CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-735

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-735
Drug Name:	terconazole vaginal cream 0.8%
Indication(s):	Treatment of vulvovaginal candidiasis
Applicant:	Altana Inc.
Date(s):	Stamp date: December 3, 2003
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	Review date: September 28, 2004
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Biometrics Division:	Division of Biometrics III (HFD-725)
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Keywords: clinical studies, NDA review, one study application, vulvovaginal candidiasis

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The results of ALT 0347-05-01 demonstrate that the efficacy of the Applicant's terconazole vaginal cream 0.8% is non-inferior to Terazol® 3 in the treatment of vulvovaginal candidiasis (VVC). Even though the results of the primary endpoint, therapeutic cure at Visit 3, show statistical significance of terconazole vaginal cream 0.8% compared to Terazol® 3, a claim of clinical superiority is not appropriate without the confirmatory evidence of a second clinical study.

1.2 Brief Overview of Clinical Studies

One clinical study has been submitted to provide support for the use of the Applicant's formulation of terconazole vaginal cream 0.8% for VVC. Study ALT 0347-05-01 was a Phase 3 randomized, double-blind, controlled trial in subjects with (VVC). Subjects were randomized to receive treatment with either terconazole 0.8% vaginal cream or Terazol® 3 vaginal cream 0.8% in a 1:1 ratio. Study medication was applied for 3 consecutive nights at bedtime. The primary efficacy endpoint was therapeutic cure at the Day 21-30 follow-up visit (Visit 3). A subject was considered a therapeutic cure if she was a clinical cure and a mycological cure.

1.3 Statistical Issues and Findings

A total of 460 subjects received study medication. Of these 460 patients, 140 terconazole patients and 153 Terazol® 3 patients were included in the Modified Intent to Treat (MITT) population. The Per Protocol (PP) population consisted of 114 terconazole and 122 Terazol® 3 patients. In the PP analysis, the therapeutic cure rates at Visit 3 were 72.8% for the Applicant's terconazole vaginal cream 0.8% group and 59.8% for the Terazol® 3 group. In the MITT analysis the therapeutic cure rates were 67.1% for the Applicant's terconazole vaginal cream 0.8% group and 52.3% for the Terazol® 3 group. The 95% confidence intervals about the difference in therapeutic cure rates are (0.2, 25.8) and (3.0, 26.6), respectively. In both analyses, the Applicant's terconazole vaginal cream 0.8% group was shown to be non-inferior to the Terazol® 3 group since the lower bounds of the 95% confidence intervals are greater than -20%.

2. INTRODUCTION

2.1 Overview

This submission contains the results of study ALT 0347-05-01 entitled "A multi-center, double-blind, randomized, parallel-group study to determine the therapeutic equivalence of two terconazole 0.8% vaginal cream formulations in the treatment of vulvovaginal

candidiasis." This study was designed as a clinical bioequivalence study to show the therapeutic equivalence of the Applicant's formulation of terconazole vaginal cream 0.8% to the reference listed drug Terazol® 3 Vaginal Cream. The study results fell outside the range of 80-120% required to demonstrate clinical bioequivalence. Therefore, Office of Generic Drugs (OGD) "refused to receive" the application as an ANDA. So the Applicant has now submitted the application as an NDA.

2.2 Data Sources

The data analyzed in this review comes from the Phase 3 study, ALT 0347-05-01. The study report and the datasets provided in the paper submission were reviewed.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design

Study ALT 0347-05-01 was a Phase 3 randomized, double-blind, controlled trial in subjects with vulvovaginal candidiasis (VVC). The study was conducted 17 sites in the United States. Subjects were randomized to receive treatment with either terconazole 0.8% vaginal cream or Terazol® 3 vaginal cream 0.8% in a 1:1 ratio. Subjects applied study medication intravaginally once daily before bedtime for 3 consecutive days.

Eligible subjects included females at least 18 years of age with a definite clinical and mycological diagnosis of VVC. A clinical diagnosis of VVC required a total score of ≥ 2 for at least one sign (erythema, edema, or excoriations) and ≥ 2 for at least one symptom (itching or burning/irritation) of the vagina and/or vulva, rated on a 4-point scale (0=none, 1=mild, 2=moderate, 3=severe). A mycological diagnosis of VVC was confirmed by the presence of hyphae/pseudohyphae and/or budding yeast cells (*Candida*) on direct microscopic examination of a KOH mount of a specimen obtained by swab of the vaginal mucosa. The study included 3 visits: a baseline (Day 1) visit and follow-up visits at Day 8-10 (Visit 2) and Day 21-30 (Visit 3). At each visit, the investigator rated the signs and symptoms of VVC and intravaginal mycology samples were cultured.

The primary efficacy endpoint was the proportion of subjects with therapeutic cure at Visit 3 (Day 21-30). A subject was considered a therapeutic cure if they were a clinical cure and a mycological cure. A subject was considered a clinical cure if all of the following were satisfied:

- Signs and symptoms with scores of 1 or 2 at entry were absent (score of 0)
- Signs and symptoms with scores of 3 at entry had scores of 0 or 1 (mild)
- The investigator indicated that the subject did not require additional therapy for VVC.

A subjects was considered a mycological cure if she had a negative KOH and culture for *Candida* species. Secondary endpoints included clinical cure, mycological cure, clinical signs and symptoms scores and response to the investigator's outcome question. The

treatment groups were compared by constructing a confidence interval about the difference in cure rates between the test product and the reference product. The confidence interval was calculated using the normal approximation to the binomial with continuity correction. Clinical signs and symptoms and the response to the investigator's outcome question were analyzed using a Cochran-Mantel-Haenszel test.

A total of 385 subjects were to be enrolled to obtain 230 evaluable subjects, 115 in each arm. The sample size was based on an estimated therapeutic cure rate of 50% and approximately 80% power to establish therapeutic equivalence of the 2 treatments. The protocol stated that therapeutic equivalence would be concluded if the confidence interval about the difference of the therapeutic cure rates is contained within the range of -20% to 20%.

***Reviewer's Comment**: It should be noted that OGD requires 90% confidence intervals to assess the bioequivalence of 2 active compounds. To assess non-inferiority of 2 active compounds, the Division uses 95% confidence intervals. For completeness, both 90% and 95% confidence intervals will be presented in this review for the primary endpoint. However, the 95% confidence intervals will be used for drawing conclusions regarding the efficacy of the generic product. It should also be noted that recent applications submitted to support the non-inferiority of VVC products have used a non-inferiority margin of -15% rather than -20%.*

The Safety population was defined as all subjects enrolled into the study who received at least one dose of study medication. The MITT population was defined as all randomized subjects who met inclusion/exclusion criteria including a positive baseline culture of *Candida*, received treatment, and returned for at least one post-baseline visit. The per protocol (PP) population was defined as an MITT subject who took 3 consecutive days of treatment, had data for all three efficacy variables at Visit 3 (KOH preparation, fungal culture, and signs and symptoms evaluation) or was discontinued from the study due to treatment failure or adverse event having received 3 days of study medication, returned to the study site within the specified window for Visit 3 (Day 21-30) unless previously declared a failure, and had no protocol violations.

***Reviewer's Comment**: The Division does not usually consider the MITT population defined by the Applicant as an ITT-type population since this population excluded subjects based on protocol violations (not meeting inclusion/exclusion criteria). Approximately 5% of subjects from each treatment arm were excluded from the MITT population for these reasons (13 terconazole subjects and 12 Terazol subjects). These exclusions do not affect the results so the Applicant's MITT population will be used throughout this review.*

Subjects who terminated the study prematurely due to treatment failure were carried forward as a treatment failure in both the PP and MITT analyses. The Applicant applied a last-observation-carried forward (LOCF) approach for subjects who had missing data in the MITT population. The Division usually considers a worst-case scenario outcome for subjects with missing data in the MITT analysis and this will be applied in all MITT analyses.

3.1.2 Patient Demographics

A total of 485 subjects were enrolled into the study, of these, 460 subjects received study medication (231 terconazole, 229 Terazol® 3) and were included in the safety population. The MITT population consisted of 140 terconazole patients and 153 Terazol® 3 patients. An additional 26 terconazole and 31 Terazol® 3 patients were excluded from the PP population leaving 114 terconazole and 122 Terazol® 3 patients in the PP population.

Table 1 summarizes the demographic and baseline characteristics of the MITT population. There were no significant differences across treatment groups. Most of the subjects were Caucasian (58.0%). The mean age of the patients was 36 years with a range of 18 to 82 years. Most subjects had moderate or severe itching, burning/irritation, and erythema at baseline. Edema was primarily mild or moderate at baseline. Only 60% of the subjects had excoriation at baseline.

Table 1

Demographic and Baseline Characteristics (MITT)

	Treatment Group	
	terconazole	**Terazol® 3**
# Patients	140	153
Age mean (SD)	35.9 (11.3)	37.4 (12.3)
min, max	18, 82	18, 72
Race		
White	82 (58.6)	88 (57.5)
Black	12 (8.6)	22 (14.4)
Hispanic	36 (25.7)	36 (23.5)
Asian	7 (5.0)	4 (2.6)
Other	3 (2.1)	3 (2.0)
Itching		
None	1 (0.7)	3 (2.0)
Mild	5 (3.6)	9 (5.9)
Moderate	69 (49.3)	67 (43.8)
Severe	65 (46.4)	74 (48.4)
Burning/Irritation		
None	11 (7.9)	3 (2.0)
Mild	18 (13.0)	26 (17.0)
Moderate	58 (41.7)	66 (43.1)
Severe	52 (37.4)	58 (37.9)
Erythema		
None	1 (0.7)	0
Mild	6 (4.3)	6 (3.9)
Moderate	70 (50.0)	83 (54.3)
Severe	63 (45.0)	64 (41.8)
Edema		
None	8 (5.7)	11 (7.2)
Mild	42 (30.0)	49 (32.0)
Moderate	56 (40.0)	58 (37.9)
Severe	34 (24.3)	35 (22.9)
Excoriation		
None	54 (38.6)	61 (39.9)
Mild	27 (19.3)	29 (19.0)
Moderate	47 (33.6)	49 (32.0)
Severe	12 (8.6)	14 (9.2)

3.1.3 Efficacy Results

The results of the primary efficacy endpoint, therapeutic cure at Visit 3, are presented in Table 2 for the PP and MITT populations. In the PP analysis, the therapeutic cure rates were 72.8% for the Applicant's terconazole vaginal cream 0.8% group and 59.8% for the Terazol® 3 group. In the MITT analysis the therapeutic cure rates were 67.1% for the Applicant's terconazole vaginal cream 0.8% group and 52.3% for the Terazol® 3 group. In both analyses, the Applicant's terconazole vaginal cream 0.8% group was shown to be non-inferior to the Terazol® 3 group since the lower bounds of the 95% confidence intervals are greater than -20%. The lower bounds are also well above a non-inferiority margin of -15%.

Table 2
Therapeutic Cure Rate at Visit 3 (Day 21-30)

	terconazole	Terazol® 3	Difference 95% CI 90% CI
PP	83/114 (72.8)	73/122 (59.8)	13.0 (0.2, 25.8) (2.1, 23.9)
MITT	94/140 (67.1)	80/153 (52.3)	14.8 (3.0, 26.6) (4.8, 24.8)

Reviewer's Comment *It should be noted that the Applicant provided a reanalysis of the data using a window of 22 – 30 days for Visit 3 as requested by OGD. This reviewer feels that it is inappropriate to shorten a protocol specified window when there is no rationale that would suggest that there would be a clinical difference for a woman was assessed on Day 21 versus Day 22. Therefore, all analyses presented in this review associated with Visit 3 are based on the window of Day 21-30 as specified in the protocol.*

Secondary endpoints included clinical cure rates and mycological cure rates at Visit 3. These results are presented in Table 3. Non-inferiority of the Applicant's terconazole vaginal cream 0.8% compared to Terazol® 3 was shown for both clinical cure and mycological cure in both analysis populations.

Table 3
Clinical Cure and Mycological Cure at Visit 3

Population	Endpoint	terconazole	Terazol® 3	Difference (95% CI)
PP	Clinical Cure	96/114 (84.2)	90/122 (73.8)	10.4 (-0.7, 21.5)
	Mycological Cure	88/114 (77.2)	80/122 (65.6)	11.6 (-0.7, 23.9)
MITT	Clinical Cure	111/140 (79.3)	101/153 (66.0)	13.3 (2.5, 24.0)
	Mycological Cure	99/140 (70.7)	87/153 (56.9)	13.8 (2.2, 25.4)

The individual clinical signs and symptoms of VVC were also secondary endpoints. Most subjects in both populations had no signs or symptoms at Visit 3. There were no differences between the treatment groups in any of the signs and symptoms in the PP population. In the MITT population, signs and symptoms were comparable with the exception of itching and

burning/irritation. The Applicant's terconazole vaginal cream 0.8% group had fewer subjects with moderate and severe itching and burning/irritation than the Terazol® 3 group.

3.2 Evaluation of Safety

A total of 48 (20.8%) subjects in the terconazole group and 47 (20.5%) subjects in the Terazol® 3 group experienced at least one adverse event. A serious adverse event was reported in 1 subject who received terconazole and the event was considered to be unrelated to the study medication. Four subjects (2 from each treatment group) discontinued study drug due to a treatment-emergent adverse event. There were no deaths during the study.

For a detailed review of the safety data, please see the medical officer's review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

All patients are female so there is no gender analysis to perform. There was no significant difference in therapeutic cure rates by race when compared to the overall study population. The majority of the subjects in this study were less than the age of 55 (92%). Therefore differences due to age cannot be assessed using this data.

4.2 Other Special/Subgroup Populations

There are no other subgroups of interest.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

All evidence provided to support the efficacy of terconazole vaginal cream 0.8% was from a single clinical study. The results of this study support the non-inferiority of terconazole vaginal cream 0.8% to Terazol® 3. Even though the results of the primary endpoint, therapeutic cure at Visit 3, show statistical significance of terconazole vaginal cream 0.8% compared to Terazol® 3, a claim of clinical superiority is not appropriate without the confirmatory evidence of a second clinical study.

5.2 Conclusions and Recommendations

The results of ALT 0347-05-01 demonstrate that the efficacy of the Applicant's terconazole vaginal cream 0.8% is non-inferior to Terazol® 3 in the treatment of VVC.

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