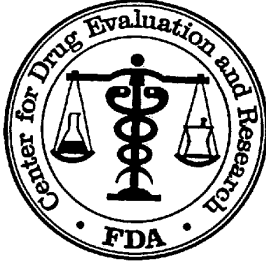


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22404Orig1s000

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number: NDA 22-404
Drug Name: Miconazole 50 mg (b) (4) buccal tablets (Oravig)
Indication(s): Oropharyngeal candidiasis
Applicant: BioAlliance Pharma
Date(s): Submission date: June 15, 2009
PDUFA due date: April 16, 2010
Review Priority: Standard

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Keywords: Clinical studies, NDA review, noninferiority

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The clinical efficacy and safety of Oravig (50 mg miconazole buccal tablets) administered once daily for 14 days in the treatment of oropharyngeal candidiasis (OPC) in immunocompromised patients was supported by one randomized, double-blind noninferiority study and one open-label, multi-center, active-controlled study. The first study was to compare the efficacy of Oravig administered once daily and Mycelex troches (clotrimazole 10 mg) administered five times a day in the treatment of oropharyngeal candidiasis (OPC) in immunocompromised patients. The second study was to compare the efficacy of Oravig and miconazole gel, a non-FDA approved comparator, in head and neck cancer patients with OPC. These two studies demonstrated that Oravig was efficacious in the treatment of OPC by showing that it was noninferior to Mycelex troches using a noninferiority margin of -15% and noninferior to miconazole gel using a noninferiority margin of -12.5%.

1.2 Brief Overview of Clinical Studies

This review focuses on the two controlled clinical studies. The objective of the first study was to compare the efficacy and safety of Oravig administered once daily and Mycelex troches (clotrimazole 10 mg) administered five times a day in the treatment of oropharyngeal candidiasis (OPC) in immunocompromised patients. The primary efficacy endpoint was clinical cure rate at days 17-22, which was defined as a complete resolution of signs and symptoms (extent of lesions score=0 and symptoms score=0).

The objective of the second study was to compare clinical efficacy of Oravig with that of miconazole gel 125 mg, 4 times per day, for 14 days, in the treatment of OPC in head and neck cancer patients receiving radiotherapy. The primary efficacy was clinical success (complete or partial response) rate at day 14, which was defined as a complete or partial disappearance of OPC lesions, where partial clinical response was improvement by at least 2 points of the score for extent of oral lesion compared with the score at day 1 according to the Murray scoring scale.

1.3 Statistical Issues and Findings

In the first study, 578 HIV positive patients were enrolled in 3 countries (USA, Canada, and South Africa), randomized to Oravig (291) and clotrimazole (287) groups. A noninferiority margin of -15% was selected by the sponsor and the lower limit of a two-sided 95% confidence interval of the difference in clinical cure rates was used to determine noninferiority of efficacy in the intent-to-treat (ITT) population and per-protocol (PP) population. The sponsor supplied a non-inferiority margin justification. Based on the statistical and clinical reviewers' assessment of the non-inferiority margin justification, it was determined that a -15% margin was justified for this study for the primary endpoint as defined. At days 17-22, in the ITT population, the cure rate was 60.7% (176/290) and 65.2% (187/287) in the miconazole group and clotrimazole group, respectively, with a difference of -4.5% (95% CI: [-12.3%, 3.4%]). In the PP population, this cure rate was 68.3% (164/240) and 74.2% (175/236) in the miconazole group and clotrimazole group, respectively, with a

difference of -5.8% (95% CI: [-13.9%, 2.3%]). It was concluded that Oravig was non-inferior to clotrimazole in clinical cure in both the ITT population and PP population. At days 35-38, in the ITT population, 42.8% (124/290) and 46.3% (133/287) remained cured, 16.6% (48/290) and 18.1% (52/287) relapsed after cure at day 17-22 in the Oravig and clotrimazole group, respectively. In the PP population 48.8% (117/240) and 53.4% (126/236) remained cured, 17.9% (43/240) and 20.3% (48/236) relapsed after cure at day 17-22, in the Oravig and clotrimazole groups, respectively.

The treatment effect was numerically different between countries (61.4% (43/70) on Oravig and 75.4% (49/65) on clotrimazole in the USA/Canada vs. 60.5% (133/220) on Oravig and 62.2% (138/222) on clotrimazole in South Africa). This might be an effect of the different demographics and baseline variables at those sites. In the USA and Canada, the majority of subjects was male (89%) and was on anti-retroviral therapy (68%), while in South Africa, the majority of subjects were female (75%) and were not on anti-retroviral therapy (13%).

In the second study, a total of 308 head and neck cancer patients with OPC were enrolled in four countries (France, Tunisia, Algeria, and Morocco) and 154 were randomized to each group. A noninferiority margin of -20% was selected by the sponsor and the lower limit of a two-sided 95% confidence interval of the difference in success rates was used to determine noninferiority of efficacy in the modified-ITT (mITT) population and PP population. FDA reviewed the justification of the noninferiority margin and concluded that a margin of -12.5% was justifiable for an endpoint of complete resolution of lesions, rather than the primary endpoint of complete and partial resolution of lesions (complete and partial clinical response). Additionally, we redefined the mITT population as all randomized subjects who received study medication. In the FDA defined mITT population, the complete clinical response rate at day 14 was 50.0% (74/148) and 43.8% (64/146) in the Oravig and miconazole gel group, respectively, with a difference of 6.2% (95% CI [-5.2%, 17.6%]). In the PP population, the complete clinical success rate was 53.3% (57/107) and 51.9% (55/106) in the Oravig and miconazole gel group, respectively, with a difference of 1.4% (95% CI [-12.0%, 14.8%]). In both populations, noninferiority of Oravig to miconazole gel was demonstrated. At day 60, in the mITT population, 38.5% (57/148) and 38.4% (56/146) remained cured, 10.8% (16/148) and 7.5% (11/146) relapsed after being cured at day 14 in the Oravig and miconazole gel group, respectively. In the PP population 40.6% (43/107) and 44.3% (47/106) remained cured, 13.2% (14/107) and 7.5% (8/106) relapsed after being cured at day 14, in the Oravig and miconazole groups, respectively.

Additionally, in France, Tunisia, and Algeria, clinical success rates in the Oravig were numerically higher (41.3% (26/63), 82.9% (34/41), and 100% (8/8)) than in the miconazole gel group (23.1% (15/65), 72.5% (29/40), and 71.4% (5/7)). In Morocco, the opposite occurred (20.7% (6/29) vs. 51.7% (15/29)). This resulted in a significant treatment by country interaction. The differences in demographic and baseline characteristics might contribute to the difference in cure rates between the two groups in this country and the differences in cure rates between different countries.

2 INTRODUCTION

2.1 Overview

Oravig 50 mg is a fixed-dose (b) (4) buccal tablet. The applicant conducted 3 clinical studies to investigate its efficacy. Study BA/2004/01/04 was a randomized, double-blind noninferiority study to compare the efficacy of Oravig administered once daily and Mycelex troches (clotrimazole 10 mg) administered five times a day in the treatment of oropharyngeal candidiasis (OPC) in immunocompromised patients. Clotrimazole troches are approved for the treatment of OPC in the USA. Study BA/2002/01/02 was an open-label, multi-center, active-controlled study to compare the efficacy of Oravig and miconazole gel in head and neck patients with OPC. Miconazole gel is not an approved regimen for OPC in the USA. Study 2002/01/03 was an open-label, non-comparative, phase III trial, to evaluate the anti-fungal activities and tolerance of Oravig tablets in the treatment of OPC in 26 HIV-positive patients, which will not be reviewed here. The two studies BA/2004/01/04 and BA/2002/01/02 (hereafter 04 and 02 for short, respectively) will be reviewed in sections 3 and 4.

2.2 Data Sources

The data sets for these studies were submitted electronically and can be found at the following location: <\\Cdsesub1\evsprod\NDA022404>. The reviewer found the data sets to be well organized and of good quality.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Objectives

Study 04

The objectives of Study 04 was to compare the efficacy and safety of Oravig administered once daily and Mycelex troches (clotrimazole 10 mg) administered five times a day in the treatment of oropharyngeal candidiasis (OPC) in immunocompromised patients.

Study 02

The objective of Study 02 was to compare clinical efficacy of Oravig with that of miconazole gel 125 mg, 4 times per day, for 14 days, in the treatment of OPC in head and neck cancer patients receiving radiotherapy.

3.1.2 Study Design

Study 04

Study 04 was a randomized, double-blind, double-dummy, parallel group, multi-center noninferiority study, conducted between 7/25/2006 and 12/27/2007. Eligible male or female HIV positive patients with OPC at 28 sites in the USA, Canada, and South Africa were randomized to one of the following two treatment groups:

- Oravig 50 mg, administered once daily for 14 days
- Clotrimazole troches 10 mg, 5 times per day for 14 days

After screening (Visit 1), randomization and treatment (Visit 2, day 1), patients were followed up at Visit 3 (On therapy, days 6-8), 4 (End of Treatment, days 14-15), 5 (Test of Cure, TOC, days 17-22), and 6 (Late Post-therapy, days 35-38).

Study 02

Study 2 was an open-label, randomized, 2-arm parallel-group, multi-center phase III noninferiority study, conducted between 5/28/2002 and 6/13/2004. According to the study report (page 34), a double blind dummy design would have introduced bias due to chewing and mouth wash, which could have favored the detachment of the Oravig because chewing and mouth wash may disturb Oravig adhesion. Due to the difficulty to reproduce the taste and appearance of Oravig for placebo, the study was designed as an open-label study. However, clinical efficacy was assessed blind in each center by a healthcare team member. Eligible head and neck cancer adult patients who had undergone radiotherapy were enrolled and randomized at day 1 to one of the following treatments for 14 days:

- Oravig 50 mg, once daily
- Miconazole gel, 125 mg per administration, 4 time daily

Patients were followed up at days 7, 14 (end of treatment visit), 30 and 60.

Comment: Note the study was conducted between 5/28/2002 and 6/13/2004. The final version of the protocol was dated 3/10/2005. The statistical analysis plan was dated 11/10/2004. It is obvious that both the statistical analysis plan and Protocol were not finalized when the study was initiated. For this open-label study, both should have been finalized before the initiation of the study.

There were 12 protocol amendments after initiation of the study. Note that changes to the protocol or statistical analysis plan after the start of the study for an open label study is of concern. The following is a summary of the statistics-related protocol amendments, made after the initiation of the study based on Protocol Appendix 9.1:

- #3. 09/19/2002. Statistic amendment (increase of number of patients from 126 to 227)
- #4. 10/14/2002. Addition of an “independent evaluator” at the end of study visit;
Change of inclusion about mycological result
- #6. 06/26/2003. Change of the study completion date to 03/31/2004.
- #11. 09/21/2004. Change of end of study as 11/30/2004.

Most of the changes were adding study centers and investigators and change of study completion dates. The amendment on 9/19/2002 included statistics related changes following the recommendations of the French Agency for the Safety of Health Projects, which included concluding a comparative test (superiority or noninferiority) for the study. The sponsor chose a noninferiority design with a 20% noninferiority margin. Assuming an efficacy of 50% for the gel, one-sided alpha=5%, and beta=10%, the sample sizes were increased to 206 evaluable patients (103 in each group) by including more centers rather than increasing the number of patients in each center. Therefore, the number to be included in the study was increased from 126 to 227 to have 206 evaluable patients. Though a sample size increase in an ongoing open label study may be a cause for concern, since the decision

to increase the sample size occurred fairly early into the study and appears to be a result of information external to the study (i.e., not based on ongoing study results), we do not see this as a major concern.

Note as stated in the study report the end of study was 6/13/2004. However, based on protocol amendments (#11, 9/21/2004) it was extended to 11/30/2004. It is unclear why a protocol amendment would be made after the end of the study. Additionally, it is not clear why the protocol would need to include a study end date. The last patient visit reported in the data set was 6/8/2004 except for one patient whose randomization date and last visit date were 11/5/2004 (not included in the ITT population).

Comment: An independent evaluator was added after protocol amendment #4 (10/14/2002). Therefore, patients evaluated in the first few months were possibly not evaluated by an independent evaluator. We will address the difference in using different evaluators in Section 3.1.4.3.

3.1.3 Statistical Considerations

3.1.3.1 Primary Endpoint and Secondary Endpoints

3.1.3.1.1 Primary Efficacy Endpoint

Study 04

The primary efficacy endpoint was clinical cure rate at TOC visit (Visit 5, days 17-22), which was defined as a complete resolution of signs and symptoms (extent of lesions score=0 and symptoms score=0).

Comment: The Visit 5 window was days 17-19 as stated in the protocol. However, based on a blind review of the data on 3/10/2008, an independent medical advisory board recommended to extend the Visit 5 window to days 17-22 to include more patients (SN46 10/28/2008, Statistical Analysis Plan Amendment 2 dated 4/1/2008). The extension is acceptable since this was based on blinded review. Previously, in our response to pre-NDA meeting (SN41 and 42, 8/1/2008, 8/27/2008), we requested an analysis that used the original window (days 17-19 after randomization) and the sponsor agreed to include a sensitivity analysis using the original window in the NDA. However, this sensitivity analysis was not included in the study report. This reviewer will conduct the analysis which is reported in Section 3.1.4.3 below.

The scoring scale for extent of oral lesions (signs) was defined as: 0=none; 1=single, localized; 2=multiple, localized; 3=extensive or confluent (Murray scoring scale).

The scoring scale for symptoms (soreness/burning) of OPC was defined as: 0=absent; 1=mild; 2=moderate; 3=severe.

Study 02

The primary efficacy endpoint was clinical success rate at day 14, which was defined as a complete or partial disappearance of OPC lesions. Partial clinical response was improvement

by at least 2 points of the score for extent of oral lesion compared with the score at day 1 according to the Murray scoring scale.

Comments:

The primary efficacy endpoint was defined based on only signs (lesions), not including symptoms, and it considered complete and partial responses as successes. Both of these points differ from the definition of the endpoint for study 04.

For the mITT population in Study 02, the analysis of the primary endpoint was performed on success rate at the day 14 visit based on either blind assessment of candidiasis lesions by a healthcare team member unaware of the assigned study treatment or the investigator's evaluation (study report, page 48). Therefore, the assessment of lesions was not conducted in a completely blind manner since some were based on the assessment of an unblinded investigator.

In addition, if the value of the primary endpoint was not available at day 14 visit, the success at day 7 visit was used (study report, page 49). This was stated in the statistical analysis plan (final version 11/10/2004), but not in the protocol (final version 3/10/2005). Given that this is an open label study any changes to the planned analyses after study start may be a cause of concern.

These two issues (the blinded assessor and the use of day 7 results) will be addressed in the Additional Analysis section (3.1.4.3).

3.1.3.1.2 Secondary Efficacy Endpoints

Study 04

There were 11 secondary efficacy endpoints in the study report (Efficacy Results section), majority of which were defined in the protocol and/or statistical analysis plan. Main secondary efficacy endpoints included the following:

- Clinical cure at day 7 (days 6-8, On Therapy Visit)
- Clinical success rate at the TOC visit. Clinical success was defined as clinical cure or clinical improvement (having no visible lesion, i.e. extent of lesions score=0 and minimal symptoms (soreness/burning score<2)
- The time of relapse and the rate of relapse at Late Post-therapy Visit (days 35-38)

Study 02

There were 9 secondary efficacy endpoints included in the study report, including the following:

- Clinical cure at day 7
- Clinical cure rate of candidiasis symptoms and oral lesions, defined as both the absence of symptoms and the complete disappearance of oral lesions
- Efficacy in patients with prior antifungal treatment
- Relapse rate at day 60 after initiation of treatment for patients with complete or partial response

Comment: There were 6 secondary efficacy endpoints included in the protocol. Efficacy in patients with prior antifungal treatment is one of those which were not included in the protocol.

3.1.3.2 Primary Analysis

3.1.3.2.1 Analysis population and missing data

Study 04

The intention-to-treat (ITT) population included all randomized patients who received at least one dose of study medication. This was defined identically both in the protocol and study report.

In the sponsor's efficacy analysis, subjects with missing data for the primary endpoint were imputed as failures in the analysis of the ITT population.

The Per Protocol (PP) population included all patients in the ITT population who did not have a major protocol deviation, had confirmation of OPC diagnosis with a positive fungal culture, completed at least 10 days of study treatment, had main efficacy criteria at the TOC visit, were compliant within the 71.4% to 120% range, and had not taken forbidden medications.

The co-primary populations for efficacy analyses were the ITT population and the PP population.

For sensitivity analyses, 2 additional populations/methods for handling missing data were defined by the sponsor as follows:

- LOCF-ITT population: ITT population with the LOCF endpoint defined as follows: if the clinical cure evaluation was missing at the TOC visit (days 17-22), it was replaced by the clinical cure evaluation at day 7 (days 6-8), if available, or by a clinical failure if the day 7 visit was also missing.
- Partial LOCF-ITT population: ITT population with the partial LOCF endpoint defined as follows: if the evaluation at the TOC visit was missing, it was replaced with the efficacy evaluation at day 7. Patients with missing day 14 and day 7 efficacy evaluations were excluded from the analysis.

Comment: In the ITT population, 49 missing values (22 on Oravig and 27 on clotrimazole) in the primary endpoint were treated as failure in the study report. Please see the Efficacy Analysis Results for detail. Among these patients, 3 patients in each group were considered as cures in the LOCF population, and remaining patients were considered as failures. In the partial LOCF-ITT population, 3 and 8 were considered as cures and failures, and 11 were excluded in the Oravig group; and 3 and 10 were considered as cures and failures, and 14 were excluded in the clotrimazole group.

Study 02

The efficacy analyses were performed on 2 populations:

- mITT population: all randomized patients with one efficacy evaluation after randomization and having received at least one treatment dose.
- PP population: all randomized patients without major protocol deviation at inclusion or during the study, and fulfilling the following conditions: completion of a pre-specified minimal treatment exposure (10 days), clinical response recorded at day 14, 15, or 16, and blind clinical efficacy evaluation at day 14, 15, or 16.

Comment: Given Study 02 was an open-label study, the definition of the mITT population which excluded patients without one efficacy evaluation and who did not have at least one treatment dose might bias the study results. Typically the mITT population is defined as all randomized patients except those who do not have a positive pre-randomization culture. Since culture results were often not known at the time of randomization, this exclusion was valid. Exclusion in any type of ITT population should not be based on post-randomization, post-therapy information, as these events could be sequelae of the treatment under study. For this reason, we will analyze the primary endpoint in the mITT population without requiring efficacy evaluation.

An additional concern with this open label study is that the definition of the analysis populations changed during the study from what was defined in the protocol to that stated in the statistical analysis plan. Changes in the protocol and the statistical analysis plan should not take place after the start of an open label study, due to concerns that the ongoing study results influenced the changes to the protocol and statistical analysis plan. In the final version of the statistical analysis plan (dated 11/10/2004, post study end), the definition of the mITT population is the same as in the study report. There was no version of statistical analysis plan dated prior to study start in this NDA submission. However, in the protocol final version (dated 3/10/2005, after study end), only two populations were defined: intended treatments (ITT) and assessable patients (AP), where ITT was defined as all randomized patients who have at least started treatment (1 day's treatment). This ITT definition in the protocol differs from the mITT population defined in the statistical analysis plan in that does not exclude subjects without an efficacy assessment.

For these two reasons, we do not agree with the sponsor's definition of mITT and will conduct additional analysis.

The applicant's principal analysis was performed on the PP population with consideration for the results from the mITT population.

Comment: According to the statistical analysis plan, if the value of the primary endpoint was not available at visit Day 14, the analysis would be performed on the success on candidiasis at Day 7 visit. In a sensitivity analysis, missing values at Day 14 would be considered as missing. Note that there was no discussion in the protocol regarding how missing data would be handled in the analysis, although there were discussions about early withdrawal, early stopping of treatment, and discontinuation of trial in the protocol. See section 3.1.4.3 Reviewer's Additional Analysis Results for an analysis which treats all missing outcomes at day 14 as failures.

3.1.3.2.2 Analysis Methods

Study 04

A one-sided noninferiority test based on binomial distribution with a type I error $\alpha=0.025$ was performed for efficacy analysis. The inferiority evaluation was based on the lower limit of a two-sided 95% confidence interval of the difference in cure rates. If the lower limit of the two-sided 95% confidence interval for the difference in clinical cure rates was higher than the pre-specified non-inferiority margin (-15%), Oravig was considered not inferior to clotrimazole.

Comment: The sponsor submitted justifications for the chosen non-inferiority margins. Based on the submitted studies and additional studies identified by the clinical reviewer, a noninferiority margin of 15% was determined to be justifiable for Study 04. The justification of the noninferiority margins is given in the appendix.

Study 02

In order to test that Oravig was not to be inferior to miconazole gel, a lower limit of a two-sided 95% confidence interval for the difference between the two regimens (Oravig – miconazole gel) would need to be greater than the non-inferiority margin, specified by the sponsor to be -20%.

No interim analysis was planned or performed.

Comment: As stated above, the sponsor submitted justification for the chosen non-inferiority margins. Based on the submitted studies and additional studies identified by the clinical reviewer, a noninferiority margin of 12.5% was considered justifiable for Study 02 for an endpoint of complete resolution of lesions, as opposed to the primary endpoint of complete and partial resolution of lesions. This is due to most of the literature used in the justification of the margin reporting resolution of lesions as the endpoint rather than complete and partial resolution. Therefore, the assessment of efficacy for this study will be based on complete resolution of lesions. The justification of the noninferiority margins is given in the appendix.

3.1.3.2.3 Sample Size Calculation

Study 04

Sample size calculation in Study 04 was based on an expected cure rate of 70% in the control group and a non-inferiority margin of -15%, and a one-sided type I error of 0.025. A sample size of 242 patients (270 patients, considering a 10% dropout rate) per group was required to achieve a 95% statistical power.

Comment: According to SN27 (8/2/2007), when 250 patients were enrolled, the sponsor submitted a letter regarding increasing number of patients at the South Africa to 400 patients due to difficulty of enrolling patients in the USA. At that point, 87 subjects were enrolled in the USA, 4 in Canada, and 159 in South Africa. We agreed upon the proposed increase.

Study 02

Assuming a success rate of 50%, a non-inferiority margin of 20%, and a one-sided type I error of 5%, 206 patients (103 patients per group) would provide 90% statistical power.

Comment: As discussed previously, the total number of subjects to be included in the study was increased from 126 to 227 to have 206 evaluable patients (Protocol Appendix).

Comment: Though the sample size was based on a one-sided 0.05 type I error rate, the analyses conducted by the sponsor used a two-sided 0.05 type I error rate.

3.1.4 Study Results

3.1.4.1 Patient Disposition, Demographic and Baseline Characteristics

Study 04

Table 1 contains the patient disposition by treatment group in Study 04.

Table 1. Patient disposition by treatment group in Study 04

	Oravig	Clotrimazole
Enrolled/Randomized	291	287
Patients who withdrew from the study	23	27
Screening failure	0	1
Inclusion criteria not all satisfied	0	2
Noncompliance or protocol deviation	7	4
Consent withdrawn	1	2
Adverse events	1	0
Investigator's decision	3	1
Lost to follow up	3	7
Serious adverse event	1	7
Death	1	5
Other reasons	10	6
Patients who completed the study	268 (92.1%)	260 (90.6%)
ITT population	290*	287
PP population	240 (82.5%)	236 (82.2%)

Adapted from sponsor's Table 5 and 6 (page 58 and 59).

*One patient reported losing all study drugs and discontinued.

Patients with multiple reasons for withdrawal were counted in more than one category.

Deaths included only those which resulted directly in withdrawal, but not those occurred after withdrawal or after study completion.

As Table 1 shows, among 291 and 287 subjects randomized to the two groups, 268 (92.1%) and 260 (90.6%) subjects completed the study. Subjects withdrew due to screening failure, not meeting the inclusion and exclusion criteria, noncompliance or protocol deviation, etc. Approximately 82% of subjects in each group were included in the PP population. In addition to 23 and 27 withdrawals listed in the table, there were 28 and 24 subjects included in ITT but excluded from PP population, in the Oravig and clotrimazole group, one and two of whom (Patno: 401004; 101029 and 405066) in the two groups, respectively, had no protocol deviation information available in the data set (Subject 401004 in the Oravig group had a treatment failure and subjects 101029 and 405066 clotrimazole group had a cure and failure, respectively).

Comment: If these three subjects with no protocol deviation information were included in the PP population, the cure rate was 68.0% (164/241) and 73.9% (176/238), with a difference of -5.90% [95% CI: -14.0%, 2.21%], still meeting a -15% noninferiority margin.

The most common protocol deviations were noncompliance, TOC visit out of acceptable observation window period, missing TOC visit, less than 10 days on study drug, or less than 2 months on stable antiretroviral therapy prior to enrollment.

Study 02

A total of 308 patients were enrolled and 154 were randomized to each group (Table 2). Two patients in the miconazole gel group were excluded from the study after randomization because one patient was randomized after inclusion period and one patient randomized before informed consent. These two patients had no outcome data available. Considering them as failures would favor Oravig in comparison. Therefore, these two subjects will not be considered in the ITT population.

Six patients in each group did not receive treatment, and one patient in the Oravig group crossed over to the miconazole gel group.

There were 147 subjects in each group in the safety population. However, 6 patients in each group did not have assessment for efficacy due to various reasons listed in the table. Therefore, there were 141 patients in each group in the mITT population. Excluding those with at least one major deviation (34 and 35), leave 107 and 106 in the Oravig and gel groups, respectively, in the PP population.

Comments:

The patient (#3082) who crossed over to the miconazole gel group had a treatment failure. Including this patient in the miconazole gel group instead of the group to which this patient was randomized in the mITT analysis would potentially make the noninferiority comparison anti-conservative. Based on ITT rules, this patient should have remained in the Oravig group. Additionally, given that this is an open label study, it is more important than in blinded studies to analyze the trial as it was randomized, as the knowledge of treatment assignment may have led to the patient/investigator to switch from the experimental treatment arm to the control.

According to Protocol amendment history, there was no change in the definition of analysis population. Only one complete version of the protocol (dated 3/10/2005) was submitted. There were two populations defined, ITT and PP populations. There was no mITT population defined. Based on the statistical analysis plan final version (11/10/2004), MITT populations included all randomized subjects having taken at least one treatment dose and one exploitable efficacy measure after application of treatment. However, the sponsor's analysis for the mITT population was based on the treatment actually received, rather than intended (randomization). For this reason we will include this patient in the Oravig group.

Additionally, we do not agree with the exclusion of patients from the mITT population for post-treatment reasons such as having no efficacy assessment. We will include these patients in an analysis and their outcomes will be considered as failures in the reviewer's analysis. Additionally, as stated earlier, an analysis population as described in the protocol did not exclude subjects for lack of an efficacy assessment. The patient who was assigned to the Oravig group but received miconazole gel will be considered as failure in the Oravig group in the reviewer's analysis.

Table 2. Patient disposition by treatment group in Study 02

	Oravig	Miconazole gel
Enrolled/Randomized	154	154
Randomized after exclusion	154	152*
Not taking treatment	6	6
<i>Informed consent withdrawn before starting (knowing) allotted treatment</i>	1	1
<i>Negative mycological culture</i>	4	1
<i>Lost to follow-up during screening</i>	0	3
<i>No on-site available treatment</i>	1	1
Crossover to the other group	1	0
Safety Population	147	147
No assessment for efficacy	6	6
<i>Consent withdrawal</i>	1	2
<i>OPC not confirmed by mycological culture</i>	3	3
<i>Lost to follow-up</i>	2	0
<i>Death due to cancer</i>	0	1
mITT population	141	141
Having at least one major deviation	34	35
PP population	107	106

Adapted from sponsor's Figure 1 and Table 6 & 7 (page 52, 54 & 55).

*One patient randomized after inclusion period and one patient randomized before informed consent were excluded. There were no treatment and outcome data listed for those two patients.

Study 04

Table 3 contains the demographic and baseline data for study 04. Age, sex, race, and country were evenly distributed between the two groups. ECOG health status score distributions were also comparable between the two groups (p-value=0.19).

In the ITT population, 48 (16.6%) in the Oravig group and 50 (17.4%) in the clotrimazole group had previous episodes of OPC. Of these with subjects, 36 subjects had one episode and 12 subjects had two or more episodes in the Oravig group; 41 subjects had one episode and 9 subjects had two or more episodes in the clotrimazole group.

Comment: Note that the numbers reported here regarding how many previous episodes of OPC a subject had are based on the submitted data and are different than those reported in the study report where it stated that 32 patients had one episode and 16 had 2 previous episodes in the Oravig group; 38 patients had 1 episode and 12 had 2 episodes in the clotrimazole group. However, the general trends are consistent.

Table 3. Demographic and baseline data in the ITT population in Study 04

	Oravig N=290	Clotrimazole N=287
Sex (males (%))	117 (40.3%)	119 (41.5%)
Age (years)		
Mean(SD)	37.5 (9.7)	36.5 (9.1)
Median[range]	37.0 [18-73]	36.0 [18-72]
Race		
Caucasian	40 (13.8%)	37 (12.9%)
African American	232 (80.0%)	226 (78.7%)
Hispanic	9 (3.1%)	10 (3.5%)
Other	9 (3.1%)	14 (4.9%)
Country		
USA/Canada	70 (24.1%)	65 (22.6%)
South Africa	220 (75.9%)	222 (77.4%)
ECOG health status at screening		
Grade 0	230 (79.3%)	218 (76.0%)
Grade 1	60 (20.7%)	69 (24.0%)
OPC history	48 (16.6%)	50 (17.4%)
HIV seropositivity prior to the study		
CD ₄ ⁺ (cell/mm ³)		
N	143	157
Mean (SD)	254 (185)	224 (170)
Median [min, max]	212 [7, 1380]	180 [2, 886]
<50	5 (3.5%)	15 (9.6%)
50–<250	80 (55.9%)	89 (56.7%)
250 or more	58 (40.6%)	53 (33.8%)
Viral Load prior to the study		
N	30	32
Mean (SD)	119325 (186626)	116130 (196527)
Median [min, max]	16678 [50, 740200]	22230 [50,711169]
Antiretroviral therapy	65 (22.4%)	83 (28.9%)
CD ₄ ⁺ (cell/mm ³) at screening	N=284	N=285
<50	23 (8.1%)	30 (10.5%)
50–<250	147 (51.8%)	140 (49.1%)
250 or more	114(40.1%)	115 (40.4%)

Adapted from Table 8 and 9 (page 61 and 62) in the study report.

ECOG: Eastern Cooperative Oncology Group score: 0=normal activity without restriction; 1=difficulties performing taxing activities but ambulatory and capable of light tasks; 2=ambulatory and able to take care of self but incapable of working. Up and active >50% of working time.

Table 4. Demographic and baseline data in the mITT population in Study 02

	Oravig N=141	Miconazole gel N=141
Sex (males (%))	103 (73.1%)	109 (77.3%)
Age (years)		
Mean(SD)	51.1 (14.5)	52.7 (14.4)
Median[range]	53.0 [17-83]	54.0 [17-83]
Weight (kg)		
Mean(SD)	64.1 (13.3)	62.5 (13.0)
Median[range]	63.0 [37-100]	60.0 [35-105]
Country		
France	63 (44.7%)	65 (46.1%)
Tunisia	41 (29.1%)	40 (28.4%)
Morocco	29 (20.6%)	29 (20.6%)
Algeria	8 (5.7%)	7 (5.0%)
ECOG health status at inclusion		
Grade 0	89 (63.1%)	95 (67.4%)
Grade 1	47 (33.3%)	69 (27.7%)
Grade 2	5 (3.6%)	7 (5.0%)
Medical and surgical history	78 (55.3%)	85 (60.3%)
Candidiasis	31 (22.0%)	32 (22.7%)
Liver disease	5 (3.6%)	10 (7.1%)
Infectious diseases	8 (5.7%)	11 (7.8%)
Candidiasis symptoms		
Burning/soreness		
Mild	40 (28.4%)	46 (32.6%)
Moderate	23 (16.3%)	19 (13.5%)
Severe	8 (5.7%)	7 (5.0%)
Absent	70 (49.7%)	69 (48.9%)
Odynophagia		
Mild	34 (24.1%)	33 (23.4%)
Moderate	12 (8.5%)	15 (10.6%)
Severe	6 (4.3%)	7 (5.0%)
Absent	89 (63.1%)	86 (61.0%)
Candidiasis lesion		
Unique, localized	49 (34.8%)	57 (40.4%)
Multiple, localized	75 (53.2%)	64 (45.4%)
Spread or confluent	17 (12.1%)	20 (14.2%)

Adopted from Table 10, 11, and 18 (page 58, 59, 64) in the study report.

ECOG: Eastern Cooperative Oncology Group score: 0=normal activity without restriction; 1=difficulties performing taxing activities but ambulatory and capable of light tasks; 2=ambulatory and able to take care of self but incapable of working. Up and active >50% of working time.

Data prior to the study (historical data) indicated that the percentage of people with CD₄⁺ cell counts less than 50 cell/mm³ in the Oravig group was lower than that in the clotrimazole group. However, the p-value from a Chi-square test was 0.08, indicating no statistically significant difference in CD₄⁺ cell distribution between the two treatment groups. In addition, there was no statistically significant difference in proportions of receiving antiretroviral treatment (p=0.07, Chi-square test). At Visit 1 (screening) CD₄⁺ cells were similarly distributed as CD₄⁺ cells prior to the study.

Comment: The CD₄⁺ cell distribution reported in is based on the data submitted with the NDA. It is slightly different from applicant's results, but the qualitative conclusions are the same.

In the ITT population, 163 (56.2%) patients in the Oravig group and 146 (50.9%) in the clotrimazole group had past medical conditions, and 195 (67.2%) in the Oravig and 199 (69.3%) in the clotrimazole group reported present medical conditions. The most commonly reported body systems with past and present medical conditions were similar between the two treatment groups. The most commonly reported past and present medical conditions were in the respiratory system, and “other” categories, respectively.

There were 46 (15.9%) patients in the Oravig group and 46 (15.9%) patients in the clotrimazole group taking prior medications. There were 236 (81.4%) patients in the Oravig group and 238 (89.2%) in the clotrimazole taking concomitant medications at randomization. Additionally, 102 (35.2%) and 114 (39.7%) subjects had change in concomitant medications, which was defined as having started on or after day 1.

There were differences in some baseline characteristics between USA/Canada and South Africa. These differences will be described in Section 4.2.

Study 02

Table 4 contains the demographic and baseline data for study 02.

The majority of subjects were males, which were almost evenly distributed in the two groups. Age, sex, height, weight, country, ECOG, medical and surgical history, and candidiasis symptoms/lesions were similar between the two groups.

3.1.4.2 Efficacy Results

Study 04

Primary Efficacy Endpoint

The primary efficacy (clinical cure) at the TOC visit is presented in Table 5. In the ITT population, the cure rate was 60.7% and 65.2% in the Oravig group and clotrimazole group, respectively, with a difference of -4.5% (95% CI: [-12.3%, 3.4%]). In the PP population, the

cure rate was 68.3% and 74.2% in the Oravig group and clotrimazole group, respectively, with a difference of -5.8% (95% CI: [-13.9%, 2.3%]). Oravig was concluded to be noninferior to clotrimazole in clinical cure using a -15% noninferiority margin in both the ITT population and PP population since both confidence intervals excluded -15%.

Table 5. Clinical cure at TOC visit by treatment group in the ITT and PP population in Study 04

Population	Oravig	Clotrimazole	Difference [95% CI]
ITT	176/290 (60.7%)	187/287 (65.2%)	-4.5% [-12.3%, 3.4%]
PP	164/240 (68.3%)	175/236 (74.2%)	-5.8% [-13.9%, 2.3%]

Adopted from Table 13 (page 68) in the study report

Comment: There were 22 missing values in the Oravig group and 27 missing values in the clotrimazole groups which were treated as failures in the ITT analysis.

Main Secondary Efficacy Endpoints

Summary of symptoms and signs of oral candidiasis at TOC in the ITT population is included in Table 6. The two treatment groups were comparable in both symptoms and signs.

Table 7 shows the mycological cure rates at TOC visit in Study 04. The mycological cure rates were similar; however, the cure rates were less than 30% for each treatment in both analysis populations.

The results by clinical cure and mycological cure are presented in Table 8. It appears that in the ITT population patients in the Oravig group were less likely to have cure-failure and more likely to have failure-failure in clinical and mycological outcomes. Only approximately 20% of patients were both clinically and mycologically cured in both groups. The kappa statistic for clinical cure and mycologic cure in the Oravig group was 0.12 (95% CI [0.03, 0.21]), and 0.04 (95% CI [-0.04, 0.12]), indicating a very low agreement between clinical cure and mycologic cure in this study.

Table 6. Candidiasis symptoms and signs at TOC visit by treatment group in the ITT population in Study 04

	Oravig N=290	Clotrimazole N=287
Symptoms		
Missing data	22 (7.6%)	27 (9.4%)
Absent	234 (80.7%)	236 (82.2%)
Mild	31 (10.7%)	22 (7.7%)
Moderate	3 (1.0%)	2 (0.7%)
Severe	0	0
Signs		
Missing data	22 (7.6%)	27 (9.4%)
Absent	189 (65.2%)	198 (68.9%)
Single, localized	38 (13.1%)	25 (8.7%)
Multiple, localized	35 (12.1%)	29 (10.1%)
Extensive or confluent	6 (5.0%)	8 (2.8%)

Table 7. Mycological cure at TOC visit by treatment group in the ITT and PP population in Study 04

Population	Oravig	Clotrimazole
ITT	79/264 (29.9%)	71/256 (27.7%)
PP	73/237 (30.8%)	64/232 (27.6%)

Adopted from Table 18 (page 73) in the study report

Table 8. Clinical outcome and mycological outcome at TOC visit in the ITT and PP population in Study 04

Clinical outcome	Mycological outcome	Oravig	Clotrimazole
ITT		N=290	N=287
Cure	Cure	61 (21.0%)	54 (18.8%)
Cure	Failure	113 (39.0%)	129 (45.0%)
Cure	Missing	2 (0.7%)	4 (1.4%)
Failure	Cure	18 (6.2%)	17 (5.9%)
Failure	Failure	72 (24.8%)	56 (19.5%)
Failure	Missing	24 (8.3%)*	27 (9.4%)†
PP		N=240	N=236
Cure	Cure	56 (23.3%)	50 (21.2%)
Cure	Failure	106 (44.2%)	121 (51.3%)
Cure	Missing	2 (0.8%)	4 (1.7%)
Failure	Cure	17 (7.1%)	14 (5.9%)
Failure	Failure	58 (24.2%)	47 (19.9%)
Failure	Missing	1 (0.4%)	0(0%)

Adopted from Table 19 (page 74) in the study report

*22 out of 24 and †27 had missing clinical data at the TOC visit but treated as clinical failure

Analysis results of the clinical cure on day 7 are included in Table 9. The cure rates were comparable between the two treatment groups both in the ITT and PP populations.

Table 9. Clinical cure at day 7 visit by treatment group in the ITT and PP population in Study 04

Population	Oravig	Clotrimazole	Difference [95% CI]
ITT	67/290 (23.1%)	71/287 (24.7%)	-1.6% [-8.6%, 5.3%]
PP	60/240 (25.0%)	63/236 (26.7%)	-1.7% [-9.6%, 6.2%]

Adopted from Table 14 (page 69) in the study report. There were 13 and 15 missing values considered as failure in the ITT population and 0 and 1 missing values in the PP population, in the Oravig and clotrimazole group, respectively.

Relapse rates at post-therapy visit (Visit 6, days 35-38) based on the submitted data are shown in Table 10. The relapse rates were comparable in the two treatment groups. Note the results are different from the results in Table 20 of the study report, where some uncured patients at TOC were included in the numbers of patients eligible for relapse at the post-therapy visit. The numbers of relapse were also slightly different (51 and 53 in the ITT population; 45 and 49 in the PP population, for the two treatment groups, respectively). The

relapse rates were approximately 18% in both groups in both analysis populations in cured patients. Among all ITT patients, approximately 43% and 46% of subjects in the two groups were cured at TOC and remained cured at days 35-38.

Table 10. Relapse at post-therapy visit (Days 35-38) by treatment group in the ITT and PP population in Study 04

Clinical Cure and Relapse	Oravig	Clotrimazole
ITT	N=290	N=287
Cured at TOC	176 (60.7%)	187 (65.2%)
<i>Relapse</i>	48 (16.6%)	52 (18.1%)
<i>No relapse</i>	124 (42.8%)	133 (46.3%)
<i>Missing</i>	4 (1.4%)	2 (0.1%)
PP	N=240	N=236
Cured at TOC	164 (68.3%)	175 (74.2%)
<i>Relapse</i>	43 (17.9%)	48 (20.3%)
<i>No relapse</i>	117 (48.8%)	126 (53.4%)
<i>Missing</i>	4 (1.7%)	1 (0.4%)

Table 11. Clinical cure at TOC visit by treatment group in the LOCFITT and partial LOCFITT population in Study 04

Population	Oravig	Clotrimazole	Difference [95% CI]
LOCFITT	179/290 (61.7%)	190/287 (66.2%)	-4.5% [-12.3%, 3.4%]
PLOCFITT	179/279 (64.2%)	190/273 (69.6%)	-5.4% [-13.2%, 2.4%]

In the LOCFITT and partial LOCFITT population (Table 11), 3 failures in each group in the ITT population were considered as cures. Furthermore, 11 and 14 subjects with missing clinical outcomes at both day 14 and 7 in the two groups were excluded in the partial LOCFITT population. Therefore, the cure rates in the LOCFITT and partial LOCFITT populations were slightly higher than the primary endpoint analysis in the ITT population.

The analysis results from LOCFITT and partial LOCFITT populations were very consistent with the sponsor's primary analysis in the ITT population.

Study 02

Primary Efficacy Endpoint

The primary efficacy endpoint (complete or partial clinical response) at day 14 is shown in the following table. In the mITT population, the difference in complete or partial clinical response (CR+PR) was 7.1%, with a two-sided 95% confidence interval [-4.5%, 18.7%], meeting the noninferiority margin of -20% proposed by the sponsor. Results for complete clinical response (CR) were similar.

Table 12. Clinical response at TOC visit by treatment group in the mITT and PP population in Study 02

		Oravig	Miconazole gel	Diff (Oravig-Gel) [95% CI]
mITT	CR	74/141 (52.4%)	64/141 (45.4%)	7.1% [-4.5%, 18.7%]
	CR+PR	79/141 (56.0%)	69/141 (48.9%)	7.1% [-4.5%, 18.7%]
PP	CR	57/107 (53.3%)	55/106 (51.9%)	1.4% [-12.0%, 14.8%]
	CR+PR	62/107 (56.9%)	58/106 (54.7%)	3.2% [-10.1%, 16.5%]

CR: complete response; PR: partial response. Primary endpoint was CR or PR.

Adapted from Table 23 (page 68) in the study report

Comments:

In the mITT population, there were only 10 subjects whose clinical response at day 7 was used as the primary endpoint due to missing values at TOC, 4 on Oravig and 6 on miconazole gel. Please see the review's analysis in Section 3.1.4.3 below.

The justification of the noninferiority margin of 12.5% was based on complete resolution of lesions rather than complete and partial. Note that the endpoint of complete response would meet the noninferiority margin of 12.5%.

As discussed earlier, we do not agree with the sponsor's defined mITT population. See section 3.1.4.3 for the primary analysis using an alternate MITT definition.

Main Secondary Efficacy Endpoints

Candidiasis symptoms and lesions at TOC visit are summarized in the following table.

Table 13. Candidiasis symptoms and lesions at TOC visit by treatment group in the mITT population in Study 02

	Oravig N=141	Miconazole gel N=141
Candidiasis symptoms		
Burning/soreness		
Missing data	4 (2.8%)	6 (4.3%)
Absent	103 (73.1%)	100 (70.9%)
Mild	26 (18.4%)	29 (20.6%)
Moderate	7 (5.0%)	4 (2.8%)
Severe	1 (0.7%)	2 (1.4%)
Odynophagia		
Missing data	4 (2.8%)	6 (4.3%)
Absent	113 (80.1%)	106 (75.2%)
Mild	14 (10.0%)	22 (15.6%)
Moderate	6 (4.3%)	5 (3.6%)
Severe	4 (2.8%)	2 (1.4%)
Candidiasis lesions		
Absent	74 (52.5%)	64 (45.4%)
Unique, localized	38 (27.0%)	49 (34.8%)
Multiple, localized	49 (34.5%)	20 (14.2%)
Spread or confluent	10 (7.1%)	8 (5.7%)

There were no significant differences in distributions of candidiasis symptoms and lesions between the two treatment groups. There were no significant differences in candidiasis lesions between the two groups (Chi-square test, p-value=0.50).

Negative fungal culture was listed but not defined in the protocol. We created a fungal culture variable, which was positive if at least one culture had greater than 0 colonies at one visit and negative if all available culture had 0 colonies at one visit. The results in Table 14 were the same as the fungal culture results shown in Table 34 of the study report.

Table 14. Fungal culture at TOC visit in the mITT and PP population in Study 02

Culture	Oravig	Miconazole gel	Diff (Oravig - gel) [95% CI] p-value
mITT	N=141	N=141	
Positive	69 (48.9%)	50 (35.5%)	13.5% [2.1%, 24.9%] 0.022
Negative	64 (45.4%)	77 (54.6%)	
Missing	8 (5.7%)	14 (9.9%)	
PP	N=107	N=105	
Positive	52 (48.6%)	34 (32.3%)	16.2% [3.2%, 29.2%] 0.016
Negative	53 (49.5%)	65 (61.3%)	
Missing	2(1.9%)	7 (6.6%)	

The p-value from the Chi-square test for culture in the mITT population was 0.053. Excluding the missing category, the p-value from the Chi-square test was 0.043. Note the p-values in the table were from the comparison of two positive proportions of the two treatment groups. The p-value from Fisher's exact test for culture in the PP population was 0.038. These tests and confidence intervals show that Oravig had higher positive culture rates than miconazole gel in both mITT and PP populations. Oravig had numerically higher clinical cure rates, but significantly higher positive culture rates.

The following table shows clinical response and fungal culture in the mITT and PP population. It appears that a larger proportion of subjects in the Oravig group were clinically cured but culture positive in both populations and that there was a larger number of subjects in the miconazole gel group who were a clinical failure but culture negative. This goes along with the results that Oravig had a numerically higher clinical response but a significantly lower mycological outcome compared to Miconazole gel.

Table 15. Clinical response and fungal culture at TOC visit in the mITT and PP population in Study 02

	Clinical outcome	Fungal culture	Oravig	Miconazole gel
mITT			N=141	N=141
	Cure	Positive	40 (28.4%)	25 (17.7%)
	Cure	Negative	35 (24.8%)	37 (26.2%)
	Cure	Missing	4 (2.8%)	7 (5.0%)
	Failure	Positive	29 (20.6%)	25 (17.7%)
	Failure	Negative	29 (20.6%)	40 (28.4%)
	Failure	Missing	4 (2.8%)	7 (5.0%)
PP			N=107	N=106
	Cure	Positive	32 (22.7%)	19 (13.5%)
	Cure	Negative	29 (20.6%)	34 (24.1%)
	Cure	Missing	1 (0.7%)	5 (3.5%)
	Failure	Positive	20 (14.2%)	15 (10.6%)
	Failure	Negative	24 (17.0%)	31 (22.0%)
	Failure	Missing	1 (0.7%)	2 (1.4%)

The following table shows clinical response at day 7 by treatment group. It appears that cure rates for Oravig were lower than those for miconazole gel. However, all 95% confidence intervals included 0.

Table 16. Clinical response at day 7 by treatment group in the mITT and PP population in Study 02

		Oravig	Miconazole gel	Diff (Oravig - gel) [95% CI]
mITT	CR	17/141 (12.1%)	21/138 (15.2%)	-3.2% [-11.2%, 4.9%]
	CR+PR	20/141 (14.2%)	28/138 (20.3%)	-6.1% [-14.9%, 2.7%]
PP	CR	11/107 (10.3%)	17/104 (16.4%)	-6.1% [-15.2%, 3.1%]
	CR+PR	14/107 (13.1%)	23/104 (54.7%)	-9.0% [-19.3%, 1.2%]

The sponsor defined relapse two different ways, one in the study report (defined as the reappearance of the oral lesion in a candidiasis-cured patient) and one in the protocol (defined as an increase in the score for extent of oral lesions compared with the score obtained at day 14). The following table shows the relapse rate at day 30 defined as reappearance of the oral lesion in a candidiasis cured patient. The relapse numbers were the same as in the study report. However, no relapse and missing were considered as relapse-free in the study report. Patients in the Oravig group had numerically higher relapse rates than miconazole gel at day 30 (the difference was not statistically significant).

Table 17. Relapse at day 30 in patients with complete clinical response at day 14 by treatment group in the ITT and PP population in Study 02

	Clinical cure and relapse	Oravig	Miconazole gel	Diff (Oravig - gel) [95% CI] p-value
mITT		N=141	N=141	
	Cured	74 (52.5%)	64 (45.4%)	
	Relapse	14 (9.9%)	8 (5.7%)	4.3% [-2.0%, 10.5%] 0.18
	No relapse	59 (41.8%)	56 (39.3%)	2.1% [-9.3%, 13.6%] 0.72
	Missing	1 (0.7%)	0	
PP		N=107	N=106	
	Cured	57 (53.3%)	55 (51.9%)	
	Relapse	12 (11.2%)	6 (5.7%)	5.6% [-1.9%, 13.0%] 0.15
	No relapse	45 (42.1%)	49 (46.2%)	-4.2% [-17.5%, 9.2%] 0.54

Adapted from Table 30 (page 75) in the study report
Proportions are based on the total sample size.

Table 18 shows the relapse rate at day 60. At day 60, the relapse rates in the Oravig group were still higher than those in the miconazole gel group; however the differences were not statistically significant. The “no relapse” rates remained similar between the two arms.

Table 18. Relapse at day 60 in patients with complete clinical response at day 14 by treatment group in the ITT and PP population in Study 02

	Clinical cure and relapse	Oravig	Miconazole gel	Diff (Oravig - gel) [95% CI] p-value
mITT		N=141	N=141	
	Cured	74(52.5%)	64(45.4%)	
	Relapse	16 (11.3%)	11 (7.8%)	3.5% [-3.3%, 10.4%] 0.31
	No relapse	57 (40.4%)	53 (37.6%)	2.8% [-8.5%, 14.2%] 0.72
	Missing	1 (0.7%)	0	
PP		N=107	N=106	
	Cured	57 (53.8%)	55 (51.9%)	
	Relapse	14 (13.2%)	8 (7.5%)	5.5% [-2.6%, 13.7%] 0.18
	No relapse	43 (40.6%)	47 (44.3%)	-4.1% [-17.4%, 9.1%] 0.54

Adapted from Table 31 (page 76) in the study report
Proportions are based on the total sample size.

3.1.4.3 Reviewer’s Additional Analysis Results

Cure rate at day 17-19 for study 04

In the original design, the TOC visit was 17-19 days. It was then extended to 17-22 for the analysis as stated in the study report. However, in the primary analysis in the ITT population, the TOC visit occurred between day 10 and day 29. The TOC visit for 8 and 3

subjects in the two treatment groups was between day 10 to 16, 2 and 1 of whom were assessed at days 10, 15, and 16, and coded as cures. The TOC visit for 4 and 6 subjects was between day 23-29 in the two treatment groups, 3 and 3 of whom were assessed at day 23 (for 5 subjects) and day 29 (for 1 subject on clotrimazole) and considered as cures. In order to examine the efficacy using the original TOC window, we consider all of these subjects with TOC visit out of window 17-22 as failures, as in the primary efficacy analysis all missing values were considered as failures.

Table 19. Clinical cure at day 17-19 visit by treatment group in the ITT and PP population in Study 04

Population	Oravig	Clotrimazole	Difference [95% CI]
ITT	148/290 (51.0%)	149/287 (51.9%)	-0.9% [-9.0%, 7.3%]
PP	140/240 (58.3%)	143/236 (60.6%)	-2.3% [-11.2%, 6.6%]

Obviously, the cure rates were lower than those using the TOC window of day 17-22 (actually day 10-29). However, the differences and their confidence intervals were consistent with the sponsor’s primary analysis results.

FDA Primary analysis of study 02

As discussed above, we did not agree with the sponsor’s definition of the mITT population which assigned subjects to the treatment received rather than the treatment to which they were randomized and which excluded subjects without a post-baseline efficacy assessment. As this exclusion could have been affected by the treatment, we did not consider it a valid exclusion from an mITT population. In addition, one subject who did not receive assigned Orgvig but received miconazole gel was considered as failure in the Oravig group in the following analysis.

Table 20. FDA primary analysis of the mITT population Clinical response at TOC visit by treatment group in the mITT and PP population in Study 02

		Oravig	Miconazole gel	Diff (Oravig-Gel) [95% CI]
mITT	CR	74/148 (50.0%)	64/146 (43.8%)	6.2% [-5.2%, 17.6%]
	CR+PR	79/148 (53.4%)	69/146 (47.3%)	6.1% [-5.3%, 17.5%]

CR: complete response; PR: partial response. Primary endpoint was CR or PR.

Comment: Because most of the outcomes in the literature used for the noninferiority justification are resolution of lesions, we are able to conclude that a 12.5% noninferiority margin was justifiable for complete response. The lower bound of the 95% confidence interval for complete response indicates that the study results still met the noninferiority criterion. Please see the non-inferiority margin justification in the Appendix.

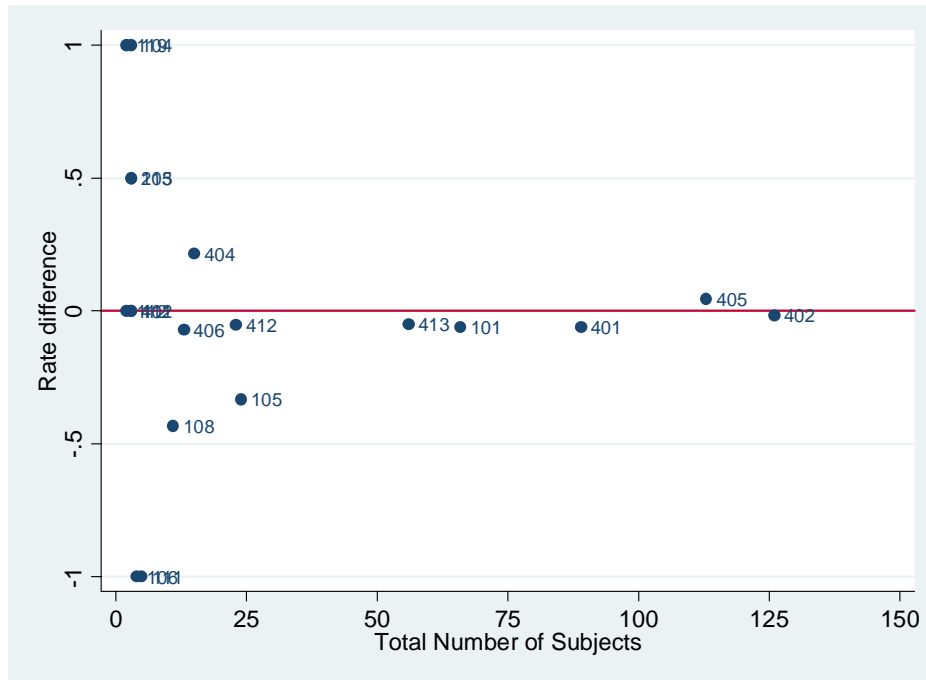
Cure rate by study site

Study 04

In Study 04, there were 28 study sites in the ITT population. Only 19 sites had both treatment groups. Nine sites only had one treatment group with 1 to 3 patients. As a means

of assessing if any site had an exceptionally large influence on the results of the study, the differences in cure rates between the two groups (Oravig-clotrimazole) for each site is plotted against the total number of subjects in each site. This is shown in the following graph.

Figure 1. Difference in cure rates by total number of subjects in a study site in ITT population in Study 04

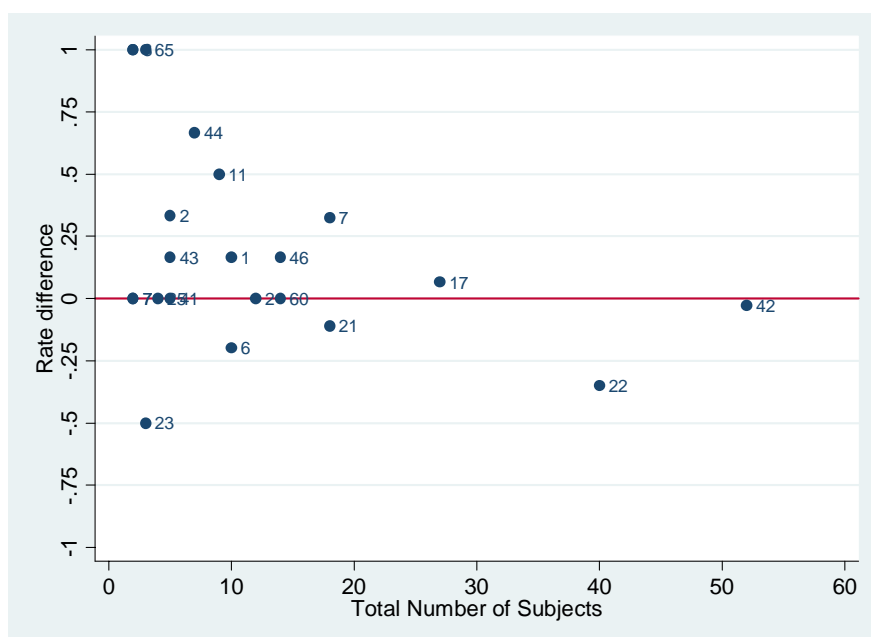


The differences were scattered around the 0 line. As the number of subjects increased, the differences were closer to 0. Therefore, there were no dominant differences in cure rates.

Study 02

The following figure shows the difference in cure rate by study site in Study 02.

Figure 2. Difference in cure rates by total number of subjects in a study site in ITT population in Study 02



In most study sites the treatment difference (Oravig - gel) was around 0 or slightly larger than 0. Noticeably, study site 22 had a much lower treatment difference. However, it was not a concern in determination of non-inferiority, since the results favored the control arm. There were a few study sites with treatment effect favoring Oravig, especially sites 7, 11, and 44. Since the total numbers of subjects from these three sites were not very large, this should not be a serious concern.

Cure rates by CD₄⁺ count in Study 04

In order to examine the effect of CD₄⁺ on the treatment effects, we analyzed the primary endpoint by CD₄⁺ (Table 21).

Table 21. Clinical cure at TOC visit by treatment group and CD₄⁺ cell count at randomization in the ITT and PP population in Study 04

Baseline CD ₄ ⁺	Oravig	Clotrimazole	Difference (95% CI)
ITT population	N=290	N=287	
<50	11/23 (47.8%)	11/30 (36.7%)	11.2% (-15.6%, 37.9%)
50-<250	93/147 (63.3%)	93/140 (66.4%)	-3.2% (-14.2%, 7.9%)
250+	67/114 (58.8%)	81/115 (70.4%)	-11.7% (-24.0%, 0.6%)
Missing	5/6 (83.3%)	2/2 (100%)	
PP population	N=240	N=236	
<50	8/14 (57.1%)	10/17 (58.8%)	-1.7% (-36.6%, 33.6%)*
50-<250	88/127 (69.3%)	87/121 (71.9%)	-2.6% (-14.0%, 8.7%)
250+	64/94 (68.1%)	76/96 (79.2%)	-11.1% (-23.5%, 1.4%)
Missing	4/5 (80.0%)	2/2 (100%)	

*Exact method

There were a numerically higher proportion of clinical cures in patients with CD₄⁺ counts <50 and a numerically lower proportion of clinical cures in patients with CD₄⁺ counts ≥250 in the Oravig group than in the clotrimazole group in the mITT population. In the PP population, the trend was similar in patients with CD₄⁺ counts ≥250.

Cure rates by blind assessment of clinical outcome in MITT population in Study 02

As mentioned before, in Study 02, the analysis of the primary endpoint was performed on success rate at the day 14 visit based on either blind assessment of candidiasis lesions by a healthcare team member unaware of the assigned study treatment or investigator's evaluation (study report, page 48). An independent evaluator was added after protocol amendment #4. Hence, patients evaluated in the first few months were not evaluated by an independent evaluator. Therefore, it is not completely blind. The following table includes cure rates by blind assessment only in the MITT population in Study 02.

Table 22. Cure rates by blind assessment of clinical outcome in MITT population in Study 02

	Oravig	Miconazole gel	Diff (Oravig - gel) [95% CI]
Blinded			
CR	69/128 (53.9%)	63/130 (48.6%)	5.4% [-6.7%, 17.6%]
CR+PR	74/128 (57.8%)	68/130 (52.3%)	5.5% [-6.6%, 17.6%]
Non-Blinded			
CR	5/13 (38.5%)	1/11 (9.1%)	29.4% [-8.7%, 61.6%]
CR+PR	5/13 (38.5%)	1/11 (9.1%)	29.4% [-8.7%, 61.6%]

Numerically, non-blinded assessment by investigator yielded more complete cure in the Oravig group, with larger differences between treatment groups (29%) than for blinded assessments (5%). However, the difference was not statistically significant due to small sample sizes. The results based on blinded outcome assessment were similar to the sponsor's primary endpoint results and would also be able to exclude the noninferiority margin if results were limited to this population only. In the PP population, all primary endpoint scores were blindly assessed.

If all outcomes from non-blinded assessment were treated as treatment failure, the cure rates would be 48.9% (69/141), and 44.7% (63/141), with a 95% two-sided confidence interval of [-7.4%, 15.9%], meeting the noninferiority margin of -12.5%.

Missing clinical response at day 14 replaced by values at day 7 in MITT population in Study 02

As mentioned above, there was no discussion in the protocol as to how missing data would be handled in the analysis. In the statistical analysis plan (dated post study end), it states that if the value of the primary endpoint was not available at visit Day 14, the analysis would be performed on the success on candidiasis at Day 7 visit. Therefore it is worthwhile to conduct more analyses to evaluate the effects of mode of assessment and the method of last value carry forward on the primary endpoint.

In the mITT population, there were only 10 subjects whose clinical response at day 7 was used as the primary endpoint due to missing value at TOC, 4 on Oravig and 6 on miconazole gel. Of these subjects, 1 out of 4 and 1 out of 6 were completely cured, in the Oravig and miconazole gel group, respectively. Given these small numbers and the fact that there were

more subjects with missing values on the control, this was not seen as a large enough problem to raise this reviewer’s concern.

3.2 Evaluation of Safety

Study 04

The following table lists adverse events by treatment group in the safety population in Study 04.

Table 23. Adverse Events by treatment group in the safety population in Study 04

	Oravig N=290	Clotrimazole N=287
Patients with adverse events	161 (55.5%)	152 (53.0%)
Patients with serious events	10 (3.4%)	9 (3.1%)
Patients who died	5 (1.7%)	6 (2.1%)

In total, 161 (55.5%) and 152 (53.0%) subjects in the two treatment groups had at least one adverse event, 10 (3.4%) and 9 (3.1%) of whom had serious adverse events, including 5 and 6 deaths, respectively. The reasons for deaths included renal failure, dehydration, etc. No deaths were considered as drug related by the sponsor.

Table 24 classifies all adverse events by severity by treatment group in the safety population. As the table shows there were no concerning differences in severity.

Table 24. Severity of all adverse events by treatment group in the safety population in Study 04

Severity	Oravig N=290	Clotrimazole N=287
Mild	322 (73.7%)	326 (80.1%)
Moderate	92 (21.1%)	64 (15.7%)
Severe	17 (3.9%)	9 (2.2%)
Life Threatening	0	1 (0.3%)
Fatal*	6 (1.4%)	7 (1.7%)
Total	437	407

*One subject in each arm counted twice due to two different AE terms.

Common treatment-emergent AEs (AEs started on or after the first dose of study drug) and number of subjects with these AEs are listed in the following table. The most common AEs included gastrointestinal system disorders, infections and infestations, and nervous system disorders. The adverse event incidences were comparable between the two groups. The difference in proportions of subjects with nervous system disorders was numerically higher in the Oravig group, though not statistically significantly different (p-value=0.066).

Table 25. Adverse events occurring in no less than 2% population by treatment group in the safety population in Study 04

	Oravig N=290		Clotrimazole N=287	
	Events	Patients	Events	Patients
Total number of adverse events or total number of patients with adverse events	417	158 (55.5%)	391	146 (53.0%)
Blood and lymphatic system disorder	26	20 (6.9%)	27	24 (8.4%)
Gastrointestinal disorders	134	76 (26.2%)	126	68 (23.7%)
General disorders and administration site conditions	28	19 (6.6%)	36	23 (8.0%)
Infections and infestations	55	46 (15.9%)	53	49 (17.1%)
Investigations	25	16 (5.5%)	26	18 (6.3%)
Metabolism and nutrition disorders	12	8 (2.8%)	7	6 (2.1%)
Musculoskeletal and connective tissue disorders	20	15 (5.2%)	20	17 (5.9%)
Nervous system disorders	47	38 (13.1%)	31	24 (8.4%)

Study 02

The following table shows adverse events and serious adverse events in the two treatment groups. The rates were comparable between the two groups.

Table 26. Adverse events by treatment group in the safety population in Study 02

Number of Patients	Oravig N=147	Miconazole gel N=147
Adverse events	43 (30.5%)	40 (28.4%)
Serious adverse events	1 (0.7%)	7 (2.8%)

The following table includes severity of adverse events by treatment group. It appears that Oravig group had a lower percentage of severe adverse events (10.1% versus 14.5%).

Table 27. Severity of all adverse events by treatment group in the safety population in Study 02

Severity	Oravig N=147	Miconazole gel N=147
Mild	26 (37.7%)	14 (28.4%)
Moderate	29 (42.0%)	29 (46.8%)
Severe	7 (10.1%)	9 (14.5%)
Missing	7 (10.1%)	10 (16.1%)
Total	69 (100%)	61 (100%)

Adverse events by body system in Study 02 are summarized in the following table. Nervous system and skin subcutaneous tissue disorders occurred slightly more often in the Oravig

group. However, the numbers were small (p-values from Fisher's exact were greater than 0.1).

Table 28. Adverse events by body system and treatment group in the safety population in Study 02

	Oravig N=147		Miconazole gel N=147	
	Events*	Patients	Events*	Patients
Total number of adverse events or total number of patients with adverse events	69	43 (29.3%)	62	40 (27.2%)
Blood and lymphatic system disorder	1	1 (0.7%)	0	0
Cardiac disorder	0	0	1	1(0.7%)
Ear and labyrinth disorder	2	2 (1.4%)	0	0
Gastrointestinal disorders	22	17 (11.6%)	30	22 (15.0%)
General disorders and administration site conditions	7	6 (4.1%)	5	5(3.4%)
Infections and infestations	8	7 (4.8%)	10	8 (5.4%)
Investigations	1	1 (0.7%)	0	0
Musculoskeletal and connective tissue disorders	5	5 (3.4%)	2	2 (1.4%)
Neoplasm benign, malignant and unspecified	1	1 (0.7%)	2	2 (1.4%)
Nervous system disorders	11	11 (7.5%)	4	3 (2.0%)
Respiratory, thoracic and mediastinal disorders	3	2 (1.4%)	6	6 (4.1%)
Skin and subcutaneous tissue disorders	6	6 (4.3%)	2	1 (0.7%)
Vascular disorders	0	2 (1.4%)	0	0

*One patient could have more than one AE episode in more than one system.

4 Findings in Special/Subgroup Populations

4.1 Gender, Race and Age

Study 04

Clinical cure rates at TOC visit by treatment group and by sex, race, and age in the ITT and PP populations in Study 04 are included in the following table.

Table 29. Clinical cure at TOC visit by treatment group, gender, race, and age in ITT and PP population in Study 04

	Oravig	Clotrimazole	Difference [95% CI]
ITT population	N=290	N=287	
Sex			
Female	113/173 (65.3%)	115/168 (68.5%)	-3.1% [-13.1%, 6.9%]
Male	63/117 (53.9%)	72/119 (60.5%)	-6.7% [-19.3%, 5.9%]
Race			
Caucasian	24/40 (60.0%)	28/37 (75.7%)	-15.7% [-36.0%, 4.9%]
Black or Africa American	140/232 (60.3%)	143/226 (63.3%)	-2.9% [-11.8%, 6.0%]
Other	12/18 (66.7%)	16/24 (66.7%)	0% [-28.8%, 28.8%]
Age			
18-29	43/65 (66.2%)	40/64 (62.5%)	3.7% [-12.9%, 20.2%]
30-49	111/190 (58.4%)	131/197 (66.5%)	-8.1% [-17.7%, 1.5%]
50-73	22/35 (62.9%)	16/26 (61.5%)	1.3% [-23.3%, 25.9%]
PP population	N=240	N=236	
Sex			
Female	108/148 (73.0%)	111/144 (77.1%)	-4.1% [-14.0%, 5.8%]
Male	56/92 (60.9%)	64/92 (69.6%)	-8.7% [-22.4%, 5.0%]
Race			
Caucasian	24/34 (70.6%)	23/29 (79.3%)	-8.7% [-30.0%, 12.5%]
Black or Africa American	130/192 (67.7%)	136/186 (73.1%)	-5.4% [-14.6%, 3.8%]
Other	10/14 (71.4%)	16/21 (76.2%)	-4.8% [-37.2%, 25.5%]*
Age			
18-29	42/55 (76.4%)	36/49 (73.5%)	2.9% [-13.8%, 19.6%]
30-49	103/157 (65.6%)	124/162 (76.5%)	-10.9% [-20.8%, 1.1%]
50-73	19/28 (67.9%)	15/25 (60.0%)	7.9% [-18.0%, 33.7%]

*Exact method.

There are appear to be some differences, though not statistically significant, in the treatment effect across the demographic subgroups with males, Caucasians, and the middle age group having lower cure rates on Oravig. Since this study was conducted in two very different geographic areas (North America and South Africa) which have different patient populations, a further exploration of the interaction of gender, race and age was explored in the ITT population (Table 30). Differences in selected baseline characteristics by country are included in Section 4.2.

Table 30. Clinical cure at TOC visit by treatment group and classification of race, gender, and age in the ITT population in Study 04

	Oravig	Clotrimazole	Difference [95% CI]
ITT population	N=290	N=287	
Race, Sex, and Age			
Caucasian female	0/2 (0.0%)	3/4 (75.0%)	
18-29	0	0	
30-49	0/1 (0%)	3/4 (75.0%)	
50-73	0/1 (0%)	0	
Caucasian male	24/38 (63.2%)	25/33 (75.7%)	-12.5% [-33.8%, 8.6%]
18-29	1/1 (100.0%)	2/2 (100%)	
30-49	15/25 (60.0%)	17/22 (77.3%)	-17.3% [-43.3%, 8.7%]
50-73	8/11 (72.3%)	6/9 (66.7%)	
Black or Africa American female	109/165 (66.1%)	104/152 (68.4%)	-2.4% [-12.7%, 8.0%]
18-29	37/51 (72.6%)	30/47 (63.8%)	8.7% [-9.7%, 27.1%]
30-49	64/102 (62.8%)	68/96 (70.8%)	-8.1% [-21.2%, 5.0%]
50-73	8/12 (66.7%)	6/9 (66.7%)	
Black or Africa American male	31/67 (46.3%)	39/74 (52.7%)	-6.4% [-22.9%, 10.1%]
18-29	3/9 (33.3%)	7/13 (53.9%)	
30-49	23/49 (46.9%)	28/53 (52.8%)	-5.9% [-25.3%, 13.5%]
50-73	5/9 (55.6%)	4/8 (50.0%)	
Other female	4/6(66.7%)	8/12(66.7%)	
18-29	2/2(100.0%)	0/1(0.0%)	
30-49	2/2 (100.0%)	8/11(72.7%)	
50-73	0	0	
Other male	8/12 (66.7%)	8/12 (66.7%)	
18-29	0/1 (0.0%)	1/1 (100.0%)	
30-49	7/9 (77.8%)	7/11 (63.6%)	
50-73	1/1(100%)	0	

In Study 04, it appears that the cure rates of Oravig were lower than those of clotrimazole consistently among male subjects and among Caucasians. The cure rates of Oravig were lower than these of clotrimazole in age group 30-49 (overall, Caucasian males, and Black African American females or females) and higher in age group 50-73. However, all differences were not statistically significant as indicated by their 95% confidence intervals.

Study 02

The following table includes complete clinical response at day 14 by sex and age in the mITT population in Study 02.

Table 31. Complete clinical response at day 14 visit by treatment group, sex, and age in the mITT population in Study 02

	Oravig N=141	Miconazole gel N=141	Difference (95% CI)
Sex			
Female	18/38 (47.4%)	16/32 (50.0%)	-0.3% [-26.1%, 20.9%]
Male	56/103 (54.4%)	48/109 (44.0%)	10.3% [-3.1%, 23.7%]
Age			
17-29	9/15 (60.0%)	13/15 (86.7%)	-26.7% [-56.8%, 3.5%]
30-49	21/34 (61.8%)	16/33 (48.5%)	13.3% [-10.3%, 36.9%]
50-83	44/92 (47.8%)	35/93 (37.6%)	10.2% [-4.0%, 24.4%]

In females the cure rates between the two treatment groups were similar. However, in males the cure rate in the Oravig group was higher than that in the miconazole gel group. In the age group of 17-29 years the cure rate in the Oravig was lower than in the miconazole gel group. Compared with age group of 17-29 years old, in older age groups, Oravig had higher cure rates than miconazole gel. However, all these differences were not statistically significant.

There was no race information available. Therefore, there was no analysis by race in the table.

4.2 Other Special/Subgroup Populations

Cure rate by country

Study 04

Table 32. Clinical cure at day 17-22 by country in the ITT population in Study 04

Country	Oravig	Clotrimazole	Diff (Orvig-Clotrimazole) [95% CI]
USA	N=67 41 (61.2%)	N=62 47 (75.8%)	-14.6% [-30.4%, 1.2%]
Canada	N=3 2 (66.7%)	N=3 2 (66.7%)	
South Africa	N=220 133 (60.5%)	N=222 138 (62.2%)	-1.7% [-10.8, 7.4%]

There were 3 countries included in Study 04 (Table 32). The cure rate in the Oravig group in the USA was approximately 15% lower than that in the clotrimazole group, which may be explained by the differences in baseline characteristics, such as sex, health status, baseline CD₄⁺ count, anti-retroviral therapy, as shown in Table 33, but the difference in cure rates between the two groups in the USA/Canada was not statistically significant. In South Africa, two cure rates were comparable. However, there was no interaction between country and treatment based on the observed data.

Table 33. Sex, CD₄+ count, antiretroviral therapy, and ECOG, by country in the ITT population in Study 04

Country	Oravig	Clotrimazole	All
USA/Canada			135
Sex	N=70	N=65	
Male	62 (88.6%)	54 (83.1%)	116 (85.9%)
Female	8 (11.4%)	11 (16.9%)	19 (14.1%)
CD ₄ +	N=67	N=64	N=131
<50	11 (16.4%)	7 (10.9%)	18 (13.7%)
50-<250	21 (31.3%)	16 (25.0%)	37 (28.2%)
250+	35 (52.2%)	41 (64.1%)	76 (58.0%)
Antiretroviral therapy	N=70	N=65	N=135
Yes	43 (61.4%)	49 (75.4%)	92 (68.2%)
No	27 (38.6%)	16 (24.6%)	43 (31.9%)
ECOG	N=61	N=63	N=124
0	58 (95.1%)	56 (88.9%)	114 (91.9%)
1+	3 (4.9%)	7 (11.1%)	10 (8.1%)
South Africa			
Sex	N=220	N=222	N=442
Male	55 (25.0%)	65 (29.3%)	120 (27.2%)
Female	165 (75.0%)	157 (70.7%)	322 (72.9%)
CD ₄ +	N=217	N=221	N=438
<50	12 (5.5%)	23 (10.4%)	35 (8.0%)
50-<250	126 (58.1%)	124 (56.1%)	250 (57.1%)
250+	79 (36.4%)	74 (33.5%)	153 (34.9%)
Antiretroviral therapy	N=220	N=222	442
Yes	22 (10.0%)	34 (15.3%)	56 (12.7%)
No	198 (90.0%)	188 (84.7%)	386 (87.3%)
ECOG	N=206	N=197	N=403
0	156 (75.7%)	155 (78.7%)	311 (77.2%)
1+	50 (24.3%)	42 (21.3%)	92 (22.8%)

Study 02

Complete clinical response at day 14 by country in Study 02 is included in the following table. In France, Tunisia, and Algeria, clinical success rates in the Oravig were numerically higher than in the miconazole gel group. In Morocco, the opposite occurred. There was a significant treatment by country interaction and Oravig showed significant improvement over miconazole gel in France and miconazole gel showed a significant improvement over

Oravig in Morocco. Patients in Morocco had higher percentages of OPC lesions with score of 2 (multiple, localized) (72.4%, 21/29) and 3 (spread or confluent) (24.1%, 7/29) in the Oravig group than in the miconazole gel group (48.3% (14/29) and 13.8% (4/29)), while in France lower percentages of patients with score of 2 (36.5% (23/63)) and 3 (12.7% (8/63)) in the Oravig group than in the miconazole gel group (35.4% (23/65) and 20.0% (13/65)). While in France about 13% of subjects were female in both groups, in Morocco, 51.7% (15/29) were female in the Oravig group, compared 31% (9/29) in the miconazole gel group. In addition, a high percentage of subjects (62.1%, 18/29) had a score of 2 or more in burning severity at inclusion in the Oravig group, compared with 48.3% (14/29) in the miconazole group, while in France, 54.0% (34/69) had a score of 2 or more in burning severity at inclusion in the Oravig group and 67.7% (44/65) in the miconazole group. In France, 88% of subjects were 50 years old or older, compared with 50% in Morocco. The differences in demographic and baseline characteristics might contribute to the difference in cure rates between the two groups in this country and the differences in cure rates between different countries.

Table 34. Complete clinical response at day 14 by country in the mITT population in Study 02

Country	Oravig	Miconazole gel	Diff (Oravig - gel) [95% CI] p-value
France	N=63 26 (41.3%)	N=65 15 (23.1%)	18.2% [2.0%, 33.7%] 0.027
Tunisia	N=41 34 (82.9%)	N=40 29 (72.5%)	10.4% [-8.3%, 29.1%] 0.279*
Morocco	N=29 6 (20.7%)	N=29 15 (51.7%)	-31.0% [-53.5%, -5.3%] 0.015*
Algeria	N=8 8 (100%)	N=7 5 (71.4%)	

*Exact method

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Two studies were reviewed in this statistical review. In the first study, 578 HIV positive patients were enrolled in 3 countries (USA, Canada, and South Africa) and randomized to Oravig (291) and clotrimazole (287) groups.

A noninferiority margin of -15% was selected by the sponsor and the lower limit of a two-sided 95% confidence interval of the difference in clinical cure rates was used to determine noninferiority of efficacy in the ITT population and PP population. In the ITT population, the cure rate at days 17-22 was 60.7% (176/290) and 65.2% (187/287) in the miconazole group and clotrimazole group, respectively, with a difference of -4.5% (95% CI: [-12.3%, 3.4%]). In the PP population, this cure rate was 68.3% (164/240) and 74.2% (175/236) in the miconazole group and clotrimazole group, respectively, with a difference of -5.8% (95% CI: [-13.9%, 2.3%]). It was concluded that Oravig was non-inferior to clotrimazole in clinical cure in both the ITT population and PP population. At days 35-38, in the ITT

population, 42.8% (124/290) and 46.3% (133/287) remained cured, 16.6% (48/290) and 18.1% (52/287) relapsed after cure at day 17-22 in the Oravig and clotrimazole group, respectively. In the PP population, 48.8% (117/240) and 53.4% (126/236) remained cured, 17.9% (43/240) and 20.3% (48/236) relapsed after cure at day 17-22, in the Oravig and clotrimazole groups, respectively.

In the second study, a total of 308 head and neck cancer patients with OPC were enrolled in four countries (France, Tunisia, Algeria, and Morocco) and 154 were randomized to each group. A noninferiority margin of -20% was selected by the sponsor and the lower limit of a two-sided 95% confidence interval of the difference in success rates was used to determine noninferiority of efficacy in the mITT population and PP population. There were 12 protocol amendments after the initiation of this open-label study, including a sample size increase and adding a noninferiority comparison. However, these changes were made following the recommendations of an external regulatory agency and were not a serious concern.

FDA reviewed the justification of the noninferiority margin and concluded a -12.5% noninferiority was justifiable for an endpoint of complete resolution of lesions, rather the primary endpoint of complete and partial resolution of lesions (complete and partial clinical response). Additionally, we redefined the mITT population as all randomized subjects who receiving study medication. In the FDA defined mITT population, the clinical success rate at day 14 was 50.0% (74/148) and 43.8% (64/146) in the Oravig and miconazole gel group, respectively, with a difference of 6.2% (95% CI [-5.2%, 17.6%]). In the PP population, the complete clinical success rate was 53.3% (57/107) and 51.9% (55/106) in the Oravig and miconazole gel group, respectively, with a difference of 1.4% (95% CI [-12.0%, 14.8%]). In both populations, noninferiority of Oravig to miconazole gel was demonstrated. At day 60, in the mITT population, 38.5% (57/148) and 38.4% (56/146) remained cured, 10.8% (16/148) and 7.5% (11/146) relapsed after being cured at day 14 in the Oravig and miconazole gel group, respectively; in the PP population 40.6% (43/107) and 44.3% (47/106) remained cured, 13.2% (14/107) and 7.5% (8/106) relapsed after being cured at day 14, in the Oravig and miconazole groups, respectively.

Additionally, in France, Tunisia, and Algeria, clinical success rates in the Oravig were numerically higher (41.3% (26/63), 82.9% (34/41), and 100% (8/8)) than in the miconazole gel group (23.1% (15/65), 72.5% (29/40), and 71.4% (5/7)). In Morocco, the opposite occurred (20.7% (6/29) vs. 51.7% (15/29)).

This resulted in a significant treatment by country interaction. The differences in demographic and baseline characteristics might contribute to the difference in cure rates between the two groups in this country and the differences in cure rates between different countries.

5.2 Conclusions and Recommendations

The clinical efficacy and safety of Oravig (50 mg miconazole buccal tablets) administered once daily for 14 days in the treatment of oropharyngeal candidiasis (OPC) in immunocompromised patients was supported by one randomized, double-blind noninferiority study and one open-label, multi-center, active-controlled study. The first study

was to compare the efficacy of Oravig administered once daily and Mycelex troches (clotrimazole 10 mg) administered five times a day in the treatment of oropharyngeal candidiasis (OPC) in immunocompromised patients. The second study was to compare the efficacy of Oravig and miconazole gel, a non-FDA approved comparator, in head and neck cancer patients with OPC. These two studies demonstrated that Oravig was efficacious in the treatment of OPC by showing that it was not inferior to Mycelex troches using a noninferiority margin of -15% and not inferior to miconazole gel using a noninferiority margin of -12.5%.

APPENDIX

Justification of Noninferiority Margins for Study 04 and 02

Justification of noninferiority margins was available in this NDA as an appendix in 2.7.3.6 Appendix section in SN000 (2/5/2009). We conducted the following review on the justification of the two noninferiority margins.

The justifications of noninferiority margins were based on published papers submitted from the sponsor and identified by the medical reviewer. Since the two studies enrolled different patients populations (HIV+ subjects in Study 04 and head and neck cancer subjects in study 02) and used different comparators (clotrimazole troches in Study 04 and miconazole gel in Study 02), there needs to be two margin justifications for the two non-inferiority studies. These are discussed below in Section 1 and Section 2.

1. Study 04

Study 04 is a non-inferiority study in HIV+ patients designed to compare the efficacy and safety of miconazole Lauriad buccal tablets (new name: Oravig) and clotrimazole (active control) with a noninferiority margin of -15%. Clotrimazole Troches (Clotrimazole Lozenges) are approved for treatment of OPC in the US. The primary endpoint in this study is complete resolution of signs and symptoms which includes resolution of lesions at days 17 - 22.

Note: The treatment difference (Oravig-clotrimazole) in the current non-inferiority study 04 was -4.5% with a 95% confidence interval of [-12.3%, 3.4%].

Based on the literature review conducted by both the sponsor and the medical officer, there were two placebo-controlled studies for clotrimazole in chronic mucocutaneous candidiasis and in hematologic malignancy, but no placebo-controlled trials in HIV positive patients with OPC. There was one study in HIV+ patients that compared ketoconazole and nystatin (Nyst 1992). Since there were no valid placebo controlled studies to estimate the effect of clotrimazole over placebo from within studies, the sponsor chose to estimate the placebo effect and the clotrimazole effect from separate studies. They then compare these two estimates to justify the non-inferiority margin.

1.1 Estimate placebo effect

The sponsor identified 3 studies and the clinical reviewer identified 3 additional studies. There is only one study conducted in HIV positive patients. This study did not have a placebo control, but the active control, nystatin, will be considered as a placebo in this analysis. The other 5 studies were conducted in immunocompromised patients (Table 1).

Table 1: Placebo controlled OPC studies in immunocompromised subjects

Author	Design & Population	Rx arm Dose Duration	Endpoint	Results
Kirckpatrick 1978	RDBPC, chronic mucocutaneous candidiasis	Clotrimazole 10mg 5x/d Placebo 2 weeks	Resolution of lesions	Clotrimazole: 6/10 (60%) Placebo: 1/10 (10%)
Petersen 1980	RDBPC, chronic mucocutaneous candidiasis	Ketoconazole 200 mg/d Placebo 6 months	Resolution of lesions	Ketoconazole: 6/6(100%) Placebo: 0/6 (0)
Hughes 1983	RDBPC Hematologic malignancy	Ketoconazole 200 mg/m ² /d Placebo 2 weeks	Sum of % of 12 areas with visible lesions- reponse if <5%	Ketoconazole 26/36(72.2%) Placebo 4/20(20%)
Schechtman 1984	DBPC Hematologic malignancy	Clotrimazole 10mg 4/d Placebo Rx till cure or progression, ranging 2-28 days	Resolution of lesions	Clotrimazole 5/7 (71.4%) Placebo 1/6(16.7%)
Nyst 1992	Open label HIV+ adults Zaire OPC and Esophageal C	Ketonazole 200 mg/d Nystatin 200,000 u qid Gentian violet 1.5 ml 0.5% bid 2 weeks	Resolution of lesions	Ketonazole 10/23(43%) Gentian 11/26(42%) Nystatin 2/23(9%) Considered pseudo-placebo rate
Bastian 2004	DBPC Denture-related, steroid inhaler, post antibiotics, smokers	Miconazole gel 50 mg 4/d Miconazole chewing gum 4/d Placebo 4 weeks	Resolution of lesions	Gel 13/27 (48.2%) Gum 23/52 (44.2%) Placebo 1/9(11.1%)

Adapted from table in medical officer's review.

(R)DBPC: (randomized,) double-blind, placebo-controlled

Nystatin will be considered as a "placebo" in the Nyst study.

Kirckpatrick: clinical cure + improvement rate was 1/10 in the placebo group

Schechtman: no patients with improvement in the placebo group

Bastian: clinical cure. No number of improvements is reported

The study populations range from chronic mucocutaneous candidiasis (2), hematologic malignancy (2), HIV+ adults (1), denture related, steroid inhaler, post antibiotics, smokers (1). Though these subjects are not all HIV+ subjects, it is felt that these populations might constitute a slightly less ill population and therefore would result in a conservative estimate for a placebo response rate. The endpoints in these studies were mostly resolution of lesions measured at various time points ranging from 2 weeks to 6 months. The following table contains the author and date, study design and results of the 6 studies.

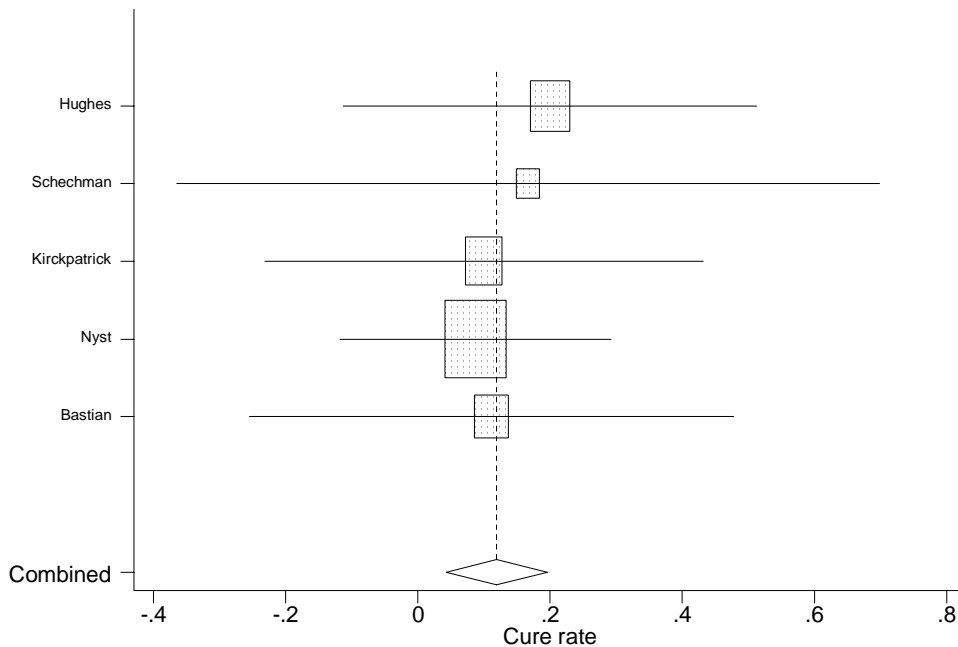
A meta-analysis using a random effect model was conducted to combine the results from the studies. In the first meta-analysis (figure 1) only 5 studies were pooled in order to calculate an overall cure rate, with the one study with a 0 cure rate being excluded.

Figure 1: Meta-analysis of 5 placebo response rates from OPC studies in immunocompromised subjects

 Test for heterogeneity: $Q=1.262$ on 4 degrees of freedom ($p=0.868$)

Random effects estimation

Est	Lower	Upper	z_value	p_value
0.119	0.043	0.195	3.060	0.002



In this analysis the placebo effect was estimated to be 11.9%, with a 95% confidence interval of [4.3%, 19.5%] (both a fixed effects model and a random effects model created the

same results). Since we excluded one study with 0 cure rate, we may have overestimated the placebo effect, which is deemed as conservative when we calculate a treatment effect later.

If we add 0.5 cures to the study with 0 cures, the new estimate from the 6 studies was 11.5% with a 95% confidence interval [4.3%, 18.7%] (both a fixed effects model and a random effects model created the same results).

In the Nyst study the mortality was high, which was not the case in Study 04. Therefore, the two study populations were not comparable and it is reasonable to exclude this study in the meta-analysis. If the Nyst study is excluded from the 6 studies, the new estimate was 13.4% with a 95% confidence interval of [4.1%, 22.6%] (both a fixed effects model and a random effects model created the same results).

If the Peterson and the Huges studies are excluded along with the Nyst study due to the use of a different endpoint either not measured within a similar time frame or was not defined as resolution of lesions, the new estimate was 11.6 with a 95% confidence interval of [-0.1%, 24.1%] (both a fixed effects model and a random effects model created the same results).

Therefore, using the largest upper bounds from the confidence intervals from these analyses, **a placebo effect of 24%** could be used in the justification of a noninferiority margin.

1.2 Estimate the effect of clotrimazole (active control)

The sponsor identified 9 randomized, controlled trials with clotrimazole troche in immunocompromised patients, 6 of which were conducted in HIV+ patients and were considered by the sponsor to contain sufficient information. The clinical reviewer also considered these results when identifying studies for this meta-analysis.

Table 2: Studies of clotrimazole in HIV+ subjects with OPC

Lead Author	Clinical response	Clinical response rate
Koletar 1990	Resolution of disease	11/17 (64.7%)
Linpiyawan 2000	Clinical cure	11/15 (73.3%)
Murray 1997	Clinical cured or improved	52/74 (70.3%)
Pons 1993	Clinical cure (resolution of signs and symptoms)	116/136 (85.3%)
Redding 1992	Clinical cure (absence of lesions)	8/11 (72.7%)
Roxane 2003	Clinical cure: complete disappearance of all symptoms and all oral lesion	73/97 (75.3%) Both groups

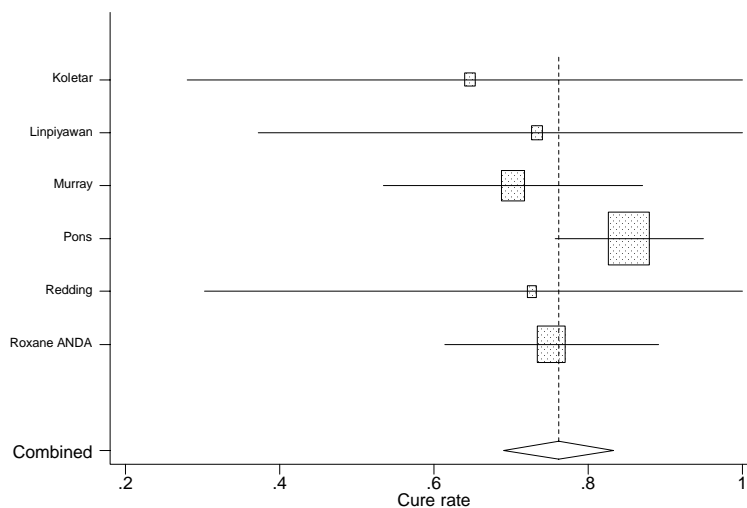
Many design aspects of these trials were different from each other and from the design used in study 04. The treatment duration was 14 days in all studies including study 04 except in Linpiyawan which used only 7 days. The evaluation criteria used in Murray was the same criteria as Study 04, while the other studies used different evaluation criteria. Most often,

evaluation criteria were a composite endpoint where erythema, plaques, patches, oral discomfort, taste or others, even mycology culture, were considered. For example, in Koletar, clinical responses were defined as resolution or failure (persistence or relapse) [of disease]. In Murray, clinical responses were classified as cured (clearance of all symptoms), improved (minimal symptoms remaining with no residual visible lesions or candidiasis), unchanged, or deteriorated. In Pons, patients were classified clinically as cured (resolution of signs and symptoms of OPC), improved (substantial resolution of signs and symptoms), or failed (little or no change or progression and confirmation by microscopy and culture). In Roxane, clinical cure was defined as complete disappearance of all symptoms and all oral lesions originally attributed to the diagnosis of oral candidiasis at the day 21 evaluation.

The time of assessment was the last day of treatment for all studies except for Roxane which assessed subjects at days 14 and 21, while study 04 used 3 to 8 days following treatment discontinuation. Other differences included severity of OPC and severity of HIV at baseline. Given the dates of these studies, HIV-positive patients were not receiving antiretroviral treatments, while in Study 04, 25.6% of subjects in the intent-to-treat population received antiretroviral therapy. Therefore, none of the referenced studies are strictly comparable to Study 04.

The same meta-analysis of the cure rates of clotrimazole using these 6 studies was conducted by both the sponsor and the reviewer. The estimated cure rate from a random effects model was 76.2% from 6 studies, with a two-sided 95% confidence interval of [69.1%, 83.3%]. See figure 2. Therefore, using the lower bound from this confidence interval, a conservative cure rate for clotrimazole in HIV+ subjects is 69%.

Figure 2: Meta analysis of 6 clotrimazole response rates from OPC studies in HIV+ subjects



Clinical cure and improvement was the primary endpoint in Murray’s study. To avoid the effect of including improvement in the analysis, we exclude it from the following meta-analysis. From the fixed effects model the estimated cure rate was 80.7% with a 95% confidence interval of 76.1%, 85.3%; from the random effects model, the cure rate was 78.2% with a confidence interval of [70.7%, 85.6%]. The estimated cure rates and the low

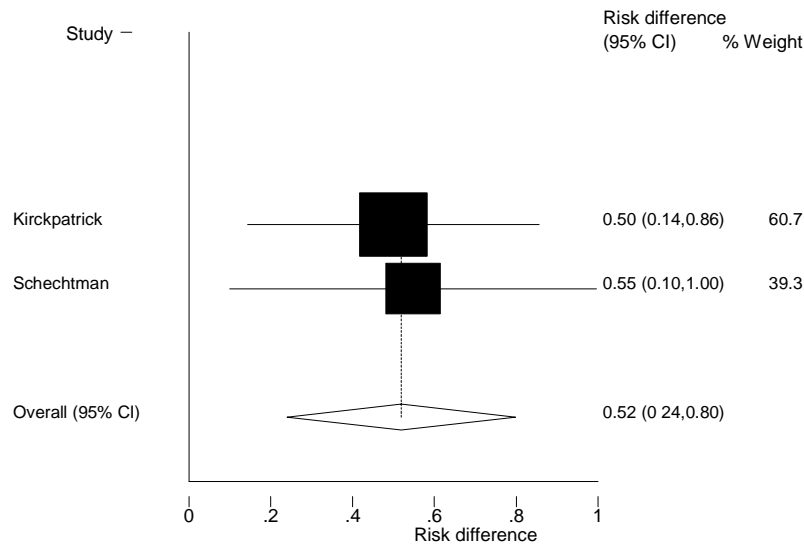
bounds of the confidence intervals were even higher than those of the analysis using all six studies, because the observed rate from Murray was lower than overall average. Therefore, 69% was still used as the estimated cure rate as a more conservative estimate.

1.3 Treatment effect [Active control-placebo]

A conservative estimate of the true treatment effect of clotrimazole over placebo was calculated by taking the difference of the lower limit of active control effect (i.e., 69%) and the upper limit of the placebo effect (i.e., 24%). This difference is 45%. Therefore, even if discounted by 50% due to the differences in study populations and use of separate studies to estimate the two rates, it appears that a noninferiority margin of 15% is justifiable.

An additional analysis was conducted by this reviewer and is included here. The above analysis was conducted by comparing the clotrimazole effect with the placebo effect from separate studies. This is because there were no placebo controlled OPC studies of clotrimazole conducted in HIV+ subjects where an estimate of the effect of clotrimazole could be estimated from within randomized studies. There are however two placebo controlled studies of clotrimazole conducted in immunocompromised patient populations. Schechtman’s (1984) and Kirckpartick’s (1978) studies compared clotrimazole and placebo in chronic mucocutaneous candidiasis and hematological malignancy patients, respectively, rather than in HIV positive patients. Though these populations are not completely comparable to the HIV + patients population, it can lead to a supportive analysis of that done above. Figure 3 contains the results of a meta-analysis of these two studies.

Figure 3: Meta analysis of two placebo controlled clotrimazole studies in OPC



The heterogeneity test for the two studies was not statistically significant. The overall difference in cure rates from a fixed effects model was 51.9% with a 95% confidence interval of [24.0%, 79.8%]; from a random effects model 51.8% with a 95% confidence interval of [24.0%, 79.7%]. From the lower bounds of the 95% confidence intervals (i.e., 24%), it seems that choosing a 15% noninferiority margin is reasonable and supportive of the results above.

2. Study 02

Study 02 is a non-inferiority study in head and neck cancer patients designed to compare the efficacy and safety of miconazole laurid buccal (Oravig) tablets and miconazole gel (active control) with a noninferiority margin of -20%. Note miconazole oral gel is marketed and approved for use in European countries since 1973. It is not approved in the US for the treatment of OPC. The primary endpoint used in study 02 was defined as (complete or partial) clinical response at day 14, where complete response is complete disappearance of OPC lesions and partial response is improvement by at least 2 points of the score for extent of oral lesion compared with the score at day 1 according to the Murray scoring scale (0=none; 1=single, localized; 2=multiple, localized; 3=extensive or confluent).

Note: The reported treatment difference (Oravig-active control) from Study 02 was 7.1% (95% CI [-4.8%, 19.0%]) in complete or partial clinical response in the ITT population, and 3.2% [-10.3%, 16.7%] in the PP population; 7.1% [-4.8, 19.0%] in complete clinical response in the ITT population, and 1.4% [-12.3%, 15.1%] in the PP population. We will focus on the complete clinical response because most of the outcomes in the literature are resolution of lesions.

Since the clinical outcomes in the studies used to estimate the placebo and miconazole gel effects below were resolution of lesions, the justification was for the margin for the complete clinical response.

Based on the literature review conducted by both the sponsor and the medical officer, there were no placebo-controlled studies of miconazole gel in head and neck cancer patients. As with the justification for study 04, since there were no valid placebo controlled studies to estimate the effect of the active control (miconazole gel) over placebo from within studies, the sponsor chose to estimate the placebo effect and the miconazole gel effect from separate studies. They then compare these two estimates to justify the non-inferiority margin.

2.1 Estimate placebo effect

There were no placebo controlled studies in head and neck cancer patients. The placebo information in immunocompromised patients reviewed in section 1.1 for Study 04 was considered relevant for the population of head and neck cancer patients as well. However, it was felt necessary to remove the one study, by Nyst, in HIV+ subjects as this population might have a lower untreated response rate than head and neck cancer patients and the mortality rate was high.

Excluding the Nyst study and the Petersen study with 0 cures, the estimated resolution rate of lesions from 4 studies was 14.4% with a two-sided 95% confidence interval of [4.2%, 24.6%] (same results from a fixed effects model and a random effects model). When 0.5 cures are added to the Petersen study, the estimated cure rate was 13.4% with a two-sided 95% confidence interval of [4.1%, 22.6%] (same results from a fixed effects model and a random effects model).

Therefore, using the upper bounds from the confidence intervals, a **placebo effect of 25%** could be used in justification of a noninferiority margin.

2.2 Estimate active control effect

2.2.1 Head and neck cancer trial

No published clinical trials have been found on the efficacy of miconazole oral gel 500 mg in the treatment of OPC in head and neck cancer patients. Only one related trial was identified (Lefebvre et al, 2002). This was a randomized, multi-center, open, noninferiority trial of fluconazole 50 mg once daily and amphotericin B 0.5 g 3 times daily in 268 **head and neck cancer patients** with OPC. A total of 147 patients discontinued prematurely (72 on fluconazole and 75 on amphotericin B), 109 of which were treatment failures and were included in the efficacy analysis. The clinical response (cure defined as resolution of all signs and symptoms or improvement defined as reduction in the number of lesions and symptoms with persistence of characteristic lesions) rates were 53% (65/123), and **52% (62/120)**, respectively, in the two arms. The cure rate were 21% (26/123) and 14% (17/120), respectively, in the two groups.

Based on these clinical response data, the sponsor determined that the efficacy rate of miconazole oral gel was fixed at 50%.

Comment: The clinical cure rates in both groups were very low, because most of clinical responses were improvements, not cures in this study.

The sponsor did not consider the variability of the estimate of the treatment effect. The 95% CIs were [43.6%, 61.9%] and [42.4%, 60.9%], respectively, in the fluconazole and amphotericin B arms. Therefore a conservative estimate for the treatment effect of these different treatments which takes into account the variability of the estimates is 42%. However these rates and confidence intervals do not take into account the missing data from this study. Given that this study did not assess the efficacy of the current active control, miconazole gel, this study is of limited use.

2.2.2 Meta analysis of Miconazole gel for all OPC

The sponsor identified 7 trials on miconazole gel for the treatment of OPC and the FDA medical officer found an additional 4 studies. However, 3 studies in infants were deemed not applicable by the medical officer and were not used in the analysis. The 8 remaining studies are listed in Table 3. The endpoints were most often resolution of lesions by 7 to 28 days. There were a few situations where the endpoint was not clearly defined in the article.

Table 3: Studies of miconazole gel for the treatment of OPC

Authors	Design & Population	Endpoint	Results
Roed-Pertersen 1978	Open uncontrolled No apparent underlying disease	Resolution of lesions	5/11(45.5%) at day 14
Schaad 1983	Randomized unblinded Hospitalized pediatric patients	Resolution of lesions at day 7 or 14.	15/23(65%) at day 7 23/23 (100%) at day 14*
Tsubura 1991	Open	Not clear	Miconazole

	HIV+, solid tumors, hematological malignancy		Overall 28/32 (87.5%) Highly effective 16/32 (50%) Effective 12/32(37.5%)
Brickner 1976, 1977	Open Hematological malignancy	Resolution of lesions	24/24
Ravera 1999	Randomized HIV + adults with OPC and EC Uganda	Resolution of lesions at EOT (day 7)	40/40(100%)
Blignaut 1999	Open HIV + South Africa	Not clear	69/73(94.5%)
Bastian 2004	DBPC Denture-related, steroid inhaler, post antibiotics, smokers	Resolution of lesions EOT (d 28)	13/27(48.1%)
Van Roey 2004	Randomized HIV + adults Uganda	Resolution of lesions EOT (7 or 14 days)	ITT 7 days MBT 135/178(75.8%)

Adopted from medical reviewer's table

DBPC: (randomized,) double-blind, placebo-controlled

* Day 14's data was used in the meta analysis because TOC was day 14 in Study 02

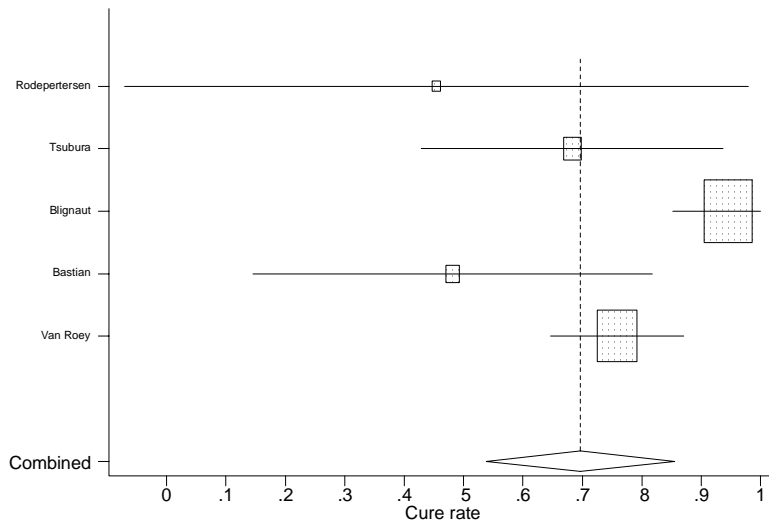
Figure 4: Meta-analysis of 5 miconazole gel cure rates from OPC studies

Test for heterogeneity: $Q = 49.071$ on 4 degrees of freedom ($p = 0.000$)

Der Simonian and Laird estimate of between studies variance = 0.028

Random effects estimation

Est	Lower	Upper	z_value	p_value
0.697	0.538	0.855	8.616	0.000



A meta-analysis using a random effect model was conducted to combine the results from the studies. In the first meta-analysis (figure 4) only 5 studies were pooled in order to calculate an overall cure rate, with the three studies with 100% cure rates being excluded. This leads to a conservative estimate, because three studies with 100% cure rate were excluded.

Note that the cure rates from these 5 studies are heterogeneous, meaning that there is a large amount of between-study variability. It is questionable to pool the study results. Nevertheless, the pooled cure rate was 69.7%. The lower bound of 95% CI was 53.8% from the random effects model.

An additional meta-analysis was conducted by reducing the number of cures by 0.5 cures for each of the three trials with a 100% cure rate. The results from the 8 studies are given in figure 5.

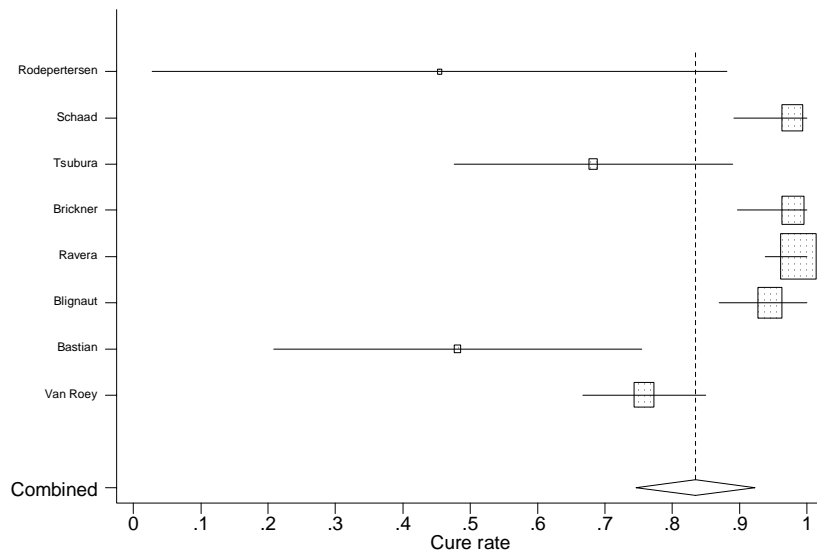
Figure 4: Meta-analysis of 8 miconazole gel cure rates from OPC studies

Test for heterogeneity: $Q = 90.891$ on 7 degrees of freedom ($p = 0.000$)
 Der Simonian and Laird estimate of between studies variance = 0.013

Random effects estimation

Est	Lower	Upper	z_value	p_value
0.835	0.746	0.923	18.531	0.000

As with the previous meta-analysis the results from the studies are significantly heterogeneous. The estimate of the effect of miconazole gel is 83.2% with a lower bound of the 95% confidence interval of 74.2%.



An additional analysis was conducted that excluded those studies whose definition of the primary endpoint was not clearly defined (Tsubura and Blignaut). The estimated cure rate was 93.9% with a 95% confidence interval of [91.5%, 96.3%] from the fixed effects model; and 82.9% with a 95% confidence interval [71.7%, 94.1%].

Using the information from these meta-analyses, an estimated 50% cure rate, defined as resolution of lesions, will be used as the miconazole cure rate in all OPC trials. This estimate is lower than the lower bounds of the confidence intervals obtained from the various meta-analyses. This conservative estimate would seem reasonable given the differences in patient populations of this group of studies.

2.3 Treatment Effect

A conservative estimate of the true treatment effect of miconazole gel over placebo was calculated using the treatment effect estimated the meta-analysis in section 2.2.2 of 50% and subtracting from it the placebo effect of 25% (as estimated in section 2.1). This gives a difference of 25%. This can be discounted by as much as 50% to still support a margin of 12.5%, the smallest margin that will support the conclusion of non-inferiority for study 02.

Note that a supportive analysis using the Bastian study (2004) which compared miconazole gel and gum were compared with placebo could not lead to a margin justification due to the small size of the study. The difference in cure rate between gel and placebo was large at 37%. However, the exact 95% confidence interval of [-5.4%, 62.1%] was not able to exclude zero and support a margin.

Given that miconazole gel is not approved in the USA (albeit approved in Europe) and no solid data were available to establish miconazole effect in head and neck cancer patients, some caution is needed.

3. Conclusion

As with most non-inferiority justifications, there are limitations in the data available in which to support a margin. For this NDA submission there were two studies for the treatment of OPC, one study in HIV+ subjects and one in head and neck cancer subjects. The two studies used different controls, one of which is approved in the US and one that is not.

Ideally, the non-inferiority margin justifications would be based on numerous placebo controlled trials of the control drug in a same population and using the same study design as the current trials. That, not surprisingly, did not exist for these justifications.

For these justifications it was necessary to obtain an estimate of a placebo rate from controlled studies using different active drugs and in different patient populations. In our analyses, we tried to calculate a placebo rate that would be conservative. This rate was then compared to an estimate of the active control rate observed from multiple studies.

There were numerous studies of clotrimazole, the active control for study 04, for the treatment of OPC in HIV + subjects. Though there were some inconsistencies with the exact definition of the endpoints used in these studies, they all did consider resolution of lesions and we used resolution of lesions as the primary endpoint in the meta-analysis

There were no studies where miconazole gel, the control used in study 02, was used as a treatment in head and neck cancer patients with OPC. Instead, for the justification, we focused on all studies of miconazole gel used as the treatment of OPC in various patient populations.

The endpoint that was most consistently measured in the literature studies was resolution of lesions which was very similar to the primary endpoint used in the study 04. Study 02 had a defined primary endpoint of complete and partial resolution of lesions; however, for our assessment of efficacy for Study 02, we will rely on complete resolution of lesions, since that is the basis of the non-inferiority justification.

Based on our analysis, for Study 04, a study in HIV+ subjects using a control of clotrimazole troches we believe that a 15% noninferiority margin is justifiable. For Study 02, a 12.5% noninferiority margin for complete clinical response is justifiable with some caution due to the limitations of the miconazole gel information for the treatment of OPC in head and neck cancer patients.

References

- Bastian HL, Rindum J, Lindeberg H. A double-dummy, double-blind, placebo-controlled phase III study comparing the efficacy and efficiency of miconazole chewing gum with a known drug (Brentan gel) and a placebo in patients with oral candidosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004;98:423-8
- Blignaut E, Messer S, Hollis RJ, Pfaller MA. Antifungal susceptibility of South African oral yeast isolates from HIV/AIDS patients and healthy individuals. *Diagn Microbiol Infect Dis* 2002;44:169-174
- Brincker H. Treatment of oral candidiasis in debilitated patients with miconazole. A new potent antifungal drug. *Scand J Infect Dis* 1976; 8:117-20
- Brincker H. Miconazole in oral candidiasis. *Proc R Soc Med* 1977;70:29-31
- Hughes, WT, Bartley, DL, Patterson, GG, & Tufenkeji, H. (1983). Ketoconazole and candidiasis: a controlled study. *J. Infect. Dis.* 147, 1060-1063.
- Kirkpatrick, CH, & Alling, DW (1978). Treatment of chronic oral candidiasis with clotrimazole troches. A controlled clinical trial. *N. Engl. J. Med.* 299, 1201-1203.
- Koletar, SL, Russell, JA, Fass, RJ & Plouffe, JF (1990). Comparison of oral fluconazole and clotrimazole troches as treatment for oral candidiasis in patients infected with human immunodeficiency virus. *Antimicrob Agents Chemother.* 34, 2267-2268.
- Lefebvre JL, Domenge C. A Comparative Study of the Efficacy and Safety of Fluconazole Oral Suspension and Amphotericin B Oral Suspension in Cancer Patients with Mucositis. *Oral Oncology* 2002; 38:337
- Linpiyawan, R., Jittreprasert, K., & Sivayathorn, A. (2000). Clinical trial: clotrimazole troche vs. itraconazole oral solution in the treatment of oral candidosis in AIDS patients. *Int. J. Dermatol.* 39, 859-861.
- Murray, PA, Koletar, SL, Mallegol, I, Wu, J, & Moskovitz, B.L. (1997). Itraconazole oral solution versus clotrimazole troches for the treatment of oropharyngeal candidiasis in immunocompromised patients. *Clin. Ther.* 19, 471-480.
- Nyst MJ et al. Gentian violet, ketoconazole and nystatin in oropharyngeal and esophageal candidiasis in Zairian AIDS patients. *Ann Soc Belg Med Trop.* 1992;72:45-52
- Petersen E, Alling D, Kirkpatrick C. Treatment of chronic mucocutaneous candidiasis with ketoconazole. A controlled clinical trial. *Ann Intern Med* 1980; 93:791-795
- Pons, V, Greenspan, D, Debruin, M., & the Multicenter Study Group. (1993). Therapy for oropharyngeal candidiasis in HIV-infected patients: a randomized, prospective multicenter

study of oral fluconazole versus clotrimazole troches. *J. Acquir. Immune Defic. Syndr.* 6, 1311-1316.

Ravera M et al. Evaluating diagnosis and treatment of oral and esophageal candidiasis in Ugandan AIDS patients. *Emerg Infect Dis* 1999; 5:274-277

Redding, SW, Farinacci, G.C., Smith, J.A., Fothergill, A.W., Rinaldi, M.G. (1992). A comparison between fluconazole tablets and clotrimazole troches for the treatment of thrush in HIV infection. *Spec. Care. Dentist.* 12, 24-27.

Roed-Petersen B. Miconazole in the treatment of oral candidosis. *Int J Oral Surg* 1978;7:558-63

Roxane Laboratories Clotrimazole Troche 10 mg ANDA 76-387. A prospective randomized, blinded, parallel group study of clotrimazole troches vs. Mycelex troches (10 mg troches five times a day for 14 days) in patients with human immunodeficiency virus (HIV) infection for the treatment of oropharyngeal candidiasis. Review date: December 12, 2003.

Schaad U, Bachmann D. Prospective comparison of miconazole gel and nystatin suspension in the treatment of oral candidiasis. *Schweiz Med Wochenschr* 1983; 113:1356-1362

Shechtman LB, Funaro, L, Robin, T, Bottone, EJ, & Cuttner, J (1984). Clotrimazole treatment of oral candidiasis in patients with neoplastic disease. *Am. J. Med.* 76, 91-94.

Tsubura E, Noma K et al. Clinical effect of miconazole gel against upper digestive tract mycosis. *Jpn J Antibiot* 1991; 44:324-336

Van Roey J et al. Comparative efficacy of topical therapy with a slow-release mucoadhesive buccal tablet containing miconazole nitrate versus systemic therapy with ketoconazole in HIV positive patients with oropharyngeal candidiasis. *J Acquir Immune Defic Syndr* 2004;35:144-150

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22404	ORIG-1	BIOALLIANCE PHARMA	Lauriad (miconazole (b) (4) tablet)

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/s/

XIANBIN LI
03/25/2010

KAREN M HIGGINS
03/26/2010
I concur

MOHAMMAD F HUQUE
03/26/2010

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 022404

Applicant: BioAlliance

Stamp Date: 6/15/2009

Drug Name: Lauriad

NDA/BLA Type: Standard

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups (if applicable).	x			Safety analyses by age and gender were included only in Study 02. The sponsor submitted pooled subgroup analyses for safety.
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			Analysis data sets for Study 04 and 02 were submitted on March 5 and 23.

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	x			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	x			Study 03.
Appropriate references for novel statistical methodology (if	x			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

present) are included.				
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	x			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	x			

Xianbin Li 07/23/2009
 Reviewing Statistician Date

Karen Higgins 07/23/2009
 Supervisor/Team Leader Date

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22404	ORIG 1		Lauriad (miconazole (b) (4) tablet)

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/s/

XIANBIN LI
08/17/2009

KAREN M HIGGINS
08/18/2009

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 022404

Applicant: BioAlliance

Stamp Date: 2/5/2009

Drug Name: Lauriad

NDA/BLA Type: Standard

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups (if applicable).		x		Safety analyses by age and gender were included only in Study 02. The sponsor will submit other subgroup analyses by April 3.
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			Analysis data sets for Study 04 and 02 were submitted on March 5 and 23.

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	x			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	x			Study 03.
Appropriate references for novel statistical methodology (if present) are included.	x			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Safety data organized to permit analyses across clinical trials in the NDA/BLA.	x			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	x			

Xianbin Li 03/27/2009

Reviewing Statistician Date

Karen Higgins 03/27/2009

Supervisor/Team Leader Date

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/s/

Xianbin Li
3/27/2009 02:46:22 PM
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Karen Higgins
4/7/2009 01:23:21 PM
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