug-Drug Interactions

The proposed label for Solodyn conveys the following concerns:

1) Patients on anticoagulant therapy may require downward adjustment of their anticoagulant dosage because tetracyclines depress plasma prothrombin activity.
2) Because bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid 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 antacids containing aluminium, calcium or magnesium and iron-containing preparations.
5) The sponsor conducted a multi-center study to evaluate effect of Solodyn on low-dose oral contraceptives. Study results showed that minocyline-related changes in estradiol, progestinic hormone, and FSH and LH levels cannot be ruled out. Based on these results, females are advised to use a second form of contraceptive during treatment with minocycline.

The sponsor conducted a study to assess effects of food on absorption of minocycline and it was shown that its absorption was unimpaired in the presence of food. The dosage and administration part of the label mentions that minocycline may be taken with or without food and that ingestion of food along with Solodyn may help to reduce risk of esophageal irritation and ulceration.

1.3.6 Special Populations

Solodyn was appropriately studied in patients more than 12 years of age since acne vulgaris is not commonly seen in the younger age groups. Efficacy and safety of Solodyn was tested in subgroups - age, race and gender and based on subgroup analysis, there are no special dosing considerations for different demographic populations. However, both pivotal clinical studies did not include adequate Asian/Pacific Islander or American Indian/Alaskan subjects.

Pregnant and breast-feeding subjects were excluded from the studies; this was based on the teratogenic adverse effects of minocycline. Minocycline has a Pregnancy category D based on the known teratogenic profile of tetracyclines.

Introduction and Background

2.1 Product Information

The sponsor, Medicis Pharmaceutical Corporation has submitted NDA # 50-808 as a 505(b)(1) application for Solodyn™ tablets, a new extended-release formulation of minocycline hydrochloride (HCl) in 45 mg, 90 mg and 135 mg strengths. The indication sought is the once daily treatment of inflammatory lesions of moderate-severe acne vulgaris (AV) in patients 12 years of age and above. This extended-release formulation includes the identical active pharmaceutical ingredient as the currently marketed minocycline as well as additional excipients required for an extended-release formulation, but is not bioequivalent to the marketed product.

Minocycline, an antibiotic, is an approved prescription drug product originally marketed in the United States as Minocin® (Lederle/Wyeth Laboratories) in 1965. It is available as several different oral formulations, and is also available as a generic prescription drug. It is currently marketed by Medicis as an immediate-release formulation under the trade name Dynacin®. Minocycline is a second generation semi-synthetic derivative of tetracycline that is indicated for a number of bacterial infections (caused by gram-positive and gram-negative organisms) as well as adjuvant therapy for severe acne vulgaris. Tetracyclines are primarily bacteriostatic and are thought to exert antimicrobial effects via inhibition of protein synthesis. The tetracycline class of drugs is not curative in the treatment of acne; in the vast majority of cases, acne recurs when the drug is stopped.

In addition to its antibacterial effects, minocycline is thought to have anti-inflammatory properties, including inhibition of bacterial production of lipases and cytokines as well as inhibition of oxidizing agents by polymorphonuclear leukocytes. Minocycline is more lipophilic than first-generation tetracyclines and has a long half-life (15 to 25 hours).

The sponsor's rationale for development of an extended-release formulation is that slowing the rate of absorption of minocycline may minimize vestibular adverse effects associated with the immediate-release formulation that are usually seen within the first 5 days of treatment. A pharmacokinetic study that compared Solodyn to the immediate-release formulation did not show a substantial difference in absorption profile between the two formulations. Its once-daily dosing regime is hoped to help improve compliance in the adolescent age groups. The extended-release formulation would be the first in its class for the treatment of acne vulgaris.

2.2 Currently Available Treatment for Indications

Minocycline HCl products (immediate release forms) are approved as adjunctive therapy for severe acne vulgaris (AV). The sponsor's currently approved immediate-release minocycline product (Dynacin) is labeled for the acne indication as follows: "in severe acne, minocycline may be useful adjunctive therapy". The currently labeled dose for adults is 200 mg initially, followed by 100 mg every 12 hours. For children above eight years, the usual dosage is 4 mg/kg initially, followed by 2 mg/kg every 12 hours.

Depending upon the severity of lesions, there are a number of other drugs available in topical and oral formulations for the treatment of AV. These include antibiotics such as erythromycin, clindamycin, other tetracyclines (doxycycline) as well as the retinoids in various strengths. The oral formulation of isotretinoin is well described as being effective for severe, nodular acne.

2.3 Availability of Proposed Active Ingredient in the United States

Minocycline was patented in the US in 1965 and is currently an approved prescription drug for a number of antibacterial indications, as well as for adjuvant therapy for severe acne vulgaris. Minocycline hydrochloride was originally marketed in the US under the trade name Minocin® (Lederle/Wyeth Laboratories) and is currently marketed by several different sponsors in a range of strengths; generic formulations are also available.

Minocycline HCl is indicated for the following infections: Rocky Mountain spotted fever, typhus fever, other tick-borne infections, Mycoplasma pneumoniae, Chlamydia trachomatis, Yersinia pestis, etc; gram-negative susceptible organisms such as Escherichia coli, Enterobacter aerogenes, Shigella, H. Influenzae, Klebsiella; gram-positive susceptible organisms such as Streptococcus pneumoniae, Staphylococcal aureus, Neisseria gonorrhoae; in patients in whom penicillin may be contraindicated; and in asymptomatic carriers of Neisseria meningitides.

2.4 Important Issues with Pharmacologically Related Products

The tetracycline-class antibiotics (tetracycline, doxycycline and other minocycline products such as Minocin and Dynacin) are known to be associated with a number of adverse events (AEs) as follows:

1) Tetracycline-class antibiotics, including minocycline are known to be teratogenic (Pregnancy Category D). Warnings for all tetracycline class drugs include permanent yellow-brown discoloration of teeth if these drugs are administered during last half of pregnancy, infancy and childhood up to age 8 years. This AE is more common during long-term use of the drug, but has also been observed following repeated short-term courses. Enamel hypoplasia has also been reported. The label for Minocin (Minocycline Hydrochloride) mentions that congenital anomalies including limb reduction have been reported in post-marketing experience.

2) Tetracyclines form a stable calcium complex in bone forming tissues by virtue of calcium chelation. Animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can cause retardation of skeletal development on the developing fetus. The labels for Minocin and Dynacin also describe evidence of embryotoxicity in animals treated early in pregnancy.

3) Tetracyclines have been associated with a variety of systemic adverse events as follows: fever, discoloration of secretions, gastrointestinal (nausea, vomiting, diarrhea, enterocolitis, pseudomembranous colitis, pancreatitis), hepatic toxicity (hepatitis, fatal hepatic failure, cholestasis, increases in liver enzymes), skin (rashes, alopecia, erythema nodosum, toxic epidermal necrolysis, vasculitis, erythema multiforme, Stevens-Johnson syndrome), musculoskeletal, renal (interstitial nephritis, acute renal failure), blood (agranulocytosis, hemolytic anemia, leucopenia, neutropenia, etc).

4) Photosensitivity manifested by an exaggerated sunburn reaction has been observed in patients taking tetracyclines (including minocycline).
5) Pseudotumor cerebri (benign intracranial hypertension) has been described in adults and adolescents associated with the use of tetracyclines, although the risk remains highest with minocycline because of its higher lipid solubility and potential ability to penetrate the blood-brain barrier. The headache and blurred vision associated with it are usually reversible upon discontinuation of treatment, but the possibility for permanent sequelae such as visual deficits exists.
The likelihood of developing pseudotumor cerebri (PTC) is higher if tetracyclines are used in combination with systemic isotretinoin products (used to treat severe acne) that also known to cause PTC on their own.
6) Drug-induced hepatitis and lupus like syndromes have been reported with tetracycline-class antibiotics as follows: a) Hypersensitivity syndrome - cutaneous reaction, eosinophilia, hepatitis, pneumonitis, nephritis, myocarditis, etc. b) Lupus-like syndrome – positive antinuclear antibody, arthralgia, arthritis, joint stiffness or swelling with fever, rash, etc. c) Serum-Sickness like syndrome – fever, urticaria, rash, arthritis, eosinophilia, etc
These reactions are usually reversible, although possibility for permanent sequelae exists.
7) When given over prolonged periods, tetracyclines have been reported to produce brown-black discoloration of the thyroid gland. Cases of abnormal thyroid function and papillary cancer have been reported in the setting of 'black thyroid'.

2.5 Pre-Submission Regulatory Activity

Following are salient meetings held with the sponsor:
Pre-IND meeting on 2/11/2002:
a) A 505(b)(1) versus 505(b)(2) approach was discussed with the sponsor; the sponsor chose to opt for the 505(b)(1) route that would require two Phase 3 safety and efficacy trials in patients 12 years and older.
b) An mg/kg dosing regime was chosen for the dose-ranging study.
c) Division noted that adequate numbers of patients from 12 to 17 years should be studied.

IND submission on 7/12/2002:
a) Pre and post-treatment labs to be done on all patients. Thyroid function tests to be monitored in the acne setting, where use is longer than for most infectious indications.
b) The interaction between oral contraceptives and minocycline was asked to be explored further.
c) Vertigo, dizziness, nausea and vomiting were to be classified as AEs throughout the trial.
d) Patients were to avoid concomitant use of high dose vitamin A supplements and Accutane to avoid the risk of Pseudotumor cerebri.
e) This study would not support any anti-microbial claims.
f) It was recommended that the global evaluation scale be shortened from 7 categories to 5 and that a static assessment of disease status be made.

Regulatory Guidance Meeting on 5/28/03:
a) Phase 3 studies that included a minocycline reference product arm would allow comparison for both safety and efficacy of a new dosage or formulation and provide valuable information to users of the drug product.
b) The sponsor would need sufficient numbers of patients treated with their drug product to meet ICH E1A if seeking an indication different from the reference drug product.
c) Safety comments included evaluation of growth plate closure in pediatric age groups, vestibular AEs, PK/PD studies evaluating effects of tetracyclines on oral contraceptives in view of the teratogenic potential of minocycline and effects of minocycline on spermatogenesis. A long-term, 2 year, open-label safety study was to be conducted in subjects with moderate to severe acne.

End-of-Phase 2 meeting on 9/17/03:
a) Design of long-term safety study discussed - recommended that 300 subjects be enrolled and safety data to be collected for one year and submitted to the NDA. The bone/growth study in children was to be conducted as part of the open-label safety study.
b) The Agency agreed with the sponsor's request of the partial waiver of the Pediatric Rule as long as large proportions of patients were between 12 and 16 years of age.

Agency comments regarding proposed Phase 3 clinical trials on 3/8/04:
a) IGA scale should include non-inflammatory as well as inflammatory lesions.
b) Proposed non-inferiority margin [redacted] for the percent change in non-inflammatory lesion counts relative to placebo was discussed.
c) An ethical escape clause to be added for those with worsening acne.
d) The Dermatology Specific Quality-of-Life Questionnaire had limited regulatory significance.

Regulatory Guidance Meeting on 8/18/04:
a) Open-label safety study – Unbiased patient selection discussed. The denominator for the long-term study should be those patients included in the initial efficacy study.
b) Agency reiterated the need to include non-inflammatory and inflammatory lesions in the IGA scale. IGA scale to include score (1 to 5) and description of each score but should avoid grades. Since the indication sought is moderate to severe AV, patients with grades 3 to 5 per the IGA scale to be included in all Phase 3 studies; patients with nodular-cystic acne could be excluded from the trial and this would be reflected in labeling. The inclusion criteria were to be enriched with patients who have primarily inflammatory lesions while imposing a cap on non-inflammatory lesions.
c) Human spermatogenesis study requested in view of the findings from the rat spermatogenesis study.
d) It was recommended that photographs of patients be submitted.
e) Growth Study in children - include appropriate imaging methods such as MRI or CT scans.

The sponsor agreed that it was important to assess effect of Minocycline ER [redacted] on non-inflammatory lesions (in addition to inflammatory lesions) and that the IGA scale would include both. The sponsor mentioned that other suggestions regarding IGA would not be incorporated since the Phase 3 safety and efficacy studies were already underway. The Agency responded that

it did not know that the trials were already underway and that recommended changes were intended to be before the study began.

Minocycline effects on spermatogenesis Protocol on 2/2/05:
a) A negative study would not necessarily imply that there was no co-relation between minocycline and human spermatogenesis. Not possible to clearly opine on a negative co-relation based on a small, open-label study design.

b) Sponsor encouraged to provide as much information as possible about this potential adverse effect; otherwise labeling would have to be adequately cautious.

A consult was obtained from the division of Reproductive and Urologic Drug Products to evaluate this protocol. Relevant comments were as follows:

a) A study to determine the effects of the drug on semen analysis should be placebo-controlled, double-blind, preferably have a non-inferiority design, and have a larger number of subjects.
b) Six-month study duration was acceptable. Because of the variability in semen analyses, collection of 3 semen analyses at each time point for each subject was optimal. If at least 2 semen analyses are collected at each time point, these data can be averaged.
c). Performance of semen analyses at one and two months may be too early to see a drug effect on spermatogenesis because spermatogenesis and maturation within the epidydymis require approximately 3 months.

Pre-NDA meeting on 3/28/2005:
a) Study report for spermatogenesis study to be included in NDA submission. Sponsor's Pharm/Tox consultant mentioned that the effects of minocycline on spermatogenesis may be due to suppression of thyroid function and that the rodent is particularly sensitive to its effects.
b) Claim sought by the sponsor that the new extended release formulation of minocycline may reduce vestibular side-effects will be a review issue.
c) Sponsor was reminded that they did not have Agency agreement with regard to study design, study endpoints and statistical evaluation. Agency stated that protocol changes are not encouraged after study initiation and the original intent of the study would be taken into account during the review process.

2.6 Other Relevant Background Information

Solodyn has not been approved in other countries; therefore no other relevant regulatory information is available at this time.

3 Significant Findings from Other Review Disciplines

3.1 CMC (and Product Microbiology, if Applicable)

Minocycline is a second generation semi-synthetic derivative of tetracycline and is an approved prescription drug originally marketed in the US under the trade name Minocin® (Lederle/Wyeth Laboratories). The drug substance is available as a generic prescription drug and it is marketed in an immediate-release formulation under the trade name Dynacin® by Medicis.

Solodyn (minocycline hydrochloride) tablets containing 45, 90 or 135 mg minocycline were developed by Medicis as an extended-release formulation; the pharmacokinetic study that compared it to the immediate-release product (Dynacin®) showed that there was no substantial difference in exposure duration between the two formulations.

Minocycline HCl is a yellow crystalline powder that is slightly hygroscopic. It is sensitive to light and surface oxidation. The lipid solubility of minocycline is higher than tetracycline and doxycycline.

The inactive ingredients in Minocycline HCl [redacted] are [redacted] lactose monohydrate NF, colloidal silicon dioxide NF, magnesium stearate NF, and an Opadry II film coating (gray, [redacted]). These are commonly recognized pharmaceutical ingredients with a safe history of use in oral formulations. They are listed in the FDA CDER Inactive Ingredients in Approved Drug Products administered by the oral route. They are also considered GRAS for food use or are FDA approved as direct food or color additives.

3.2 Animal Pharmacology/Toxicology

Please see Pharmtox review by Dr. Norman See

Salient points from Pharmtox summary for Solodyn are as follows:

- In the 90 day repeat-dose toxicology studies in mice, rats and monkeys, minocyline was reasonably well tolerated. The primary toxicological target organ for all species was the thyroid with treatment-related effects manifesting as grossly visible enlargement, increased mean weight, dark red discoloration, increased colloid content, accumulation of brown pigment in follicular cells, follicular cell hypertrophy and elevated plasma levels of T4 and TSH.
- Minocycline was negative in a battery of genetic toxicology studies and is apparently not genotoxic.
- Minocycline may be capable of impairing fertility in human males. In male rats, minocyline adversely affected spermatogenic endpoints; these included a significant reduction in the mean number of sperm cells per gram of epididymis, an apparent reduction in the percentage of sperm that were motile and increased numbers of morphologically abnormal sperm cells. Morphological abnormalities included absent heads, misshapen heads and abnormal flagella.
- Teratogenic effects

  Rats – Minocycline reduced mean fetal weight and induced skeletal malformations

(bent limb bones) and skeletal variations (reduced skeletal ossification).
Female rabbits - During period of organogenesis, minocycline induced abortion in a minority of does, reduced maternal weight gain, gravid uterine weight and mean fetal body weight and induced skeletal malformations (bent limb bones). Gross external anomalies in pups included smallness of size, malrotated forelimbs and micromelia.

- In safety pharmacology studies, minocycline had no effect on behavior, psychological state, arterial blood pressure, heart rate, ECG or (at clinically relevant levels of exposure) respiration.

Carcinogenicity studies: The label for Dynacin® notes that "dietary administration of minocycline in a long-term tumorigenicity study in rats resulted in evidence of thyroid tumor production. Minocycline has also been found to produce thyroid hyperplasia in rats and dogs. In addition, there has been evidence of oncogenic activity in rats in studies with a related antibiotic, oxytetracycline (i.e. adrenal and pituitary tumor)."

Supplemental studies to be conducted by the sponsor:
Carcinogenicity bioassay studies in mice and rats based on current toxicology testing designs have not been initiated; these 2 year studies are part of the Phase 4 post-approval commitment and will be scheduled upon concurrence with the FDA Cancer Assessment Committee on the maximum dose to be tested. The clinical reviewer agrees that these are appropriate given the few human cases of papillary thyroid cancer that have been reported in the 'black thyroid' setting.

4 Data Sources, Review Strategy, and Data Integrity

4.1 Sources of Clinical Data

The clinical development program for minocycline consisted of the following studies conducted in the US:

1) Four pharmacokinetic (PK) studies – bioequivalence/bioavailability, dose-proportionality, food-effect and steady-state studies.
2) Four pharmacodynamic (PD) studies – antimicrobial effects, interaction with oral contraceptives, effects on spermatogenesis (2 studies).
3) One Phase 2 dose-ranging study.
4) Two Phase 3, randomized, double-blind, placebo-controlled safety and efficacy studies.
5) One open-label, two-year safety study (ongoing), which will incorporate a pediatric growth study to evaluate effects of minocycline on bone growth.

In response to Agency's request for a worldwide safety update for all minocycline formulations, the sponsor provided literature reports. The reviewer consulted literature reports regarding safety and efficacy of minocyline, especially pertaining to its use in acne and Office of Drug Safety (ODS) provided a consult/safety update for minocycline in relation to its use in acne vulgaris.

4.2 Tables of Clinical Studies

Table No. 1
Bioavailability (BA) & Pharmacokinetic (PK) studies

Study Type	Description	Objective	Study Design	Test Products	Subjects	Study Duration	Comment
Bio-availability (BA)	AA1-US-110	BE of two 150 mg tablets with marketed 75 mg capsule	3-way crossover	Tablet, 150 mg, single dose, oral	24 healthy adult male	Single dose	Complete
Bio-availability	AA1-US-190	Relative BA of 135 mg caplet, single dose, fed vs. fasted	2-way, crossover	Caplet, 135 mg, single-dose, oral	24 healthy adults (12 male and 12 female)	Single dose	Complete
Bio-availability	AA1-US-233	Dose proportionality BA of 45 mg, 90 mg and 135 mg caplet compared to 100 mg minocycline capsule	4-way crossover	Caplet, 45, 90 & 125 mg, single dose, oral	24 healthy adults (14 male, 10 female)	Single dose	Complete
Pharmaco-kinetics (PK)	MP-0104-15	Steady-state PK – 135 mg caplet and 100 mg Minocin capsule	2-way crossover	Caplets, 135 mg once daily	28 Healthy adult male	7 days	Complete

Table No. 2 Pharmacodynamic (PD) and Clinical Studies

Study Type	Description	Objective	Study Design	Test Products	Subjects	Study Duration	Comment
Pharmaco-dynamic	MP-0104-09	In vivo antimicrobial effects	Open-label, uncontrolled	Caplets, 45, 90 and 135 mg, once daily	28 subjects with moderate-severe AV; age 12 or older	12 weeks of 1 mg/kg mino. HCl caplets	Complete
Pharmaco-dynamic	MP-0104-10	Drug interaction with oral contraceptives	Open-label, 2-period	Caplets, 45, 90 and 135 mg, once daily	30 healthy adult females taking low-dose oral contraceptives	7 days of 1 mg/kg mino. HCl caplets	Complete
Pharmaco-dynamic	MP-0104-13	Effects on spermatogenesis	Open-label, uncontrolled	Caplets, 45, 90 and 135 mg, once daily	30 (26 for interim summary)healthy adult males	12 weeks of 1 mg/kg/day mino. HCl caplets	Study was ongoing, site affected by Hurricane Katrina; interim report
Pharmaco-dynamic	MP-0104-16	Effects on spermatogenesis	Cohort	Caplets, 45, 90 and 135 mg, once daily	42 (31 on 1 mg/kg/day mino; 11 on no mino.). moderate-severe inflammatory AV, age 16 or older	Participated in MP-0104-04 or MP-0104-05. Up to 68 weeks	Complete
Safety & Efficacy	MP-0104-01	Dose-ranging	Randomized, double-blind, placebo-controlled	Caplets, 45, 135 and 150 mg, once daily	241 (181 active doses, 60 placebo); moderate-severe AV, 12 to 30 years old	12 weeks of 1, 2 or 3 mg/kg/day of mino HCL caplets	Complete
Safety & Efficacy	MP-0104-04	Pivotal efficacy & safety	Randomized, double-blind, placebo-controlled	Caplets, 45, 90 or 135 mg once daily	451 (300 active, 151 placebo); moderate-severe AV, age 12 or older	12 weeks of 1 mg/kg mino. HCl caplets	Complete
Safety & Efficacy	MP-0104-05	Pivotal efficacy & safety	Randomized, double-blind, placebo-controlled	Caplets, 45, 90 or 135 mg once daily	473 (315 active, 158 placebo); moderate-severe AV, age 12 or older	12 weeks of 1 mg/kg mino. HCl caplets	Complete
Safety	MP-0104-07	Long-term safety	Open-label, uncontrolled	Caplets, 45, 90 or 135 mg once daily	345 subjects with moderate-severe AV, age 12 or older	2 years of 1 mg/kg mino. HCl caplets	Ongoing, interim report

4.3 Review Strategy

Efficacy of modified-release minocycline HCl caplets in the treatment of facial inflammatory lesions of acne vulgaris was assessed based on results from the two pivotal Phase 3, placebo-controlled safety and efficacy studies MP-0104-04 and MP-0104-05.

The integrated safety review was based on results from the two Phase 3 pivotal studies as well as results from a Phase 2 dose-ranging study MP-0104-01, 8 PK/PD studies and the ongoing open-label, 2 years' safety study MP-0104-07. The PD studies included an open-label, cohort spermatogenesis study MP-0104-16 (complete report) as well as another open-label, spermatogenesis study MP-0104-13 (incomplete, interim report).

The protocol for study MP-0104-13 was compromised because of its open-label nature, lack of placebo arm, inadequate number of patients (30) and other study design issues. The sponsor had been advised to revise study design and submit a complete study report; however, the sponsor chose to continue with the compromised study design and since the study was still ongoing at the time of NDA submission, an interim report for MP-0104-13 was submitted with the NDA application. It was later revealed that the single study site for this study that was based in New Orleans was destroyed by Hurricane Katrina in August, 2005. The sponsor informed that Agency that this study could not continue and that study reports were destroyed, it would be hard to retrieve adequate information for a full study report and as such, the study could not be completed. The interim report for this study revealed that minocycline therapy may have adverse effects on human spermatogenesis. The sponsor subsequently submitted a revised protocol that was reviewed as a 45 day Special Protocol Assessment on 12/16/2005; this study will be included as a post-marketing commitment.

Since minocycline has been used for many years to treat acne vulgaris, literature reports have been reviewed regarding its use in the treatment of acne vulgaris.

4.4 Data Quality and Integrity

Division of Scientific Investigations was not consulted to audit applicant's data or analyses.

4.5 Compliance with Good Clinical Practices

Clinical studies were conducted in accordance with acceptable ethical standards and Good Clinical Practice guidelines. Informed consent was obtained from all patients participating in the studies.

4.6 Financial Disclosures

The sponsor has submitted Form FDA 3454: Certification of Financial Interests and Arrangements of Clinical Investigators. It does not describe financial arrangements with clinical investigators that would compromise the integrity of data submitted for NDA review.

Clinical Pharmacology

Solodyn™ (minocycline HCl) extended release tablets have been developed in strengths of 45 mg, 90 mg and 135 mg; this extended release formulation was developed by the sponsor in the expectation that this would lower the adverse effects (AEs) reportedly associated with rapid absorption of minocycline, mainly vestibular AEs. The clinical pharmacology program explored the pharmacokinetics (PK) and pharmacodynamics (PD) of the extended-release formulation and compared aspects of it to the immediate-release formulation.

Please refer to Biopharmaceutical review for further details.

5.1 Pharmacokinetics

Human pharmacokinetics of oral minocycline is well described. Minocycline (immediate-release formula 100 mg dose) is readily absorbed from the gastrointestinal tract (>95%) with a C_{max} of 1.7 to 5.7 µg/mL observed within 2 to 4 hours. The elimination half-life is 15 to 25 hours. Due to its high lipid solubility, it has a high volume of distribution, binds substantially to plasma proteins, and is re-absorbed by the renal tubules and gastrointestinal tract; this contributes to the long half-life of the drug.

The extended-release formulation of minocycline was developed in an effort to lower the systemic side effects associated with immediate-release minocycline formulations. Solodyn tablets produce a slightly delayed T_{max} at 3.5 - 4.0 hours as compared to a non-modified release reference minocycline product (T_{max} at 2.25 - 3 hours). At steady-sate (Day 6), the mean AUC(0-24) and C_{max} were 33.32 µg×hr/mL and 2.63 µg/ml for SOLODYN tablets and 46.35 µg×hr/mL and 2.92 µg/ml for Minocin capsules respectively at dose adjusted to 135 mg per day for both products.

Metabolism: Minocycline is partially degraded in the liver to 3 inactive metabolites and is eliminated predominately by the fecal route. The label for Solodyn states that 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. Under such conditions, lower than usual total doses are indicated, and if therapy is prolonged, serum level determinations of the drug may be advisable.

Bioavailability (BA)/pharmacokinetics (PK) studies:

1) Study AAI-US-110: A single-dose three-way crossover pilot bioequivalence/bioavailability study of minocycline tablets and capsules in healthy male volunteers.
2) Study AAI-US-190: A randomized, single-dose, two-way crossover study of the effect of food on the pharmacokinetics of minocycline tablets in healthy volunteers.
3) Study AAI-US-233: A single-dose four-way crossover dose proportionality study of minocycline tablets in healthy volunteers
4) Study MP-0104-15: A two-way crossover steady-state study of minocycline caplets in healthy volunteers

Results of BA/PK studies: These studies indicated that Solodyn is not bioequivalent to the marketed immediate-release formulations. The single-dose, four-way crossover study demonstrated that all strengths of Solodyn tablets (45mg, 90mg, 135 mg) exhibited dose-proportional pharmacokinetics. The food effect study demonstrated that when Solodyn tablets were administered concomitantly with a meal that included dairy products, the extent and timing of absorption of minocycline did not differ from that of administration under fasting conditions.

Drug Interactions
The label for Solodyn contains the following:
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 antacids containing aluminum, calcium or magnesium and iron-containing preparations
5. In a multi-center study to evaluate the effect of Solodyn on low dose oral contraceptives, hormone levels over one menstrual cycle with and without Solodyn 1 mg/kg once-daily were measured. Based on the results, minocycline-related changes in estradiol, progestinic hormone, FSH, and LH plasma levels can not be ruled out. To avoid contraceptive failure, females are advised to use a second form of contraception during treatment with minocycline.

The label also mentions that false elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

5.2 Pharmacodynamics

Pharmacodynamic studies:
1) Study MP-0104-10: An open-label Phase 1 study to examine the effects of minocycline on low-dose ethinyl estradiol contraceptive therapy.
2) Study MP-0104-09: An evaluation of the anti-microbial effects in vivo of minocycline in humans.
3) Study MP-0104-13: An open-label Phase 1 study to examine the effects of minocycline on spermatogenesis in human males (inadequate study design and incomplete study; will be repeated)
4) Study MP-0104-16: An open-label cohort study to investigate the effects of minocycline 1 mg/kg/day on sperm characteristics in male subjects with acne vulgaris.

Results
- Study MP-0104-10 was a multi-center study to evaluate the effect of Solodyn on low dose oral contraceptives, where hormone levels over one menstrual cycle with and without Solodyn 1 mg/kg once-daily were measured. Based on the results, minocycline-related changes in estradiol, progestinic hormone, FSH, and LH plasma levels could not be ruled out. Females will be advised

to use a second form of contraceptive during treatment with minocycline to avoid contraception failure.
- Study MP-0104-13, the human spermatogenesis study was initiated to assess effects of minocycline on male spermatogenesis. This open-label study was found to be inadequate in study design by the Agency and had been initiated by the sponsor already at a single-center site in New Orleans, Louisiana. According to the sponsor, Hurricane Katrina destroyed the study site and affected the conduct of this study. This study is to be repeated utilizing an improved study design.
- Study MP-0104-16 was an open-label, retrospective cohort study initiated by the sponsor without Agency input to assess effects of minocycline on sperm characteristics. Preliminary results from both studies indicate that minocycline may have effects on human spermatogenesis. (Both spermatogenesis studies have been discussed in Section 7.1.12)
- In Study MP-0104-09, therapeutic outcomes showed no evidence of association with the P acnes culture results. Although minocycline has been shown to have in vitro activity against P. acnes an organism associated with acne vulgaris, the clinical significance of this activity against P. acnes in patients with acne vulgaris is not known.
Please refer to Microbiology review for further details of this study.

5.3 Exposure-Response Relationships

The sponsor conduced a Phase 2 dose-ranging study, MP-0104-01, that helped determine the dose chosen for Solodyn at 1 mg/kg once a day in the treatment of non-nodular, moderate-severe lesions of acne vulgaris. The three doses chosen were 1, 2 and 3 mg/kg and the studies were conducted in subjects 12 years and older, with moderate-severe acne vulgaris over a 12 week treatment period.

Study MP-0104-01
Title: A randomized, double-blind, placebo-controlled, Phase 2, dose-ranging study of an oral modified formulation of minocycline as primary therapy for acne vulgaris in participants 12 – 30 years of age.
Study centers: 13 US centers
Study objective: To determine the lowest concentration of a new formulation of minocycline given orally in caplet form once daily that can demonstrate efficacy in the treatment of participants with moderate-to-severe acne vulgaris with the safest side effect profile.
Number of subjects: 241 enrolled; 55 in placebo group; 59 in 1 mg/kg minocycline group; 59 in 2 mg/kg minocycline group; 60 in the 3 mg/kg minocycline group.
Main inclusion criteria:
1. Male or female subjects 12 to 30 years of age with moderate-to-severe facial acne vulgaris.
2. Subjects were to have ≥20 and ≤ 100 inflammatory facial lesions and <5 nodules or cysts.
3. Females of childbearing potential had to have a negative urine pregnancy test and have been practicing contraception (or abstinence) for at least 6 months, and be willing to continue on the contraceptive for the duration of the study.
4. Written, informed consent.

Study Design: A multi-center, 12 week, randomized, double-blind, placebo-controlled, dose-ranging study. Subjects with moderate-severe facial acne vulgaris received Solodyn™ extended-release tablets at 1 mg/kg, 2 mg/kg or 3 mg/kg once daily in the morning from day 1 to day 84. In addition to screening and baseline visits, study visits were on days 28, 56 and 84.

Efficacy endpoints:

- Primary efficacy endpoint was the reduction in the number of inflammatory lesions (papules and pustules) from Baseline (Day 1) to Day 84, analyzed as change in absolute lesion counts a well as percent change from baseline.
- Secondary efficacy endpoints included a change in Static Global Evaluation of acne severity at days 28, 56 and 84; dichotomized Static Global Evaluation at days 28, 56 and 84; reduction in the number of non-inflammatory lesions (open or closed comedones) at days 28, 56 and 84; and the reduction in the total number of lesions, inflammatory and non-inflammatory at days 28, 56 and 84.

Safety:
This included assessment of adverse events and lab evaluations (complete blood counts, serum chemistries and urinanalysis were monitored at baseline and at the end of the study). Adverse events were coded using the Medical Dictionary for Regulatory Affairs (MedDRA) terminology. Adverse events were also tabulated by severity and relationship to study drug.

Statistical Analysis:
Demographic characteristics were summarized using descriptive statistics. Interval data were compared between treatment groups using the 2-way analysis of variance (treatment, center) with interaction. Categorical data were compared between groups using Cochran-Mantel-Haenszel (CMH) statistics, adjusting for center. Subgroup analyses were performed for the efficacy endpoints by weight, gender, body mass index (BMI), and number of lesions at Baseline.

Efficacy Results:
Primary efficacy endpoints:

- Mean number of inflammatory lesions decreased from baseline in all three dose groups.
- The percent decrease was highest in the 1 mg/kg group and no dose-dependent effects were observed.

Table No. 3
Mean and Percent Change in Inflammatory Lesion Counts at Day 84

	Minocycline 1 mg/kg	Minocycline 2 mg/kg	Minocycline 3 mg/kg	Placebo
Baseline.	38.8±2.02	47.0±2.63	39.1±2.33	40.3±2.39
Mean Change at Day 84	-21.8±2.21	-23.7±2.63	-18.3±2.56	-17.2±2.92
% Change at Day 84	-56.8±4.21	-49.3±4.40	-46.6±6.10	-39.4±5.74

Source: Sponsor briefing document, Module 5

Subgroup analyses revealed minocycline to be less effective in subjects weighing ≥ 171 pounds and in those with BMI ≥ 25.

Secondary efficacy endpoints:

- Non-inflammatory lesions showed smaller percent decreases from Baseline to Day 84 in all treatment groups compared to inflammatory lesions. Percent change in non-inflammatory lesion count from Baseline to Day 84 was –18.0% for 1 mg/kg, –29.5% for 2 mg/kg, and –7.5% for 3 mg/kg, compared to –15.7% for placebo.
- Analysis of global assessment scores showed an overall improvement, with mean change of approximately 1 unit in all 4 treatment groups.
- Percentage of subjects who had a static global assessment of clear or almost clear at Day 84 was 23.7% in the 1 mg/kg group, 16.9% in the 2 mg/kg group, and 30.0% in the 3 mg/kg group, compared to 14.5% in the placebo group.
- Percentage of subjects who had an improvement in global assessment score of at least 2 units from Baseline to Day 84 was 25.4% in the 1 mg/kg group, 25.4% in the 2 mg/kg group, and 33.3% in the 3 mg/kg group, compared to 20.0% in the placebo group.

Efficacy conclusion:
Efficacy results showed the 1 mg/kg group to be the lowest effective dose for treating inflammatory, non-nodular lesions of moderate-severe facial acne vulgaris. No trends of efficacy were observed for doses higher than 1 mg/kg.

Safety analysis:

The incidence of treatment-emergent AEs in the 1 mg/kg, 2 mg/kg, and 3 mg/kg dose groups was 70%, 68%, and 78%, respectively; the incidence in the placebo group was 71%. The most commonly reported treatment-emergent events included nausea, fatigue, malaise, dizziness, headache, and nasopharyngitis. Incidence of vestibular AEs (nausea, vomiting, dizziness, vertigo or ringing in the ear) was 24%, 32%, and 42% in the 1 mg/kg, 2 mg/kg, and 3 mg/kg dose groups, respectively, while the incidence in the placebo group was 26%.

There were no deaths, serious adverse events or other significant adverse events. Most commonly reported events leading to treatment discontinuation were associated with the gastrointestinal system and skin disorders. Other AEs leading to treatment discontinuation included headache, dizziness, pruritus, urticaria and severe acne.

AEs of interest are discussed for the 1 mg/kg, 2 mg/kg, 3 mg/kg and placebo groups respectively:

- Headache was the most commonly reported treatment-related AE reported by > 20% in all groups (29%, 34%, 33% and 24%)
- Dizziness was reported by 14%, 22%, 22% and 6%
- Nausea was reported by 7%, 14%, 22% and 13%
- Vertigo was reported by 2%, 2%, 5% and 0%
- Gastrointestinal pain NOS was reported by 3%, 5%, 7% and 13%
- Fatigue was reported by 3%, 5%, 10% and 4%
- Malaise was reported by 5%, 10%, 12% and 4%

- Mood alteration NOS was reported by 0%, 3%, 7% and 6%

Table No. 4
Incidence {N (%)} of Treatment-Emergent Adverse Events MP-0104-01

	Minocycline			Placebo
	1 mg/kg N =59	2 mg/kg N = 59	3 mg/kg N = 60	N = 55
At Least One Treatment-Emergent Adverse Event	**41 (70)**	**40 (68)**	**47 (78)**	**39 (71)**
Body System				
Ear and Labyrinth Disorders	**3 (5)**	**5 (9)**	**5 (8)**	**1 (2)**
Vertigo	1 (2)	1 (2)	3 (5)	0
Gastrointestinal Disorders	**9 (15)**	**18 (31)**	**20 (33)**	**23 (42)**
Diarrhea NOS	3 (5)	1 (2)	3 (5)	1 (2)
Gastrointestinal pain NOS	2 (3)	3 (5)	4 (7)	7 (13)
Nausea	4 (7)	9 (15)	13 (22)	9 (16)
Vomiting	1 (2)	1 (2)	3 (5)	4 (7)
General Disorders and Administration Site Conditions	**8 (14)**	**10(17)**	**16 (27)**	**9 (16)**
Fatigue	3 (5)	3 (5)	6 (10)	4 (7)
Malaise	4 (7)	6 (10)	7 (12)	3 (6)
Infections and Infestations	**5 (9)**	**8 (14)**	**9 (15)**	**11 (20)**
Upper respiratory tract infection NOS	2 (3)	4 (7)	3 (5)	4 (7)
Sinusitis NOS	0	1 (2)	0	3 (6)
Immune System Disorders	**0**	**1 (2)**	**0**	**4 (7)**
Seasonal allergy	0	1 (2)	0	3 (6)
Nervous System Disorders	**24 (41)**	**29 (49)**	**32 (53)**	**17 (31)**
Dizziness	9 (15)	13 (22)	14 (23)	3 (6)
Headache	21 (36)	23 (39)	25 (42)	15 (27)
Migraine NOS	0	3 (5)	1 (2)	0
Psychiatric Disorders	**3 (5)**	**6 (10)**	**8 (13)**	**7 (13)**
Mood alterations	0	3 (5)	4 (7)	3 (6)
Respiratory, Thoracic and Mediastinal Disorders	**10 (17)**	**5 (9)**	**9 (15)**	**9 (16)**
Nasopharyngitis	6 (10)	2 (3)	4 (7)	4 (7)
Skin and Subcutaneous Tissue Disorders	**7 (12)**	**8 (14)**	**12 (20)**	**7 (13)**
Acne aggravated	1 (2)	1 (2)	3 (5)	0
Pruritus	1 (2)	3 (5)	2 (3)	2 (4)

Source: Sponsor briefing document, Module 5

Lab evaluations:
Lab evaluation revealed sporadic changes in liver enzymes as well as 1 neutropenic event, and 1 event each of increased alkaline phosphatase and decreased platelet count. No consistent patterns of change were observed.

Safety conclusions:
Overall, majority of AEs reported in the Phase 2 dose-ranging study MP-0104-04 are known AEs of minocycline. AEs were in general higher in the 2 and 3 mg/kg groups compared to the 1 mg/kg group. The incidence of dizziness and vertigo were higher in the all minocycline groups compared to the placebo group. Subjects in the placebo group had a relatively high incidence of gastrointestinal disorders such as pain and nausea.

Conclusions for Phase 2 Dose-Ranging Study MP-0104-01
In conclusion, efficacy results showed the 1 mg/kg group to be the lowest effective dose for treating inflammatory, non-nodular lesions of moderate-severe facial acne vulgaris. No trends of efficacy were observed for doses higher than 1 mg/kg. Safety analysis revealed the overall incidence of AEs to be generally higher in the 2 and 3 mg/kg groups compared to the 1 mg/kg group. This was the basis for the sponsor choosing the 1 mg/kg dose for Phase 3 pivotal safety and efficacy studies.

6 Integrated Review of Efficacy

The efficacy of modified release minocycline tablets (Solodyn™) 45 mg. 90 mg and 135 mg was determined based on review of two pivotal Phase 3 safety and efficacy studies MP-0104-04 and MP-0104-05. These two studies have been reviewed in detail in the following sections. A total of 1038 patients were included in the Intent-to-Treat (ITT) population for efficacy analysis, out of which, 674 subjects received minocycline 1 mg/kg and 364 subjects received placebo.

6.1 Indication

The indication sought by the sponsor for Solodyn™ (minocycline modified release) tablets is the once a day treatment of inflammatory lesions of moderate to severe acne vulgaris in patients 12 years of age and older.
Since only subjects with < 2 nodules/cysts were included in clinical studies, the indication will be modified to 'treatment of only inflammatory lesions of non-nodular, moderate-severe acne vulgaris'.

6.1.1 Methods

The efficacy review is based on an analysis of results obtained from the two pivotal safety and efficacy studies MP-0104-04 and MP-0104-05. Both studies lasted 12 weeks and were conducted in patients 12 -63 years of age (either sex or any race) with moderate to severe acne vulgaris. Studies included patients with inflammatory and non-inflammatory lesions; non-inflammatory lesions were included to ensure that there was no worsening of lesions with minocycline. Pediatric patients < 12 years of age were not included since acne vulgaris is not commonly seen in that age group and the sponsor has requested a partial pediatric waiver. Per Agency recommendations, adequate numbers of patients in the 12 to 17 years age groups were included in the studies and subgroup analyses by age, sex and gender have been conducted by the sponsor.

6.1.2 General Discussion of Endpoints

Two types of assessments were performed in the 12 week pivotal studies MP-0104-04 and MP-0104-05 to assess subject's acne vulgaris. These evaluations were performed at screening, baseline and on days 28, 56, 84 (week 12) and post-treatment (day 112). The evaluator was the

investigator or the investigator's designee and the same rater performed all evaluations for a subject.

Primary efficacy endpoints in ITT population were as follows:

1) Percent change from baseline to day 84 (end-of-treatment) in inflammatory lesion counts and
2) Proportion of subjects who achieved success defined as a score of 0 (clear) or 1 (almost clear) on the dichotomized Evaluator's Global Severity Assessment (EGSA) scale (inflammatory lesion counts only) at day 84.

Minocycline was considered to be superior to placebo if both primary efficacy endpoints were statistically significantly in favor of minocycline compared to placebo. The EGSA was a static scale, such that each assessment made at study visits was independent from baseline or any other prior assessment. Since most inflammatory lesions are superseded by non-inflammatory lesions, the effect of minocycline on non-inflammatory lesions was also assessed.

Based on a protocol amendment dated March 31, 2004, two assessments were completed at each visit for each subject; these included an assessment for inflammatory lesions (papules and pustules) only and a second assessment for inflammatory and non-inflammatory lesions. An EGSA that included noninflammatory lesions was added to the study and was included as a secondary efficacy endpoint.

Secondary efficacy endpoints in ITT population were as follows:

1) Two-grade reductions on ESGA scale on days 28, 56 and 84.
2) Percent reduction in non-inflammatory lesion counts from baseline on days 28, 56 and 84.
3) Percent reduction in inflammatory lesion counts from baseline on days 28 and 56.

Other efficacy endpoint:

1) Percent reduction in total lesion counts on days 28, 56 and 84.

Subset analysis for the primary efficacy endpoints were conducted for the subgroups of gender, age and race and baseline EGSAs.

6.1.3 Study Design

Both Phase 3 safety and efficacy studies MP-0104-04 and MP-0104-05 were nearly identical in design and are discussed together as far as possible.

Pivotal Phase 3 studies (MP-0104-04 and MP-0104-05)
These were 12 week, multi-center, randomized, double-blind, placebo-controlled studies of minocycline ER tablets, at 1 mg/kg daily in subjects with moderate-severe facial acne vulgaris.

STUDY MP-0104-04

Study title: A randomized, double-blind, placebo-controlled phase 3 study of an extended-release formulation of minocycline for the treatment of inflammatory lesions of acne vulgaris.

Investigators and Study centers: Elizabeth Arthur, MD et al at 14 US centers
Study period: 23rd February, 2004 – 29th December, 2004
Study objective: To show safety and efficacy of a modified-release minocycline formulation when used as a once daily therapy for the treatment of inflammatory lesions of moderate-severe acne vulgaris
Number of subjects: 451 subjects enrolled at 14 study centers in the US; 300 in the minocycline arm and 151 in the placebo arm. All were analyzed in the ITT population.

Table No. 5
List of Investigators for Study MP-0104-04

Site Number	PI Name & Site Address	IRB Name & Address for all sites
030	Wiltz, Hector MD	New England Institutional Review Board 40 Washington Street, Suite 130 Wellesley, MA 02481
031	Harrison, Paul MD	
032	Parish, Larry MD	
033	Gold, Michael MD	
040	Arthur, Elizabeth MD	
041	Bucko, Alicia DO	
042	Fleischer, Alan MD	
043	Jarratt, Michael MD	
044	Kempers, Steven MD	
045	Loven, Keith MD	
046	Stewart, Daniel DO	
047	Swinyer, Leonard M, MD	
048	Weiss, Jonathan MD	
049	Zeide, Donna MD	

Inclusion criteria:
Subjects were eligible for inclusion in the study who -
1. Were at least 12 years of age at the time of enrollment
2. Weighed 45 kg to 136.36 kg (99 to 300 lbs)
3. Had ≥25 and ≤75 inflammatory facial lesions (papules/pustules)
4. Had <2 nodules/cysts on the face
5. Had an Evaluator's Global Severity Assessment of moderate or severe acne
6. If female of childbearing potential, practiced abstinence, or used a reliable method of contraception, and remained on that same contraceptive method for the duration of the study
7. If female using oral contraception, used the same therapy for a period of at least three months prior to the start of the study, and remained on that particular therapy throughout the duration of the study;
8. Had received an explanation of the study procedures, and signed the Informed Consent Form

Exclusion criteria:
Subjects were excluded from the study who –
1. Were pregnant or lactating, or planned to become pregnant within 1 month of study completion
2. Had an allergy/sensitivity to minocycline or any of the other drug product components
3. Used antacids or other dietary supplements containing aluminum, calcium, iron, or magnesium, or subjects taking Vitamin A or supplements containing Vitamin A in an amount greater than the amount contained in an over-the-counter multivitamin (5000 International Units [IU])
4. Had a history of vestibular incidents including vertigo, lightheadedness, nausea, or vomiting within 30 days prior to enrollment
5. Had a history or current risk of hepatic dysfunction
6. Had a history or current risk of renal dysfunction, eg, uncontrolled diabetes
7. Had systemic lupus erythematosus (SLE) or a positive test for antinuclear antibodies (ANA) at Screening
8. Had a history of alcohol or drug dependency
9. Had received any experimental drugs within 30 days prior to Study Day 1
10. Had Baseline safety laboratory values outside the normal range for non-liver function tests (LFTs) determined to be clinically significant
11. LFTs (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma glutamyl transpeptidase [GGT]) greater than 1.5 times the upper limit of normal
12. Had facial hair that, in the investigator's estimation, could interfere with the assessment of facial acne
13. Had underlying diseases or dermatological conditions that required the continued use of interfering topical medications applied to the face, or systemic therapy
14. Had received:
    - oral isotretinoin (ie, Accutane® or Soriatane®) within 6 months of baseline visit
    - oral antibiotics (ie, tetracyclines, erythromycin) within 4 weeks of baseline visit
    - systemic corticosteroids within 4 weeks of Baseline visit,
    - topical retinoid or retinol containing products for facial acne within 2 weeks of baseline visit
    - topical antibiotics for facial acne (ie, tetracyclines, erythromycin, clindamycin) within 2 weeks of Baseline visit,
    - topical corticosteroids applied to the face within 2 weeks of Baseline visit,
    - topical benzoyl peroxide (BPO) for facial acne within 2 weeks of Baseline visit
    - topical over-the-counter remedies for facial acne (salicylic acid) within 2 weeks of baseline visit

Interruption or Discontinuation of Treatment:
Subjects were permitted to withdraw from the study for the following reasons:
1. Withdrawal of consent by subject or legal guardian
2. Noncompliance with study procedures, loss to follow-up, etc.
3. Incidence of an AE (eg., pregnancy or worsening of acne such that scarring was likely unless standard therapy was instituted), which in the investigator's opinion required withdrawal of subject from study therapy.

Pregnancies occurring during the treatment period or up to 14 days after study completion of drug therapy were to be reported to the investigator and were to be followed until resolution.

Study design:
This was a multi-center, 12-week, randomized, double-blind, placebo-controlled study of the extended-release formulation of minocycline (Solodyn™) tablets in the treatment of moderate-severe lesions of facial acne vulgaris.

Study drugs:
The active drug, minocycline tablets - 45 mg, 90 mg and 135 mg were all of the same shape, size and total weight, and each tablet was expected to release the active ingredient over approximately 4 hours. The placebo tablet was identical in formulation and appearance to all strengths of the active tablet with the exception of the active ingredient.

Treatment assignment and blinding:
Each subject was assigned a unique, consecutive, 3-digit number used for identification throughout the study. Subjects who satisfied all entry criteria were randomized to a treatment group or placebo in a 2:1 ratio. Assignment to a treatment group was stratified by the Evaluator's Global Severity Assessment (EGSA) as moderate or severe. Subject's study drug was determined by body weight and available tablet strengths and was designed to achieve an approximate dose of 1 mg/kg. Subjects self-administered their assigned medication, i.e. 1 tablet in the morning each day for 12 weeks; the tablet could be taken with or without food. Dose assignment for minocycline HCl was as follows:

Table No. 6
Dose assignments for Study MP-0104-04

Patient's Weight (lbs)	Patient's Weight (kg)	Available Caplet Strength (mg)	Actual mg/kg Dose
99 – 131	45.00 – 59.54	45	1.00 – 0.76
132 – 199	60.00 – 90.45	90	1.50 – 1.00
200 – 300	90.91 – 136.36	135	1.48 – 0.99

Source: Sponsor briefing document: Module 5

Study drugs were packaged according to randomization tables and were delivered to study sites pre-labeled to ensure blinding.

Study schedule:
At the screening visit, within 30 days prior to the baseline visit, subjects were screened for entrance criteria, including medical history, weight, laboratory evaluations, urine pregnancy test for females of childbearing potential, inflammatory and non-inflammatory lesion counts and Evaluator's Global Severity Assessment (EGSA). Males < 16 years and females < 15 years, who were between the 5^{th} and 95^{th} percentiles for normal height were given the option to enroll in a bone-growth sub-study. For those who enrolled in the linear bone growth sub-study, a left hand and wrist X-ray were taken prior to the first dose of study drug and height was recorded.

Table No. 7
Study Schedule for MP-0104-04

Study Day	Screening Day -30 to -1*	Baseline Day 1†	Day 7 ± 2	Day 28 ± 2	Day 56 ± 2	Day 84 ± 3	Day 112 ± 3 (Post-treatment)
Informed consent	X						
Inclusion/exclusion‡	X						
Medical history	X						
Weight and height	X	X					
Laboratory evaluations§	X			X		X	
Urine pregnancy test	X	X		X	X	X	
Overall Disease State Evaluation (inflammatory and noninflammatory lesion count)‖	X	X		X	X	X	X
Evaluator's Global Severity Assessment	X	X		X	X	X	X
Dermatology-Specific Quality-of-Life Questionnaire (DSQL)		X				X	
Subject randomization		X					
Distribute study drug		X		X	X		
Distribute diary		X¶					
First dose of study drug		X					
Concomitant medications		X	X	X	X	X	
AEs			X	X	X	X	X
Coordinator call to subjects#			X				
Left wrist and hand X-rays and height measurements **	X						

* If the subject did not require a washout period, these procedures served as Baseline procedures.
† This visit occurred as soon as possible after the washout period or no later than 7 days after the Screening visit if no
‡ washout period was required. Laboratory tests were repeated if Day 1 occurred more than 31 days after Screening laboratory tests were performed.
After the washout period or if Day 1 occurred more than 7 days after Screening, eligibility was reevaluated at the Baseline
§ visit. If subject did not meet inclusion/exclusion criteria (eg, lesion counts, weight, negative pregnancy test, etc), the subject
‖ was considered a screen failure.
¶ Laboratory assessments were performed at Screening, Day 28, and at Day 84.
\# Evaluation for the number of inflammatory and noninflammatory lesion counts was performed after the study begun.
** Diaries were completed for the first 5 days of dosing, then returned to the investigational site.
Phone contacts: Day 7 and 48 hours after a missed visit.
For those subjects who elected to be enrolled in the long-term safety and bone growth study upon completion of Phase 3 treatment.

Source: Sponsor briefing document: Module 5

After screening and baseline evaluations, eligible subjects were randomized to two treatment groups in a 2:1 ratio of active (1 mg/kg minocycline HCl) to placebo. For this 12-week study, study visits were conducted on days 28, 56 and 84, with a follow-up visit on day 112 to assess relapses for those subjects who chose to not enter into the long-term safety study. For those subjects who did not elect to enter the long-term safety study, the final visit was the day 112 visit.

Although the Agency had advised the sponsor to include a 12 week follow-up period after study completion to assess relapse rate, the sponsor chose a 4 week period.

Subjects were contacted on day 7 (± 2 days) concerning compliance and returned to study site at day 28 (± 2 days), day 56 (± 2 days) and day 84 (± 3 days) for lesion counts and EGSA, assessment of AEs, lab evaluations (day 28 and day 84), urine pregnancy tests for females of childbearing potential, and collection and distribution of study medications.

Efficacy Assessments:
The two assessments used to evaluate subject's skin condition throughout study period included: lesion counts and the Evaluator's Global Severity Assessment (EGSA). The investigator recorded the number of inflammatory lesions (papules, pustules, nodules or cysts) and the number of non-inflammatory lesions (open and closed comedones) on the following facial regions: the right forehead, left forehead, right cheek, left cheek, the nose and area below nose and the chin.

Primary Efficacy Endpoints:

1. Mean percent change in inflammatory lesion counts from baseline to Day 84
2. Percentage of subjects with an EGSA (inflammatory lesions only) of clear or almost clear at day 84

Secondary Efficacy Endpoints:

1. Percentage of subjects with at least a 2-grade reduction in the EGSA from baseline to day 84
2. Percentage change in non-inflammatory lesion counts at day 84
3. Percentage of subjects with an EGSA (inflammatory and non-inflammatory lesions) clear or almost clear at day 84

Lesion counts
These were performed at screening, baseline, days 28, 56, 84 and on day 112 (post-treatment). Raters counted the number of individual inflammatory (papules and pustules) and noninflammatory lesions (open and closed comedones) in specific areas of the face, and recorded these counts on a template divided into 5 sections: forehead, right and left cheek, nose, and chin.

Evaluator's Global Severity Assessment (ESGA)
This was a static assessment, independent of baseline score; the evaluator made this assessment without referring to the baseline score and prior to performing lesion counts. Two versions of EGSA were used; the primary one evaluated inflammatory lesions only and a secondary version assessed inflammatory and non-inflammatory lesions. Assessments were performed at screening, baseline, days 28, 56, 84 and on day 112 (post-treatment). The secondary version was added to the protocol in an Amendment (March 3, 2004) at Agency request, after study enrollment had commenced; therefore this assessment was not performed on all subjects.

Table No. 8
Evaluator's Global Severity Assessment Scale - MP-0104-04 (Inflammatory lesions only)

Score	Grade	Description
0	Clear	No evidence of papules or pustules (inflammatory lesions)
1	Almost clear	Rare (eg, <5) non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red)
2	Mild	Few (eg, <10) inflammatory lesions (papules/pustules only; no nodulocystic lesions)
3	Moderate	Multiple (eg, between 25 and 40) inflammatory lesions present; many papules/pustules; there may or may not be a few nodulocystic lesions
4	Severe	Inflammatory lesions are more apparent, many papules/pustules (eg, between 40 and 75); there may or may not be a few nodulocystic lesions
5	Very Severe	Highly inflammatory lesions predominate, many papules/pustules, and many nodulocystic lesions

Table No. 9
Evaluator's Global Severity assessment Scale - MP-0104-04 (Inflammatory & Non-Inflammatory lesions)

Score	Grade	Description
0	Clear	Normal, clear skin with no evidence of acne vulgaris
1	Almost clear	Rare noninflammatory lesions present, with rare non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red)
2	Mild	Some noninflammatory lesions are present, with few inflammatory lesions (papules/pustules only; no nodulocystic lesions)
3	Moderate	Noninflammatory lesions predominate, with multiple inflammatory lesions evident: several to many comedones and papules/pustules, and there may or may not be one small nodulocystic lesion
4	Severe	Inflammatory lesions are more apparent, many comedones and papules/pustules, there may or may not be a few nodulocystic lesions
5	Very Severe	Highly inflammatory lesions predominate, variable number of comedones, many papules/pustules and many nodulocystic lesions

Safety Assessments
These consisted of recording of all adverse events (and following patients till resolution); laboratory assessments and monitoring those subjects who chose to enroll in the bone growth study.

Safety has been discussed in detail in Section 7 – Integrated Review of Safety.

Protocol Amendments

Salient protocol amendments were as follows:

Amendment 1 on September 29, 2003.

- Long- term follow- up study included in protocol based on Agency comments

Amendment 2 on January 8, 2004.

- Long- term bone growth study enrollment procedures added to protocol.

Amendment 3 on March 31, 2004

- Primary efficacy endpoint would be EGSA of inflammatory lesions only
- EGSA (Inflammatory and Noninflammatory Lesions) added. Noninflammatory lesions added to the EGSA at Agency's request

Statistical Methods:

Statistical significance was based on 2- tailed tests of the null hypothesis resulting in P values of 0.05 or less.

Study Population and Handling of Missing data

The two analysis populations were the Intent-to-Treat (ITT) population which included all subjects who received study drug and the Per-Protocol (PP) population, which included all subjects who completed the 12 week treatment period without major protocol violations. In the PP population, subjects completed study treatment through day 84, within a 7-day visit window, were at least 80% compliant with study medication took no prohibited medications. Missed visits included - subject unable to complete a scheduled visit, lost to follow- up, or discontinued the study. In order to provide a value for missing efficacy parameters, the last observation was carried forward (LOCF).

Efficacy Evaluation:

Inflammatory and non-inflammatory lesion counts were recorded for each subject at Baseline and at Days 28, 56, and 84. Total lesion count was the sum of inflammatory and noninflammatory lesion counts.

Percent change from Baseline of inflammatory lesion count, noninflammatory lesion count, and total lesion count were derived for each subject at Days 28, 56, and 84.

Evaluator's Global Severity Assessments were recorded for each subject and dichotomized to success (clear or almost clear, a score of 0 or 1), or failure at Days 28, 56, and 84.

Primary Efficacy Analysis (PEA)

The PEA was conducted for the ITT population. Analyses of percent change from baseline in lesion count were based on ANOVA results, which included factors for treatment group and analysis center. Frequency distributions were presented by treatment group for the Evaluator's Global Severity Assessment and for the dichotomized Evaluator's Global Severity Assessment.

Secondary Efficacy Analysis (SEA)

Secondary efficacy analyses were conducted to characterize the treatment effect for those subjects who achieved an Evaluator's Global Severity Assessment (inflammatory and

noninflammatory lesions) at Day 84 of clear or almost clear, or who showed at least a 2- grade reduction from Baseline in Evaluator's Global Severity Assessment (inflammatory lesions only) at Day 84.

A test for demonstrating the noninferiority of the percent change from Baseline in noninflammatory lesion count for minocycline relative to placebo at Day 84 was conducted based on the 1- sided 97.5% confidence interval approach with a noninferiority margin of 15%. Noninferiority for the percent change from Baseline in noninflammatory lesion count was established if the lower limit of the 1- sided 97.5% confidence interval was not less than - 15%.

Subset analysis
Subset analyses were conducted on ITT and PP populations for the subgroups of

- gender
- age
- race
- Baseline EGSA

Pooling of Sites
The common clinical protocol was used for each investigational site such that data could be poled for analysis. A minimum of 10 subjects were to be enrolled in each treatment arm for any investigator. If there were too few subjects in a treatment arm, then the investigator's data was combined to achieve the desired sample size minimum per arm. This resulted in re-defining treatment groups for statistical analysis. The combined groups were referred to as 'analysis centers' for the ANOVA and Breslow- Day analyses, and for CMH testing.

Study Subjects:
Disposition of Subjects -ITT Population (MP-0104-04)
All 451 subjects randomized to the study received at least one dose of study medication and were included in the ITT population; 300 of these received minocycline and 151 received placebo. Out of the 300 randomized to minocycline, 34 (11.3%) withdrew before study completion, while out of the 151 subjects randomized to placebo, 20 (13.2%) withdrew before study completion. In the minocycline arm, the most frequent reasons were withdrawal of consent 11 (3.7%), lost to follow-up 10 (3.3%), and AE 9 (3%). In the placebo arm reasons were lost to follow-up 8 (5.2%) and withdrawal of consent 7 (4.6%). Out of the 397 subjects who completed the 12 week treatment period, 117 (39%) in the minocycline group and 50 (33%) in the placebo group entered the long-term safety study.

Protocol Deviations (MP-0104-04)
85 subjects in the minocycline group and 38 subjects in the placebo group deviated from the protocol and were not include in the PP population.

- 25 (8.3%) of 300 subjects in the minocycline group and 19 (12.6%) out of 151 in the placebo group withdrew before completing treatment.
- 75 (25%) in the minocycline group and 35 (23.2%) in the placebo group had a day 84 visit that was outside the study visit window of 81 to 89 days.

- 36 (12%) in the minocycline group and 23 (15.2%) in the placebo group had < 80% compliance.

Table No. 10
Subject Disposition MP-0104-04

	Minocycline N=300	Placebo N=151	Total N=451
ITT subjects (Safety)	300 (100.0)	151 (100.0)	451 (100.0)
PP subjects	215 (71.7)	113 (74.8)	328 (72.7)
Subjects not included in the PP population*			
Did not complete treatment phase	25 (8.3)	19 (12.6)	44 (9.8)
Day 84 visit outside window	75 (25.0)	35 (23.2)	110 (24.4)
Compliance < 80%	36 (12.0)	23 (15.2)	59 (13.1)
Other protocol violation	1 (0.3)	0	1 (0.2)
Subjects completing through Day 84	**266 (88.7)**	**131 (86.8)**	**397 (88.0)**
Subjects not completing through Day 84	34 (11.3)	20 (13.2)	54 (12.0)
Subjects completing through Day 112	149 (49.7)	79 (52.3)	228 (50.6)
Subjects entering long-term follow-up	117 (39.0)	50 (33.1)	167 (37.0)
Reason that subject did not complete treatment phase			
Adverse Event	9 (3.0)	2 (1.3)	11 (2.4)
Protocol violation/noncompliance	2 (0.7)	2 (1.3)	4 (0.8)
Withdrawal of consent	11 (3.7)	7 (4.6)	18 (4.0)
Lost to follow-up	10 (3.3)	8 (5.2)	18 (4.0)
Other	2 (0.7)	1 (0.7)	3 (0.7)

* Subjects could be excluded from the PP population for more than one reason.
Source: Sponsor briefing document, Module 5

Please see Section 7.1.3.2 for AEs leading to study discontinuation.

Patient Demographics (MP-104-04)
57% of subjects were male, 69% were White, 18% were Hispanic and 11% were Black. Mean age of subjects in the minocycline group was 19.2 years, the range being 12.2 to 63.1 years. Mean age in the placebo group was 21.3 years, range being 12.3 years to 45.0 years.

The majority of patients enrolled in both groups were White; there were only 4 (1.3%) Asian patients in the minocycline group and 0 Asian patients in the placebo group.

Table No. 11
Demographics, ITT Population – Study MP-0104-04

	Minocycline N=300	Placebo N=151	Total N=451	*P* value*
Age (years)				
Mean ± SD	19.2 ± 6.61	21.3 ± 8.24	19.9 ± 7.26	0.003
Range	12.2 – 63.1	12.3 – 45.0	12.2 – 63.1	
Gender – n (%)				
Male	171 (57.0)	85 (56.3)	256 (56.8)	0.920
Female	129 (43.0)	66 (43.7)	195 (43.2)	
Race – n (%)				
White	214 (71.3)	97 (64.2)	311 (69.0)	
Black	26 (8.7)	22 (14.6)	48 (10.6)	
Hispanic	51 (17.0)	29 (19.2)	80 (17.7)	0.056
American Indian/Alaskan	0	2 (1.3)	2. (0.4)	
Asian/Pacific Islander	4 (1.3)	0	4 (0.9)	
Other	5 (1.7)	1 (0.7)	6 (1.3)	
Height (inches)				
Mean ± SD	67.1 ± 3.56	67.3 ± 3.65	67.2 ± 3.58	0.396
Range	57.0 – 80.0	59.0 – 75.0	57.0 – 80.0	
Weight (lbs)				
Mean ± SD	159.5 ± 36.18	158.6 ± 36.07	159.2 ± 36.11	0.800
Range	101.0 – 299.0	103.0 – 297.0	101.0 – 299.0	
BMI†				
Mean ± SD	24.9 ± 5.41	24.7 ± 5.58	24.8 ± 5.46	0.509
Range	16.3 – 49.8	16.6 – 47.9	16.3 – 49.8	

* *P* value for treatment group comparisons was obtained using a 2-way ANOVA model for age, height, weight, and BMI: CMH statistics were used for gender and race.
† BMI=(weight x 703)/ height^2

Source: Sponsor briefing document, Module 5

STUDY MP-0104-05:

Study title: A randomized, double-blind, placebo-controlled phase 3 study of an extended-release formulation of minocycline for the treatment of inflammatory lesions of acne vulgaris.

Investigators and Study centers: Carole Aponte, MD et al at 16 US centers

Study period: 23rd February, 2004- 22nd December, 2004

Study objective: To show safety and efficacy of a modified-release minocycline formulation when used as a once daily therapy for the treatment of inflammatory lesions of moderate-severe acne vulgaris

Number of subjects: 473 subjects enrolled at 16 study centers in the US; 315 in the minocycline arm and 158 in the placebo arm. All were analyzed in the ITT population.

Inclusion criteria:

Please see study MP-0104-04

Exclusion criteria:

Please see study MP-0104-04

Interruption or Discontinuation of Treatment:

Please see study MP-0104-04

Table No. 12
List of Investigators for Study MP-0104-05

Site Number	PI Name & Site Address	IRB Name & Address for all sites
050	Karl Reinhard Beutner, MD	New England Institutional Review Board 40 Washington Street, Suite 130 Wellesley, MA 02481
051	Scott Michael Dinehart, MD	
052	Jo Lynne Herzog, MD	
053	Terry M Jones, MD, PA J&S	
054	Robert W. Loss, MD	
055	Stacy R Smith, MD	
056	Dow B Stough, MD	
057	Helen M. Torok, MD	
058	Paul Steven Yamauchi, MD, PhD	
059	Jeffrey A Carmel, MD	
061	Carole C. Aponte, MD	
062	Frank E Dunlap, MD	
063	Toivo E Rist, MD	
064	Patricia C Lee, MD	
065	Stephen Keith Tyring, MD, PhD, MBA	
066	James Henry Herndon, Jr, MD	

Study design and schedule:
Please see study MP-0104-04
Efficacy and Safety Assessments:
Please see study MP-0104-04
Protocol Amendments
Please see study MP-0104-04
Statistical evaluation:
Please see study MP-0104-04 for statistical methods.

Study Subjects
Disposition of Subjects (ITT Population)
473 subjects randomized to the study received at least one dose of study medication and were included in the ITT population; 315 of these received minocycline and 158 received placebo. Out of the 315 randomized to minocycline, 21 (6.7%) withdrew before study completion, while out of the 158 subjects randomized to placebo, 15 (9.5%) withdrew before study completion. In the minocycline arm, the most frequent reasons were lost to follow-up 11 (3.5%), AE 8 (2.5%) and withdrawal of consent 7 (2.2%). In the placebo arm the most frequent reason was withdrawal of consent 8 (5.1%). Out of the 428 subjects who completed the 12 week treatment period, 116 (36.8%) in the minocycline group and 63 (39.9%) in the placebo group entered the long-term safety study.

Table No. 13
Subject Disposition Study MP-0104-05

	Minocycline N=315	Placebo N=158	Total N=473
ITT subjects (Safety)	315 (100)	158 (100)	473 (100)
PP subjects	258 (81.9)	126 (79.7)	384 (81.2)
Subjects not included in the PP population*			
Did not complete treatment phase	21 (6.7)	15 (9.5)	36 (7.6)
Day 84 visit outside window	50 (15.9)	27 (17.1)	77 (16.3)
Compliance < 80%	27 (8.6)	21 (13.3)	48 (10.1)
Other protocol violation	0	0	0
Subjects completing through Day 84	287 (91.1)	141 (89.2)†	428 (90.5)
Subjects not completing through Day 84	28 (8..9)	17 (10.8)	45 (9.5)
Subjects completing through Day 112	171 (54.3)	76 (48.1)	247 (52.2)
Subjects entering long-term follow-up	116 (36.8)	63 (39.9)	179 (37.8)
Reason that subject did not complete treatment phase			
Adverse Event	8 (2.5)	3 (1.9)	11 (2.3)
Protocol violation/noncompliance	2 (0.6)	2 (1.3)	4 (0.8)
Withdrawal of consent	7 (2.2)	8 (5.1)	15 (3.2)
Lost to follow-up	11 (3.5)	4 (2.5)	15 (3.2)
Other	0	0	0

* Subjects could be excluded from the PP population for more than one reason.

† Two subjects (52-014 and 53-059) completed the treatment period through Day 84, but did not return for Day 112.

Source: Sponsor Briefing Document, Module 5

Protocol Deviations (MP-0104-05):

Sixty-four (64) subjects in the minocycline group and 34 subjects in the placebo group deviated from the protocol for one or more reasons and were not included in the PP population.

- 21 (6.7%) of 315 subjects in the minocycline group and 15 (9.5%) of 158 subjects in the placebo group withdrew before completing treatment
- 50 (15.9%) subjects in the minocycline group and 27 (17.1%) subjects in the placebo group had a Day 84 visit that was outside the visit window of 81 to 89 days
- 27 (8.6%) subjects in the minocycline group and 21 (13.3%) subjects in the placebo group had < 80% compliance
- 1 subject in the minocycline group had an EGSA of 'mild' at baseline. This subject was <80% compliant and was excluded from the PP population

Patient Demographics (MP-0104-05):

Mean age of subjects in the minocycline group was 20 years, with a range of 12 to 51 years. Majority of subjects were male and white. The majority of patients were in the 12-17 years age group, which is in keeping with the age group where acne vulgaris is most commonly seen.

Table No. 14
Demographics ITT Population – MP-0104-05

	Minocycline N=315	Placebo N=158	Total N=473	*P*value*
Age (years)				
Mean ± SD	20.0 ±7.83	19.6 ± 7.72	19.8 ± 7.78	0.696
Range	12.0 – 51.0	12.0 – 53.7	12.0 – 53.7	
Gender – n (%)				
Male	182 (57.8)	88 (55.7)	270 (57.1)	0.694
Female	133 (42.2)	70 (44.3)	203 (42.9)	
Race – n (%)				
White	237 (75.2)	121 (76.6)	358 (75.7)	
Black	37 (11.7)	17 (10.8)	54 (11.4)	
Hispanic	26 (8.3)	11 (7.0)	37 (7.8)	0.614
American Indian/Alaskan	0	0	0	
Asian/Pacific Islander	7 (2.2)	7 (4.4)	14 (3.0)	
Other	8 (2.5)	2 (1.3)	10 (2.1)	
Height (inches)				
Mean ± SD	67.1 ± 3.80	66.7 ± 3.62	67.0 ± 3.74	0.861
Range	55.0 – 80.0	59.0 – 76.0	55.0 – 80.0	
Weight (lbs)				
Mean ± SD	159.1 ± 37.37	155.3 ± 34.68	157.9 ± 36.50	0.324
Range	100.0 – 289.0	100.0 – 290.0	100.0 – 290.0	
BMI†				
Mean ± SD	24.9 ± 5.60	24.6 ± 5.28	24.8 ± 5.49	0.365
Range	16.6 – 47.6	16.3 – 45.9	16.3 ± 47.6	

* *P* values for treatment group comparisons were obtained using a 2-way ANOVA model for age, height, weight, and BMI; CMH statistics were used for gender and race.

† BMI=(weight x 703)/ height2

Source: Sponsor Briefing Document, Module 5

Please see Section 7.1.3.2 for AEs leading to study discontinuation.

6.1.4 Efficacy Findings

Efficacy evaluation for the two pivotal studies MP-0104-04 and MP-0104-05 are presented in this section.

Data sets analyzed:
Results from the ITT population have primarily been considered for efficacy analysis and are discussed in the following sections. PP results have been reviewed and overall, the results for the PP population are similar to the ITT population. There was no significant treatment-by-center interaction in either study.

In Study MP-0104-04, 451 subjects were enrolled at 14 study centers. The ITT population included 451 subjects; 300 in the minocycline arm (1 mg/kg) and 151 in the placebo arm. The mean age of patients was 19.2 years, with a range of 12.2 to 63.1 years; mean age in placebo group was 21.3 years, with a range of 12.3 to 45 years. Majority of patients were in the 12 to17 years age group. Male patients were in the majority 256/451 (56.8%) compared to female 195/451 (43.2%). Majority of patients were White 311/451 (69%), followed by Hispanic 80/451 (17.7%), Black 48/451 (10.6%), American Indian/Alaskan 2/451 (0.4%), Asian/Pacific Islander 4/451 (0.9%) and Other 6/451 (1.3%). The medical history profile was characteristic of young, healthy adults in general.

In Study MP-0104-05, 473 subjects were enrolled at 16 study centers. The ITT population included 473 subjects; 315 in the minocycline arm (1 mg/kg) and 158 in the placebo arm. Mean age of patients in the minocycline group was 20 years, with a range of 12 to 57 years; mean age in placebo group was 19.6 years, with a range of 12 to 53.7 years. Majority of patients were in the 12 to17 years age group. Male patients were in the majority 270/473 (57.1%) compared to female 203/473 (42.9%). Majority of patients were White 358/473 (75.7%), followed by Black 54/473 (11.4%), Hispanic 37/473 (7.8%), American Indian/Alaskan 0, Asian/Pacific Islander 14/473 (3%) and Other 10/473 (2.1%). The medical history profile was characteristic of young, healthy adults in general.

Race distribution was not considered optimal across both studies since the majority of patients were White; gender distribution was evenly represented and age distribution was maximum in the 12 to 17 years age group, which is in keeping with age prevalence of acne vulgaris.

Table No. 15
Analysis Populations for Studies MP-0104-04 and MP-0104-05

	MP-0104-04			MP-0104-05		
	Minocycline	Placebo	Total	Minocycline	Placebo	Total
ITT population	300	151	451	315	158	473
PP population	215	113	328	258	126	384

Inflammatory Counts at Baseline:
In Study MP-0104-04, mean inflammatory counts at baseline were 39.1 in the minocycline group versus 38.7 in the placebo group.

In MP-0104-05, mean inflammatory lesion counts at baseline were 38.9 in the minocycline group versus 38.4 in the placebo group.

Analysis of Efficacy:
Primary Efficacy Analyses, including subgroup analyses for primary efficacy endpoints conducted on the ITT population are discussed in detail in this section.

Table No. 16
Study Drug Compliance for MP-0104-04:

	Minocycline	Placebo
N	292	144
Mean ± SD	90.07 ± 18.23	90.57 ± 17.51
Proportion at least 80% compliant	85.0%	84.1%

Table No. 17
Study Drug Compliance for MP-0104-05

	Minocycline	Placebo
N	304	156
Mean ± SD	92.90 ± 15.64	91.62 ± 16.11
Proportion at least 80% compliant	89.2	85.4

Primary Efficacy Analysis:
The two primary efficacy endpoints analyzed for both studies are as follows

1) Percent change from baseline in inflammatory lesion count at day 84 *and*
2) Dichotomous analysis of the EGSA (inflammatory lesions) at day 84, where treatment was considered a success if EGSA was clear (0) or almost clear (1) and failure if the score was mild (2), moderate (3), severe (4) or very severe (5).

Primary Efficacy Endpoint # 1
Percent reduction in lesion counts
Study MP-0104-04
In MP-0104-04, the mean percent decrease from baseline to day 84 (end-of-treatment ETT) in inflammatory lesion counts was statistically significantly higher in the minocycline group 43.1% compared to the placebo group 31.7% (P = 0.001). At day 28, the mean percent decrease was 30.3% in the minocycline group and 18.1% in the placebo group, and at day 56, it was 38.2% in the minocycline group and 28.5% in the placebo group.

Table No. 18
Change in mean percent inflammatory lesions over time MP-0104-04

	Minocycline	Placebo	P value
Day 28	30.3%	18.1%	
Day 56	38.2%	28.5%	
Day 84 (ETT)	43.1	31.7	P = 0.001

Table No. 19
Summary of Inflammatory Lesion Counts MP-0104-04

	Minocycline	Placebo	P value
N	300	151	
Baseline Mean	39.1	38.7	0.789
Mean absolute change from Baseline to Day 84	16.5	12.3	
Mean percent change from baseline to day 84	43.1	31.7	0.001

Study MP-0104-05

In Study MP-0104-05, the mean percent decrease from baseline to day 84 in inflammatory lesion counts was statistically significantly higher in the minocycline group 45.8% compared to the placebo group 30.8% ($P < 0.001$). At day 28, the mean percent decrease was 32.8% in the minocycline group and 24.9% in the placebo group, and at day 56, it was 41.5% in the minocycline group and 29.6% in the placebo group.

Table No. 20
Change in mean percent inflammatory lesions over time MP-0104-05

	Minocycline	Placebo	P value
Day 28	32.8%	24.9%	
Day 56	41.5%	29.6%	
Day 84 (ETT)	45.8%	30.8%	$P < 0.001$

Table No. 21
Summary of Inflammatory Lesion Counts MP-0104-05

	Minocycline	Placebo	P value
N	315	158	
Baseline Mean	38.9	38.4	0.847
Mean absolute change from Baseline to Day 84	17.2	11.3	
Mean percent change from baseline to Day 84	45.8	30.8	< 0.001

The decrease in mean percent inflammatory lesions was greater over the course of the 12 week therapy for both studies in the minocycline group compared to the placebo group; the decrease was slightly greater in the minocycline group in MP-10104-05 compared to MP-0104-04.

Subgroup Analysis (ITT Population) Study MP-0104-04

Subgroup analyses of inflammatory lesion counts for the ITT population was performed by gender, age, race and EGSA at baseline for both studies MP-0104-04 and MP-0104-05.

a) *Gender*

MP-0104-04

The mean percent decrease in inflammatory lesion counts from baseline to day 84 in males for M/P was 38%/23.5%, and in females it was 49.8%/42.2%.

Table No. 22
Inflammatory lesion Counts by Gender in ITT Population MP-0104-04

	Minocycline	Placebo
Males		
N	171	85
Mean counts at baseline	40.2	40.3
Mean percent change from baseline to day 84	38	23.5
Females		
N	129	66
Mean counts at baseline	37.5	36.6
Mean percent change from baseline to day 84	49.8	42.2

MP-0104-05
The mean percent decrease in inflammatory lesion counts from baseline to day 84 in males for M/P was 44.9%/27.2%, and in females it was 47%/35.3%.

Table No. 23
Inflammatory lesion Counts by Gender in ITT Population MP-0104-05

	Minocycline	Placebo
Males		
N	182	88
Mean counts at baseline	40.9	40.6
Mean percent change from baseline to day 84	44.9	27.2
Females		
N	133	70
Mean counts at baseline	36.1	35.7
Mean percent change from baseline to day 84	47.0	35.3

Although the baseline mean inflammatory counts were slightly higher in males compared to females, the percent decrease in inflammatory lesion counts at end-of-treatment was higher in females compared to males in both treatment groups, especially in MP-0104-04.

b) *Age*
MP-0104-04
The mean percent change from baseline to day 84 for M/P in those < 18 years of age was 36%/21.8% and for those ≥ 18 years of age, it was 55%/42.8%.

Table No. 24
Inflammatory lesion Counts by Age in ITT Population MP-0104-04

	Minocycline	Placebo
< 18 years of age		
N	188	80
Mean counts at baseline	40.3	41.0
Mean percent change from baseline to day 84	36.0	21.8
≥ 18 years of age		
N	112	71
Mean counts at baseline	37.0	36.0
Mean percent change from baseline to day 84	55	42.8

MP-0104-05

The mean percent change from baseline to day 84 for M/P in those < 18 years of age was 43.5%/21.1% and for those ≥ 18 years of age, it was 49.5%/45.4%.

Table No. 25
Inflammatory lesion Counts by Age in ITT Population MP-0104-05

	Minocycline	Placebo
< 18 years of age		
N	188	80
Mean counts at baseline	40.3	41.0
Mean percent change from baseline to day 84	36.0	21.8
≥ 18 years of age		
N	119	63
Mean counts at baseline	36.2	36.2
Mean percent change from baseline to day 84	49.5	45.4

Improvement was greater in patients' ≥ 18 years of age in both active and placebo arms compared to those < 18 years of age in both studies.

c) Race

MP-0104-04

The percent change from baseline to day 84 for M/P in White subjects was 39.7/25.5 and in non-White subjects, it was 51.5/42.7.

Table No. 26
Inflammatory lesion Counts by Race in ITT Population MP-0104-04

	Minocycline	Placebo
White subjects		
N	214	97
Mean counts at baseline	40	40.5
Mean percent change from baseline to day 84	39.7	25.5
Non-White subjects		
N	86	54
Mean counts at baseline	36.7	35.4
Mean percent change from baseline to day 84	51.5	42.7

MP-0104-05

The mean percent change from baseline to day 84 for M/P in White subjects was 45%/26.1% and in non-White subjects, it was 48.2%/46.2%.

Table No. 27
Inflammatory lesion Counts by Race in ITT Population MP-0104-05

	Minocycline	Placebo
White subjects		
N	237	121
Mean counts at baseline	39.2	39.1
Mean percent change from baseline to day 84	45	26.1
Non-White subjects		
N	78	37
Mean counts at baseline	37.7	36.3
Mean percent change from baseline to day 84	48.2	46.2

Improvement was greater in non-White subjects in both active and placebo arms compared to White subjects in both studies.

d) *Baseline Evaluator's Global Severity Assessment*

MP-0104-04

The mean percent change from baseline to day 84 for M/P in those with EGSA ≤ 3 was 44.5/29.6 and in those with EGSA ≥ 4 it was 39.8/36.4.

Table No. 28
Inflammatory lesion Counts by EGSA in ITT Population MP-0104-04

	Minocycline	Placebo
EGSA ≤ 3		
N	210	105
Mean counts at baseline	33.3	32.7
Mean percent change from baseline to day 84	44.5	29.6
EGSA ≥ 4		
N	90	46
Mean counts at baseline	52.5	52.3
Mean percent change from baseline to day 84	39.8	36.4

MP-0104-05

The mean percent change from baseline to day 84 for M/P in those with EGSA ≤ 3 was 48.2%/31.7% and in those with EGSA ≥ 4 it was 38.4%/27.8%.

Table No. 29
Inflammatory lesion Counts by EGSA in ITT Population MP-0104-05

	Minocycline	Placebo
EGSA ≤ 3		
N	210	105
Mean counts at baseline	33.3	32.7
Mean percent change from baseline to day 84	44.5	29.6
EGSA ≥ 4		
N	77	37
Mean counts at baseline	52.1	51
Mean percent change from baseline to day 84	8.4	27.8

The mean percent improvement in inflammatory lesion counts was higher in those with EGSA ≤ 3 in the minocycline group in both studies.

Primary Efficacy Endpoint # 2

Evaluator's Global Severity assessment (Inflammatory lesions only) dichotomized as success or failure.

Study MP-0104-04

In MP-0104-04, percentage of subjects who were clear or almost clear based on EGSA (inflammatory lesions only) at day 84 was 17.3% in the minocycline group and 7.9% in the

placebo group (P = 0.006). The percentage of subjects who showed at least a 2 grade reduction in the EGSA (inflammatory lesions only) was 23.7% in the minocycline group and 13.9% in the placebo group (P = 0.011).

Table No. 30
Evaluator's Global Severity Assessment (Inflammatory lesions) Dichotomized as Success or Failure ITT Population MP-0104-04

	Minocycline		Placebo		P-Value
	N	Success N (%)	N	Success N (%)	
Baseline	300		151		
Day 28	300	9 (3%)	151	0	0.031
Day 56	300	25 (8.3%)	151	5 (3.3%)	0.036
Day 84	300	52 (17.3%)	151	12 (7.9%)	0.006

Study MP-0104-05
In MP-0104-05, percentage of subjects who were clear or almost clear based on EGSA (inflammatory lesions only) at day 84 was 15.9% in the minocycline group and 9.5% in the placebo group (P = 0.018). The percentage of subjects who showed at least a 2 grade reduction in the EGSA (inflammatory lesions only) was 19.7% in the minocycline group and 12% in the placebo group (P = 0.012).

Table No. 31
Evaluator's Global Severity Assessment (Inflammatory lesions) Dichotomized as Success or Failure ITT Population MP-0104-05

	Minocycline		Placebo		P-Value
	N	Success N (%)	N	Success N (%)	
Baseline	315		158		
Day 28	315	13 (4.1%)	158	2 (1.3%)	0.071
Day 56	315	38 (12.1%)	158	5 (3.2)	<0.001
Day 84	315	50 (15.9%)	158	15 (9.5%)	0.018

Statistically significant success rates were seen in the Minocycline group at all study visits and success rates increased progressively over time in both studies.

Subgroup Analysis (ITT Population) Study MP-0104-04
Subgroup analyses of the EGSA, dichotomized as success or failure were performed on inflammatory lesion counts for the ITT population by gender, age, race and EGSA at baseline.
a) *Gender*
MP-0104-04
Dichotomized analysis of the EGSA by gender for the ITT population showed success rates in males for M/P 14.6%/8.2% and in females for M/P 20.9%/7.6%.

MP-0104-05
Dichotomized analysis of the EGSA by gender for the ITT population showed success rates in males for M/P 13.7%/11.4% and in females for M/P 18.8%/7.1%.

b) *Age*
MP-0104-04

Dichotomized analysis of the EGSA by age for the ITT population showed success rates in those < 18 years of age for M/P 14.4%/3.8%, and in those ≥ 18 years, for M/P 22.3%/12.7%.

MP-0104-05
Dichotomized analysis of the EGSA by age for the ITT population showed success rates in those < 18 years of age for M/P 12.2%/7.4%, and in those ≥ 18 years, for M/P 21.8%/12.7%.

c) *Race*
MP-0104-04
Dichotomized analysis of the EGSA by race for the ITT population showed success rates in White subjects for M/P 18.7%/5.2%, and in non-White subjects, for M/P 14%/13%.

MP-0104-05
Dichotomized analysis of the EGSA by race for the ITT population showed success rates in White subjects for M/P 14.3%/7.4%, and in non-White subjects, for M/P 20.5%/16.2%.

d) *Baseline EGSA*
MP-0104-04
Dichotomized analysis of the EGSA by baseline EGSA for the ITT population showed success rates in those with baseline EGSA ≤ 3 for M/P 21.4%/8.6% and in those with baseline EGSA ≥ 4 for M/P 7.8%/6.5%.

MP-0104-05
Dichotomized analysis of the EGSA by baseline EGSA for the ITT population showed success rates in those with baseline EGSA ≤ 3 for M/P 19.3%/10.7%, and in those with baseline EGSA ≥ 4 for M/P 5.2%/5.4%.

Subgroup analysis revealed success rates to be higher in females and in ≥ 18 years age groups for both studies; it is possible that these findings may be related to a difference in compliance between groups. It also showed that success rates for minocycline were much lower in patients with more severe disease at baseline, i.e. those with baseline EGSA scores ≥ 4 in both studies. In general, White subjects had better efficacy rates than Non-White subjects; the majority of subjects in clinical studies were White.

Table No. 32
EGSA (Inflammatory lesions) dichotomized as Success/ Failure in MP-0104-04 - Subgroup Analysis by Gender, Age, Race and Baseline EGSA at Day 84

		Minocycline	Placebo
Gender			
Males N (%)	Success	25 (14.6%)	7 (8.2%)
	Failure	146 (85.4)	78 (91.8)
Females N (%)	Success	27 (20.9)	5 (7.6)
	Failure	102 (79.1)	61 (92.4)
Age			
< 18 years N (%)	Success	27 (14.6)	3 (3.8)
	Failure	161 (85.6)	77 (96.3)
≥ 18 years N (%)	Success	25 (22.3)	9 (12.7)

	Failure	87 (77.7)	62 (87.3)
Race			
White N (%)	Success	40 (18.7)	5 (5.2)
	Failure	174 (81.3)	92 (94.8)
Non-White N (%)	Success	12 (14.0)	7 (13.0)
	Failure	74 (86.0)	47 (87.0)
Baseline EGSA			
≤3 N (%)	Success	45 (21.4)	9 (8.6)
	Failure	165 (78.6)	96 (91.4)
≥4 N (%)	Success	7 (7.8)	3 (6.5)
	Failure	83 (92.2)	43 (93.5)

Table No. 33
EGSA (Inflammatory lesions) dichotomized as Success/ Failure in MP-0104-05 - Subgroup Analysis by Gender, Age, Race and Baseline EGSA at Day 84

		Minocycline	Placebo
Gender			
Males N (%)	Success	25 (13.7)	10 (11.4)
	Failure	157 (86.3)	78 (88.6)
Females N (%)	Success	25 (18.8)	5 (7.1)
	Failure	108 981.2)	65 (92.9)
Age			
< 18 years N (%)	Success	24 (12.2)	7 (7.4)
	Failure	172 (87.8)	88 (92.6)
≥ 18 years N (%)	Success	26 (21.8)	8 (12.7)
	Failure	93 (78.2)	55 (87.3)
Race			
White N (%)	Success	34 (14.3)	9 (7.4)
	Failure	203 (85.7)	112 (92.6)
Non-White N (%)	Success	16 (20.5)	6 (16.2)
	Failure	62 (79.5)	31 (83.8)
Baseline EGSA			
≤3 N (%)	Success	46 (19.3)	13 (10.7)
	Failure	192 (80.7)	108 (89.3)
≥4 N (%)	Success	4 (5.2)	2 (5.4)
	Failure	73 (94.8)	35 (94.6)

Secondary Efficacy Analysis:

1. Percentage of subjects with at least a 2-grade reduction in the EGSA from baseline to day 84 (end-of-treatment)
2. Percentage change in non-inflammatory lesion counts at day 84
3. Percentage of subjects with an EGSA (inflammatory and non-inflammatory lesions) clear or almost clear at day 84

Secondary Efficacy Endpoint 1:
Percentage of subjects with at least a 2-grade reduction in the EGSA from baseline to day 84
For this endpoint, the proportion of subjects with a decrease of at least 2 points in the EGSA (inflammatory lesions) was assessed.

MP-0104-04

In the ITT population, the proportion of subjects with a decrease of at least 2 points in the EGSA increased over the course of the study in both the minocycline and placebo groups, but was greater in the minocycline group at all time points and was statistically significant on Day 84.

Table No. 34
Proportion of Patients with 2-grade reduction EGSA (Inflammatory lesions) MP-0104-04

Study visit	Disease status	Minocycline	Placebo	P-value
Day 28 N (%)	Improvement of 2-points No improvement	13 (4.3%) 287 (95.7%)	2 (1.3%) 149 (98.75)	0.083
Day 56 N (%)	Improvement of 2-points No improvement	39 (13.0%) 261 (87.0%)	11 (7.3%) 140 (92.75)	0.052
Day 84	Improvement of 2-points No improvement	71 (23.7%) 229 (76.3%)	21 (13.9%) 130 (86.1%)	0.011

MP-0104-05

In the ITT population, the proportion of subjects with an improvement of at least 2 points in the EGSA (inflammatory lesions) increased over the course of time in both groups and the proportion was statistically significantly higher in the minocycline group at all time points. It was noted however, that the p-value was 0.030 on day 28, 0.003 on day 56 and increased to 0.020 on day 84 (Table No....)

Table No. 35
ITT- Proportion of Patients 2-grade reduction EGSA Inflammatory lesions MP-0104-05

Study visit	Disease status	Minocycline	Placebo	P-value
Day 28 N (%)	Improvement of 2-points No improvement	18 (5.7) 297 (94.3)	3 (1.9) 155 (98.1)	0.047
Day 56 N (%)	Improvement of 2-points No improvement	48 (15.2) 267 (84.8)	10 (6.3) 148 (93.7)	0.002
Day 84	Improvement of 2-points No improvement	62 (19.7) 253 (80.0)	19 (12.0) 139 (88.0)	0.012

N = 473 ITT population LOCF

Results of the PP population also showed similar results, with p-values 0.030 on day 28, 0.003 on day 56 and 0.020 on day 84.

Table No. 36
PP - Proportion of Patients 2-grade reduction EGSA Inflammatory lesions MP-0104-05

Study visit	Disease status	Minocycline	Placebo	P-value
Day 28 N (%)	Improvement of 2-points No improvement	17 (6.6) 241 (93.4)	2 (1.6) 124 (98.4)	0.030
Day 56 N (%)	Improvement of 2-points No improvement	45 (17.4) 213 (82.6)	9 (7.1) 117 (92.9)	0.003
Day 84	Improvement of 2-points No improvement	55 (21.3) 203 (78.7)	16 (12.7) 110 (87.3)	0.020

N = 384 PP population LOCF

For the secondary efficacy endpoint of a 2-grade improvement in acne status at day 84, in Study MP-0104-04, 23.7% of patients in the minocycline group compared to 13.9% of placebo patients (p= 0.011) had the 2-grade improvement and were considered 'success'. This is compared to the primary efficacy endpoint of EGSA 'clear' or 'almost clear' to be considered success at day 84, where 17.3% of patients in the minocycline group compared to 7.9% of patients in the placebo group (p-value 0.006) achieved success.
Similarly, in Study MP-0104-05, 19.7% of patients in the minocycline group compared to 12% of placebo patients (p = 0.012) had the 2-grade improvement and were considered 'success'. This is compared to the primary efficacy endpoint of EGSA 'clear' or 'almost clear' to be considered success at day 84, where 15.9% of patients in the minocycline group compared to 9.5% of patients in the placebo group (p-value 0.018) achieved success.
Higher success rates were achieved when 2-grade reduction in EGSA scores was used to assess efficacy.

Secondary Efficacy Endpoint 2:
Percentage change in non-inflammatory lesion counts at day 84
MP-0104-04
The percent change in non-inflammatory lesion counts from baseline to day 84 was 15.6% in the minocycline group and 14.3% in the placebo group.

Table No. 37
Percent Change in Non-Inflammatory lesion counts ITT Population MP-0104-04

	Minocycline	**Placebo**
Baseline N	300	151
Baseline mean lesion count	47.8	47.8
Day 84 N	299	150
Percent change from Baseline to Day 84	15.6	14.3
Subgroup Analyses		
Males		
Baseline N	171	85
Baseline mean lesion count	50.8	49.8
Percent change from Baseline to Day 84	6.1	13.0
Females		
Baseline N	129	66
Baseline mean lesion count	42.7	42.8
Percent change from Baseline to Day 84	23.9	11.9
Age < 18 years		
Baseline N	188	80
Baseline mean lesion count	55.8	55.8
Percent change from Baseline to Day 84	12.8	8.2
Age ≥ 18 years		
Baseline N	112	71
Baseline mean lesion count	33.1	36.5
Percent change from Baseline to Day 84	15.4	17.6
White subjects		
Baseline N	214	97
Baseline mean lesion count	49.1	50.2
Percent change from Baseline to Day 84	12.2	11.0

Non-White subjects		
Baseline N	86	54
Baseline mean lesion count	42.8	40.4
Percent change from Baseline to Day 84	17.7	15.3
EGSA ≤3		
Baseline N	210	105
Baseline mean lesion count	42.9	40.3
Percent change from Baseline to Day 84	12.4	13.0
EGSA ≥4		
Baseline N	90	46
Baseline mean lesion count	57.6	61.4
Percent change from Baseline to Day 84	16.8	11.4

MP-0104-05

The mean baseline non-inflammatory count was similar between the minocycline (42.1) and placebo (41.7) groups. The percent change in non-inflammatory lesion counts from baseline to day 84 was 13.8% in the minocycline group and -1.6% in the placebo group.

Table No. 38
Percent Change in Non-Inflammatory lesion counts ITT Population MP-0104-05

	Minocycline	**Placebo**
Baseline N	315	158
Baseline mean lesion count	42.1	41.7
Day 84 N	314	158
Percent change from Baseline to Day 84	13.8	-1.6
Subgroup Analyses		
Males		
Baseline N	182	88
Baseline mean lesion count	47.8	47.4
Percent change from Baseline to Day 84	10.7	6.8
Females		
Baseline N	133	70
Baseline mean lesion count	39.8	40.7
Percent change from Baseline to Day 84	19.7	-10.7
Age < 18 years		
Baseline N	196	95
Baseline mean lesion count	49.4	49.0
Percent change from Baseline to Day 84	9.5	-4.9
Age ≥ 18 years		
Baseline N	119	63
Baseline mean lesion count	36.2	37.5
Percent change from Baseline to Day 84	22.9	5.1
White subjects		
Baseline N	237	121
Baseline mean lesion count	44.4	46.1
Percent change from Baseline to Day 84	16.3	1.7
Non-White subjects		
Baseline N	78	37
Baseline mean lesion count	44.7	39.1
Percent change from Baseline to Day 84	9.1	-9.4
EGSA ≤3		
Baseline N	238	121

Baseline mean lesion count	42.8	42.5
Percent change from Baseline to Day 84	15.9	-4.8
EGSA ≥4		
Baseline N	77	37
Baseline mean lesion count	49.5	50.8
Percent change from Baseline to Day 84	10.3	11.6

This secondary efficacy endpoint was added to ensure that minocycline did not worsen non-inflammatory lesions. The efficacy analysis showed that minocycline did not exacerbate the severity of non-inflammatory lesions, although there was not much difference in efficacy rates between the minocycline and placebo arms. This implies that minocycline has no effect on non-inflammatory lesions. Interestingly, the mean percent decrease was higher in the placebo group compared to minocycline in males, subject's ≥ 18 years, and those with baseline EGSA ≤3 for MP-0104-04, while similar effects were seen in those with EGSA ≥4 in MP-0104-05.

Secondary efficacy endpoint # 3
Percentage of subjects with an EGSA (inflammatory and non-inflammatory lesions) clear or almost clear at day 84

The assessment for percentage of subjects with an EGSA that included inflammatory and non-inflammatory lesions was initiated after study enrollment had begun; therefore number of subjects in each treatment group is less than the full ITT population. The EGSA assessment was dichotomized as success or failure.

MP-0104-04

The incidence of success increased progressively over time in both treatment groups, and on day 84, the success rate in the minocycline group was 17% compared to 9.7% in the placebo group (p = 0.040).

Table No. 39
EGSA (Inflammatory & Non-Inflammatory lesions) MP-0104-04

Study visit	Minocycline	Placebo	P-value
Day 28			
N	242	122	
Success N (%)	8 (3.3)	0	0.041
Failure N (%)	234 (96.7)	122 (100)	
Day 56			
N	279	139	
Success N (%)	22 (7.9)	3 (2.2)	0.020
Failure N (%)	257 (92.1)	136 (97.8)	
Day 84			
N	294	145	
Success N (%)	50 (17)	14 (9.7)	0.040
Failure N (%)	244 (83)	131 (90.3)	

MP-0104-05

In Study MP-0104-05, the success rate increased over time in both treatment groups, but was statistically significantly higher in the minocycline group compared to the placebo group only at the day 28 visit (p = 0.015).

Table No. 40
EGSA (Inflammatory & Non-Inflammatory lesions) MP-0104-05

Study visit	Minocycline	Placebo	P-value
Day 28			
N	235	120	
Success N (%)	11 (4.7)	0	0.015
Failure N (%)	224 (95.3)	120 (100)	
Day 56			
N	271	136	
Success N (%)	19 (7)	3 (2.2)	0.055
Failure N (%)	252 (93)	133 (97.8)	
Day 84			
N	299	149	
Success N (%)	30 (10)	7 (4.7)	0.065
Failure N (%)	269 (90)	142 (95.3)	

Additional Analysis:

Total lesion counts

MP-0104-04

The percent change form baseline to day 84 was M/P 31.8%/24.1%, p = 0.015. The change was progressively greater over the study period and was greater in the minocycline group compared to the placebo group at all time points.

Table No. 41
Total Lesion Counts ITT Population MP-0104-04

	Minocycline	Placebo	P-value
Baseline	86.4	85.4	
Mean percent change form baseline to day 84	31.8	24.1	0.015

MP-0104-05:

The percent change form baseline to day 84 was M/P 32%/17.5%, p <0.001. The change was progressively greater over the study period and was greater in the minocycline group compared to the placebo group at all time points.

Table No. 42
Total Lesion Counts ITT Population MP-0104-04

	Minocycline	Placebo	P-value
Baseline	83.3	82.8	
Mean percent change form baseline to day 84	32.1	17.5	<0.001

6.1.5 Clinical Microbiology

Minocycline is a bacteriostatic antibiotic that has been shown to have some in vitro activity against P. acnes, however, the clinical significance of this activity in the treatment of acne vulgaris is not known.

The sponsor conducted study MP-0104-09, entitled 'An evaluation of the anti-bacterial effects in vivo of minocycline in humans'. The objective of this study was to determine the relative antimicrobial effects of a new extended-release formulation of minocycline in measuring its inhibitory action against P. acnes counts in vivo. In this open-label, 16-week, uncontrolled, single-center study, Solodyn was administered at 1 mg/kg/day in subjects with moderate-severe facial acne for 12 weeks and follow-up was after 4 weeks of study treatment completion.

The primary efficacy endpoint was the change from baseline to day 84 in log P. acnes counts. Secondary efficacy endpoints included 1) Change from baseline to days 28 and 56 in log P. acnes counts, 2) percentage of subjects with and EGSA of clear or almost clear at days 28, 56 and 84, 3) number of subjects with a 2-point improvement in EGSA at days 28, 56 and 84 and 4) number and percentage of subjects with a change in P. acnes susceptibility from baseline to days 28, 56, 84 and 112.

Efficacy results showed that P. acnes cultures/counts were inconsistent and did not co-relate with facial improvement. Most cultures (~ 75%) were negative for P. acnes.

Conclusion of Study MP-0104-09: Therapeutic outcomes in subjects with acne vulgaris using Solodyn for 12 weeks did not show evidence of association with the P. acnes culture results. Study findings reiterate that clinical significance of activity of Solodyn against P. acnes in *in vitro* studies is unknown; the role of P. acnes in causation of acne is not entirely clear.

6.1. 6 Efficacy Conclusions

Results from the two pivotal studies MLP-0104-04 and MP-0104-05 indicate that Solodyn™ (minocycline HCl) extended-release tablets were effective in meeting the pre-defined primary and secondary efficacy endpoints. The studies were conducted in subjects with non-nodular, moderate-severe acne vulgaris (< 2 nodules/cysts included) and the primary efficacy endpoint involved assessment of only inflammatory lesions.

Study MP-0104-04
Primary efficacy endpoints:

- Mean percent reduction from baseline in inflammatory lesion counts at day 84, minocycline/placebo = 43.1%/31.7% (p=0.001) and
- Dichotomized analysis (success = clear/almost clear) of the Evaluator's Global Severity Assessment scale at day 84, minocycline/placebo = 17.3%/7.9% (p=0.006).

Results in the ITT population were supported by those in the PP population.

Secondary efficacy endpoints – Minocycline demonstrated superiority over placebo for two endpoints and was shown to be non-inferior to placebo in the treatment of non-inflammatory lesions.

- 2-grade reduction in EGSA from baseline to day 84 in inflammatory lesion counts - success rate in the minocycline group (23%) was higher than the success rate in the placebo group (13.9%) ($p = 0.011$).
- Percentage change in non-inflammatory counts at day 84 - decrease was 15.6% in the minocycline group and 14.3% in the placebo group; minocycline was shown to be non-inferior to placebo in the effect on non-inflammatory lesions.
- Percentage of subjects with an EGSA (inflammatory and non-inflammatory lesion) clear or almost clear at day 84 – Success rates in minocycline group (17%) were higher than placebo (9.7%) ($p = 0.040$).

Study MP-0104-05

Primary efficacy endpoints:

- Mean percent reduction from baseline in inflammatory lesion counts at day 84, minocycline/placebo = 45.8%/30.8% ($p < 0.001$) and
- Dichotomized analysis (success = clear/almost clear) of the Evaluator's Global Severity Assessment scale at day 84, minocycline/placebo = 15.9%/9.5% ($p = 0.018$).

Results in the ITT population were supported by those in the PP population.

Secondary efficacy endpoints – Minocycline demonstrated superiority over placebo for two endpoints and was shown to be non-inferior to placebo in the treatment of non-inflammatory lesions.

- 2-grade reduction in EGSA from baseline to day 84 in inflammatory lesion counts - success rate in the minocycline group (19.7%) was higher than the success rate in the placebo group (12%) ($p = 0.012$).
- Percentage change in non-inflammatory counts at day 84 - decrease was 13.8% in the minocycline group and -1.6%% in the placebo group; minocycline was shown to be non-inferior to placebo in the effect on non-inflammatory lesions.
- Percentage of subjects with an EGSA (inflammatory and non-inflammatory lesion) clear or almost clear at day 84 – Success rates in minocycline group (10%) were higher than placebo (4.7%), but were not statistically significant ($p = 0.065$).

Efficacy Analysis conclusions:

Solodyn extended-release tablets were shown to be effective over the 12 week period in the treatment of non-nodular, moderate-severe inflammatory lesions of facial acne vulgaris in subjects' $\geq$ 12 years of age. No claims for efficacy should be made for non-facial areas, since they were not included in the efficacy analysis.

For non-inflammatory lesions, it was shown that minocycline had no effect on non-inflammatory lesions, i.e. no benefit/worsening. In clinical practice minocyline is often combined with adjunctive topical therapy for non-inflammatory lesions.

Subgroup analyses revealed success rates to be generally higher in females and in $\geq$ 18 years age groups; this may be related to compliance. It also showed that success rates were much

lower in patients with more severe disease at baseline, i.e. those with EGSA scores ≥ 4 in both studies. Success rates were in general higher in White subjects compared to Non-White subjects; however, both pivotal clinical studies did not include adequate Asian/Pacific Islander or American Indian/Alaskan subjects.

7 Integrated Review of Safety

7. 1 Methods and Findings

The integrated summary of clinical safety for Solodyn tablets combines safety from the following clinical studies (Please refer to Section 4 for Table of Clinical Studies):

1) Three Bioavailability studies
2) One Pharmacokinetic and four Pharmacodynamic studies
3) One Phase 2 placebo-controlled dose-ranging study
4) Two pivotal Phase 3 safety and efficacy studies
5) One 2-year, open-label safety study (ongoing)

Overall Extent of exposure:

Single-dose Bioavailability Studies in Healthy Subjects:

These were single-dose, bioavailability studies. Safety assessments included recording AEs and evaluation of labs (chemistry and hematology) for all studies.

1) Study AA1-US-110 – A 3-way crossover pilot bioequivalence/bioavailability study of two new formulations of minocycline HCl compared to a marketed formulation in healthy male volunteers (n = 24). Reference drug was Dynacin® 150 mg.
2) Study AA1-US-190 – A 2-way crossover study of the effects of food on the pharmacokinetics of minocycline in healthy volunteers (n = 24).
3) Study AA1-US-223 – A 4-way crossover dose proportionality study of increasing doses of minocycline on healthy volunteers (n = 24). Reference drug was Minocin 100 mg.

Repeat-dose Pharmacokinetic and Pharmacodynamic Studies in Healthy Subjects:

Pharmacokinetic Study:

Study MP-0104-15 – A 2-way, crossover, steady-state study of minocycline tablets in healthy volunteers; 28 healthy subjects received treatment with 135-mg extended-release minocycline HCl tablets once daily for 6 days. The reference product was 100 mg Minocin® twice daily for 6 days. Safety assessments included recording AEs and evaluation of labs (chemistry and hematology).

Pharmacodynamic Studies:

1) Study MP-0104-10 – Open-label study to examine effects of minocycline on low-dose ethinyl estradiol therapy in healthy female subjects (n = 30). Safety assessments included recording AEs and evaluation of labs (chemistry, hematology, thyroid function tests and anti-nuclear antibodies).

2) Study MP-0104-13 – Open-label, twelve-week study to examine effects of minocycline on spermatogenesis (sperm count, motility, morphology and effects on FSH, LH and testosterone) in human males in healthy male subjects. Safety assessments included recording AEs and evaluation of labs (chemistry, hematology, thyroid function tests and anti-nuclear antibodies). Although the protocol for this study was found to be inadequate by the Agency, the sponsor chose to proceed with the study. 30 subjects were planned for enrollment; however, according to the sponsor, study site and documentation were destroyed by Hurricane Katrina. Therefore, limited study results are available.
3) Study MP-0104-16 – Open-label, cohort study to investigate effects of minocycline on sperm characteristics in male subjects with acne vulgaris. This study compared sperm count, motility and morphology in 2 cohorts of male subjects with acne vulgaris, 16 years and older; one cohort underwent treatment with minocycline 1 mg/kg/day for at least 24 weeks (n = 31); the other cohort was naïve of any antibiotic treatment for at least 32 weeks (n = 11). No additional safety evaluations were performed in this study. This study was performed without Agency input.
4) Study MP-0104-09 – Evaluation of the anti-microbial effects inhibitory action against *Propionibacterium acnes*) in vivo of minocycline caplets in subjects with moderate-severe acne vulgaris (n = 28). Safety assessments included recording AEs and evaluation of labs (chemistry, hematology, thyroid function tests and anti-nuclear antibodies).

Phase 2 and 3 Safety and Efficacy Studies:
This included MP-0104-01, a dose-ranging study; *and* MP-0104-04 and MP-0104-05 the two pivotal Phase 3 studies. Across all three studies that included subjects with moderate-severe AV, 674 subjects received Solodyn 1 mg/kg/day and 364 received placebo. The mean duration of exposure for Solodyn was 82 days. Safety assessments included recording AEs and evaluation of labs (hematology, chemistry and urinalysis) for all three studies.

1) Study MP-0104-01 – Phase 2, randomized, double-blind, placebo-controlled, dose-ranging study. This study was conducted using minocycline ER as primary therapy for moderate-severe facial acne vulgaris in patients 12 -30 years. Subjects received minocycline at 1 mg/kg/day (59), 2 mg/kg/day (59), 3 mg/kg/day (60), or placebo (55).

2) Study MP-0104-04 – Phase 3, randomized, double-blind, placebo-controlled study of minocycline ER at 1 mg/kg/day in subjects with moderate-severe facial acne. 451 subjects were enrolled, 300 in the minocycline arm and 151 in the placebo arm.

3) Study MP-0104-05 – Phase 3 study that was almost identical in design to MP-0104-04. 473 subjects were enrolled, 315 in the minocycline arm and 158 in the placebo arm.

Table No. 43
Overall Number of Patients for Safety evaluation (Minocycline at 1 mg/kg/day)

Single-dose studies, healthy subjects	
Study	N
AAI-US-110	24
AAI-US-190	24
AAI-US-233	24
Repeat-dose, Pharmacodynamic and Pharmacokinetic Studies, healthy subjects	

MP-0104-15	28
MP-0104-10	29
MP-0104-13	26 (study to be repeated)
MP-0104-16	42 (M/P = 31/11)
12-week Pharmacodynamic Study, Acne Vulgaris subjects	
MP-0104-09	28
12-week, Phase 2 dose-ranging study	
MP-0104-01	59
12-week, Phase 3 safety and efficacy Studies	
MP-0104-04	451 (M/P = 300/151)
MP-0104-05	473 (M/P = 315/158)

Table No. 44
Study Drug Exposure Pooled Phase 2 and 3 Studies

Duration of Exposure (by 2-week periods)	Minocycline 1 mg/kg N = 674	Placebo N = 364
1 – 14 days	5 (0.8)	2 (0.6)
15 – 28 days	15 (2.3)	3 (0.8)
29 – 42 days	12 (1.8)	11 (3.1)
43 – 56 days	3 (0.5)	10 (2.8)
57 – 70 days	7 (1.1)	10 (2.8)
71 – 84 days	246 (37.7)	144 (40.7)
>84 days	365 (55.9)	174 (49.2)
Unknown	21 (3.1)	10 (2.7)

Open-label, 2 year safety study

1) Study MP-0104-07 – This is an ongoing open-label, 2 year safety study of Solodyn at 1 mg/kg/day in subjects with moderate-severe facial acne. All subjects enrolled were to have participated in either MP-0104-04 or MP-0104-05. 345 subjects enrolled (233 treated with minocycline and 112 with placebo previously). Subset of subjects enrolled in this study is to be evaluated for linear growth.

Demographics of Study Population:

Table No. 45
Age Range of Patients enrolled in Studies MP-0104-04 & MP-0104-05

Age (years)	MP-0104-04		MP-0104-05	
	Minocycline	Placebo	Minocycline	Placebo
12-14 N (%)	66 (22)	26(17.2)	73(23.2)	42(26.6)
15-17 N (%)	122 (40.7)	54 (35.8)	123 (39.0)	53 (33.5)
18-22 N (%)	51 (17.0)	26 (17.2)	55 (17.5)	27 (17.1)
>22 N (%)	61 (20.3)	45 (29.8)	64 (20.3)	36 (22.8)

In the Phase 2 and 3 safety and efficacy studies in moderate-severe acne patients, there were 674 subjects (minocycline 1 mg/kg/day) who were 12 to 63 years, with a mean age of 19.4 years; 40.2% of these subjects were between 12 to 17 years. Out of the total of 674 subjects, 58% (391) were male and 42% (283) were female. 74% (501) were White, 10% (66) were Black and 12% (82) were Hispanic.

The majority of patients enrolled in both pivotal studies were in the teenage age groups, i.e. 12-17 years, which is in keeping with the age group where acne vulgaris is most commonly seen.

7.1.1 Deaths

There were no deaths reported in any of the clinical studies conducted during the drug development program for Solodyn™ caplets.

7.1.2 Other Serious Adverse Events

Severe Adverse Events:

Table No. 46
Severe Treatment-Emergent AEs in Combined Phase 2 and 3 studies

	Minocycline 1 mg/kg N=674	**Placebo N=364**
At least one severe AE	20 (3%)	7 (2%)
Headache	2	4
Gastrointestinal pain	2	0
Ruptured ovarian cyst	2	0
Abdominal pain	1	0
Aggravated acne	1	0
Back pain	1	0
Contusion	1	0
Facial bone fracture	1	0
Hypoaesthesia	1	0
Migraine	1	0
Nasal septum deviation	1	0
Nasal turbinate hypertrophy	1	0
Nasopharyngitis	1	0
Neck pain	1	0
Otitis externa	1	0
Otitis media	1	0
Pharyngolaryngeal pain	1	0

Rash	1	0
Restlessness	1	0
Sunburn	1	0
Urticaria	1	0
Vomiting	1	0
Acne	1	1
Pruritus	1	1
Fatigue	0	1
Ligament injury	0	1

Source: Sponsor briefing document, Module 2

Severe treatment-emergent AEs were reported by 20 (3%) of subjects in the minocycline group and 7 (2%) of subjects in the placebo group. In the minocycline/placebo groups, these included headache 2/4, GI pain 2/0, abdominal pain 1/0, vomiting 1/0, aggravated acne 1/0, acne 1/0, rash 1/0, sunburn 1/0, urticaria 1/0 and pruritus 1/0.

Treatment-related severe AEs included GI and skin related AEs (both included in minocycline label); these AEs were slightly higher in the minocycline group compared to placebo.

Serious Adverse events:

Table No. 47
Serious AEs in Phase 2 and 3 Studies

Site/ Subject No.	Adverse Event	Severity	Relation to Treatment	Onset Day	Action Taken/Outcome
MP-0104-04, Minocycline 1 mg/kg					
32/14	Depression	Moderate	Unrelated	2	Remedial drug therapy; hospitalization; event resolved.
42/53	Ovarian cyst	Severe	Unrelated	56	Remedial drug therapy; hospitalization; cyst removal and elective appendectomy; event resolved.
	Ruptured ovarian cyst	Severe	Unrelated	95	Hospitalization; IV fluids; event resolved.
42/63	Asthma NOS	Severe	Unrelated	103	Remedial drug therapy; hospitalization; event resolved.
MP-0104-05, Minocycline 1 mg/kg					
57/12	Neck pain	Severe	Possibly	9	DC study med; remedial drug therapy; hospitalization; outcome unknown.
	Hypoaesthesia	Mild	Possibly	13	DC study med; hospitalization; outcome unknown.
	Paraesthesia	Mild	Possibly	13	DC study med; hospitalization; outcome unknown.

Source: Sponsor briefing document Module 2

Narratives of Serious AEs:

1. MP-0104-04 – Minocycline arm – Subject 31/14 was a 15 year old White female who experienced an episode of depression, 1 day after starting treatment and was hospitalized. Patient had a past history of depression for which she had been previously hospitalized and was on ongoing quetiapine fumarate and fluoxetine hydrochloride. Event resolved after 12 days and patient completed study treatment.
This event does not appear to be related to study treatment.

2. MP-0104-04 – Minocycline arm – Subject 42/53 was a 17 year old black female with no significant past medical history who experienced periumbilical pain on day 43 of study treatment that worsened, leading to hospitalization on day 56 . Patient had a ruptured right ovarian cyst and was discharged on day 58 after event resolved. Patient was re-admitted on day 85 for abdominal pain and required surgical removal of benign right ovarian cyst and also had an appendectomy. Subject completed study treatment.
This event does not appear to be related to study treatment.

3. MP-0104-04 – Minocycline arm – Subject 42/63 was a 15 year old black male who had completed full study treatment. However, this patient who had a past history of asthma and seasonal allergies experienced mild fatigue on day 95 (12 days after study treatment completion) and an exacerbation of asthma requiring hospitalization on day 103. Patient was discharged after 2 days, event resolved and patient completed study treatment per protocol.
This event does not appear to be related to study treatment.

4. MP-0104-05 – Minocycline arm – Subject 57/12 experienced severe neck pain after strenuous yard work which led to hospitalization. 4 days later, patient had mild episodes of hypoaesthesia and paraesthesia for which he required re-hospitalization. These events did not continue; study medication was discontinued, subject outcome is unknown and both events were considered possibly related to study treatment by the investigator.

7.1.3 Dropouts and Other Significant Adverse Events

Study dropouts and adverse events noted in Phase 2 and 3 studies are discussed in the following section. For MP-0104-01, only subjects exposed to minocycline 1 mg/kg will be discussed in this section.

In MP-0104-01, adverse events as reason for discontinuation were higher in the minocycline group (25%) compared to placebo group (10%), and 'Other' reasons were 58% in the minocycline group compared to 20% in the placebo group. 30% of patients in the placebo group withdrew consent compared to 8% in the minocycline group and 40% were lost to follow-up in the placebo group compared to 8% in the minocycline group.

In Studies MP-0104-04 and MP-0104-05, about 89% of subjects completed study through day 84 in all groups, while about 50% completed through day 112 (follow-up visit); however, about 35% of patients chose to enter the open-label long-term study across all groups. Patients who entered the open-label safety study on day 84 were not seen at Day 112. Adverse event as

reason for discontinuation was slightly higher in the minocycline groups (3%) in both studies, compared to 1% in placebo in MP-0104-04 and 2% in placebo in MP-0104-05.

Overall, adverse events as reasons for discontinuation were higher in the minocycline groups compared to placebo across Phase 2 and 3 studies.

Table No. 48
Reasons for Study Discontinuation - Phase 2 study MP-0104-01

	Minocycline 1 mg/kg N (%)	Placebo
ITT (Safety)	59 (100)	55 (100)
PP Subjects	53 (89)	42 (76)
Completed through Day 84	54 (91)	47 (86)
Discontinued prior to day 84	5 (9)	8 (15)
Completed through Day 91*	47 (78)	45 (82)
Discontinued prior to Day 91	12 (20)	10 (18)
Reasons for discontinuation prior to Day 91		
Withdrawal of consent	1 (8)	3 (30)
Adverse experience	3 (25)	1 (10)
Lost to follow-up	1 (8)	4 (40)
Other	7 (58)	2 (20)
Missing	0	0

* Study treatment end-Day 84, Follow-up call-Day 91

Table No. 49
Reasons for Study Discontinuation Phase 3 studies MP-0104-04 & MP-0104-05

	MP-0104-04 Minocycline N (%)	MP-0104-04 Placebo N (%)	MP-0104-05 Minocycline N (%)	MP-0104-05 Placebo N (%)
ITT (Safety)	300 (100)	151 (100)	315 (100)	158 (100)
PP Subjects	215 (72)	113 (75)	258 (82)	126 (80)
Subjects completing through Day 84	266 (89)	131 (87)	287 (91)	141 (89)
Subjects who discontinued prior to day 84	34 (11)	20 (13)	28 (9)	17 (11)
Subjects completing through Day 112	149 (50)	79 (52)	171 (54)	76 (48)
Subjects entering long-term follow-up	117 (39)	50 (33)	116 (37)	63 (40)
Reasons for discontinuation of study treatment				
Adverse event	9 (3)	2 (1)	8 (3)	3 (2)
Protocol violation/non-compliance	2 (0.7)	2 (1)	2 (0.6)	2 (1)
Withdrawal of consent	11 (4)	7 (5)	7 (2)	8 (5)
Lost to follow-up	10 (3)	8 (5)	11 (6)	4 (3)
Other	2 (0.7)	1 (0.7)	0	0

7.1.3.1 Overall profile of dropouts

Of the 674 subjects in pooled Phase 2 and 3 studies treated with minocycline 1 mg/kg, 20 (3%) had AEs that led to treatment discontinuation; in the placebo group, out of 364 subjects, 6 (2%) had AEs leading to treatment discontinuation.

In the minocycline group, majority of AEs were skin-related and included pruritus (7), urticaria (7) and rash (3). Other AEs included GI pain, diarrhea, nausea, fatigue and neck pain, hypoaesthesia, paraesthesia and dermatitis medicamentosa, upper respiratory tract infection, insomnia and mood alteration. Most AEs were of mild-moderate intensity and resolved; few cases (especially pruritus and urticaria) required remedial drug therapy.
In the placebo group, AEs included headache, GI pain and aggravation of acne.

Overall profile of AEs associated with discontinuation of treatment in the minocycline groups are in keeping with known AEs of minocycline.

7.1.3.2 Adverse events associated with dropouts

In MP-0104-01, 3 subjects had AEs in the minocycline 1 mg/kg arm leading to discontinuation of treatment. One patient had pruritus and rash NOS, another had gastrointestinal pain (GI) NOS and the last one had acne aggravated. Aggravated acne was the only AE considered severe, but unrelated to study drug and required remedial drug therapy; other AEs were considered related and resolved in all cases.

In the pooled analysis for MP-0104-04 and MP-0104-05, out of the 674 subjects in Phase 2 and 3 studies treated with minocycline 1 mg/kg, 20 (3%) subjects had AEs that led to treatment discontinuation.

Table No. 50
Adverse events leading to subject discontinuation in MP-0104-04

Site/ Subject No.	Adverse Event	Severity	Relation to Treatment	Onset Day	Action Taken/Outcome
MP-0104-04, Minocycline 1 mg/kg					
30/61	Diarrhea NOS	Mild	Probably	10	DC study med; event resolved.
42/70	Urticaria NOS	Severe	Possibly	18	DC study med; remedial drug therapy; event resolved.
43/24	Pruritus	Moderate	Definitely	40	DC study med; outcome unknown.
44/9	Urticaria NOS	Moderate	Probably	20	DC study med; event resolved.
45/1	Nausea	Mild	Possibly	Unknown	DC study med; event resolved.
	Fatigue	Moderate	Possibly	Unknown	DC study med; event resolved.
	Headache	Moderate	Possibly	Unknown	DC study med; event resolved.
45/15	Arthralgia	Moderate	Definitely	17	DC study med; event resolved.
	Pruritus, Rash NOS	Severe	Definitely	17	DC study med; remedial drug therapy; events resolved.
46/9	Pruritus	Moderate	Possibly	25	DC study med; remedial drug therapy; events resolved.
	Rash NOS	Mild	Possibly	27	DC study med; remedial drug therapy; events resolved.
	Swelling face	Mild	Possibly	26	DC study med; event resolved.
46/56	Urticaria NOS	Moderate	Possibly	16	DC study med; remedial drug therapy; event resolved.
47/46	Fatigue	Mild	Possibly	4	DC study med; events resolved.
	Dizziness	Mild	Possibly	8	DC study med; events resolved.
	Migraine NOS	Severe	Probably	4	DC study med; events resolved.
	Insomnia	Mild	Possibly	4	DC study med; events resolved.

	Mood alteration NOS	Moderate	Possibly	8	DC study med; events resolved.
MP-0104-04, Placebo					
42/66	Pregnancy NOS	Mild	Unrelated	Unknown	DC study med; outcome unknown.
46/54	Acne NOS	Severe	Possibly	68	DC study med; remedial drug therapy; event resolved.

Source: Sponsor briefing document: Module 2

Adverse events leading to discontinuation of study treatment in MP-0104-04 was higher in the minocycline arm compared to placebo. Most AEs resolved; outcome of 1 subject in the minocycline group with pruritus was unknown. 1 subject in the placebo group had a pregnancy, resulting in a premature delivery; infant had surgery for patent ductus arteriosus and passed away at 5 months of age due to Sudden Infant Death syndrome (SIDS.

Severe AEs leading to discontinuation were noted in the minocycline group, 1 case of urticaria and 1 of pruritus; both resolved with remedial drug treatment. In the minocycline group, 1 patient had arthralgia and 2 patients had pruritus that was felt to be definitely related to study drug. All AEs leading to study discontinuation are labeled AEs of minocycline.

Table No. 51
Adverse events leading to subject discontinuation in MP-0104-05

Site/ Subject No.	Adverse Event	Severity	Relation to Treatment	Onset Day	Action Taken/Outcome
MP-0104-05 Minocycline 1 mg/kg					
51/18	Pruritus	Mild	Possibly	21	DC study med; remedial drug therapy; event resolved.
51/21	Upper respiratory tract infection NOS	Mild	Unrelated	30	DC study med; remedial drug therapy; event unresolved.
52/41	Urticaria NOS	Moderate	Possibly	23	DC study med; remedial drug therapy; event resolved.
57/09	Pruritus	Moderate	Definitely	18	DC study med; remedial drug therapy; event resolved.
	Urticaria NOS	Mild	Definitely	18	DC study med; remedial drug therapy; event resolved.
57/12	Neck pain	Severe	Possibly	9	DC study med; remedial drug therapy; hospitalization; outcome unknown.
	Hypoaesthesia	Mild	Possibly	13	DC study med; hospitalization; outcome unknown.
	Paraesthesia	Mild	Possibly	13	DC study med; hospitalization; outcome unknown.
57/24	Pruritus	Moderate	Definitely	17	DC study med; remedial drug therapy; event resolved.

	Urticaria NOS	Moderate	Definitely	17	DC study med; remedial drug therapy; event resolved.
57/41	Urticaria NOS	Moderate	Definitely	25	DC study med; event resolved.
59/15	Dermatitis medicamentosa	Moderate	Possibly	16	DC study med; event resolved.

MP-0104-05 Placebo					
53/27	Headache	Moderate	Possibly	1	DC study med; event resolved.
53/76	Arthralgia	Mild	Possibly	2	DC study med; event resolved.
	Arthralgia	Mild	Possibly	2	DC study med; event resolved.
	Neck pain	Mild	Possibly	2	DC study med; event resolved.
	Headache	Mild	Possibly	2	DC study med; event resolved.
50/54	Vision blurred	Mild	Possibly	24	Remedial drug therapy; event resolved.
	Gastrointestinal pain NOS	Mild	Possibly	27	None; event resolved.
	Nausea	Mild	Possibly	1	None; event resolved.
	Pharyngitis streptococcal	Moderate	Unrelated	41	Interrupted study med; remedial drug therapy; event resolved.
	Vaginosis fungal NOS	Moderate	Probably	48	Remedial drug therapy; event resolved.
	Headache	Moderate	Probably	31	Remedial drug therapy; event resolved.

Source: Sponsor briefing document: Module 2

In MP-0105-05, adverse events leading to discontinuation of treatment were higher in the minocycline group compared to the placebo group. With the exception of 1 patient in the minocycline group whose outcome was unknown (patient- subject # 57/12 with neck pain, hypoaesthesia and paraesthesia), and 1 patient with upper respiratory tract infection whose outcome was unresolved, all other AEs resolved. Subject 57/12 experienced severe neck pain after strenuous yard work and neurological symptoms of hypoaesthesia and paraesthesia were considered possibly related to study drug; however, they may also have been related to the 'strenuous yard work'. In the minocycline group, AEs such as urticaria and pruritus were considered definitely related. All AEs leading to study discontinuation are labeled AEs of minocycline.

7.1.3.3 Other significant adverse events

Treatment-emergent AEs related to vestibular function:

These included dizziness, nausea, tinnitus, vertigo and vomiting. Dizziness was noted to be higher in the minocycline group (8.8%) compared to placebo (4.7%), and the incidence of vertigo was 1.2% in the minocycline group compared to placebo (0.8%). Minocycline is known to be associated with vestibular AEs.

Table No. 52
Vestibular Function Related Treatment-Emergent AEs in Combined Phase 2 & 3 Studies

	Minocycline 1 mg/kg N=674	Placebo N=364
Nausea	64 (9.5)	41 (11.3)
Dizziness	59 (8.8)	17 (4.7)
Vomiting	14 (2.1)	9 (2.5)
Tinnitus	10 (1.5)	5 (1.4)
Vertigo	8 (1.2)	3 (0.8)

Source: Sponsor Briefing Document Module 2

7.1.4 Other Search Strategies
An ODS safety review for minocycline was obtained and is discussed in Section 7.2.2.2. Literature reports regarding minocycline use in acne are discussed in Section 7.2.2.3.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

The primary clinical safety population for Solodyn included 647 subjects in the combined 12-week Phase 2 and Phase 3 studies, treated with minocycline 1 mg/kg and the control group treated with placebo. Clinical safety evaluation plan for Solodyn was designed to assess all AEs, and especially known AEs of minocycline/tetracyclines for eg., vestibular AEs, autoimmunity syndromes, thyroid disorders, CNS disorders, skin and hypersensitivity reactions, hyperpigmentation, etc.

All adverse events (AEs) occurring after administration of study drug were recorded, whether or not considered related to study drug. All AEs considered to be related to study drug, and all serious AEs (SAEs) were followed until resolution or until clinically stable.

During the 12 week studies, subjects were contacted on Day 7 to assess AEs and had clinic visits on days 28, 56 and 84 to assess AEs amongst other study procedures. Similar safety assessment approaches were adopted amongst all pivotal safety and efficacy studies.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

All local and systemic AEs were collected and AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA). For the combined safety population, the most frequently reported AEs were in the MedDRA SOCs as follows:

- Nervous System Disorders M/P = 29%/26% (headache, dizziness, somnolence, migraine, hypoaesthesia, paraesthesia, etc)
- Gastrointestinal (GI) Disorders M/P = 21%/26% (diarrhea, nausea, vomiting, abdominal pain, dry mouth, etc)
- Skin and Subcutaneous Tissue Disorders M/P = 9%/7% (pruritus, urticaria, rash, acne dermatitis, etc)
- Infections and Infestations M/P = 9%/11% (nasopharyngitis, upper respiratory tract infection, sinusitis, pharyngitis, etc)

7.1.5.3 Incidence of common adverse events

The incidence of common adverse events is analyzed for the single and multiple dose PK/PD studies, the 12 week PD study and the pivotal safety and efficacy studies.

7.1.5.4 Common adverse event tables

AEs in single-dose studies in healthy subjects:
Most commonly reported AEs in single-dose PK/PD studies in healthy subjects were headache (6 patients) and dizziness or lightheadedness (3 subjects). These are labeled AEs of minocycline and majority was of mild intensity. There were no serious AEs and no patients discontinued from the studies.

AEs in repeat-dose PK/PD studies in healthy subjects:
Most common AE in repeat-dose PK/PD studies in healthy subjects were headache and dizziness; these are labeled AEs of minocycline. There were no serious AEs; majority of AEs were mild/moderate and no patient discontinued form the study due to an AE.

AEs in 12-week safety and efficacy studies in subjects with acne vulgaris:
Study population included combined patients from the two identical 12-week Phase 3 studies MP-0104-04 and MP-0104-05 as well as the 12-week Phase 2 dose-ranging study MP-0104-01 (only patients treated with 1 mg/kg minocycline + placebo group). Primary safety population for this analysis is 674 subjects treated with minocycline 1 mg/kg and 364 subjects treated with placebo.

Across Phase 2 (dose ranging) and Phase 3 (safety and efficacy) studies, 379 (56%) of subjects on minocycline 1 mg/kg and 197 (54%) on placebo (P) reported treatment-emergent AEs in the 12 week period. Most commonly reported AEs in the minocycline/placebo groups included headache 23%/23%, nausea 10%/11%, fatigue 9%/7%, dizziness 9%/5%, diarrhea 5%/6%, gastrointestinal pain 5%/7%, upper abdominal pain 3%/4%, and pruritus 5%/4%. Other AEs in

the M/P groups included mood alteration 3%/3%, vomiting 2%/3%, urticaria 2%/0.3%, tinnitus 1.5%/1.4%, vertigo 1.2%/0.8%.

Table No. 53
Treatment-Emergent AEs in at least 1% of Subjects in Combined Phase 2 and 3 Studies

	Minocycline (1mg/kg) N = 674	Placebo N=364
At least one treatment-emergent event	379 (56.2)	197 (54.1)
Headache	152 (22.6)	83 (22.8)
Nausea	64 (9.5)	41 (11.3)
Fatigue	62 (9.2)	24 (6.6)
Dizziness	59 (8.8)	17 (4.7)
Diarrhea	35 (5.2)	21 (5.8)
Gastrointestinal pain	34 (5.0)	25 (6.9)
Pruritus	31 (4.6)	16 (4.4)
Malaise	26 (3.9)	9 (2.5)
Abdominal pain, upper	22 (3.3)	14 (3.8)
Nasopharyngitis	22 (3.3)	10 (2.7)
Mood alteration	17 (2.5)	9 (2.5)
Insomnia	15 (2.2)	11 (3.0)
Vomiting	14 (2.1)	9 (2.5)
Upper respiratory tract infection	13 (1.9)	6 (1.6)
Somnolence	13 (1.9)	3 (0.8)
Urticaria	10 (1.5)	1 (0.3)
Tinnitus	10 (1.5)	5 (1.4)
Arthralgia	9 (1.3)	2 (0.5)
Pharyngolaryngeal pain	9 (1.3)	8 (2.2)
Vertigo	8 (1.2)	3 (0.8)
Vision blurred	8 (1.2)	6 (1.6)
Dry mouth	7 (1.0)	5 (1.4)
Myalgia	7 (1.0)	4 (1.1)

Source: Sponsor briefing document Module 2

Safety analysis conclusions:
Overall, AEs were mild to moderate and were in keeping with labeled AEs of minocycline. Commonly occurring treatment-emergent AEs in at least 1% of the population in the minocycline group included headache, dizziness, nausea and fatigue. Vestibular and skin-related AEs were in general higher in the minocycline group.

For safety evaluation purposes, it would have been useful if the extended-release formulation of minocycline had been compared to the immediate release formulation; although the Agency had recommended such comparison studies to the sponsor, they were not conducted.

7.1.5.5 Identifying common and drug-related adverse events

Common and drug-related adverse events identified in combined safety population from Phase 2 and 3 studies were as follows (M/P = minocycline/placebo):

- Drug-related AEs were highest in the Nervous System Disorders class; M/P = 25.2%/23.4%; headache and dizziness were the most common AEs.
- This was followed by the GI Disorders class; M/P = 17%/22%; nausea, abdominal pain and diarrhea were the most common AEs
- The next common class was General Disorders and Administration Site Conditions; M/P = 10.4%/8%; fatigue and malaise were the most common AEs
- Skin and Subcutaneous Tissue Disorders; M/P = 6.7%/5.2%; pruritus and urticaria were the most common AEs
- Investigations; M/P = 0.6%/1.1%; 4 patients in the minocycline group and 1 in placebo group had liver function abnormalities thought to be related to drug treatment

In general, drug-related AEs were in keeping with known AEs of minocycline and included headache, dizziness, nausea, diarrhea, abdominal pain, fatigue, pruritus and urticaria. Dizziness, tinnitus and vertigo were higher in the minocycline group compared to the placebo group.

Table No. 54
Significant Drug-related Adverse Events in Phase 2 and 3 studies (N = 1038)

	Minocycline 1 mg/kg N (%) AEs related to treatment	Placebo N (%) AEs related to treatment
Subjects with at least 1 AE	292 (43.3)	154 (42.3)
Ear and Labyrinth Disorders	**2.4%**	**2.2%**
Tinnitus	9 (1.3)	4 (1.1)
Vertigo	7 (1)	3 (0.8)
Eye Disorders	**1.3%**	**2.5%**
Vision blurred	8 (1.2)	6 (1.6)
Eye pruritus	1 (0.1)	0
Gastrointestinal disorders	**17%**	**22%**
Abdominal pain upper	16 (2.4)	13 (3.6)
Diarrhea NOS	29 (4.3)	17 (4.7)
Dyspepsia	3 (0.4)	7 (1.9)
GI pain NIS	30 (4.5)	25 (6.9)
Nausea	59 (8.8)	35 (9.6)
Vomiting NOS	10 (1.5)	4 (1.1)
General Disorders & Administration Site Conditions	**10.4%**	**8%**
Asthenia	3 (0.4)	2 (0.5)
Fatigue	50 (7.4)	18 (4.9)
Malaise	23 (3.4)	18 (2.2)
Investigations	**0.6%**	**1.1%**
ALT increased	1 (0.1)	1 (0.3)
AST increased	2 (0.3)	0
Alk Phosphatase decreased	1 (0.1)	0
Musculoskeletal & Connective tissue disorders	**0.9%**	**1.1%**

Arthralgia	1 (0.1)	2 (0.5)
Neck pain	2 (0.3)	1 (0.3)
Nervous System Disorders	**25.5%**	**23.4%**
Dizziness	55 (8.2)	17 (4.3)
Headache	134 (19.9)	76 (20.9)
Hypoaesthesia	2 (0.3)	0
Migraine	2 (0.3)	0
Somnolence	9 (1.3)	3 (0.8)
Psychiatric Disorders	**4.7%**	**5.2%**
Insomnia	12 (1.8)	7 (1.9)
Mood Alteration NOS	16 (2.4)	9 (2.5)
Skin & Subcutaneous Tissue Disorders	**6.7%**	**5.2%**
Pruritus	29 (4.3)	14 (3.8)
Rash NOS	5 (0.7)	0
Urticaria NOS	8 (1.2)	0
Swelling face	2 (0.3)	0

7.1.5.6 Additional analyses and explorations

Adverse events are analyzed in this section based on the subgroups of age, gender and race in the combined Phase 3 studies. This included 615 subjects treated with minocycline and 309 subjects treated by placebo in the control group.

In the analysis of AEs by age, some AEs that were higher in the minocycline group compared to placebo in those ≥ 18 years of age compared to those < 18 years of age were: fatigue (11.7%/8.9%) and dizziness (10.4%/7%).

In the analysis of AEs by gender, some AEs that were higher in the minocycline group compared to placebo in females compared to males were: dizziness (11.8%/5.7%), fatigue (11.5%/8.8%), and urticaria (2.7%/0.8%).

In the analysis by race, some AEs that were higher in the minocycline group compared to placebo in Whites compared to Non-Whites were: fatigue (10.6%/7.9%) and malaise (4.2%/1.8%).

Table No. 55
Treatment-Emergent AEs by Age Group Phase 3 studies

	Minocycline 1 mg/kg		**Placebo**	
	12 – 17 N = 384	**18 and Over N = 231**	**12 – 17 N = 175**	**18 and Over N = 134**
At least one treatment-emergent event	215 (56.0)	137 (59.3)	90 (51.4)	73 (54.5)
Headache	79 (20.6)	55 (23.8)	35 (20.0)	35 (26.1)
Nausea	36 (9.4)	25 (10.8)	15 (8.6)	19 (14.2)
Fatigue	34 (8.9)	27 (11.7)	13 (7.4)	7 (5.2)
Dizziness	27 (7.0)	24 (10.4)	10 (5.7)	4 (3.0)
Diarrhea	19 (4.9)	14 (6.1)	11 (6.3)	9 (6.7)
Gastrointestinal pain	23 (6.0)	11 (4.8)	10 (5.7)	9 (6.7)

Pruritus	14 (3.6)	17 (7.4)	11 (6.3)	4 (3.0)
Malaise	13 (3.4)	9 (3.9)	4 (2.3)	3 (2.2)
Abdominal pain, upper	18 (4.7)	4 (1.7)	9 (5.1)	1 (0.7)
Nasopharyngitis	20 (5.2)	6 (2.6)	10 (5.7)	1 (0.7)
Mood alteration	8 (2.1)	9 (3.9)	4 (2.3)	2 (1.5)
Insomnia	9 (2.3)	6 (2.6)	5 (2.9)	5 (3.7)
Vomiting	10 (2.6)	4 (1.7)	3 (1.7)	3 (2.2)
Upper respiratory tract infection	7 (1.8)	5 (2.2)	2 (1.1)	3 (2.2)
Somnolence	8 (2.1)	4 (1.7)	2 (1.1)	1 (0.7)
Urticaria	7 (1.8)	3 (1.3)	0	1 (0.7)
Tinnitus	5 (1.3)	3 (1.3)	2 (1.1)	2 (1.5)
Arthralgia	7 (1.8)	2 (0.9)	2 (1.1)	0
Pharyngolaryngeal pain	7 (1.8)	4 (1.7)	5 (2.9)	4 (3.0)
Vertigo	5 (1.3)	2 (0.9)	3 (1.7)	0
Vision blurred	5 (1.3)	3 (1.3)	2 (1.1)	3 (2.2)
Dry mouth	3 (0.8)	4 (1.7)	1 (0.6)	3 (2.2)
Myalgia	5 (1.3)	1 (0.4)	1 (0.6)	2 (1.5)

Source: Sponsor briefing document, Module 2

Table No. 56
Treatment-Emergent AEs by Gender Phase 3 studies

		Minocycline 1 mg/kg	**Placebo**	
		Male Female N=353 N=262	**Male N=173**	**Female N=136**
At least one treatment-emergent event	184 (52.1)	168 (64.1)	173 (49.1)	78 (57.4)
Headache	62 (17.6)	72 (27.5)	32 (18.5)	38 (27.9)
Nausea	36 (9.4)	25 (10.8)	15 (8.6)	19 (14.2)
Fatigue	31 (8.8)	30 (11.5)	8 (4.6)	12 (8.8)
Dizziness	20 (5.7)	31 (11.8)	8 (4.6)	6 (4.4)
Diarrhea	19 (5.4)	14 (5.3)	10 (5.8)	10 (7.4)
Gastrointestinal pain	18 (5.1)	16 (6.1)	9 (5.2)	10 (7.4)
Pruritus	12 (3.4)	19 (7.3)	8 (4.6)	7 (5.1)
Malaise	12 (3.4)	10 (3.8)	4 (2.3)	3 (2.2)
Abdominal pain, upper	14 (4.0)	8 (3.1)	9 (5.2)	1 (0.7)
Nasopharyngitis	18 (5.1)	8 (3.1)	10 (5.8)	1 (0.7)
Mood alteration	7 (2.0)	10 (3.8)	4 (2.3)	2 (1.5)
Insomnia	7 (2.0)	8 (3.1)	6 (3.5)	4 (2.9)

Vomiting	11 (3.1)	3 (1.1)	4 (2.3)	2 (1.5)
Upper respiratory tract infection	6 (1.7)	6 (2.3)	2 (1.2)	3 (2.2)
Somnolence	4 (1.1)	8 (3.1)	1 (0.6)	2 (1.5)
Urticaria	3 (0.8)	7 (2.7)	0	1 (0.7)
Tinnitus	5 (1.4)	3 (1.1)	1 (0.6)	3 (2.2)
Arthralgia	4 (1.1)	5 (1.9)	1 (0.6)	1 (0.7)
Pharyngolaryngeal pain	6 (1.7)	5 (1.9)	5 (2.9)	4 (2.9)
Vertigo	3 (0.8)	4 (1.5)	3 (1.7)	0
Vision blurred	4 (1.1)	4 (1.5)	2 (1.2)	3 (2.2)
Dry mouth	3 (0.8)	4 (1.5)	1 (0.6)	3 (2.2)
Myalgia	3 (0.8)	3 (1.1)	2 (1.2)	1 (0.7)

Source: Sponsor briefing document, Module 2

Table No. 57
Treatment-Emergent AEs by Race Phase 3 studies

	Minocycline 1 mg/kg		**Placebo**	
	White N=451	**Non-White N=164**	**White N=218**	**Non-White N=91**
At least one treatment-emergent event	264 (58.5)	88 (53.7)	121 (55.5)	42 (46.2)
Headache	100 (22.2)	34 (20.7)	50 (22.9)	20 (22.0)
Nausea	52 (11.5)	9 (5.5)	25 (11.5)	9 (9.9)
Fatigue	48 (10.6)	13 (7.9)	15 (6.9)	5 (5.5)
Dizziness	38 (8.4)	13 (7.9)	13 (6.0)	1 (1.1)
Diarrhea	24 (5.3)	9 (5.5)	16 (7.3)	4 (4.4)
Gastrointestinal pain	27 (6.0)	7 (4.3)	13 (6.0)	6 (6.6)
Pruritus	20 (4.4)	11 (6.7)	13 (6.0)	2 (2.2)
Malaise	19 (4.2)	3 (1.8)	6 (2.8)	1 (1.1)
Abdominal pain, upper	19 (4.2)	3 (1.8)	9 (4.1)	1 (1.1)
Nasopharyngitis	20 (4.4)	6 (3.7)	8 (3.7)	3 (3.3)
Mood alteration	12 (2.7)	5 (3.0)	5 (2.3)	1 (1.1)
Insomnia	13 (2.9)	2 (1.2)	9 (4.1)	1 (1.1)
Vomiting	13 (2.9)	1 (0.6)	4 (1.8)	2 (2.2)
Upper respiratory tract infection	8 (1.8)	4 (2.4)	4 (1.8)	1 (1.1)
Somnolence	9 (2.0)	3 (1.8)	1 (0.5)	2 (2.2)
Urticaria	9 (2.0)	1 (0.6)	0	1 (1.1)
Tinnitus	6 (1.3)	2 (1.2)	3 (1.4)	1 (1.1)
Arthralgia	6 (1.3)	3 (1.8)	2 (0.9)	0
Pharyngolaryngeal pain	8 (1.8)	3 (1.8)	8 (3.7)	1 (1.1)

Vertigo	7 (1.6)	0	3 (1.4)	0
Vision blurred	6 (1.3)	2 (1.2)	3 (1.4)	2 (2.2)
Dry mouth	5 (1.1)	2 (1.2)	2 (0.9)	2 (2.2)
Myalgia	6 (1.3)	0	1 (0.5)	2 (2.2)

Source: Sponsor briefing document, Module 2

7.1.6 Less Common Adverse Events

Following are clinically significant less common adverse events in combined Phase 2 and 3 studies.

1) Myalgia was seen in 7/674 (1%) patients in the minocycline group.
2) Dry mouth was seen in 7/674 (1%) of patients in the minocycline group.
3) Acne and aggravated acne were seen in 1/674 (0%) patients each in the minocycline group; both were reported to be severe AEs.
4) Sunburn was seen in 1/674 (0%) in the minocycline group; reported to be a severe AE.

Photosensitivity, including sunburn reaction is a labeled AE for minocycline; myalgia, dry mouth and acne are not labeled AEs.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory (lab) assessments performed at baseline and treatment completion included

- compete blood count (CBC)
- metabolic profile – sodium, potassium, chloride, blood urea nitrogen (BUN), serum creatinine
- liver function tests (LFTs) – alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase, bilirubin
- Thyroid function tests (TFTs) – triiodothyronine (T3), tetraiodothyronine (T4) and thyroid stimulating hormone (TSH)
- Antinuclear antibodies (ANA)

A blood sample for future evaluations was also drawn: C-reactive protein, anti-Smith and anti-double-stranded DNA, auto-antibodies anti-Sjogren's syndrome, anti-ribonuclear protein, complement factors, antihistone and a hepatitis panel. Clinically significant findings at end of treatment were recorded as AEs. Subjects were to be monitored until results returned to normal or were no longer considered clinically significant.

For the subset of patients enrolled in the 2-year Growth Study, baseline height and left wrist X-rays were conducted. Height was to be repeated every 3 months and X-rays annually.

No drug concentrations were measured in the pivotal clinical studies.

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

Table No. 58
Subjects with lab abnormalities Phase 2 and 3 Studies-ITT Population

	n/N (%)	
Parameter	Minocycline 1 mg/kg N=674	Placebo N=364
GGT	1/611 (0.2)	3/302 (1.0)
ALT	39/586 (6.7)	15/335 (4.8)
AST	10/621 (1.6)	3/338 (0.9)
T3	12/505 (2.4)	10/252 (4.0)
Thyroxine	3/565 (0.5)	1/283 (0.4)
TSH	4/555 (0.7)	0/282
ANA	2/576 (0.3)	0/290

Source: Sponsor briefing document; Module 2

Lab abnormalities at day 84 in subjects who had normal values at baseline in the ITT population in Phase 2 and 3 studies are as follows:

Electrolytes – There were no significant changes in sodium, potassium, chloride and creatinine values across both minocycline (M)/Placebo (P) groups in all studies. For BUN, 13/611 (2%) in M group versus 5/334 (2%) in the P group reported high values at day 84.

Liver function tests

Alkaline phosphatase - 4/546 (0.7%) in the M group versus 3/299 (1%) in the P group reported high values at day 84

GGT – 1/611 (0.2%) subjects in the M group versus 3/286 (1%) in the P group reported high values at day 84

ALT – 39/586 (7%) subjects in the M group versus 15/315 (5%) in the P group reported high values at day 84

AST – 10/621 (2%) subjects in the M group versus 3/338 (1%) in the P group reported high values at day 84

Total bilirubin – 15/609 (2%) subjects in the M group versus 7/330 (2%) in the P group reported high values at day 84

Thyroid function tests

T3 – 12/505 (2%) subjects in the M group versus 10/252 (4%) in the P group reported high values at day 84. No subjects in either group reported low values at day 84.

Thyroxine (T4) – 3/565 (0.5%) subjects in the M group versus 1/283 (0.4%) in the P group reported high values at day 84.
2/565 (0.4%) subjects in the M group versus 0/283 subjects in the P group reported low values on day 84.

TSH – 4/555 (0.7%) subjects in the M group versus 0/282 reported high values at day 84
2/555 (0.4%) subjects in the M group versus 1/282 (0.4%) subjects in the P group reported low values on day 84.

Blood counts

Hemoglobin – 5/580 (0.9%) subjects in the M group versus 6/317 (1.9%) subjects in the P group reported low values on day 84

Red blood cells – 11/602 (1.8%) subjects in the M group versus 16/318 (5%) subjects in the P group reported low values on day 84

White blood cells – 11/595 (1.8%) subjects in the M group versus 2/322 (0.6%) subjects in the P group reported low values on day 84.
14/595 (2.4%) subjects in the M group versus 11/322 (3.4%) subjects in the P group reported low values on day 84

Platelets – 5/589 (0.8%) subjects in the M group versus 0/308 subjects in the P group reported low values at day 84.

ANA

2/576 (0.3%) subjects in the M group versus 0/290 in the P group reported high values at day 84

Conclusions:

In 12-week studies, most common lab abnormalities in the minocycline group were elevations of LFTs, i.e. ALT and AST. There were also slight elevations in TSH, thyroxine and ANA values. None of these patients exhibited clinically relevant signs and symptoms and most AEs were considered mild and resolved. Overall, a small proportion of subjects exhibited lab abnormalities in the 12-week studies and these were all labeled AEs of minocycline.

While lab abnormalities and associated clinical symptoms were not commonly seen in 12-week studies, this is not necessarily reflective of long-term treatment; the label should convey that prescribers should be aware of these AEs and monitor patients periodically as indicated.

Further lab assessments - open-label safety study MP-0104-07

Subjects who completed the 12 week studies were given the option of enrolling into the 2 year open-label, safety study where patients were to receive minocycline 1 mg/kg/day for 12 week intervals as needed for flare-ups. Please refer to Section 7.1.12 for further discussion about this study and results obtained at time of interim report as well as a safety update.

7.1.7.3 Standard analyses and explorations of laboratory data

Comparative trial data analyses were not performed since Solodyn was not compared to the immediate-release formulation of minocycline.

7.1. 7.4 Additional analyses and explorations

Analyses of AEs related to lab abnormalities for MP-0104-07 that include dose, time dependency and those that take into account other factors will be conducted once final results are obtained for this open-label, 2-year study.

7.1.7.5 Special assessments

Tests for autoimmunity are discussed under Section 7.1.12 –Special Safety Studies/Study MP-0104-07.

7.1.8 Vital Signs

There were no safety-related observations of changes in vital signs in clinical studies for Solodyn.

7.1.8.1 Overview of vital signs testing in the development program

There were no safety related changes in assessment of vital signs in the integrated safety analysis of clinical studies.

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

Not conducted for this NDA

7.1.8.3 Standard analyses and explorations of vital signs data

Not conducted for this NDA

7.1.9 Electrocardiograms (ECGs)

Not conducted for this NDA

7.1.10 Immunogenicity

Not applicable.

7.1.11 Human Carcinogenicity

No malignancies were reported during any of the clinical studies for Solodyn as part of this NDA. Per the interim report and safety update, no malignancies have been reported in the ongoing 2-year, open-label safety study MP-0104-07.

7.1.12 Special Safety Studies

This section includes the following studies:

- MP-0104-07, the open-label safety study (*ongoing*)
- MP-0104-13 and MP-0104-16, the two spermatogenesis studies

MP-0104-07: Subjects who completed the 12 week studies were given the option of enrolling into the 2 year open-label, multi-center, uncontrolled safety study where patients were to receive only minocycline 1 mg/kg/day for 12 week intervals plus topical treatment as needed for flare-

ups of their acne. Safety assessments arising from long-term use of minocycline were to be obtained on completion of this study. At the time of NDA submission, study MP-0104-07 was ongoing; this review discusses study design and incorporates study results at two time-points as relevant; the Interim Report submitted with original NDA that spanned time period 5/26/204 to 12/31/2004 and the Safety Update report that spanned time period 12/31/2004 to 7/31/2005 (submitted to Agency on 11/16/05).

Study MP-0104-07 (ongoing)

Study title: An open-label safety study of a new formulation of minocycline for treatment of moderate-severe acne.

Study objectives: *Primary* objective was to assess long-term safety of extended-release minocycline HCl tablets as monotherapy for acne vulgaris or with other concomitant medications. *Secondary* objective was to assess patterns of use of the new formulation of minocycline by following circumstances for treatment discontinuation and re-initiation of therapy.

Study period: 5/26/2004 through 12/31/2004 (interim cut-off).

Study centers: 25 US centers.

Number of subjects: 300 planned; 345 enrolled and analyzed. Enrollment complete on 12/31/2004 with 233 subjects who had been treated with minocycline and 112 subjects who had been treated with placebo in Phase 3 studies.

Inclusion criteria:

1) All subjects who participated and completed one of the two Phase 3 studies MP-0104-04 and MP-0104-05 and were compliant with study requirements (including inclusion/exclusion criteria for those studies).
2) Subjects at least 12 years old at time of Phase 3 study entry (baseline).
3) Weight 45 kg to 136.36 kg (99 to 300 lbs).
4) Moderate-severe inflammatory facial acne vulgaris with $\geq$25 and $\leq$75 inflammatory facial lesions (papules/pustules) and < 2 nodules/cysts on the face.
5) In good physical health.
6) Submitted informed consent, or if < 18 years, whose parent or legal guardian had submitted informed consent.
7) Willing to comply with study instructions.

Exclusion Criteria:

Subjects were excluded from the study if at the Day 84 visit of the Phase 3 study:
1. Showed non-liver function test (LFT) clinical laboratory values outside the normal range, determined to be of clinical significance.
2. Showed LFT values (alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transpeptidase) greater than 1.5 times the upper limit of normal.
3. Showed a positive pregnancy test.
4. Showed an AE which, in the investigator's judgment, should preclude enrollment of the subject in the long-term trial.

Study drug:
All subjects received minocycline HCl as 45, 90 or 135 mg caplets. Daily dose adjusted so as to receive a once-daily dose equal to approximately 1 mg/kg (range 0.76 mg/kg - 1.5 mg/kg) for up to 2 years. Subjects allowed to use concomitant topical acne medication and allowed to start and stop treatment as their acne status changes.

Study design:
This is an ongoing, 2 year open-label, multi-center, uncontrolled safety study of modified-release minocycline conducted at 25 centers in the US. Subjects completing Phase 3 studies MP-0104-04 and MP-0104-05 have been given the chance to enroll in this study at the day 84 visit; the day 84 will be coincident with day 1 of the long-term safety study.

Study treatment determination is done by the investigator based on the Evaluator's Global Severity Scale (EGSS) assigned at each visit. Solodyn tablets at 1 mg/kg/day are prescribed if the EGSS is mild, moderate or severe. If the EGSS is clear or almost clear, treatment is to be discontinued by the investigator and monthly follow-up visits continued. If treatment is continued, a rationale for continuing therapy is required from the sponsor.

Study visits:
Study visits are once monthly for 24 months, when study medication provided in bottles of 30 tablets. At each monthly visit, procedures include: query regarding AEs, concomitant medications, urine pregnancy test, EGSS and investigator's rationale for continuing treatment.

On day 1 and every 3rd month (months 3, 6, 9, 12, etc.), subjects are to be weighed, a physical exam (including skin for blue-black discoloration of scars and gums, fundus, joint exam for pain and stiffness and vestibular dysfunction) is to be done and labs are to be drawn.

Subset of subjects enrolled in MP-0104-07 is to be evaluated for linear growth. On day 1 and every 3rd month, subjects will be measured for height using a Harpenden stadiometer and left hand and wrist X-rays will be taken at months 12 and 24.

Safety evaluation is based on review of AEs, physical exam findings and clinical labs.

Efficacy Assessments:
The Evaluator's Global Severity Score is a static assessment, independent of baseline score.

Safety Assessments:
This includes monitoring of AEs, (local and systemic), serious AES as well as monitoring labs. All AEs occurring after minocycline administration will be recorded. AEs are to be coded using MedDRA.

Lab Assessments:
Performed every third month and include: CBC, BUN, creatinine, ALT, AST, GGT, alkaline phosphatase, bilirubin and TFTs (TSH, T3 and T4) and ANA. Clinically significant labs will be recorded as AEs and all subjects with abnormal labs will be followed till normal.

Table No. 59
EGSS for Study MP-0104-07

Score	Grade	Description
0	Clear	Normal, clear skin with no evidence of acne vulgaris
1	Almost clear	Rare noninflammatory lesions present, with rare non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red)
2	Mild	Some noninflammatory lesions are present, with few inflammatory lesions (papules/pustules only; no nodulocystic lesions)
3	Moderate	Noninflammatory lesions predominate, with multiple inflammatory lesions evident: several to many comedones and papules/pustules, and there may or may not be one small nodulocystic lesion
4	Severe	Inflammatory lesions are more apparent, many comedones and papules/pustules, there may or may not be a few nodulocystic lesions
5	Very Severe	Highly inflammatory lesions predominate, variable number of comedones, many papules/pustules and many nodulocystic lesions

Source: Sponsor Briefing Document, Module 5

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Table No. 60
Study Schedule for MP-0104-07

Study Day	Initial Day 1	Monthly*	Months 3, 6, 9, ..., 24	Months 12 and 24
Informed consent	X			
Physical Examination†	X		X	X
Laboratory Evaluations‡ §	X		X	X
Urine Pregnancy Test‡	X	X	X	X
Evaluator's Global Severity Score‡	X	X	X	X
Distribute/Collect Study Drug‖	X	X	X	X
Concomitant Medications	X	X	X	X
Adverse Events¶		X	X	X
Weight Measurement	X		X	X
Height Measurement#	X		X	X
Hand/Wrist X-Rays**				X

* Monthly visits occur at intervals of 30 days ± 2 days after from Day 1.
† Standard physical examination in addition to a skin examination for blue-black discoloration of scars and gums, a funduscopic examination, examination for joint/pain stiffness, and testing for vestibular dysfunction.
‡ Procedure completed for Day 84 of the Phase 3 study is used as the initial procedure for the long-term safety study.
§ Complete blood counts (CBC), ANA, serum creatinine, blood urea nitrogen (BUN), liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and bilirubin), and thyroid tests (thyroid stimulating hormone [TSH], T_3 [triiodothyronine, and T_4 [tetraiodothyronine]).
‖ Study drug is distributed when the EGSS is mild, moderate, or severe. When the EGSS is found to be clear or almost clear, the investigator could consider whether or not to discontinue minocycline therapy. In the event that the minocycline is discontinued, therapy could be recommenced if needed at the next monthly visit.
¶ AEs not resolved on Day 84 of the Phase 3 study were followed into the long-term safety study.
# For subjects enrolled in the linear growth substudy, height measurements are performed using a Harpenden Stadiometer.
** For subjects enrolled in the linear growth substudy, AP X-rays of the left hand and wrist are performed at Month 12 and Month 24. These subjects must have had a Baseline X-ray prior to the start of study medication in the Phase 3 study.

Source: Sponsor Briefing Document, Module 5

Statistical methods:

Safety evaluation – AEs will be listed individually and summarized by organ class and preferred term according to MedDRA. AEs will be categorized as treatment-emergent AEs, AEs by maximum severity, by relationship to study drug and by race, age and sex. Descriptive summary statistics for lab values and their associated change from baseline is to be presented for each parameter.

Interim Clinical Study Report for MP-0104-07 (data from 5/26/04 to 12/31/04); Subject Disposition

Interim report is based on data from beginning of study 5/26/04 to 12/31/04 for subjects who had been on minocycline for approximately 1 year. Study enrollment was completed by 12/20/2004 with total of 345 subjects, of which 233 had been on minocycline and 112 on placebo.

As of 12/31/2004, of the 345 subjects enrolled in the study, 299 (86.7%) were ongoing and 46 (13.3%) had discontinued. Out of the 46 who discontinued, 33 were in the group that had originally been on minocycline and 13 had been on placebo in Phase 3 studies. Reasons for discontinuation were as follows: adverse event M/P = 9 (4%)/1 (0%), consent withdrawn M/P = 9 (4%)/6 (5%), lost to follow-up M/P = 9 (4%)/ 3 (3%), Other M/P = 6 (3%)/3 (3%). Other reasons included lack of efficacy or worsening of acne.

More patients in the minocycline group discontinued due to adverse event (discussed in adverse events leading to study discontinuation)

Table No. 61
Subject Disposition N (%) per Interim Report for MP-0104-07

	Double-Blind Treatment Group		
	Minocycline N=233	Placebo N=112	Total N=345
Safety Population	233 (100.0)	112 (100.0)	345 (100.0)
Visit Attendance			
Initial	233 (100.0)	112 (100.0)	345 (100.0)
Month 1	223 (95.7)	103 (92.0)	326 (94.5)
Month 2	201 (86.3)	94 (83.9)	295 (85.5)
Month 3	146 (62.7)	70 (62.5)	216 (62.6)
Month 4	117 (50.2)	58 (51.8)	175 (50.7)
Month 5	78 (33.5)	32 (28.6)	110 (31.9)
Month 6	46 (19.7)	21 (18.8)	67 (19.4)
Month 7	4 (1.7)	4 (3.6)	8 (2.3)
Subjects Currently On Study	**200 (85.8)**	**99 (88.4)**	**299 (86.7)**
Subjects Discontinued			
Adverse Event	9 (3.9)	1 (0.9)	10 (2.9)
Consent Withdrawn	9 (3.9)	6 (5.4)	15 (4.3)
Lost to Follow-Up	9 (3.9)	3 (2.7)	12 (3.5)
Other	6 (2.6)	3 (2.7)	9 (2.6)
Total	33 (14.2)	13 (11.6)	46 (13.3)

Note: Double-blind treatment group is the group to which the subjects were randomized in the Phase 3 studies.

Source: Sponsor Briefing Document, Module 5

Demographics and Baseline characteristics:

Overall, the mean age of patients was 18.9 years, male subjects were > female subjects (60%/40%) and the majority of subjects were White (79%), followed by Hispanic (9%) and Black (8.1%).

Safety Evaluation:
This incorporates relevant results from the safety update provided to the Agency on 11/16/05 and spans the time period 12/31/2004 to 7/31/2005. In order to highlight minocycline-related AEs, for subjects treated with active treatment during Phase 3 studies, AEs were included in safety analysis; however, AEs reported for subjects in placebo groups in Phase 3 studies were not included in this analysis.

Adverse Events:
197 out of 345 (57%) subjects treated in MP-0104-07 up to 12/31/2004 had experienced at least 1 AE in the first 6 months of active treatment, including those on minocycline in double-blind phase of Phase 3 study.

Table No. 62
Adverse events while on minocycline in first 6 months (Interim Report)

	N (%)
Subjects Treated	**345**
Subjects with AE	197 (57.1)
Number of AEs	520
Subjects with Treatment-Related AE	123 (35.7)
Subjects with Severe AE	14 (4.1)
Subjects Discontinued Due to AE	12 (3.5)
Subjects with Serious AE	1 (0.3)

Source: Sponsor briefing document, Module 5

Over the 12 week treatment period in Phase 3 studies, out of those who entered the long-term safety study, 53.6% of subjects in the minocycline group and 61.6% in the placebo group had reported AEs. In the first 6 months of the study, subjects who reported AEs were higher in previous minocycline groups (48.1%) compared to placebo groups (42%). Most commonly reported AEs with onset in first 6 months (182 days) of minocycline treatment included headache (18.6%), nausea (10.4%), fatigue (7.2%) and dizziness (6.1%).

Subject retention appears to be progressively declining with duration; number of subjects in the first 6 months was 345, in months 7 to 12, there were 283 subjects and in months 13 to 18, there were 120 subjects. Per the 4-month safety update, the number of subjects with treatment-related AEs and discontinuations due to AEs is highest in subjects who had been in minocycline groups in Phase 3 studies.

AEs occurring in ≥ 5% in Phase 3 studies included headache, nausea, fatigue, dizziness, pruritus, gastrointestinal pain and diarrhea.
AEs occurring in ≥ 2% of subjects in MP-0104-07 were as follows:

- In the first 6 months, AEs in ≥ 2% of subjects across both treatment groups included headache, viral gastroenteritis and nausea. Positive ANA in previous minocycline/placebo subjects = 5/233 (2.1%)/1/112 (0.9%); ALT increased in M/P subjects = 7/233 (3%)/0/112; and AST increased in M/P subjects = 4/233 (1.7%)/0/112. Dizziness in M/P subjects = 3/233 (1.3%)/1/112 (0.9%)
- In months 7 to 12, AEs in ≥ 2% of subjects included headache. ALT increased in M/P subjects = 6/191 (3.1%)/1/92(1.1%); ANA positive in M/P subjects = 4/191 (2.1%)/2/92

92.2%); T3 increased in M/P subjects = 2/191 (1%)/2/92 (2.2%); AST increased in M/P subjects =3/191 (1.6%)/0/92.

Table No. 63
Summary of AEs in Long-Term Safety Study MP-0104-07

	Months 1 to 6		Months 7 to 12	Months 13 to 18
	Previous Minocycline	Previous Placebo	Combined	Combined
Number of Subjects Treated	233	112	283	120
Number of Subjects with at Least 1 Event	112 (48.1)	47 (42.0)	108 (38.2)	5 (4.2)
Number of Subjects with at Least 1 Serious Adverse Event	2 (0.9)	0	3 (1.1)	0
Number of Subjects with At Least 1 Treatment-Related Adverse Event	41 (17.6)	15 (13.4)	24 (8.5)	2 (1.7)
Numbers of Subjects with 1 Severe Adverse Event	8 (3.4)	2 (1.8)	5 (1.8)	0
Number of Subjects Discontinued Due to Adverse Events	16 (6.9)	1 (0.9)	2 (0.7)	0

Source: Sponsor briefing document - Safety Update

Deaths and Other Serious Adverse Events MP-0104-07:
Per safety update, no deaths have been reported for study MP-0104-07. 2 serious AEs have been described. They are as follows:

- A 15 year White female with past history of depression reported exacerbation of symptoms 2 days after initiating minocycline in the double-blind phase; it resolved by day 11 and was not considered related to treatment.
- A 53 year White female reported torn ligaments while on placebo in double-blind phase. Patient underwent surgery and this event was considered unrelated to treatment.

Time to First Occurrence of Select Adverse Events
AEs discussed in this section include those related to vestibular effects, skin effects and other AEs known to be related to minocycline/other tetracycline use. Subjects were analyzed for AE rates and incidence from time of initiation of active treatment, i.e. minocycline (these included initial dose-ranging studies). For subjects receiving placebo in Phase 3 double-blind studies, this meant the first day would have been the first day of receiving minocycline in the open-label safety study MP-0104-07.

Adverse events related to vestibular dysfunction
These included dizziness, nausea, tinnitus, vertigo and vomiting.

Table No. 64
AEs {N (%)} in Long-Term Safety Study MP-0104-07 per Safety Update

	Previous Minocycline (N=233)	Previous Placebo (N=112)	Combined (N=345)
	Months 1 to 6		
At least one treatment-emergent event	112 (48.1)	47 (42.0)	159 (46.1)
Headache	14 (6.0)	6 (5.4)	20 (9.8)
Gastroenteritis, viral	8 (3.4)	3 (2.7)	11 (3.2)
Pharyngolaryngeal pain	8 (3.4)	1 (0.9)	9 (2.6)
Nausea	5 (2.1)	6 (5.4)	11 (3.2)
Alanine aminotransferase increased	7 (3.0)	0	7 (2.0)
Antinuclear antibody positive	5 (2.1)	1 (0.9)	6 (1.7)
Cough	5 (2.1)	1 (0.9)	6 (1.7)
Joint sprain	4 (1.7)	1 (0.9)	5 (1.4)
Wisdom teeth removal	4 (1.7)	1 (0.9)	5 (1.4)
Sinusitis	3 (1.3)	2 (1.8)	5 (1.4)
Aspartate aminotransferase increased	4 (1.7)	0	4 (1.2)
Dizziness	3 (1.3)	1 (0.9)	4 (1.2)
Vomiting	0	4 (3.6)	4 (1.2)
	Months 7 to 12		
	N=191	**N=92**	**N=283**
At least one treatment-emergent event	72 (37.7)	36 (39.1)	108 (38.2)
Headache	7 (3.7)	3 (3.3)	10 (3.5)
Alanine aminotransferase increased	6 (3.1)	1 (1.1)	7 (2.5)
Antinuclear antibody positive	4 (2.1)	2 (2.2)	6 (2.1)
Triiodothyronine increased	2 (1.0)	2 (2.2)	4 (1.4)
Aspartate aminotransferase increased	3 (1.6)	0	3 (1.1)
Acne	2 (1.0)	2 (2.2)	4 (1.4)
Contact dermatitis	3 (1.6)	1 (1.1)	4 (1.4)
Dizziness	1 (0.5)	3 (3.3)	4 (1.4)
Nasal congestion	0	4 (4.3)	4 (1.4)
Pharyngolaryngeal pain	3 (1.6)	1 (1.1)	4 (1.4)
Vomiting	3 (1.6)	1 (1.1)	4 (1.4)
Dyspepsia	2 (1.0)	2 (2.2)	4 (1.4)
Abdominal pain, upper	1 (0.5)	2 (2.2)	3 (1.1)
Cough	1 (0.5)	2 (2.2)	3 (1.1)
Sinus congestion	2 (1.0)	1 (1.1)	3 (1.1)
Sinusitis	3 (1.6)	0	3 (1.1)
Herpes simplex	3 (1.6)	0	3 (1.1)
	N=191	**N=92**	**N=283**
Fatigue	2 (1.0)	1 (1.1)	3 (1.1)
Arthralgia	2 (1.0)	1 (1.1)	3 (1.1)
Influenza	2 (1.0)	1 (1.1)	3 (1.1)
Joint sprain	3 (1.6)	0	3 (1.1)

Source: Sponsor Briefing document - Safety Update

Although this is a preliminary report, the incidence of vestibular AEs appeared to decrease over the course of the therapy and was highest in the 3 m/kg group (Phase 2 dose-ranging study). Interestingly, for those who were on placebo in the double-blind Phase 3 study, the incidence of first occurrence of vestibular AEs remained low, even during the first few weeks of therapy. The

incidence in those who had been on minocycline in Phase 3 double blind studies remained higher than those who had been on placebo even as study duration increased.

Table No. 65
Number (%) of subjects with Select Adverse Events by time to First Occurrence while on Minocycline; Days 1 to 28

	Active Days 1 - 28				
	Placebo N=364	Previous Placebo 1 mg/kg N=112	1 mg/kg N=672	2 mg/kg N=56	3 mg/kg N=59
Vestibular Effects	**50 (13.7)**	**1 (0.9)**	**98 (14.6)**	**18 (32.1)**	**23 (39.0)**
Nausea	36 (9.9)	1 (0.9)	52 (7.7)	9 (16.1)	12 (20.3)
Dizziness	16 (4.4)	1 (0.9)	48 (7.1)	12 (21.4)	13 (22.0)
Vomiting	3 (0.8)	0	8 (1.2)	0	2 (3.4)
Tinnitus	3 (0.8)	0	4 (0.6)	1 (1.8)	2 (3.4)
Vertigo	2 (0.5)	0	7 (1.0)	1 (1.8)	3 (5.1)
Skin Effects	**14 (3.8)**	**0**	**36 (5.4)**	**3 (5.4)**	**4 (6.8)**
Pruritus	13 (3.6)	0	25 (3.7)	3 (5.4)	3 (5.1)
Urticaria	1 (0.3)	0	9 (1.3)	1 (1.8)	1 (1.7)
Dermatitis	0	0	2 (0.3)	0	0
Rash	0	0	9 (1.3)	0	1 (1.7)
Other Effects*					
Headache	68 (18.7)	1 (0.9)	128 (19.0)	18 (32.1)	23 (39.0)
Arthralgia	2 (0.5)	1 (0.9)	5 (0.7)	0	0
Myalgia	4 (1.1)	0	4 (0.6)	2 (3.6)	0
Lymphadenopathy	1 (0.3)	1 (0.9)	0	0	0

* Events listed as other effects are associated with various unrelated body systems.

Source: Sponsor briefing document – Safety Update

Table No. 66
Number (%) of subjects with Select Adverse Events by time to First Occurrence while on Minocycline; Days 29 - 84

	Active Days 29 - 84						
	Placebo N=353	Previous Placebo 1 mg/kg N=110	1 mg/kg N=652	2 mg/kg N=53	3 mg/kg N=55	Days 85 – 182 Combined N=714*	Days > 182 Combined N=306
Vestibular Effects	**11 (3.1)**	**1 (0.9)**	**29 (4.4)**	**2 (3.8)**	**1 (1.8)**	**11 (1.5)**	**10 (3.3)**
Nausea	5 (1.4)	1 (0.9)	10 (1.5)	0	1 (1.8)	7 (1.0)	4 (1.3)
Dizziness	1 (0.3)	0	10 (1.5)	1 (1.9)	0	3 (0.4)	4 (1.3)
Vomiting	6 (1.7)	1 (0.9)	6 (0.9)	1 (1.9)	1 (1.8)	4 (0.6)	3 (1.0)
Tinnitus	1 (0.3)	0	6 (0.9)	1 (1.9)	0	0	0
Vertigo	1 (0.3)	0	1 (0.2)	0	0	0	0
Skin Effects	**3 (0.8)**	**0**	**11 (1.7)**	**1 (1.9)**	**0**	**5 (0.7)**	**8 (2.6)**
Pruritus	3 (0.8)	0	9 (1.4)	0	0	2 (0.3)	1 (0.3)
Urticaria	0	0	1 (0.2)	1 (1.9)	0	1 (0.1)	0
Dermatitis	0	0	1 (0.2)	0	0	2 (0.3)	6 (2.0)
Rash	0	0	0	0	0	0	1 (0.3)
Other Effects†							
Headache	14 (4.0)	3 (2.7)	22 (3.4)	5 (9.4)	2 (3.6)	11 (1.5)	7 (2.3)
Arthralgia	0	0	5 (0.8)	0	0	1 (0.1)	3 (1.0)
Myalgia	0	0	3 (0.5)	0	0	2 (0.3)	0
Lymphadenopathy	0	0	1 (0.2)	0	0	0	1 (0.3)

* The N of 714 includes those subjects in the 1 mg/kg group who completed the randomized controlled trial at a time point beyond Day 84 but who did not continue into the long-term safety trial.
† Events listed as other effects are associated with various unrelated body systems.

Source: Sponsor briefing document – Safety Update

Skin effects:
These included pruritus, urticaria, dermatitis and rash and the highest incidence was seen in the 3 mg/kg group (Phase 2 dose-ranging study). Incidence of skin events appeared to decline over time in the active groups except for dermatitis.

Although it appeared that in general the incidence of AEs appeared to decrease as study duration progressed, a final assessment of incidence of AEs over a course can only be made after study completion.

Adverse events leading to treatment discontinuation as of 7/31/05:
Per the 4-month Safety Update, as of 7/31/2005, 19 subjects receiving minocycline had discontinued due to AEs. Sixteen (16) of the 19 subjects discontinued due to adverse events with onset during the first 182 days of active treatment; 3 subjects discontinued due to adverse events with onset during the second 6 months of treatment (i.e., after 182 days).

- 7 subjects discontinued due to elevated liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and/or gammaglutamyl transpeptidase [GGT])
- 6 subjects discontinued due to positive antinuclear antibodies (ANA)
- 1 subject discontinued due to dizziness and nausea
- 1 subject discontinued due to dizziness and headache
- 1 subject discontinued due to constipation
- 1 subject discontinued due to headache, mood swings, and flatulence
- 1 subject discontinued due to worsening acne
- 1 subject discontinued due to non-Hodgkin's lymphoma.

Most AEs described above are included in the minocycline label; the label should include lab monitoring for AEs associated with minocycline therapy.

Lab Abnormalities
Labs that were of interest included LFTs, ANAs and TFTs. Time to first occurrence of abnormalities in these labs is discussed below.

Liver function
Interim study results show that LFT abnormalities were higher in the minocycline groups than placebo. For those who had been on placebo in earlier double-blind Phase 3 studies and then started on minocycline 1 mg/kg, the incidence of lab abnormalities increased, however, as study duration progressed, the overall incidence of LFT abnormalities was still higher in those on minocycline since the inception of Phase 3 double-blind studies.

Preliminary results indicate that abnormalities in AST and GGT values appeared to be increasing as study duration progressed while there appeared to be a general trend towards improvement in other LFT values.

Antinuclear Antibodies
The number of subjects with positive ANA fluctuated over the course of the study, and was somewhat higher in those who had previously been on placebo before switching to minocycline.

Table No. 67
Number (%) of subjects with LFT Abnormalities - Time to First Occurrence

	ALT	AST	GGT	ALT/AST Ratio	Any Liver Function Test
Placebo					
Weeks 0 to 14	26/281 (9.3)	8/281 (2.8)	4/232 (1.7)	84/281 (29.9)	92/281 (32.7)
Weeks 15 to 28	0/7	0/7	1/4	2/7	1/7
Previous Placebo 1 mg/kg					
Weeks 0 to 14	14/106 (13.2)	4/106 (3.8)	3/106 (2.8)	29/106 (27.4)	36/106 (34.0)
Weeks 15 to 28	2/90 (2.2)	1/90 (1.1)	0/90	5/90 (5.6)	4/90 (4.4)
Weeks 29 to 42	2/80 (2.5)	0/80	0/80	3/80 (3.8)	3/80 (3.8)
Weeks 43 to 56	0/30	0/30	0/30	2/30 (6.7)	1/30 (3.3)
1 mg/kg					
Weeks 0 to 14	78/624 (12.5)	25/624 (4.0)	5/571 (0.9)	157/624 (25.2)	196/624 (31.4)
Weeks 15 to 28	8/224 (3.6)	8/224 (3.6)	1/222 (0.5)	24/224 (10.7)	29/224 (12.9)
Weeks 29 to 42	8/189 (4.2)	2/189 (1.1)	0/189	15/189 (7.9)	12/189 (6.3)
Weeks 43 to 56	7 /152 (4.6)	1/152 (0.7)	2/152 (1.3)	10/152 (6.6)	12/152 (7.9)
Weeks 57 +	2/73 (2.7)	2/73 (2.7)	2/73 (2.7)	3/73 (4.1)	2/73 (2.7)

Source: Sponsor briefing document, Safety Update

Thyroid Function Tests

The number of subjects with abnormal TSH levels increased over time in both treatment groups but was higher in those who had been previously on placebo and then switched to minocycline in the open-label study.

Table No. 68
Number (%) of subjects with Positive ANA or abnormal TSH values - Time to First Occurrence

	TSH	ANA
Placebo		
Weeks 0 to 14	7/231 (3.0)	1/133 (0.8)
Weeks 15 to 28	0/3 (0.0)	
Previous Placebo 1 mg/kg		
Weeks 0 to 14	4/106 (3.8)	1/104 (1.0)
Weeks 15 to 28	5/90 (5.6)	0/89 (0.0)
Weeks 29 to 42	4/80 (5.0)	4/80 (5.0)
Weeks 43 to 56	4/30 (13.3)	0/30 (0.0)
1 mg/kg		
Weeks 0 to 14	18/569 (3.2)	3/351 (0.9)
Weeks 15 to 28	11/219 (5.0)	5/213 (2.3)
Weeks 29 to 42	9/189 (4.8)	1/190 (0.5)
Weeks 43 to 56	7/152 (4.6)	3/152 (2.0)
Weeks 57 and higher	4/73 (5.5)	0/72 (0.0)

ANA = Antinuclear antibody; TSH = Thyroid stimulating hormone.

Source: Sponsor briefing document, Safety Update

These safety results indicate that minocycline is likely to cause abnormalities in LFTs, TFTs and ANA; this is in keeping with its known AE profile. Preliminary results from this study indicate that there were no associated clinical signs or symptoms. However, these labs should be monitored especially in subjects receiving more than one course of minocycline and in any patient manifesting symptoms.

Conclusions (preliminary) for 2-year, open-label safety study MP-0104-07
As this study is still ongoing, following conclusions are preliminary and are based on the interim report and safety update. The interim report indicates that subject retention may not be optimal for this 2-year study (345 subjects enrolled at baseline, 299 subjects ongoing). Most commonly reported AEs within first 6 months included headache, nausea, fatigue and dizziness. AEs leading to discontinuation of treatment included the same as well as elevated LFTs, and positive ANAs. Abnormalities in thyroid function tests were also observed and the number of subjects with abnormal TSH levels appeared to increase over time. Preliminary results indicate that lab abnormalities were not associated with clinical signs or symptoms. However, relevant labs should be monitored especially in subjects receiving more than one course of minocycline and in any patient manifesting symptoms. Overall, these are labeled AEs of minocycline; a final determination of AEs and their outcome will be made upon study completion.

Sponsor safety update as of 1/31/2006
Safety Update for Autoimmunity

Per safety update from the sponsor on 1/31/2006, 202 subjects are currently receiving ongoing therapy with minocycline 1 mg/kg/day in study MP-0104-07. Total duration of exposure ranges from 58 to 100 weeks, with a median duration of 83 weeks on active therapy. Positive ANA at Screening was a criterion for disqualification from enrollment in Phase 3 studies. However, there were 2 protocol restriction violations; 2 subjects who were ANA positive were enrolled in clinical studies, out of which one converted to negative and no subsequent test results are available for another.

Phase 3 and long-term study databases contain 757 subjects with at least one ANA test result, including screening and post-treatment tests. Of these 757 subjects, 31 have had at least one positive-ANA test, of which 24 subjects converted while receiving active minocycline (13 of these subsequently became ANA-negative while continuing on drug) and 7 subjects had a positive ANA test prior to minocycline exposure. 2 of these subjects converted while on minocycline and experienced an infectious disease (infectious mononucleosis in one subject and acute or sub clinical hepatitis infection in two subjects). One subject may have had a false positive ANA test.

Per the safety update and interim report, ANA positive subjects did not demonstrate substantive signs and symptoms of lupus-like illnesses. The average time before seroconverting has been 286 days (range 30 to 567 days). So far, out of the 13 subjects who spontaneously converted to negative ANA while on minocycline, 9 have stayed ANA-negative upon re-testing.

Description of ANA-Positive Subjects:
Per the safety update, majority of subjects were white {92% (22/24)} females and the mean age was 18.5 years with the range being 12 -20 years. Most subjects converted to ANA-positive after having been on minocycline for at least 9 months, but the range was 1 to 20 months.

These are findings from the safety update and complete results will be available after completion of the 2 year long-term safety study. Age range and gender fits in with known epidemiology of lupus syndromes, but while lupus is commonly seen in Black subjects, in this study, White subjects were in the majority. The majority of subjects enrolled in clinical studies were White and studies did not include adequate numbers of non-White subjects.

Table No. 69
Description of 24 ANA-Positive Subjects at Time of Conversion

Gender	N (%) male	9 (37.5%)
	N (%) female	15 (62.5%)
Age	Mean	18.5
Conversion Day	Mean	285.7
	Median	270.5
	Range	30 to 567
Drug Exposure (g)	Mean	19.5
	Median	19.4
	Range	2.4 to 51.3

Source: Sponsor Safety Update 2/16/2006

Conclusions of autoimmunity safety update:

This interim report and safety update for autoimmunity testing with minocycline therapy demonstrates that minocycline therapy can induce serological autoimmune expressions without necessarily inducing clinical signs and symptoms of lupus-like syndromes. This is in keeping with the known AE profile of minocycline; lupus-like syndromes (clinical and serological), autoimmune and drug-induced hepatitis, vasculitis and serum sickness have all been reported to be induced by minocycline. While clinical manifestations of lupus were not manifest per the safety update, this may not necessarily reflect clinical outcome over a longer period.

This study report demonstrates the importance of monitoring for autoimmune syndromes while on minocycline therapy, especially when used over a longer period. While all subjects may not require routine testing, clearly testing should be done in those that manifest clinical signs and symptoms of autoimmunity. It is also important to obtain a thorough medical and family history before starting minocycline therapy and to closely monitor subjects who are on minocycline. It is not entirely clear if minocycline induced autoimmune syndromes are fully reversible; thus it is recommended that minocycline therapy not be initiated in subjects who show clinical or serological manifestations of autoimmunity and that therapy be discontinued in those who seroconvert or show signs and symptoms of autoimmune syndromes while on therapy.

Sub-study of MP-0104-07 - *Linear Growth Study*

Rationale: All tetracyclines are known to form a stable calcium complex in bone-forming tissues and get concentrated in the epiphyseal growth plates of children exposed to these drugs. Since acne vulgaris is considered a chronic indication the sponsor was asked to perform a growth evaluation study as part of the long-term safety study in order to evaluate the potential effects on linear growth in teenagers who may undergo long-term treatment with minocycline.

Study centers: 10 out of the 25 investigational sites for the long-term safety study participated in the growth study.

Study population: Subjects between the 5th and 95th percentile for height; males < 16 years and females < 15 years.

Study design: Those study subjects electing to enroll in this study received a left wrist and hand x-ray (bone age) at baseline prior to receiving study drug and height was measured with a

Harpenden Stadiometer. As part of the long-term safety study, these subjects had height measurements in triplicate every third month and X-rays at months 12 and 24. Bone age is to be interpreted by a single observer. Study parameters include annual growth velocity and predicted adult height determined on the basis of current height and bone age.
Study status: study ongoing. No data submitted at time of interim report.

Studies addressing effects of minocycline on human spermatogenesis (MP-0104-13 & MP-0104-16):

This section covers two studies, MP-0104-13 and MP-0104-16. Both were open-label studies that attempted to assess effects of minocycline on human spermatogenesis.

Rationale - There are concerns that the tetracycline class of antibiotics may have an effect on spermatogenesis and seminiferous tissues. In addition, animal (rat) studies conducted by the sponsor (at much higher doses than human doses) have suggested effects of minocycline on sperm morphology and concentration. Therefore, the sponsor was asked to conduct a well-designed, placebo-controlled, double-blind study to evaluate the effects of minocycline on spermatogenesis from long-term use.

The protocol for MP-0104-13 was submitted to the Agency; this was reviewed in liaison with a consult from the Division of Reproductive and Genito-Urinary Drugs. The sponsor was advised that the protocol was inadequate: it was open-label, there was no placebo arm, and number of subjects was small (n = 30), and there were limitations in sperm sample collections at study visits, etc. The sponsor chose to proceed with the study as originally planned, but according to the sponsor, Hurricane Katrina affected the completion of this study that was being conducted at a single site in Louisiana. Study results are not available for all subjects and case records are apparently destroyed; the sponsor has tried to retrieve as much information as possible given the circumstances.

MP-0104-16 was another open-label cohort study in which single semen samples were obtained from 2 groups of subjects; one that had received minocycline and one that had not. The protocol for this single time-point survey was not submitted to the Agency; thus there was no Agency input in the conduct of this study.

Both studies are likely to yield limited information given the shortcomings described above and are discussed briefly; individual study design is discussed, followed by study results.

Study MP-0104-13
Title: An open-label study to examine the effects of minocycline on spermatogenesis in human males with acne vulgaris.

The primary objective of this study was to investigate the effects of minocycline on sperm count, motility and morphology, while the secondary objective was to investigate effects of minocycline on levels of FSH, LH and testosterone. 30 male subjects with acne vulgaris had been planned for enrollment, but 26 were enrolled at the time of interim analysis. Each subject

received a once-daily dose of 1 mg/kg minocycline for 84 consecutive days and the total duration of the study was 156 days.

Labs at baseline and pre-dose on days 28, 56, 84 and 156 included levels of minocycline, FSH, LH and testosterone. Semen samples (2 samples per subject) for sperm analysis were collected at screening and days 28, 56, 84 and 156.

As mentioned above, this study was being conducted at a single-center in New Orleans, Louisiana and according to the sponsor the study was prematurely terminated due to Hurricane Katrina in August, 2005. Out of the 30 subjects enrolled in this open-labeled, uncontrolled study, data is available for only 14 subjects through the final scheduled visit. End of study files are incomplete for 14 subjects due to premature closure of the study and the inability to retrieve the final case report forms according to the sponsor.

Study MP-0104-16
Title: An open-label cohort study to examine the effects of minocycline on sperm characteristics in males with acne vulgaris.

MP-0104-16 was a multi-center, open-label cohort study of the effects of minocycline on sperm in male subjects who had received either active or placebo treatment. This study was conducted without Agency input and was essentially a survey to assess the effects of minocycline on sperm count, motility and morphology in minocycline-treated and untreated subjects with acne vulgaris 16 years of age and older. 42 subjects participated in this study at 11 investigational sites. Of these, 31 had received minocycline for at least 24 weeks (Cohort 1) and 11 were minocycline naïve (Cohort 2).

Each subject attended a single study visit at a designated lab and provided a semen sample. Sperm analysis included volume of ejaculate, pH, total sperm count, percent of sperm motile, percent of sperm with normal morphology, white blood cell count and red blood cell count. Results were tabulated, and compared descriptively, but no statistical hypotheses were tested.

Study results for MP-0104-13 and MP-0104-16
In both studies, study data was obtained from a very small number of subjects.

Table No.7 1
Number (%) of Subjects with ≥ 50% Reduction in Sperm Count MP-0104-13

	Minocycline 1 mg/kg
	n/N (%)
Day 28	4/21 (19.0)
Day 56	4/19 (21.1)
Day 84	5/14 (35.7)
Day 156	4/12 (33.3)

Source: Sponsor briefing document, Safety Update

Table No. 70
Study Results for MP-0104-13 per 4-month Safety Update

	Total Sperm Count ($\times 10^6$)	Motility (% with Forward Movement)	Morphology (% Normal)
Baseline (N=26)			
Mean(SD)	213.3 (± 134.3)	67.0 (± 8.0)	32.9 (± 12.9)
Range	36.8, 505.3	43.0, 80.5	15.0, 62.0
Day 28 (N=21)			
Mean(SD)	234.7 (± 172.9)	63.4 (±8.9)	30.6 (± 10.2)
Range	2.0, 693.0	40.0, 73.5	15.0, 53.0
Change from Baseline			
Mean(SD)	19.5 (± 105.5)	-4.7 (± 11.1)	-2.6 (± 12.5)
Range	-161.0, 208.7	-35.0, 10.5	-30.0, 21.0
Day 56 (N=19)			
Mean(SD)	204.6 (± 146.1)	63.3 (± 8.6)	32.3 (± 11.9)
Range	17.1, 446.0	49.0, 81.5	15.0, 50.0
Change from Baseline			
Mean(SD)	-15.4 (± 134.2)	-5.3 (± 8.1)	-2.3 (± 15.8)
Range	-317.9, 325.7	-19.0, 16.0	-37.0, 23.0
Day 84 (N=14)			
Mean(SD)	134.7 (±85.0)	60.7 (±11.1)	35.8 (± 15.7)
Range	12.7, 246.4	27.5, 77.5	8.0, 66.0
Change from Baseline			
Mean(SD)	-46.7 (±139.4)	-6.5 (± 14.1)	4.4 (± 12.9)
Range	-302.8, 193.6	-40.5, 12.0	-13.0, 24.0
Day 156 (N=12)			
Mean(SD)	148.8 (±103.4)	57.2 (± 7.1)	30.0 (± 13.4)
Range	10.8, 408.0	37.5, 64.0	8.0, 57.0
Change from Baseline			
Mean(SD)	-66.8 (±101.7)	-12.01 (± 12.6)	-2.8 (± 13.1)
Range	-263.2, 71.7	-43.0, 4.0	-23.0, 19.0

Source: Sponsor briefing document, Safety Update

Table No. 72
Study Results MP-004-16

	Cohort 1 N = 31	Cohort 2 N = 11
Sperm Concentration ($\times 10^6$/mL)		
N	30	11
Mean (SD)	83.7 (105.5)	154.8 (172.8)
n (%) 0 to <20	7 (23)	2 (18)
n (%) 20 to <40	6 (20)	1 (9)
n (%) 40 to <100	8 (27)	2 (18)
n (%) 100 or more	9 (30)	6 (55)
Morphology (% Normal)		
N	22	8
Mean (SD)	38.8 (28.6)	70.6 (27.3)
n (%) 0 to <15	5 (23)	0
n (%) 15 to <50	9 (41)	1 (13)
n (%) 50 to <75	6 (27)	3 (38)
n (%) 75 to 100	2 (9)	4 (50)
Motility (% Normal)		
N	29	10
Mean (SD)	55.0 (22.6)	59.4 (28.9)
n (%) 0 to <25	5 (17)	2 (20)
n (%) 25 to <50	4 (14)	0
n (%) 50 to <75	14 (48)	4 (40)
n (%) 75 to 100	6 (21)	4 (40)

Source: Sponsor briefing document, Module 2

In MP-0104-13, out of the 26 subjects that were enrolled, only 8 had completed the day 84 visit at the time of interim analysis. Per the interim report, data is available for 12 of the 14 subjects who completed the study through day 156.

Data for MP-0104-13 were as follows:

- Sperm concentration decreases over time from a mean of 213.3×10^6 at baseline to a mean of 148.8×10^6 at Day 156. Out of 12 subjects, 1 had an abnormally low count of 10.8×10^6 and upon re-testing, sperm counts were 12 and 32.0×10^6 at 1 and 2 weeks respectively. Another subject had a sperm count of 4.7×10^6 at day164 and 69×10^6 on day 171. (Sponsor subsequently indicated that in the case of the last two subjects, one patient had a history of vasectomy and another had a history of azoospermia).
- Mean percentage of sperm with normal motility was 67% at baseline and was 57% by day 156. At day 156, it was abnormally low for 2 subjects at 37.5% and 38%.
- Mean percentage of sperm with normal morphology was 32.9% at baseline and 30% by day 156. At day 156, one subject had an abnormally low percent change in morphology at 8%.

The number of subjects with $\geq$ 50% reduction in sperm counts declined progressively as duration of therapy progressed.

In MP-0104-16, results for Cohort 1 (minocycline treated subjects from 43 to 68 weeks) compared to Cohort 2 (minocycline-naïve subjects) were as follows:

- 23% (Cohort 1) showed sperm concentration below 20×10^6/mL (Cohort 2 = 18%)
- 23% (Cohort 1) had under 15% of sperm with normal morphology (Cohort 2 = 0%)
- 31% (Cohort 1) had < 50% of sperm with normal motility (Cohort 2 = 20%)

The mean sperm concentration for the minocycline-treated cohort in MP-0104-16 was 83.7×10^6, a value slightly more than 50% of the mean for the minocycline-naïve subjects.
In Study MP-0104-16, the mean percentage of sperm with normal motility was 53.1% in the minocycline-treated subjects and 54% in minocycline-naïve subjects. The percentage of subjects with normal morphology was lower in the minocycline-treated cohort than in the minocycline-naïve cohort (37.1% compared to 62.8%).

Conclusions:

Limited results from these studies indicate that minocycline may have a deleterious effect on human male spermatogenesis. The decrease in sperm concentration and alteration in sperm morphology and motility appeared to co-relate with duration of treatment; the extent to which is affected is not entirely clear. Both studies had compromised study designs, but results obtained are of concern and may have an important implication for male subjects hoping to conceive a child while on minocycline and this would need to be reflected in labeling.

Well-designed studies that help to elucidate effects of minocycline on spermatogenesis are needed. The sponsor has submitted a revised protocol for MP-0104-13 and this has been reviewed in liaison with the Division of Reproductive and Genito-Urinary Drugs.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Minocycline, as other tetracyclines is not known to be associated with withdrawal phenomena/abuse potential. No instances of dug abuse were reported in subjects treated with active or placebo in clinical studies for Solodyn.

Vestibular AEs such as dizziness and vertigo are well known AEs of Minocycline that can impair the ability to drive or operate machinery. This is included in the Warnings section and Information for Patients in the Solodyn label.

7.1.14 Human Reproduction and Pregnancy Data

Minocycline, like other tetracyclines is a known teratogen and has a Pregnancy Category D rating. Pregnant women were exuded from the study and females of child-bearing potential were required to use reliable methods of contraception. Pregnancies occurring during study treatment were required to be followed through delivery to assess outcome.

In MP-0104-04, 5 patients reported pregnancies as described above; 3 were on minocycline and 2 were on placebo. Exposure to study drug was in the first trimester and all patients discontinued treatment upon positive pregnancy results. In the minocycline group, one patient had a spontaneous miscarriage (unavailable for further follow-up), another had an elective abortion at 6 weeks gestation and one patient was lost to follow-up (pregnancy outcome unknown). In the placebo group, one patient was lost to follow up (pregnancy outcome unknown) and one patient had a premature delivery and infant had surgery for patent ductus arteriosus and then passed away due to SIDS.
There were no pregnancies in MP-0104-05.

Table No. 73
Pregnancy Outcomes in Clinical Studies

Study/Subject #	Treatment Arm	Outcome/Comments
MP-0104-04/ # 32/4	Minocycline	Pregnancy on Day 61 [redacted]; discontinued treatment day 66. LMP = 11/29/04. Spontaneous miscarriage o [redacted]. Unavailable for further follow-up.
MP-0104-04/ # 32/22	Minocycline	Completed study per protocol. Pregnancy on day 85 [redacted]. LMP = 10/9/04. Returned for dav 112 visit on 12/6/2004. Elective abortion [redacted]
MP-0104-04/ # 41/25	Minocycline	Completed study per protocol. Pregnancy on day 85 [redacted] Lost to follow-up.
MP-0104-04/ # 42/66	Placebo	Patient took 56 days of study treatment, discontinued from study on day 85 ([redacted] when pregnancy reported. LMP = 9/04. Premature delivery by emergency Cesarean section on [redacted], infant had surgery for patent ductus arteriosus. Infant passed away on [redacted]; cause of death listed as Sudden Infant Death syndrome (SIDS).
MP-0104-04/ # 49/30	Placebo (Minocycline reported by error). Sponsor report on 2/16/2006 mentioned that patient was actually on placebo.	Patient took 58 days of study treatment, discontinued from study on day 58 [redacted] when pregnancy reported. LMP = 8/7/04. Pregnancy ongoing. Lost to follow-up.

LMP = Last menstrual period

In the minocycline group, autopsy results were not available on subjects who had miscarriage/abortion and one was lost to follow-up; unfortunately no further information is available.

Post-marketing data for minocycline exposure during pregnancy:
Please refer to Section 7.2.2.2 (Post-Marketing Experience) for ODS review that discusses minocycline associated congenital anomalies.

7.1.15 Assessment of Effect on Growth

Since all tetracyclines are known to form a stable calcium complex in any bone-forming tissue, there is concern that tetracyclines may be deposited in growing epiphyseal bone plates and affect growth in pediatric subjects. This is especially of concern because acne is commonly seen in teenage age groups and treatment may be long-term for this chronic indication.

To evaluate this concern, the sponsor is conducting a 2-year, open-label growth study in pediatric subjects who are to receive minocycline on a long-term basis for their acne vulgaris. This study is currently ongoing; hence no results are available at time of NDA review.

7.1.16 Overdose Experience

No instances of overdose with the active or placebo drug were described in clinical studies for Solodyn.

The proposed Solodyn label mentions that in case of overdosage, medication should be discontinued and patients treated symptomatically by instituting supportive measures. It also mentions that minocycline is not removed in significant quantities by hemodialysis or peritoneal dialysis.

7.1.17 Postmarketing Experience

Solodyn has never been marketed; hence, there is no post-marketing data available. Minocyline is an old antibiotic that has been marketed for many years and postmarketing data for it has been discussed under literature review and as part of the ODS review in Section 7.2.2.2.

7.2 Adequacy of Patient Exposure and Safety Assessments

Safety for Solodyn (extended-release minocycline) was assessed from clinical studies conducted as part of the drug-development program. These studies were appropriately conducted in subjects 12 years and older since acne vulgaris is not commonly seen in lower age groups. The safety review focused on AEs reported during 12-week Phase 2 and 3 studies, where 674 subjects received minocycline 1 mg/kg and 364 received placebo.

Safety was assessed based on AEs and lab evaluations that took place periodically through the 12 week studies. All local and systemic AEs were collected and AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Although all AEs were reported, AEs of special interest were reported separately; these included AEs that are well known to be

associated with minocycline such as vestibular AEs, hepatotoxicity, autoimmune syndromes, thyroid dysfunction, etc. Although the sponsor had been asked to compare Solodyn to immediate release minocycline for safety purposes, this was not performed by the sponsor.

Lab evaluations were performed appropriately; these include routine labs and also focused on AEs that are known to be associated with minocycline such as lupus-like reactions, hepatotoxicity and thyroid abnormalities.

Subgroup analysis for adverse events was based on age, gender and race in the combined Phase 3 studies. This included 615 subjects treated with minocycline and 309 subjects treated by placebo in the control group. The majority of subjects were White; studies did not include adequate Asian/Pacific Islander or American Indian/Alaskan subjects.

Unresolved safety concerns:

1. Effects of minocycline on human spermatogenesis need to be evaluated by conducting well-controlled studies. The sponsor initiated an open-label study design with no placebo control that was affected by Hurricane Katrina. Limited results obtained form the study showed that there may be deleterious effects of minocycline on spermatogenesis.
2. Minocyline induced 'black thyroid' has been linked in literature reports to cases of papillary thyroid cancer. Non-clinical studies mice and rat carcinogenicity studies are included as post-marketing commitments. Further studies/cautious labeling may be needed depending upon results from these studies.

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

Primary safety data sources for Solodyn included all clinical studies conducted as part of the drug development program.

Please refer to Sections 4 and 7.

7.2.1.1 Study type and design/patient enumeration

Please see Section 4 (Data sources, Review Strategy and Data Integrity) for tabular description of studies

7.2.1.2 Demographics

Subgroup analyses by age, race and gender were done for safety and efficacy studies. Please refer to Section 7.1.5.6 (Integrated Review of Safety).

7.2. 1.3 Extent of exposure (dose/duration)

The sponsor conducted a Phase 2 dose ranging study.

Please see Section 5.3 for further details.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Secondary clinical data for ascertaining safety of minocycline in the treatment of acne was derived from literature reports and the Office of Drug Safety review. The ODS review is discussed in Section 7.2.2.2 and literature reports under Section 7.2.2.3.

7.2.2.1 Other studies

These include two inadequately conducted human spermatogenesis studies - MP-0104-13 and MP-0104-16. Both studies have been reviewed in Section 7.1.12. Limited data available from both suggests that minocycline may have a deleterious effect on male spermatogenesis.

The open-label safety study MP-0104-07 is a 2 year study that is still ongoing; interim results obtained from this study are discussed in Section 7.1.12. A growth study in pediatric subjects is included in this study and is also ongoing.

7.2.2.2 Postmarketing experience

No post-marketing information is available for Solodyn since it is a new extended-release formulation of minocycline. However, minocycline is an old antibiotic that has been used for years for multiple anti-infective indications as well as in the treatment of acne.

Office of Drug Safety (ODS) conducted a review of the post-marketing AEs for minocycline which is discussed in this section. A brief review of literature reports is also included in this section.

Summary of ODS Review of Adverse Events associated with minocycline (3/11/2006):
ODS review was based on AERS reports as well as current literature reports; as of January 20, 2006, the AERS database contained 4795 adverse event reports associated with minocycline use, of which 733 were reports of adverse events in acne.
Modified excerpts from the review are as follows:

1). Deaths with acne indication
As of 1/20/2006, 10 deaths have been reported with minocycline use in the treatment of acne. Causes of death were:

- Acute fulminant hepatic failure in a 12 year old female; drug reaction/rash developed 25 days after starting minocyline; patient died on day 60 from fulminant hepatic failure and associated complications secondary to minocyline therapy.
- Hypersensitivity myocarditis in a 25 year old female; developed three months after initiating minocycline; also had Stevens Johnson syndrome after starting minocyline.
- Suicide in a 20 year old male approximately 6 months after staring minocycline.
- Spontaneous abortion (2). First case was at 13 weeks gestation; second case at 9 weeks gestation.
- No cause identified in 15 year old female; drug rash 1-2 months after starring minocycline.

- Unspecified hepatic reaction in17 year old female at an unknown date after receiving minocycline.
- Unspecified hepatic reaction in a 20 year old female who received minocycline for 154 days.
- Unspecified hepatic reaction in a 31 year old male who received one dose of 200 mg minocycline and died at an unknown date.
- Suicide with "diffusely black thyroid" upon autopsy in a 19 year old male who developed shortness of breath and rapid heart beat two weeks after staring minocycline. Fluoxetine prescribed, minocycline continued and subject shot himself a year later.

A literature report[1] describes another case of 'minocycline-induced black thyroid' in a 24 year old female. This subject had a depressive disorder, with repeated suicide attempts and ultimately committed suicide by gunshot to the head. The paper indicated that depression may have been caused by the minocycline-induced 'black thyroid'.

2. Liver injuries with acne indication:
165 liver injury reports; females/males = 109/54; 9 cases were severe liver injuries. Six of nine cases reported hepatic failures. Ages ranged from 12 to 49 years, with a median of 16 years and time to onset ranged from 1 week to 7 years, although the majority of cases (n = 6) experienced severe liver injury within one month of initiating minocycline. Causes of liver failure (6) included:

- Hypersensitivity syndrome and/or skin eruptions (4)
- Autoimmune hepatitis case (1)
- Unspecified cause (1)

Other 3 liver injury cases included autoimmune hepatitis with cirrhosis, granulomatous hepatitis, and an unspecified hepatitis with jaundice and encephalopathy. 1 pediatric patient died due to fulminant hepatic failure; another patient required emergent liver transplantation for recovery; and 4 patients recovered.

Literature reports[2] suggest two patterns of hepatotoxicity with minocycline use in acne: 1) hypersensitivity reaction with rapid onset within one month of treatment and 2) autoimmune hepatitis with late onset of about a year or more after therapy. Severe liver injury cases that occurred within one month of minocycline therapy were accompanied by skin eruptions and/or hypersensitivity type reactions.

ODS recommendation: 'Hepatotoxicity' section recommended in the Warnings section of the label to include serious liver injury cases, including irreversible drug-induced hepatitis and fulminant hepatic failure (sometimes fatal); autoimmune hepatitis also recommended for inclusion in label.

1 Tsokos M, Schroder S. Black thyroid report of an autopsy case; Int J Legal Med.2005 Sep 6;1-3.
2 Lawrenson RA, Seaman HE, Sundstrom A et al; Liver damage associated with minocycline use in acne. Drug safety 2000; 23: 333-349

3. Lupus/lupus-like syndromes with acne indication

18 cases of lupus/lupus-like syndrome were identified; majority in female (n = 16); ages ranged from 14 to 42 years with a median of 19 years. Time to onset ranged from 2 months to 5 years with a median of 2 years. Most common symptoms were polyarthritis/arthralgia (12), fever (5) and/or rash (3). Concurrent liver involvement was reported in 6 patients (5 had autoimmune hepatitis) and one had pulmonary lupus. Antinuclear antibodies were positive in 11 subjects; majority of patients (61%) reported recovery or improvement upon discontinuation of minocycline and one exhibited positive rechallenge. *Four subjects did not improve despite discontinuation of minocycline.*

4. Skin/Photosensitivity events with acne indication

16 skin events, including 14 cases of skin eruptions and 4 photosensitivity reactions were identified; majority were female (n = 12) and ages ranged from 15 to 65 years, with a median of 22 years. Skin eruptions included Stevens - Johnson syndrome (SJS) (3), erythema multiforme (EM) (4), bullous dermatitis (4) and pustular rash (1).
Eight subjects recovered; two patients with bullous dermatitis did not recover.

ODS recommendation: 'Serious Skin/Hypersensitivity Reaction' section be added under Precautions, to inform prescribing practitioners that post-marketing cases of anaphylaxis and serious skin reactions (such as SJS and EM) have been reported.

5. Anaphylactic reactions with acne indication

6 reports; ages ranged from 15 to 50 years (median = 29 years) and 3 were in females. All except one subject reported anaphylaxis or anaphylactoid reaction after ingesting one dose or on the same day of initiating minocycline. Serious outcomes reported in all 6 cases.

6. Congenital anomalies reported for all indications

Minocycline is labeled as pregnancy category D and its use is not recommended during pregnancy; concerns regarding effects on fetal skeletal and tooth development.

21 reports of congenital anomalies associated with minocycline use were identified, regardless of the indication. 14 women reported minocycline use around the time of conception and/or during their first trimester of pregnancy, and 1 reported drug use during her second trimester. 1 case of possible paternal exposure occurred during the time of conception. The time of minocycline exposure in the five remaining cases was not reported.

15 congenital anomalies (one possibly due to paternal exposure) were reported with live births, with 5 live births reporting limb abnormalities including missing hands and/or reduced forearms. 2 infants died within one week of delivery.

ODS recommendation: 5 post-marketing reports of limb abnormalities including missing hands and/or reduced forearms with minocycline use observed. This is concerning since the animal studies submitted with Solodyn™ demonstrated fetal skeletal malformations occurring in the offspring of rats and rabbits after maternal exposure to minocycline. Pregnancy section of Solodyn™ label should reflect that limb reductions have been reported in the post-marketing setting with minocycline use during pregnancy. This recommendation was consistent with recommendations from the Pregnancy and Lactation labeling team.

Table No. 74
Minocycline- Associated Congenital Anomalies

Infant #	Description of congenital anomalies
1	No right hand
2	Partial left forearm and absent left hand
3	Limb reduction of left forearm possessing rudimentary digits
4	No left hand and part of forearm
5	Dysmorphic features including abnormal face and ears, absent right hand, four fingers of left hand, abnormal toenails, sacral pit, Fallot's tetralogy with trisomy 6, growth retardation
6	Congenital positional talipes
7	Bilateral non varus talipes equinus
8	Right renal hypoplasia and compensated left kidney hyperplasia
9	Right testis teratoma and left testis ectopy
10	Dorsolateral diaphragmatic hernia
11	Ventricular septal defect
12	Anophthalmia, esophageal atresia
13	Microcephaly, absent palate, huge harelip, undeveloped nose, close-set eyes
14	Undefined congenital anomaly

Source: ODS Consult (1/20/2006)

Conclusions of ODS consult:

- Add Hepatotoxicity to Warnings section
- Add Autoimmune Hepatitis to the label
- Add Serious Skin/Hypersensitivity Reaction under Precautions
- Update Pregnancy section to add limb reductions

7.2.2.3 Literature

Following are salient literature reports assessing adverse effects with minocycline use in acne.

1). Side effects of minocycline in the treatment of acne vulgaris 1997 Jul 19;141(29):1424-7; Ned Tijdschr Greneeskd; Hoefnagel JJ, van Leeuwen RL, Mattie H, Bastiaens MT.
This article discussed serious adverse events such as hyperpigmentation, autoimmune disorders (systemic lupus erythematosus, autoimmune hepatitis) and serious hypersensitivity reactions (hypersensitivity syndrome reaction, pneumonitis and eosinophilia and serum-sickness like syndrome) of minocycline in the context of long-term treatment.

2) Comparative safety of tetracycline, minocycline and doxycycline; Arch Dermatol. 1997 Oct; 133(10):1224-30; Shapiro LE, Knowles SR, Shear NH.
This article discussed a study that tried to asses if doxycycline and tetracycline were associated with autoimmune and hypersensitivity syndromes are associated with minocycline. Findings:

- 19 cases of hypersensitivity syndrome reaction (HSR) due to minocycline, 2 due to tetracycline and 1 due to doxycycline

- 11 cases of serum-sickness like reaction due to minocycline, 3 due to tetracycline and 2 due to doxycycline.
- 33 cases of drug-induced lupus attributed to only minocycline
- 40 cases of isolated single organ dysfunction (SOD) due to minocycline, 37 due to tetracycline and 6 due to doxycycline.

Hypersensitivity syndrome reaction, serum-sickness like reaction and single organ dysfunction generally occurred within 4 weeks of therapy; lupus occurred on an average 2 years after initiation of therapy. The article theorized that minocycline metabolism may account for serious AEs observed with the drug.

An article by the same authors in Arch Dermatol 1996 Aug; 132(8):934-9 discussed above AEs and suggested that if minocycline were to be used on a long-term basis, (> 1 year), antinuclear antibody and hepatic transaminase levels be checked at baseline and that re-challenge is not recommended for those who experience these AEs.

3) Minocycline for acne vulgaris: efficacy and safety; Cochrane Database Syst Rev; 2003 ;(1):CD002086
This Cochrane database reviewed 27 randomized clinical trials comparing minocycline to placebo in the treatment of inflammatory lesions of acne. In only two trials, minocycline was found to be superior to other tetracyclines and no evidence was found to support benefits of minocycline in acne resistant to other therapies and dose.

4) Minocycline-induced autoimmune syndromes: an overview. Semin Arthritis Rheum 1999 Jun; 28(6):392-7; Elkayam O, Yaron M, Caspi D.
This article sought to increase awareness of minocycline-induced autoimmune syndromes. It stated that 4 minocycline-induced autoimmune syndromes were described in 82 patients: serums sickness, drug-induced lupus, autoimmune hepatitis and vasculitis. All syndromes with the exception of serum sickness (described as sporadic) occurred in patients treated for acne. Drug induced lupus and hepatitis were the most common (66/82). Generally these syndromes presented after longer use (mean 25.3 months) with the exception of serum sickness that presented shortly after treatment initiation (mean 16 days). Patients with acne were young (mean age 19.7 years) and most frequent symptoms were arthralgia, followed by arthritis, fever and rash. Antinuclear antibodies (63/68 tests) were the most common serological finding. The article concluded that minocycline has the potential to evoke variety of clinical and serological autoimmune expressions and that the number of published reports may underestimate the frequency of this condition.

5) Black pigmentation of bone due to long-term minocycline use; Surgeon 2004 Aug; 2(4):236-7; Pandit S, Hadden W.
This article discussed minocycline-induced dark pigmentation that affected the acromian and pelvis in a patient who used minocycline on a long-term basis for acne rosacea. It also described minocycline as having been described to affect affecting the oral cavity (teeth, mucosa, alveolar bone), skin, nails, eyes and thyroid.

6) Black thyroid: Report of an autopsy case: Int J Legal Med. 2005 Sep 6; 1-3; Tsokos M, Scroder S.
Discussed in Section 7.2.2.2 (Post-marketing experience/ODS Review)

7) Minocycline-induced black thyroid gland: Medical curiosity or a marker for papillary cancer? Current Surgery; Vol 58, Issue 5, Sept-Oct 2001, Pages 470-471; Christian Birkedal, William Tapscott, et al.
This article discussed thyroid cancer associated with minocycline-induced black thyroid gland in 1 case (and described another case of a nodular thyroid goiter in association with black thyroid) and reported that black thyroid syndrome had been reported in 26 other cases. Both patients in the case reports had previously used minocycline for years for acne vulgaris. The article thus reported a total of 28 cases of black thyroid caused by minocycline, out of which 11 cases have developed papillary carcinoma (39%). The authors theorized that derangements in thyroid hormone metabolism and production of metabolically active byproducts may be responsible and that history of minocycline use in a patient with thyroid mass should prompt biopsy to rule out cancer.

8) Minocycline and the thyroid: antithyroid effects of the drug and the role of thyroid peroxidase in minocycline-induced black pigmentation of the gland. Thyroid 1996 Jun; 6(3):211-9; Taurog A, Dorris ML, Doerge DR.
This article discussed the role of thyroid peroxidase (TPO) in minocycline induced black thyroid; TPO was shown to be associated with minocyline-induced black thyroid. Minocycline was shown to be more potent than other tetracycline drugs in its anti-thyroid effects. The authors recommended that in view of potent anti-thyroid effects of minocycline in *in vitro* studies, it is advisable to monitor thyroid function in patients receiving long-term minocycline therapy.

9) Mechanism for the anti-thyroid action of minocycline. Chem Res Toxicol. 1997 Jan; 10(1):49-58; Doerge DR, Divi RL et al.
This article discussed mechanisms for causation of black pigment in humans and other species of animals and antithyroid effects seen in rodents. The authors mention that they had previously shown that these effects appear to be related to interactions of minocycline with thyroid peroxidase, which is a key enzyme in thyroid synthesis.

10) Skin pigmentation due to minocycline treatment of facial dermatoses. Br J Dermatol. 1993 Aug; 129(2):158-62; Dwyer, CM, Cuddihy AM, Kerr RE, Chapman RS, Allam BF.
This article discussed AEs seen in 54 patients who had taken minocycline for acne or rosacea; their mean duration of treatment was 17 months. In these patients, while hematology, biochemistry and thyroid functions were normal, skin pigmentation was seen in 8 patients (14.8%). 5 patients had diffuse facial pigmentation and 3 had localized pigmentation at site of scar or injury. 50% of patients who had been on minocycline for $\geq$ 3 years had diffuse pigmentation. Localized pigmentation at sites of previous tissue damage was not directly related to duration of therapy. The authors concluded that long-term minocycline therapy patients should be monitored for development of pigmentation.

10) The outcome of pseudotumor cerebri induced by tetracycline therapy; Arch Neurol Scand 2004; 110: 408-411; Kesler A, Goldhammer Y et al.
This article assessed patients who had developed pseudotumor cerebri (PTC) after treatment with tetracyclines and who were followed for a minimum of 2 years after cessation of tetracycline. In this study, out of 243 patients with PTC, 18 had concurrent history of tetracycline treatment; a third experienced a limited course with no relapses; 12 had a variable course with a prolonged relapsing illness. Mean duration of tetracycline prior to diagnosis was 2.73 months. The study concluded that tetracyclines, especially *minocycline is currently considered a cause or precipitating factor for PTC and that drug withdrawal is curative in only some patients.* It recommended that every patient treated with minocycline or doxycycline should be routinely checked for papilledema after first month of treatment and a minimum of 1 year follow-up after cessation of therapy is necessary to monitor recurrence of PTC.

11. Pseudotumor cerebri induced by Vitamin A combined with minocycline; Ann Ophthalmol 1993; 25: 306-308; Moskowitz Y, Leibowitz E et al.
Minocycline is known to be associated with pseudotumor cerebri. Literature reports[3,4] suggest that isotretinoin, a systemic retinoid prescribed for severe acne vulgaris is also known to be cause pseudotumor cerebri. The label for Accutane[5] (isotretinoin) mentions that concomitant treatment of tetracyclines should be avoided.

Conclusions of salient literature reports:

- Amongst all the tetracyclines, minocycline use for acne is most associated with the development of autoimmune and hypersensitivity syndromes; this is generally associated with long-term use, however serum-sickness type syndromes may occur with relatively short duration of treatment
- Minocycline use is associated with development of various types of tissue hyperpigmentation
- Minocycline-induced black thyroid may be associated with thyroid dysfunction, notably hypothyroidism; depression may be caused by minocyline induced hypothyroidism. Patients on long-term treatment should be routinely monitored for thyroid dysfunction and development of goiters.
- Minocycline-induced black thyroid may be associated with the development of thyroid papillary cancer.
- Tetracyclines (especially minocycline because of its higher lipid solubility and ability to penetrate the blood-brain barrier) have been known to be associated with the development of pseudotumor cerebri (PTC), especially with long-term treatment. Visual AEs associated with pseudotumor cerebri may not always be reversible upon resolution of papilledema associated with PTC.

3 Pseudotumor cerebri induced by Vitamin A combined with minocycline; Ann Ophthalmol 1993; 25: 306-308; Moskowitz Y, Leibowitz E et al
4 Pseudotumor cerebri after treatment with tetracycline and isotretinoin for acne ; Cutis 1995; 55:165-168; Lee AG
5 Accutane label (Roche)

- The risk of PTC increases if isotretinoin is used in combination with minocycline since both drugs are known to individually cause PTC. The two drugs should not be used together in the treatment of acne vulgaris.

It is recommended that above findings be incorporated into labeling. It is recommended that the label for Solodyn convey that 'Concurrent use of isotretinoin and minocycline should be avoided. Each drug alone has been associated with pseudotumor cerebri'.

7.2.3 Adequacy of Overall Clinical Experience

An adequate number of subjects with acne vulgaris were exposed to the extended-release formulation of minocycline during the 12-week pivotal randomized, double-blind, placebo-controlled clinical studies. Subgroup analyses for race, gender and age were conducted appropriately, but the majority of subjects enrolled were White. The clinical studies should have been enriched for ethnic diversity.

Exposure during the 12 week duration does not necessarily co-relate with long-term use for a chronic indication such as acne vulgaris. The sponsor is assessing long-term safety by conducting the 2-year open-label, safety study MP-0104-07. The open-label, uncontrolled human spermatogenesis study conducted by the sponsor is considered inadequate and will need to be repeated.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Appropriate non-clinical studies were performed with this new extended-release formulation of minocycline with the exception of carcinogenicity studies in mice and rats which are to be performed as a post-marketing commitment.

Please see Section 3.2 and Pharmtox review for detailed discussion.

7.2.5 Adequacy of Routine Clinical Testing

Clinical studies for Solodyn included assessing acne vulgaris lesions primarily; studies also included periodic physical examinations, assessing local and systemic safety and lab monitoring. Adverse event and lab monitoring included monitoring for those AEs associated with minocyline/tetracycline use.

Overall, the clinical testing for 12-week studies for Solodyn was considered appropriate. As discussed earlier, clinical studies for human spermatogenesis were considered inadequate and will need to be repeated.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Specific drug-drug interaction studies were not conducted for Solodyn. The sponsor conducted PK/PD studies; these studies included assessing food effects on absorption and effects of minocyline on action of oral contraceptives.

Please refer to Section 5.

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

In clinical trials for Solodyn, while all AEs were reported and monitored, certain AEs of interest that are known to be associated with minocycline/tetracyclines were focused upon. These included vestibular events, hepatotoxicity, skin and hypersensitivity, lupus-like syndromes, thyroid dysfunction, central nervous system AEs, etc. Lab monitoring included routine blood counts, urinanalysis, liver function tests, thyroid function tests, anti-nuclear antibody tests and other autoimmunity tests as needed. Similar monitoring is included in the open-label, 2-year, long-term safety study MP-0104-07. Study design for human spermatogenesis studies was considered inadequate; these studies are to be repeated. Although the sponsor had been advised to compare the extended-release formulation of minocycline to the immediate-release type for safety purposes, such studies were not done.

7.2.8 Assessment of Quality and Completeness of Data

Data submitted for safety review of Solodyn was considered incomplete because of lack of complete information available from human spermatogenesis studies. Results from MP-0104-07 may help elucidate long-term safety, although this will depend upon the overall conduct of the study, subject retention, etc.

7.2.9 Additional Submissions, Including Safety Update

A 120-day safety update was submitted on 11/16/2005 and the sponsor submitted an update on autoimmune AEs seen in MP-0104-07, the open-label, 2 year safety study on 1/31/2006. These have been reviewed and incorporated in discussion about Study MP-0104-7. Please refer to Section 7.1.12 (Special Safety Studies)

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

In clinical studies, all local and systemic AEs were collected and coded using the Medical Dictionary for Regulatory Activities (MedDRA). Common and drug-related adverse events identified in combined safety population form Phase 2 and 3 studies were as follows:

- Drug-related AEs were highest in the Nervous System Disorders class; M/P = 25.2%/23.4%; headache and dizziness were the most common AEs.
- This was followed by the GI Disorders class; M/P = 17%/22%; nausea, abdominal pain and diarrhea were the most common AEs
- The next common class was General Disorders and Administration Site Conditions; M/P = 10.4%/8%; fatigue and malaise were the most common AEs

- Skin and Subcutaneous Tissue Disorders; M/P = 6.7%/5.2%; pruritus and urticaria were the most common AEs
- Investigations; M/P = 0.6%/1.1%; only 4 patients in the minocycline group and 1 in placebo group had liver function abnormalities thought to be related to drug treatment

This analysis shows that in general, drug-related AEs were in keeping with known AEs of minocycline and included headache, dizziness, nausea, diarrhea, abdominal pain, fatigue, pruritus and urticaria. Dizziness, tinnitus and vertigo were higher in the minocycline group compared to the placebo group.

5.4 General Methodology

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

A combined safety analysis was done by pooling data from all clinical studies performed for Solodyn. However, the safety review concentrated mainly on AEs seen in Phase 2 and 3 twelve week clinical studies since dose and duration of treatment in PK/PD studies were different from 12-week studies.

7.4.1.2 Combining data

The common clinical protocol was used for each investigational site such that data could be pooled for analysis. A minimum of 10 subjects were to be enrolled in each treatment arm for any investigator. If there were too few subjects in a treatment arm, then the investigator's data was combined to achieve the desired sample size minimum per arm.

Per the Biostats review by Dr. Kathleen Fritsch, all of the centers in Study 04 were large enough so that no pooling was needed for the analysis. The smallest center in Study 04 had 13 minocycline and 7 placebo subjects. Study 05, however, had several small centers that were pooled in the analyses involving center. The three smallest centers which had 6 or fewer subjects each were each pooled with the three largest centers. The sponsor's pooling differed slightly from the algorithm in the statistical analysis plan. The algorithm stated that the smallest center with fewer than 10 subjects *per treatment arm* would be pooled with the largest center *with fewer than 10 subjects per treatment arm*, and so on. The actual algorithm used by the sponsor was to pool the smallest center with fewer than 10 *total* subjects with the center with the largest enrollment (not restricted among the small centers), and so on. The impact of this change is minimal.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

The sponsor conducted a Phase 2 dose-ranging study.

Please refer to Section 5.3 for further details.

7.4.2.2 Explorations for time dependency for adverse findings

The interim report for MP-0104-07 and the safety update provided preliminary information about time to first occurrence of select adverse events.

Please see Section 7.1.12.

7.4.2.3 Explorations for drug-demographic interactions

A subgroup analysis of adverse events by age, race and gender was done for combined Phase 3 studies.

Please see Section 7.1.5.6.

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

Please see Section 7.1.5.5.

8 Additional Clinical Issues

8.1 Dosing Regimen and Administration

Per the dose-ranging study, the once a day regime was chosen in order to improve compliance and for ease of administration, especially in teenage age groups, and the 12 week duration was in keeping with most other acne trials.

Please see Section 5.

8.2 Drug-Drug Interactions

Not conducted for this NDA and no drug-drug interactions observed during clinical trials.

Please see Section 5

8.3 Special Populations

Solodyn tablets were studied in subjects 12 years of age and older since acne vulgaris is more prevalent in this age group and if approved would be indicated in similar age groups. Efficacy and safety of Solodyn was tested in subgroups – age, race and gender and based on those findings, there are no special dosing considerations for different demographic populations. Use of tetracycline class antibiotics below the age of 8 is not recommended because of the potential for tooth discoloration.

Pregnant and breast-feeding subjects were excluded from the studies based on the teratogenic adverse effects of minocyline and if approved, Solodyn would have pregnancy Category D in keeping with other tetracyclines. Limited human studies for Solodyn have suggested that minocycline may have deleterious effects on spermatogenesis. Solodyn should not be used by individuals of either gender who are attempting to conceive a child. Further, well-designed studies are needed to elucidate the effects of minocyline on human spermatogenesis.

The proposed label for Solodyn tablets mentions that in patients with significantly impaired renal function, usual doses may lead to drug accumulation and possibly liver toxicity. Under such conditions, lower doses are indicated and monitoring serum drug levels is advisable.

8.4 Pediatrics

Studies for Solodyn tablets were conducted in compliance with PREA regulations. Since acne is commonly seen in teenagers, patients12 years of age and older were included in clinical trials. The sponsor has requested a pediatric waiver since acne is not usually seen in patients less than 12 years of age and it would be difficult to enroll appropriate patients in that age group. A partial pediatric waiver will be granted to the sponsor.

8.5 Advisory Committee Meeting

No advisory committee meetings were held to discuss Solodyn.

8.6 Literature Review

Minocyline has been used for a number of years to treat inflammatory acne. A literature review was done to assess safety of minocyline, especially for the acne indication.

Please refer to Section 7.2.2.3.

8.7 Postmarketing Risk Management Plan

No risk management activity for Solodyn is planned at this time. Upon approval, the sponsor will have to closely monitor all adverse events reported for Solodyn and submit them to the Agency per 21 CFR 314.80(c). This will also include Periodic Adverse Drug Experience Reports at quarterly intervals for the first three years after drug approval per 21 CFR 314.80(c)(2).

8.8 Other Relevant Materials

DDMAC and ODS reviews for Solodyn have been reviewed and incorporated.

9 Overall Assessment

9.1 Conclusions

Medicis Pharmaceutical Corporation has submitted a NDA application for Solodyn tablets, which is an extended-release formulation of minocycline. The indication sought by the sponsor is the once a day treatment of inflammatory lesions associated with moderate-severe acne vulgaris in patients 12 years of age and older.

Solodyn was originally conceived as an extended-release formulation that would help prevent the vestibular adverse effects that may be associated with the rapid absorption of immediate-release minocycline products. However, pharmacokinetic testing for Solodyn revealed its absorption profile was not vastly different from the immediate-release formulation. Solodyn has not been compared to the immediate-release formulation of minocycline in safety and efficacy clinical trials.

Efficacy for Solodyn was determined based on two Phase 3, twelve-week, pivotal efficacy and safety studies in patient's ≥12 years while the integrated safety analysis was based on all clinical studies. Results from these studies showed that Solodyn was safe and effective in the treatment of non-nodular, inflammatory lesions of moderate-severe acne vulgaris. Solodyn did not demonstrate any effect on non-inflammatory lesions (benefit or worsening).

Minocyline, like other tetracyclines is known to have certain adverse effects that may preclude its use beyond 12 weeks. In general, these adverse effects are expected to occur over long-term therapy with minocycline, although there are some adverse effects that may not necessarily be dose or duration limited. Currently, safety of minocycline ahs not been established beyond 12 weeks of use. An ongoing 2-year, open-label safety study will attempt to elucidate long-term safety and a pediatric growth study is included as part of this study. Limited human spermatogenesis studies showed that minocycline may have a deleterious effect on male spermatogenesis; well-designed studies will need to be performed to assess this adverse effect further.

In conclusion, an Approval action is recommended for Solodyn for the once a day treatment of only non-nodular, moderate-severe inflammatory lesions of acne vulgaris. Safety has not been established beyond 12 weeks of use.

9.2 Recommendation on Regulatory Action

Please see Section 1.1

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Please see Section 8.7

9.3.2 Required Phase 4 Commitments

Post-marketing commitments include:
Clinical:
1) Submit results of ongoing 2-year, open-label safety study (MP-0104-07) which includes a growth assessment of a subset of pediatric subjects within 3 months of study completion to the Agency.

2) Conduct an appropriately designed human spermatogenesis study to evaluate effects of minocycline on male spermatogenesis within 3 months of drug approval and submit results to agency within 3 months after study completion. This study should be appropriately representative of US demographics and should include a racially diverse population.

Non-Clinical:
1) Submit protocols for non-clinical rat and mice carcinogenicity studies within 3 months of drug approval and submit results within 3 months after study completion.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

Changes to the sponsor-proposed Solodyn label are based on NDA review and ODS, DDMAC and PLT consult recommendations. These include:

1) Modify Pharmacology section to include PK/PD studies conducted for Solodyn.
2) Modify Microbiology section to include P. acnes antimicrobial study.
3) Modify Clinical Studies section to reflect salient features of studies conducted.
4) Modify Indications and Usage section to reflect use of Solodyn in *only non-nodular inflammatory lesions of moderate-severe acne vulgaris* and that this formulation of minocycline has not been evaluated in the treatment of infections.
5) Update Warnings section to reflect teratogenic, gastrointestinal, metabolic, central nervous system effects and photosensitivity.
6) Update Precautions section to include that safety beyond 12 weeks is not established. Include autoimmune syndromes, serious skin/hypersensitivity reactions and tissue hyperpigmentation.
7) Modify Information for Patients to reflect safety and correct usage concerns.
9) Update Drug Interactions to include oral contraceptive study findings.

10) Update Carcinogenesis, Mutagenesis and Impairment of Fertility to reflect genotoxic study findings and rat spermatogenesis study findings. Also mention human spermatogenesis study findings briefly.
11) Update Pregnancy section to include limb reductions/skeletal malformations.
12) Update Pediatric Use section to reflect findings from clinical studies.
13) Update Adverse Reactions section to include salient AEs from clinical studies and update post-marketing section.
14) Modify Dosage and Administration section to include 12 weeks duration.
15) Delete References in label provided by sponsor.

Patient Package Insert recommendation:
A Patient Package Insert (PPI) is recommended to be included in the Solodyn label such that it conveys safe and effective 12-week use of minocycline. It is expected that a PPI would appraise patients regarding potential adverse effects and to seek medical help when needed.

9.5 Comments to Applicant

Please address the following:
Clinical deficiency noted during NDA review:
1) Inappropriately designed and incomplete human spermatogenesis study to evaluate effects of minocyline on spermatogenesis.

Post-marketing commitments:
1) Conduct an appropriately designed human spermatogenesis study to evaluate effects of minocycline on male spermatogenesis within 3 months of drug approval and submit results to agency within 3 months after study completion

2) Submit results of ongoing 2-year, open-label safety study (MP-0104-07) and the 2-year open-label growth study in pediatric subjects within 3 months after study completion.

3) There are concerns that minocycline induced black thyroid in humans may result in papillary thyroid cancer. Conduct non-clinical rat and mice carcinogenicity studies within 3 months of drug approval and submit results to the Agency within 3 months after study completion.

10. APPENDICES

10.1 Labeling Review:

Insertions are underlined and deletions are crossed out for ease of review. The Package Insert and Patient Package Insert are both included.

SOLODYN™

17 Page(s) Withheld

_____ Trade Secret / Confidential

X Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Medical-*_____

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Bindi Nikhar
5/8/2006 02:17:50 PM
MEDICAL OFFICER

Markham Luke
5/8/2006 02:37:07 PM
MEDICAL OFFICER
See also clinical TL memo in DFS.

Stanka Kukich
5/8/2006 02:55:14 PM
MEDICAL OFFICER
Agree with the MO's recommendation that this application be approved

Dermatology Clinical Team Leader Memorandum
NDA 50-808 SOLODYN (Minocycline HCl) Extended Release Tablets

May 1, 2006

SOLODYN (Minocycline HCl) Extended Release Tablets was evaluated by a multi-disciplinary review team and recommended to be safe and efficacious when studied for the treatment of only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older, with labeling revised from the original submission. The Clinical Team Leader agrees with this assessment of the information submitted. Outstanding issues are to be assessed by the sponsor as commitments for post-approval study with these issues adequately described in labeling.

Comments on Efficacy

The clinical studies were reviewed in detail by the primary Clinical Reviewer, Dr. Bindi Nikhar. The clinical studies for acne were conducted using a subset of the full criteria needed for the complete acne indication, i.e. the application targets inflammatory lesions only as opposed to both non-inflammatory and inflammatory acne lesions. In addition, this systemically administered product was not studied for the treatment of nodular acne.

Minocycline formulated as SOLODYN demonstrated success in the treatment of acne in placebo-controlled clinical studies. Success as determined using a dichotomized win (Clear/Almost Clear) by Day 84 of a static Global Severity Score was 7.9% in study 04 and 9.5% in study 05 in the placebo arm vs. 17.3% in the minocycline arm in study 04 and 15.9% in study 05. Percent reduction of inflammatory lesion counts were as follows: 31.7% and 30.8% respectively for placebo and 43.1% and 45.8% for minocycline in the two pivotal studies.[1] See also the Biostatistics review by Dr. Kathy Fritsch.

The study designs used in the pivotal studies appear to approximate current draft Guidance recommendations for the specific subset of acne vulgaris. There is some question regarding the clinical utility of indicating treatment for inflammatory lesions only. Ideally, future products for acne vulgaris should seek to target all acne, rather than just a specific subset as was the case for SOLODYN.

Comments on Safety

Safety concerns for minocycline were carefully evaluated by the primary clinical reviewer from the clinical dataset submitted by the sponsor together with the available information from the currently approved minocycline drug products. Current labeling for other minocycline drug products were looked at carefully and information from that review, review recommendations by the Office of Drug Safety, and review

[1] Of academic interest are the rates of success achieved by the placebo in this setting free of influence of a topical vehicle. The dataset (especially the lesion count data) suggests that inflammatory lesions of moderate to severe non-nodular acne vulgaris generally improve in patients as part of the natural course of the disease.

recommendations by the Division of Anti-Infective Products were all considered in the final labeling recommended by the review team.

Informational needs for safety that were lacking in the current submission, but were thought to be allowable for post-marketing evaluation as commitments by the sponsor from the Clinical reviewer are as follows:

1) Submit results of ongoing 2 year, open-label safety study (MP-0104-07) and the 2 year open label growth study in pediatric subjects within 3 months after study completion to the Agency.
2) Conduct an appropriately designed human spermatogenesis study to evaluate effects of minocycline on male spermatogenesis within 3 months of drug approval and submit results to agency within 3 months after study completion. The spermatogenesis study should be appropriately representative of US demographics and should include a more racially diverse population.

The 2 year, open-label safety study for minocycline included 345 subjects and had safety data reported thus far with 120 subjects thus far treated for at least 18 months. There does not appear to be any increase in the rate or severity of adverse events that correlate with increased length of use from the data thus far submitted. However, complete analysis has not been conducted pending submission of the final study report. The post-marketing commitment is to submit the complete results of that study. This study also includes a pediatric growth evaluation that has not yet been submitted (see Dr. Nikhar's review). The second post-marketing commitment is with regard to whether minocycline has an effect on human spermatogenesis. At this time, there is a signal in a previous study that there may be a concern (increasing reduction in sperm count from baseline with increased length of exposure to minocycline). Please also see primary clinical review and consult reply from CDER's Division of Urology and Reproductive Products. This concern is not currently described in labels for other minocycline products as this appears to be a novel finding by this sponsor for their 505(b)1 submission. Recommended labeling for SOLODYN includes description regarding this concern under PRECAUTIONS: Impairment of Fertility.

The Pharmacology/Toxicology reviewer, Dr. Norman See, raised concerns regarding the lack of carcinogenicity information to inform longer term use for acne, a chronic condition. Dr. See proposed and the sponsor has accepted conducting mouse and rat carcinogenicity evaluations of minocycline HCl. This information is not available in the already approved and marketed minocycline products. The concern is thought to be sufficiently mitigated by the current products being available that these studies may be conducted as post-marketing commitments.

The issues regarding anti-microbial drug resistance have been explored and discussed with the Clinical Microbiology Team. Dr. Fred Marsik. Dr. John Alexander, and Dr. John Powers have attended our labeling meetings and have contributed to evaluation of this new indication for a drug product containing minocycline as the active ingredient used at an anti-microbial dosage, including drug resistance issues. The clinical

relevance of the anti-microbial effect of minocycline for acne vulgaris has not been sufficiently explored to allow an anti-microbial claim. Please see proposed labeling.

The Chemistry reviewer, Shrikant Pagay, has made a determination that the submitted information are sufficient to make a determination that "Extended-Release Tablets" is the appropriate name for this formulation. The relevance for "Extended-Release" is further delineated in the Clinical Biopharmaceutics review by Dr. Tapash Ghosh. SOLODYN tablets are "not bioequivalent to non-extended release minocycline products". There was no clinical study submitted that evaluated any advantage of the SOLODYN extended release formulation over the non-extended release minocycline, therefore no labeling claims have been allowed.

In summary, the Clinical Team Leader, in this Interdisciplinary Summary memorandum agrees that SOLODYN Tablets may be approved as is recommended by the review team for the indication of treating only inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 12 years of age and older.

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

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/s/

Markham Luke
5/1/2006 11:55:48 AM
MEDICAL OFFICER
Clinical TL interdisciplinary memo.

Stanka Kukich
5/8/2006 10:53:21 AM
MEDICAL OFFICER

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE:	December 15, 2005
FROM:	Gerard G. Nahum, MD Pregnancy and Lactation Team, OND IO
THROUGH:	Sandra Kweder, MD Deputy Director, Office of New Drugs
TO:	Stanka Kukich, MD Acting Director, Division of Dermatology and Dental Products
SUBJECT:	Solodyn (Minocycline Hydrochloride) – Review of pregnancy category for the indication of acne vulgaris [NDA 50-808]
Consult received: Due date:	October 13, 2005 January 15, 2006

I. EXECUTIVE SUMMARY

The Pregnancy and Lactation Team (PLT) has been consulted by the Division of Dermatology and Dental Products concerning the product labeling and pregnancy category for Solodyn® (minocycline hydrochloride) for the indication of acne vulgaris.

The PLT has three times before reviewed the product labeling for minocycline for the Division of Anti-infective Drug Products (on July 16, 2003, October 8, 2003 and January 5, 2005 [NDA No. 50-649/S-015, NDA No. 50-444/S-038 and NDA No. 50-445/S-022]).

Because of very limited animal and human data of pregnancy exposures to minocycline, the sponsor refers to published data pertaining to other tetracycline-class antibiotics and proposes labeling language for the pregnancy section with a pregnancy category of "D". In addition, the sponsor proposes to include new animal data concerning fetal skeletal malformations that have occurred after fetal exposures to minocycline in rats and rabbits, although the source(s) of this new data have not been specified. Based on these limited data, the sponsor proposes new language for the WARNINGS and Pregnancy sections of the product label.

In addition to the rat and rabbit data proposed for inclusion in the Solodyn® label by the sponsor, the PLT has identified two peer-reviewed reports of experimental fetal

exposures to minocycline in both rhesus monkeys and dogs that should also be considered for incorporation in the Solodyn® label. These very limited data do not confirm the lower animal findings that are proposed for inclusion by the sponsor. The PLT recommends that the rat and rabbit data proposed by the sponsor for the product label be obtained for assessment by pharm/ tox reviewers. If it is confirmed as credible as regards the occurrence of skeletal abnormalities in the offspring of rats and rabbits, the PLT recommends that a Pregnancy Category "D" rating should be retained for Solodyn®. This category rating is consistent with what is currently assigned to other minocycline products and also to both tetracycline and doxycycline products (two other related tetracycline-class antibiotics).

Based on the currently available data, the PLT offers recommendations to the labeling language for Solodyn®. In addition, although the PLT recognizes that the current application represents a new NDA with labeling that may be independently negotiated by the sponsor from previous minocycline products, the PLT recommends that the product label for Minocin®, Dynacin®, and all related generic versions of minocycline be made to conform to the WARNINGS, Pregnancy, and Nursing Mothers product label that is ultimately adopted for Solodyn®. As part of the recommended modifications to the Solodyn® label proposed by the sponsor, the PLT strongly recommends that the recently negotiated labeling changes for the Pregnancy section of the product label for Minocin® (October 2005; see below) should also be incorporated into the Solodyn® label, as well as all other related minocycline products.

II. BACKGROUND

Minocycline, like doxycycline, is a long-acting, second-generation tetracycline antibiotic.[1,2] It was first approved by the FDA in 1971. Minocycline is bacteriostatic against susceptible organisms and, at high concentrations, it may be bactericidal. Its action results from reversible binding to the 30s bacterial ribosomal subunit, thereby inhibiting protein synthesis.[1]

Minocycline is structurally related to both tetracycline and doxycycline (Fig.1) and it is active against many gram-negative and gram-positive organisms.[1-5] Like doxycycline, it is more lipophilic than tetracycline and has a longer half-life.[1-3] Doxycycline is the tetracycline-class antibiotic most similar to minocycline in terms of chemical structure, lipid solubility and serum half-life.[1-3]

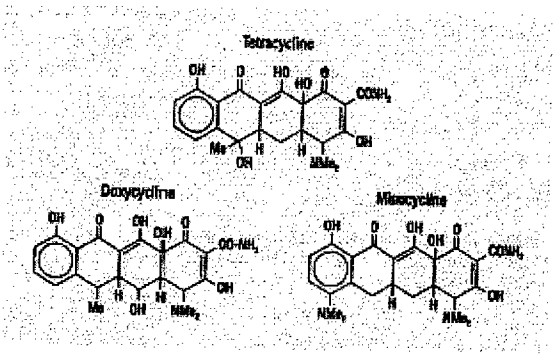


Fig. 1. Structure of tetracyclines.

Minocycline crosses the placenta.[4,5] No adequate and well-controlled human trials exist to assess the risk of fetal harm from maternal minocycline exposure. The use of tetracycline-class antibiotics during pregnancy is generally avoided because of potential hepatotoxic effects in the mother,[6-10] osteotoxic effects in the fetus,[11-13] and discoloration of the deciduous teeth of the fetus when used after the 25th week of gestation.[11-15] Although tetracycline can cause cosmetic staining of the primary dentition in human fetuses exposed during the 2nd or 3rd-trimester of pregnancy,[11-16] it is not known whether minocycline produces similar effects. Tooth discoloration in humans is more common during the long-term use of tetracycline, but has also been observed after repeated short-term exposures. The manufacturer of doxycycline has previously expressed concerns about possible enamel hypoplasia and depression of fetal bone growth.[17] While not reported with minocycline exposure, oral tetracycline given to premature infants has been associated with a decrease in fibular growth that was reversible when the drug was discontinued.[18] Although this is not typically considered a teratogenic effect, some references include tetracyclines on their lists of teratogenic drugs for this reason. While isolated cases of major fetal malformations have been reported in the offspring of mothers who received tetracycline during pregnancy (e.g., oral clefts, spina bifida, polydactyly), available data do not support an increased association of major congenital malformations with tetracycline.

An expert review of published data concerning the use of minocycline during pregnancy by the Teratogen Information System (TERIS) concludes that the "magnitude of teratogenic risk to children born after exposure during gestation" is "undetermined", with the "quality and quantity of data on which the risk estimate is based" being "very limited".[16] There is no published human data to show that fetal exposure to minocycline causes cosmetic staining of the primary teeth, however this cannot be ruled out because of potential of a tetracycline class effect.[16]

The current product labels relevant to Pregnancy for MINOCIN® (minocycline hydrochloride) and DYNACIN® (minocycline HCl tablets) are different, and both of these labels are different from the proposed product label for SOLODYN®. The portions of the WARNINGS section relevant to pregnancy, the Labor and Delivery section, and the Nursing Mothers section of the product labels of MINOCIN® and DYNACIN® are currently identical and read as follows:

2 Page(s) Withheld

_____ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Medical-_____

As part of the review by the PLT, the sponsor's proposed product labeling, prior minocycline, doxycycline and tetracycline antibiotic product labels, and the peer-reviewed literature concerning the use of minocycline and other tetracycline-class antibiotics by pregnant and lactating women were considered. A literature search was conducted using the PubMed search engine to identify relevant studies. These are listed below in the Reference section.

IV. REVIEW OF DATA

Human Data

There are no well controlled studies of minocycline use in pregnant women. The majority of reported experience with tetracycline-class antibiotics during human pregnancy is from limited case reports/ case series with short-term exposures (i.e., 7 to 10 days of therapy).[19] Some limited amount of case-control pregnancy-exposure data is also available.

Toxic Effects

A unique effect of minocycline therapy is the brown-black staining of cutaneous tissues, thyroid, bone, and breast milk.[12-15,20-23] Data from animal studies do not indicate that thyroid function is significantly impaired by the deposition of the pigmented metabolic derivatives of minocycline.[24]

Tetracycline use has been associated with fatty liver of pregnancy,[7-10] although there are no published reports of an association of this rare condition with minocycline use. This morbid and often fatal disorder has been reported to follow high dose intravenous tetracycline used to treat pyelonephritis.[8]

Teratogenicity/ Embryotoxicity

1) Major congenital anomalies were reported in 8 (4.4%) of 181 newborns whose mothers were given prescriptions for minocycline during the 1st-trimester of pregnancy in a record linkage study of Michigan Medicaid recipients (Rosa, 1993).[16] The expected background rate was 3.9%. Cardiovascular defects and oral clefts were observed in the exposed group as frequently as expected. These limited published data were based only upon claims databases and did not involve medical chart review or interview confirmation. The available data also do not permit determination of the statistical significance, the specificity of the observed associations, or possible effects of confounding factors.[16]

Animal Data

Teratogenicity/ Embryotoxicity

(a) Minocycline was administered orally at doses of 8.7-17.4 mg/kg (1-4 times the usual human dose) to rhesus monkeys during embryogenesis and the period of fetal skeletal formation. No adverse or teratogenic effects were observed.[25]

(b) Minocycline administration at high doses was seen to cause fetal abnormalities in rats and rabbits.[26] Lower doses of minocycline did not adversely affect fetal development in dogs.[26]

Breastfeeding

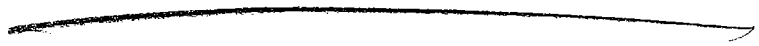
Like other tetracyclines, minocycline and its metabolites are secreted in human milk.[27,28] Although there is no quantitative data available for minocycline, the human breast milk concentrations of doxycycline are 30%-40% of that found in maternal blood.[28]

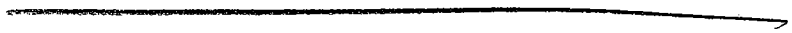
Besides its excretion into breast milk, minocycline also has had a unique effect reported concerning brown-black staining of breast milk in humans. In one case report, a 24-year old woman who ingested 100 mg of minocycline twice daily for more than four years to control her pustulocystic acne developed galactorrhea after ingesting phenothiazines for an unrelated psychiatric condition.[20] The milk that she secreted had a brown-black hue and contained numerous macrophages containing iron-staining particles, which was identified as hemosiderin. In another case, a 29-year old woman reported black discoloration of her breast milk, which occurred 18 months after she discontinued breastfeeding her infant. This developed three weeks after beginning 150 mg daily of oral minocycline for the treatment of acne vulgaris.[21]

The extent of absorption of tetracyclines, including minocycline, by breastfed infants is unknown. Tetracyclines can form nonabsorbable complexes with the calcium in breast milk. Short-term use by lactating women is considered probably safe,[29] however the effects of prolonged exposure to tetracyclines in breast milk are not known.[30] Theoretically, there is a risk of tooth discoloration, enamel hypoplasia, inhibition of linear skeletal growth, modification of bowel flora, oral and vaginal thrush, photosensitivity reactions, and hepatic damage in infants who receive tetracycline-class antibiotics. Although the quantities of the tetracycline antibiotics secreted into milk are probably too small to affect neonatal bone growth or stain teeth, even these small quantities may modify bowel flora and potentially interfere with the interpretation of culture results if an evaluation for fever is required. The American Academy of Pediatrics does not specifically include minocycline in its listing of drugs with regard to breastfeeding, but it classifies tetracycline as compatible with breastfeeding.[31] The WHO Working Group on Drugs and Human Lactation concluded the use of tetracycline antibiotics for a short (one week) period would be unlikely to have adverse effects in exposed infants.[29] No comment was made concerning longer term use.

V. LABELING RECOMMENDATIONS

Based on the information reviewed by the PLT, the following suggestions are made to the sponsor's proposed Pregnancy and Nursing Mothers sections of the product label for SOLODYN®:





VI. CONCLUSIONS

In view of the animal data for rats and rabbits that is presented by the sponsor for inclusion in the proposed product label, the PLT recommends that a pregnancy category "D" rating be retained for SOLODYN®. This pregnancy category rating is consistent with the category that is also currently assigned to other minocycline products, as well as to both tetracycline and doxycycline.

Before the proposed rat and rabbit data are incorporated into the product label, the PLT recommends that the Division query the sponsor concerning the source(s) of this data and have this information scrutinized by pharm/tox reviewers for its appropriateness and

credibility. Of note is that the very limited rhesus monkey, dog, and human data do not confirm the reported rat and rabbit findings. Due to the claims database that was used to derive the human data, the lack of medical chart review or interview confirmation of data, and the non-published nature of the information, the PLT does not recommend that the limited amount of human data be incorporated into the product label. Based on the currently available data, the PLT has made specific language recommendations to the proposed labeling (see Labeling Recommendations above).

The PLT recommends that all of the WARNINGS, Pregnancy, and Nursing Mothers sections of the product labeling for MINOCIN®, DYNACIN® and SOLOYN®, in addition to all generic equivalents, be made consistent.

If not already done, the PLT also recommends that the Division contact the Office of Drug Safety (ODS) to review the Adverse Events Reporting System (AERS) for any spontaneous case reports of adverse events relating to minocycline use during pregnancy.

VII. REFERENCES

1) Smilack JD. The tetracyclines. Mayo Clin Proc 1999;74:727-9.
2) Saivin S, Houin G. Clinical pharmacokinetics of doxycycline and minocycline. Clin Pharmacokin 1988;15:355-66.
3) Meynadier J, Alirezai M. Systemic antibiotics for acne. Dermatology 1998;196:135-9.
4) Product information DYNACIN® (Minocycline HCL tablets), October 2003, MEDICIS
5) Product information for MINOCIN® (minocycline hydrochloride), October 2005, (Wyeth)
6) Burette A, Finet C, Prigogine T, DeRoy G, Deltenre M. Acute hepatic injury associated with minocycline. Arch Intern Med 1984;144(7):1491-2.
7) Allen ES, Brown WE. Hepatic toxicity of tetracycline in pregnancy. Am J Obstet Gynecol 1966;95:12-8.
8) Schultz JC, Adamson JS, Workman WW, Norman TD. Fatal liver disease after intravenous administration of tetracycline in high dosage. N Engl J Med 1963;269:999-1004.
9) Kunelis CT, Peters JL, Edmondson HA. Fatty liver of pregnancy and its relationship to tetracycline therapy. Am J Med 1965;38:359-77.
10) Wenk RE, Gebhardt FC, Bhagavan BS, Lustgarten JA, McCarthy EF. Tetracycline-associated fatty liver of pregnancy, including possible pregnancy risk after chronic dermatologic use of tetracycline. J Reprod Med 1981;26:135-41.
11) Kline AH, Blattner RJ, Lunin M. Transplacental effect of tetracyclines on teeth. J Am Med Assoc 1964;188:178-80.
12) Rendle-Short TJ. Tetracycline in teeth and bone. Lancet 1962;1:1188.
13) Kutscher AH, Zegarelli EV, Tovell HM, Hochberg B, Hauptman J. Discoloration of deciduous teeth induced by administration of tetracycline antepartum. Am J Obstet Gynecol 1966;96(2):291-2.
14) Cohlan SQ. Tetracycline staining of teeth. Teratology 1977;15:127-30.
15) Toaff R, Ravid R. Tetracyclines and the teeth. Lancet 1966;2:281-2.

16) Friedman JM, Polifka JE. Teratogenic Effects of Drugs: A Resource for Clinicians (TERIS). Baltimore, MD: The Johns Hopkins University Press; 2000.
17) Product information Vibramycin®, 2001
18) Cohlan SQ, Bevelander G, Tiamsic T. Growth inhibition of prematures receiving tetracycline. Am J Dis Child 1963;105:453-61.
19) Tsui MS, Fang RCY, Su YM, Li YT, Lin HM, Sun LS, Tu FC. Scrub typhus and pregnancy: A case report and literature review. Chin Med J (Taipai) 1992;49:61-3.
20) Basler RSW, Lynch PJ. Black galactorrhea as a consequence of minocycline and phenothiazine therapy. Arch Dermatol 1985;121:417-8.
21) Hunt MJ, Salisbury ELC, Grace J, Armati R. Black breast milk due to minocycline therapy. Br J Dermatol 1996;134:943-4.
22) Fenske NA, Millns JL. Cutaneous pigmentation due to minocycline hydrochloride. J Am Acad Dermatol 1980;3:308-10.
23) Saul SH et al: The black thyroid: Its relation to minocycline use in man. Arch Pathol Lab Med 1983;107:173-7.
24) Kurosumi M, Fujita H. Fine structural aspects on the fate of rat black thyroids induced by minocycline. Virchows Arch (Cell Pathol) 1986;51:207-13.
25) Jackson BA, Rodwell DE, Kanegis LA, Noble JF. Effect of maternally administered minocycline on embryonic and fetal development in the rhesus monkey. Toxicol Appl Pharmacol 1975;33:156.
26) Anonymous. Minocycline HCl. Rx Bull 1971;2:67-9.
27) Knowles JA. Drugs in milk. Pediatr Curr 1972;21:28-32.
28) Morganti G, Ceccarelli G, Ciaffi G. Comparative concentrations of a tetracycline antibiotic in serum and maternal milk. Antibiotica 1968;6:216-23.
29) The WHO Working Group, Bennet PN (ed). Drugs and Human Lactation. Elsevier, Amsterdam, New York, Oxford, 1988. pp. 200-7.
30) Hale T. Medications and Mothers Milk. 9th ed. Amarillo, TX: Pharmasoft Publishing; 2000:225-6.
31) Committee on Drugs, American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. Pediatrics 2001;108(3):776-89.

Gerard G. Nahum, MD
Medical Officer

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Copies:

OND IO	Kweder, Uhl, Kennedy
DDDP	Kukich, Nikhar, Curtis F, Lindstrom J
DAIDP	Albrecht R, Miller K, Singer M, Navarro Almario, Gitterman S, Sacks L
ODS	Avigan

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/s/

Gerard Nahum
12/15/2005 12:22:27 PM
MEDICAL OFFICER

Sandra L. Kweder
12/15/2005 03:34:39 PM
MEDICAL OFFICER
In addition to recommendations by Dr. Nahum, in the future you could consider addressing in labeling (for this and other minocyline products) information about expected risk in the setting of very early gestation, though data are very limited.

Memorandum of Consultation

To: Felecia Curtis, Project Manager
Division of Dermatology and Dental Products

From: Christine P. Nguyen, MD, Medical Officer
Division of Reproductive and Urologic Products (HFD-580)

George S. Benson, MD, Urology Team Leader
Division of Reproductive and Urologic Products (HFD-580)

Daniel A. Shames, MD, Director
Division of Reproductive and Urologic Products (HFD-580)

Date consult submitted: October 13, 2005
Date consult completed: December 1, 2005

Re: **Solodyn** (Minocycline extended-released tablets)
Consult regarding the results of studies MP-01014-16 and MP-0104-13 on the effects of minocycline on spermatogenesis in human males

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Background:

Tetracycline and its derivatives have been implicated in interfering with the process of spermatogenesis based on preclinical studies. The ability of the tetracyclines to bind to metallic elements such as calcium; the adsorption of tetracyclines to the acrosomal portion of mammalian spermatozoa; and the toxicity of minocycline to bovine spermatozoa at all concentrations tested warrant clinical data on the drug-effect of tetracyclines on human spermatogenesis. Such clinical information is particularly important in a drug such as minocycline that is indicated for long-term use in a target population of young males who may desire fertility.

Based on prior discussion with the Division of Dermatology and Dental Products (HFD-540), the sponsor of Solodyn (a minocycline extended-release tablet) agreed to elucidate the effect of minocycline on spermatogenesis in human males. The Division of Reproductive and Urologic Products (DRUP) reviewed protocol MP-0104-13, a phase I, open-label study designed to investigate the effect of daily oral administration of modified-release minocycline on spermatogenesis in healthy male subjects in a consult to HFD-540, dated December 3, 2004. The sponsor informed HFD-540 on September 2, 2005, that the study site of MP-0104-13 was destroyed by Hurricane Katrina, with the subsequent loss of data and CRF's. The sponsor, however, had also completed another study, MP-0104-16, which provided additional data on the effects of minocycline on human male sperm parameters.

HFD-540 has requested a consultation from the DRUP to "evaluate the study results available from the two spermatogenesis studies MP-0104-13 and MP-0104-16."

Medical Officer Review
Materials reviewed:

1) The interim study results of MP-0104-13: "An Open-Label Phase I Study to Examine the Effects of Minocycline on Spermatogenesis in Human Males."
2) Study results of MP-0104-16: "An Open Label Cohort Study to Investigate the Effects of Minocycline 1mg/kg/day on Sperm Characteristics in Male Subjects with Acne Vulgaris."
3) Selected literature references regarding the effects of tetracyclines on spermatogenesis.

Preclinical data: Please refer to DRUP's previous consult dated 12/3/04.

Clinical Studies Review

MP-0104-13: This protocol was the subject of a previous consultation by DRUP on December 3, 2004. There is limited information available from this study due to the destruction of the study site by Hurricane Katrina. The interim report submitted by the sponsor is based on data collected during approximately the first 4 months of the study, from January 6, 2005, through April 30, 2005.

MP-0104-13 was a phase I, open-label, multiple-dose study of the effect of minocycline 1mg/kg/day on human male spermatogenesis. Enrolled subjects were to receive minocycline once daily at a dose of 1mg/kg (± 0.5mg/kg) for 84 days. Semen sample collection was to occur at screening (2 samples per subject) and was to be repeated at days 28, 56, 84, and 156. The average of the 2 baseline values were used to determine eligibility and as baseline value for comparison. The primary endpoint was the comparison of baseline values of total sperm count, percent sperm motility, and percent normal sperm morphology with values obtained on Days 28 (± 2 days), 56 (± 2 days), 84 (± 2 days), and 156 (± 7 days). Inclusion criteria included healthy adult males between the ages of 18 to 50, whose sperm parameters were within clinically acceptable limits. The definition of "normal" semen analysis was based on the 1999 World Health Organization (WHO) criteria for total sperm count $\geq 40 \times 10^6$, percent motile $\geq 50\%$, and percent normal morphology $\geq 15\%$. Exclusion criteria included major medical problems, urological disorders, and substance abuse. Prescription and over-the-counter medication were prohibited during the dosing period (through Day 84), and tetracyclines and erythromycin were prohibited within 12 weeks of the first day of dosing with minocycline.

Reviewer's comments: Although it was recommended by DRUP that "at least 2 semen analyses should be collected at each time point for each subject," semen samples were

collected only once on days other than screening. It is not clear if all the semen analyses were performed at the same laboratory.

Reviewer's comments: The semen analysis values identified by the World Health Organization are considered to be the minimum criteria for "normal" semen quality.

Results: A total of 26 subjects were enrolled and dosed. The summary of the demographics of the study subjects is shown in Table 1. As of April 30, 2005, of the 26 study subjects, 23 (88.5%) have completed Day 28 visit, 21 (80.8%) have completed the Day 56 visit, and 8 (30.8%) have completed the Day 84 visit. No subjects have completed the Day 112 or Day 156 visit.

Table 1:

Summary Demographics
Available Data as of 30 April 2005

	Minocycline 1 mg/kg N = 26
Age (yr)	
mean ± SD	29.0 ± 9
Range	18 – 46
Race – n(%)	
White	16 (61.5)
Black	10 (38.5)
Smoker – n (%)	
No	17 (65.4)
Yes	9 (34.6)

Source: Post-text Table 14.1, and Listing 16.1

Table 2 is the summary of the effects of minocycline on sperm parameters as of 4/30/05. According to the sponsor, "these preliminary data showed no evidence of an adverse effect of modified-release minocycline on spermatogenesis." In addition, none of the semen analysis parameters for the 8 subjects obtained at Day 84 were outside the "normal" range, according to the 1999 WHO definition.

Table 2:

Summary of Total Sperm Count ($x10^6$), Motility (% with Forward Movement), and Morphology (% Normal) - Available Data as of 30 April 2005

	Total Sperm Count ($x10^6$)	Motility (% with Forward Movement)	Morphology (% Normal)
Baseline (N=26)			
Mean(SD)	213.3 (± 134.3)	67.0 (± 8.0)	32.9 (± 12.9)
Range	36.8, 505.3	43.0, 80.5	15.0, 62.0
Day 28 (N=21)			
Mean(SD)	234.7 (± 172.9)	63.4 (±8.9)	30.6 (± 10.2)
Range	2.0, 693.0	40.0, 73.5	15.0, 53.0
Change from Baseline			
Mean(SD)	19.5 (± 105.5)	-4.7 (± 11.1)	-2.6 (± 12.5)
Range	-161.0, 208.7	-35.0, 10.5	-30.0, 21.0
Day 56 (N=19)			
Mean(SD)	204.6 (± 146.1)	63.3 (± 8.6)	32.3 (± 11.9)
Range	17.1, 446.0	49.0, 81.5	15.0, 50.0
Change from Baseline			
Mean(SD)	-15.4 (± 134.2)	-5.3 (± 8.1)	-2.3, (± 15.8)
Range	-317.9, 325.7	-19.0, 16.0	-37.0, 23.0
Day 84 (N=8)			
Mean(SD)	148.6 (±83.1)	63.8 (± 6.9)	37.0 (± 13.0)
Range	42.0, 245.9	55.0, 77.5	21.0, 59.0
Change from Baseline			
Mean(SD)	-37.4 (±141.6)	-4.1 (± 12.6)	0.1 (± 11.0)
Range	-302.8, 179.6	-21.0, 12.0	-13.0, 22.0

Source: Posttext Tables 14.3.1, 14.3.2, 14.3.3, and Listing 16.6
SD = Standard Deviation

Reviewer's comments:

1) *Because the duration of an entire spermatogenic cycle within the human testis is 74 days, sperm analysis performed on Day 28 and on Day 56 may not reflect the drug effect of minocycline on the analyzed sperm parameters.*
2) *The semen analysis parameters for the study subjects were well above the minimum criteria in the WHO definition at all time points.*
3) *This reviewer does not concur with the sponsor regarding lack of adverse effect on sperm characteristics after 84 days of minocycline treatment. Specifically, the total sperm count appeared to have a treatment duration-related decline, based on the mean values. A separate baseline analysis was performed by this reviewer on the 8 subjects who completed Day 84. There was a similar magnitude of decrease from baseline sperm count at Day 56 and at Day 84. In a longitudinal study such as MP-0104-13, it is more clinically relevant to evaluate the change from baseline in sperm parameters after chronic exposure to minocycline than to analyze whether sperm parameters exceed the WHO minimum criteria.*

4) *The number of subjects (N=8) who completed Day 84 visit was too small to draw any meaningful conclusion, especially when semen sample was only collected once per subject after the screening baseline.*

Study MP-0104-16: This retrospective study was designed to compare the semen parameters collected from 2 cohorts of male subjects with acne vulgaris who participated in two previous Phase III studies. This study was intended to supplement the data obtained from study MP-0104-13.

MP-0104-16 was a multi-center, open-label, retrospective, cohort study of male patients, at least 16 years of age, with acne vulgaris, who have participated in either of the 2 clinical phase III trials (MP-0104-4 or MP-0104-05). Cohort 1 included male patients with acne vulgaris who were treated with a minimum of 24 weeks of minocycline 1mg/kg/day (12 weeks of active treatment and at least an additional 12 weeks of minocycline in the long-term, open-label study MP-0104-07). Cohort 2 included male patients who were in the placebo arm of the phase III trial and who have not received any tetracycline-class antibiotic since the termination of the trial.

Reviewer's comments: According to the sponsor, the two cohorts were assumed to be well-matched at the time of their randomization to the Phase III trials. The sponsor acknowledged possible confounding factors between Cohort 1, which chose to enter the long-term, open-label trial, and Cohort 2, which chose not to enter the trial.

The subjects were instructed to abstain from ejaculation for 48-72 hours prior to their semen collection at a designated andrology lab. A single-point semen sample for the assay of sperm count, sperm morphology, and sperm motility was obtained from each subject. The primary objective was the comparison of sperm concentration, sperm motility, and sperm morphology between the minocycline-treated and the control groups. The reference ranges for the semen parameters measured in the study was based on those provided by the 1999 World Health Organization criteria (see review on MP-0104-13).

Reviewer's comments: Because of the normal variability in semen quality and analyses, a single-point semen sample would provide limited information. Various laboratories may differ in their specific techniques of semen analysis.

Results:

A total of 42 male patients were enrolled; 31 in Cohort 1 and 11 in Cohort 2. The median age of both cohorts was 18 years. The mean age of Cohort 1 was 20.0 years, ranging from 14.8 to 40.9 years old. The mean age of Cohort 2 was 25.7 years, ranging from 16.3 to 50.8 years old. The exposure of Cohort 1 subjects to minocycline 1mg/kg/day ranged from 43 to 68 weeks. Twenty-three of the 31 subjects have been treated for more than one year.

Reviewer's comments: The subjects in Cohort 1 were overall younger than those in Cohort 2. The extent of exposure to minocycline in Cohort 1 is adequate for long-term evaluation.

Table 1 provides the summary of semen analysis from Cohort 1 and Cohort 2. The volume of ejaculate and the semen pH were similar between the 2 cohorts. In regards to sperm concentration, 23% (7/30) of subjects in Cohort 1 showed concentration < 20 x 10^6 compared to 18% (2/11) in Cohort 2. Twenty–three percent of subjects in Cohort 1 (5/22) had <15% of normal sperm morphology compared to 0% in Cohort 2. And finally, 31% (9/29) of subjects in Cohort 1 showed < 50% sperm motility compared to 20% (2/10) in Cohort 2. The sponsor concluded that the sperm parameters between the minocycline (Cohort 1) and control (Cohort 2) groups were similar.

Table 1: Summary of Sperm Analysis

	Cohort 1 N = 31	**Cohort 2 N = 11**
Sperm Concentration (x10^6/mL)		
N	30	11
Mean (SD)	83.7 (105.5)	154.8 (172.8)
n (%) 0 to <20	7 (23)	2 (18)
n (%) 20 to <40	6 (20)	1 (9)
n (%) 40 to <100	8 (27)	2 (18)
n (%) 100 or more	9 (30)	6 (55)
Morphology (% Normal)		
N	22	8
Mean (SD)	38.8 (28.6)	70.6 (27.3)
n (%) 0 to <15	5 (23)	0
n (%) 15 to <50	9 (41)	1 (13)
n (%) 50 to <75	6 (27)	3 (38)
n (%) 75 to 100	2 (9)	4 (50)
Motility (% Normal)		
N	29	10
Mean (SD)	55.0 (22.6)	59.4 (28.9)
n (%) 0 to <25	5 (17)	2 (20)
n (%) 25 to <50	4 (14)	0
n (%) 50 to <75	14 (48)	4 (40)
n (%) 75 to 100	6 (21)	4 (40)

Source: Posttext Table 13.2, Data Listing 14.2.

Reviewer's comments: This reviewer does not concur with the sponsor's conclusion. The semen parameters show a lower sperm concentration and percent normal morphology when the minocycline group is compared to the control group. The

percentages of subjects with semen parameters below the WHO "normal" criteria were greater in the minocycline-treated cohort than those in the control cohort for the semen concentration and percent normal sperm morphology variables. In addition, the mean values of the semen concentration and of percent normal sperm morphology in Cohort 1 are approximately 50% of those in Cohort 2.

Protocol Violations:
Cohort 1: A subject was enrolled despite being less than 16 years old. One subject did not produce enough semen for analysis and was not included in the analysis of Cohort 1. Subject 51/15 was enrolled in Cohort 1, although he had not been receiving minocycline for 6 months. Subject 51/45 discontinued minocycline during the long-term, open-label trial but was included in Cohort 1.

Overall, morphology determination was not performed in 10 subjects, and pH was not determined in 8 subjects. The number of days since ejaculation was not available in 3 subjects.

Reviewer's comments: These protocol violations potentially adversely affect the quality of the data analyzed, especially given that the total number of subjects enrolled was limited. Sperm morphology data were not available in approximately 25% of the subjects in this study (10/41).

Summary and comments:

1. The studies MP-0104-13 and MP-0104-16 were significantly limited by the small sample size and were descriptive in nature. Study MP-0104-16 had major methodological issues, as acknowledged by the sponsor. The absence of a baseline measurement and the lack of replicate within-subject measurements resulted in data that could not be meaningfully interpreted. The retrospective nature of the study and its inherent biases can not provide evidence to support meaningful conclusions.
2. The preliminary, descriptive data from the 2 studies indicate a possible negative effect of minocycline on sperm concentration (MP-0104-13, MP-0104-16) and on % normal sperm morphology (MP-0104-16). These findings (combined with the pre-clinical findings) are of sufficient concern to warrant further evaluation with adequately powered clinical studies designed to specifically define the effects of minocycline on human spermatogenesis and spermatozoal function.
3. As recommended by DRUP (consult dated 12/3/04), such a study should be a placebo-controlled, double-blind, non-inferiority design with an adequate number of subjects. The primary endpoint should evaluate a pre-specified drug-effect on sperm concentration. A primary endpoint of "proportion of subjects with a 50% decline in sperm concentration" would be acceptable. Potential secondary endpoints are pre-specified drug-effect on % sperm motility and % normal sperm morphology.
4. Drug should be given for a minimum of 3 months. Semen analyses should be performed at baseline, 3 months, and 6 months. Because of the potentially wide

variability in semen analyses, a minimum of 2 semen samples at each time point should be collected. In addition, a single laboratory should perform the semen analyses.

Christine P. Nguyen, M.D.
Medical Officer
Division of Reproductive and Urologic Drug Products

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/s/

Christine Nguyen
11/25/2005 10:44:34 AM
MEDICAL OFFICER

George Benson
11/28/2005 06:52:03 AM
MEDICAL OFFICER

Daniel A. Shames
11/29/2005 06:23:47 PM
MEDICAL OFFICER