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RESEARCH**

APPLICATION NUMBER:
21-735

MEDICAL REVIEW

Team Leader Review

Application Type	NDA
Submission Number	21-735
Submission Code	N
Letter Date	November 25, 2003
Stamp Date	December 2, 2003
PDUFA Goal Date	October 1, 2004
Review Completion Date	September 24, 2004
Established Name	terconazole 0.8% vaginal cream
(Proposed) Trade Name	terconazole 0.8% vaginal cream
Therapeutic Class	antifungal
Applicant	ALTANA Inc.
Priority Designation	S
Formulation	vaginal cream
Dosing Regimen	once daily at bedtime for 3 days
Indication	vulvovaginal candidiasis
Intended Population	adults

Recommendation:

The Division recommends approval of terconazole 0.8% vaginal cream once daily at bedtime for 3 days for the treatment of vulvovaginal candidiasis. The review team has determined that the product is both safe and effective at the recommended dose regimen for this indication based on the review of a single randomized double blind study demonstrating that terconazole is not inferior to the reference listed drug Terazole. There are no phase IV commitments. Pediatric studies are waived for this indication.

Background:

This NDA consists of one pivotal study entitled "A multicenter, 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 originally designed to fulfill the Office of Generics Drug's requirement for the determination of bioequivalence of the candidate drug product to the RLD Terazole based on a 90% confidence interval around the difference in proportions of therapeutic cure of the two active study treatments. The OGD originally refused to file the application because their reviewer determined that bioequivalence of the candidate product to the RLD was not established in the pivotal study. The OGD's bioequivalence evaluation found that the 90% confidence interval around the difference in successful outcomes (symptom resolution and a negative KOH AND a negative culture) in the Per Protocol population exceeded the prespecified interval of -20 to +20 percentage points. While negotiations with OGD regarding alternative analyses were ongoing, ALTANA Inc filed a 505b2 NDA 21-735 with the Division of Special Pathogen and Immunologic Drug Products for Terconazole Vaginal Cream 0.8% in January, 2004 as an alternate route to market. The OGD's RTR was finally decided in August 2004 and HFD 590 proceeded with the review of the application at this time.

Study Overview and Conclusions:

NDA 21-735, terconazole 0.8% vaginal cream

Dr. Vicki Moncada's clinical review of this application finds that the candidate drug product terconazole 0.8% vaginal cream (ALTANA Inc) is not inferior in efficacy to the reference listed drug Terazol 3 vaginal cream 0.8% (Ortho-Mc Neil Pharmaceutical Corporation) as therapy for the treatment of vulvovaginal candidiasis. This conclusion is based on HFD 590's finding that the difference in proportion of therapeutic cures (clinical resolution of signs and symptoms and a negative culture) on day 21-30 exceeded the 95% confidence interval threshold required to therapeutic equivalence (1998 Draft Guidance). In the primary analysis in the Per Protocol population, the therapeutic cure rate was 73% for the test group and 60% for the reference group; (95% confidence interval on the 13 percentage point difference in therapeutic cure rate: 2.11% to 23.83%) at Visit 3 (Day 21-30). The supportive analysis in the MITT population was consistent with the findings in the per protocol population, with efficacy rates that were generally lower for both study arms. The safety analysis was favorable, with no serious drug related adverse events and no unanticipated adverse events identified. The most frequent adverse events noted were unresolved symptoms of vaginal burning and itching and occurred in the comparator treated group, consistent with their finding.

Analysis Analytic population	Successful Outcomes At Visit 3		Difference	95% CI
	Terconazole 0.8% Vaginal Cream (ALTANA) n/N (%)	Terazole 3 0.8% Vaginal cream (Ortho Mc Neil) n/N (%)		
Primary efficacy outcome				
PP Therapeutic cure	83/114 (73%)	73/122 (60%)	13%	(0.2 %, 25.8%)
Supportive analyses (2ndary outcomes)				
MITT Therapeutic cure	100/140 (71%)	86/153 (56%)	15%	(2.0 %, 28.0%)
PP Clinical cure	96/114 (84%)	90/122 (74%)	10%	(-1.1 %, 21.1 %)
MITT Clinical cure	116/140 (83%)	107/153 (70%)	13%	(2.8 %, 23.2 %)
PP Mycological cure	88/114 (77%)	80/122 (66%)	11%	(-1.3 %, 23.3 %)
MITT Mycological cure	108/140 (77%)	97/153 (63%)	16%	(3.0 %, 25.0%)
Safety Parameters				
SAFETY			p value	
Any AE	48/231 (20.8%)	47/229 (20.5%)	0.895	
Drug related AE	4/231 (1.7%)	6/229 (2.6%)	0.462	
Severe AE	3/231 furunculosis, generalized rash, breast pain, vaginitis	4/229 allergic reaction, vaginal moniliasis, salivary gland enlargement nausea		

While the numerical outcome as presented above, shows that the product is statistically superior for therapeutic cure and some of the other analyses when compared to the control, evaluation of the available information suggests that this difference may be due to chance instead of a specific difference between products or populations. Specifically, the Altana terconazole 0.8% vaginal cream is virtually identical to the innovator's product in the active ingredient, strength, dosage and route of administration. Drs. Moncada and Dixon evaluated efficacy by center, by severity strata, by lot of drug evaluated and found no differences that would provide a plausible explanation for the difference in outcomes. The statistical superiority is demonstrated whether the review team evaluated the outcomes based on OGD's definition of successful outcome (resolution of signs and

NDA 21-735, terconazole 0.8% vaginal cream symptoms and negative KOH and culture), or HFD 590's definition of success (resolution of signs and symptoms and negative culture).

- a) By definition, the $p > 0.5$ significance level means that there is a 1 in 20 chance finding that a study will conclude that the drug is not similar to the approved product even when the converse is true, and the possibility is that this study represents that small chance finding. Therefore, the finding of statistical superiority in this case is probably due to chance rather than another factor based on the similarity of products and the absence of other clear differences. Because the lower limit of the 95% confidence interval exceeds a lower limit or delta of -15% or better, the results can be interpreted as showing noninferiority and therefore the results support approval of this application. Although only one adequate and well-controlled study is submitted, the results of this trial are convincing and supportive data exist in the literature and previous finding of safety and efficacy by the Agency regarding other terconazole vaginal products, to conclude that there is adequate evidence of efficacy and safety to support approval of this 505(b)(2) application. As noted above, the drug product is as safe as the terconazole 0.8% vaginal cream RLD despite the numerical advantage in efficacy
- b) the drug is virtually identical to the terconazole 0.8% vaginal cream RLD in composition, strength, pharmacokinetic properties and route of administration. Thus, there is no plausible explanation for its increased efficacy over the comparator.

In this application, the applicant is not requesting a claim of superiority and the division is not proposing to grant a claim of superiority. If the applicant wishes to claim superiority, a second adequate and well-controlled study showing therapeutic and statistical superiority would need to be submitted to corroborate the results of the existing study. However, there is no need for a second study to be conducted to confirm that the product is safe and effective, as summarized in the applicant's proposed labeling.

Summary:

The study provides convincing evidence that the terconazole 0.8% vaginal cream drug formulation is safe and efficacious in the treatment of vulvovaginal candidiasis and the review team recommends approval of this application. The review team also finds the proposed labeling acceptable for initial product launch.

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Through:
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NDA 21-735

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CLINICAL REVIEW

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Letter Date November 25, 2003
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Reviewer Name Victoria Moncada, MD
Review Completion Date September 24, 2004

Established Name terconazole 0.8% vaginal cream
(Proposed) Trade Name terconazole 0.8% vaginal cream
Therapeutic Class antifungal
Applicant ALTANA Inc.

Priority Designation S

Formulation vaginal cream
Dosing Regimen one applicatorful (5g) intravaginally
once daily at bedtime for 3 days
Indication vulvovaginal candidiasis
Intended Population adults

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The MO finds the candidate drug product, terconazole 0.8% vaginal cream (ALTANA Inc) to be safe and efficacious in the treatment of vulvovaginal candidiasis and recommends approval of this application.

1.2 Recommendation on Postmarketing Actions

Not applicable.

1.2.1 Risk Management Activity

Not applicable.

1.2.2 Required Phase 4 Commitments

Not applicable.

1.2.3 Other Phase 4 Requests

Not applicable.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The Agency received a 505(b)(2) submission for Terconazole Vaginal Cream 0.8% from Altana Pharmaceuticals in December 2003. The Division of Special Pathogens (HFD-590) filed the submission on January 31, 2004. Originally, this New Drug Application (NDA) had been submitted to The Office of Generic Drugs (OGD) as a bioequivalence study to the reference listed drug (RLD). Upon review of the ALTANA study, OGD refused to file the application because the proposed drug failed to show bioequivalence to the RLD. They found that although Terconazole Vaginal Cream 0.8% contains the same active ingredient and is identical in strength, dosage form and route of administration to Terazol @ 3 Vaginal Cream 0.8%, the candidate product showed a slight improvement over the RLD with a confidence interval of 102-124%, just outside the range of 80-120% required to demonstrate bioequivalence. Both products demonstrated similar safety profiles.

The purpose of this multicenter, double-blind, randomized parallel-group study was to evaluate the safety and therapeutic equivalence of terconazole 0.8% vaginal cream (ALTANA Inc.) to Terazol® 3 vaginal cream 0.8% (Ortho-McNeil Pharmaceutical Corporation) in the treatment of vulvovaginal candidiasis. Subjects were randomized in a 1:1 ratio to one of two treatment groups and then required to apply either the candidate drug (terconazole 0.8% vaginal cream) or the registered listed drug (RLD) (Terazol® 3) once a day at bedtime for 3 consecutive days. Clinical evaluation of the subjects was done on Visit 2 (Day 8-10) and Visit 3 (Day 21-30).

Four hundred eighty-five (485) subjects were enrolled in the study. Four hundred sixty (460) were included in the intent-to-treat (ITT) analyses; 293 were included in the modified ITT (MITT) analyses and 236 were included in the per protocol (PP) analyses. Efficacy variables included the rates of therapeutic cures, mycological cures, clinical cures, signs and symptoms scores, and the investigator's outcome scores. Safety variables included adverse events (AEs).

Our review of the study supported OGD's conclusion of numerical superiority for the candidate drug over the reference listed comparator, using the Divisions' clinical threshold for equivalent efficacy. Further, we found no plausible explanation for the increased efficacy of the candidate drug over the RLD. We evaluated various individual study reports in an attempt to find any marked differences between the two treatment groups. Both treatment arms had a comparable number of subjects enrolled in the study (243 vs 242) and the specifically defined populations within the arms were likewise comparable in number with respect to the intent-to-treat (ITT) population (231 vs 221), the modified intent-to-treat (MITT) population (140 vs 153) and the per-protocol (PP) population (114 vs 122). See **Table 1**.

We also found that the number of subjects who completed the study in the Terconazole 0.8% vaginal cream group (164; 67%) was comparable to the number of subjects completing the study in the Terazol® 3 group (161; 67%). Likewise, there was no discrepancy between the number of subjects who left the study in the Terconazole treatment arm (79; 33%) versus the Terazol® 3 treatment group (81; 33%).

Further analysis of why subjects discontinued the study in the respective treatment arms again found no marked differences to account for the non-inferior efficacy of the candidate drug to the RLD. A negative baseline Candida culture result accounted for 55 (23%) candidate drug subjects to drop out of the study compared to 42 (17%) in the RLD group. The presence of other vaginal infectious pathogens (*Neisseria gonorrhoeae* or *Chlamydia trachomatis*) at baseline caused 1 subject to be excluded from the RLD treatment group; none were excluded from the candidate drug group. Insufficient therapeutic response after 3 days of study drug therapy caused 6 (2%) subjects in the Terazol® 3 group to drop out of the protocol; none were excluded from the candidate drug group.

Adverse events led to study discontinuation of 2 (1%) subjects from each treatment group. Protocol noncompliance caused 5 (2%) and 7 (3%) subjects to be discontinued from the candidate drug and RLD treatment arms respectively. Eleven (5%) subjects in the candidate drug group and 13 (5%) subjects in the RLD group were lost to follow-up. Other causes for discontinuance from the study accounted for the loss of 6 (2%) subjects from the Terconazole Vaginal Cream group versus 10 (4%) subjects from the Terazol ® 3 group. All results are summarized in **Table 1** below.

Table 1. Patient Disposition in the Analytic Populations and Reasons for Discontinuation

Disposition in Analytic Populations	Candidate Drug (Terconazole vaginal cream 0.8%)	RLD (Terazol ® 3 vaginal cream 0.8%)
Number Randomized	243	242
ITT	231	221
MITT	140	153
PP	114	122
Reasons for Discontinuation		
Number Randomized	243	242
Number Completed Study	164 (67%)	161 (67%)
Number Discontinued	79 (33%)	81 (33%)
Negative baseline culture	55 (23%)	42 (17%)
Presence of other pathogens	0	1 (0%)
Failure at day 3 of Study	0	6 (2%)
Adverse Event	2 (1%)	2 (1%)
Protocol Noncompliance	5 (2%)	7 (3%)
Lost to follow-up	11 (5%)	13 (5%)
Other	6 (2%)	10 (4%)

The reason for drop-outs from the study were balanced between treatment arms except for a slightly bigger proportion of patients with negative baseline cultures in the terconazole 0.8% vaginal cream group. There appeared to be no symptomatic bias in the allocation of patients to the analytic population. The review team concludes that these parameters are unlikely to explain the efficacy performance of the sponsor's candidate drug compared to the RLD.

1.3.2 Efficacy

The efficacy analyses were conducted on both the PP and the MITT subject

populations. The primary efficacy parameter was the proportion of subjects with a therapeutic cure at Visit 3 (Day 21-30). The definition of therapeutic cure for this study included a clinical cure plus a mycological cure (negative KOH and culture for *Candida* species). A subject was considered a clinical cure if the following requirements were met: all signs and symptoms of candidiasis with severity scores of 1 or 2 at the time of protocol entry were absent (score of 0) by the end of treatment; signs and symptoms of candidiasis with severity scores of 3 at protocol entry had scores of 0 or 1 (mild) after treatment, and the investigator confirmed that the subject no longer required therapy for her vulvovaginal candidiasis.

A subject was considered a clinical failure if she had signs and symptoms present at entry that had not cleared as specified in the clinical cure definition and there was evidence that active disease was still present, or the investigator indicated that the subject required additional therapy for vulvovaginal candidiasis.

Secondary efficacy parameters in this study included the number of subjects evaluated as clinical cures at Visit 2 and Visit 3; the number of subjects evaluated as mycological cures at Visit 2 and Visit 3; the clinical signs and symptoms scores at Visit 2 and Visit 3 and the response to the investigator's outcome question at Visit 3. For purposes of this summary the efficacy discussion will focus on results of the primary efficacy parameter between the two treatment groups in the PP and MITT populations. The secondary efficacy parameter results, which support the primary efficacy parameter results, are discussed in section VI of the appendix.

The claim for non-inferiority requires a 95% confidence interval for the difference in the proportions of therapeutic cures between the candidate drug and the RLD at Visit 3 (Day 21-30) contained within the interval of -15% to +15%. The primary analysis in the PP population showed that the therapeutic cure rate was higher for the sponsor drug (73%) than the RLD (60%) at Visit 3 (Day 21-30). Likewise, the sponsor drug showed a higher therapeutic cure rate (71%) in the MITT analysis compared to the reference drug (56%) at Visit 3 (Day 21-30). Thus ALTANA's terconazole 0.8% vaginal cream was found to be not inferior to Terazol® 3 vaginal cream 0.8% in the PP analysis (95% confidence interval on the difference in therapeutic cure rate: 0.2% to 25.8%) and the MITT analysis (95% confidence interval on the difference in therapeutic cure rate: 2.0% to 28.0%) at Visit 3 (Day 21-30). Results for mycological, clinical and therapeutic cures are summarized in **Table 2**

MO Comment: *The sponsor analyzed their data based on a claim of bioequivalence, using a 90% confidence interval for the difference in the proportions of therapeutic cures between the candidate drug and the RLD at Visit 3 (Day 21-30), contained within the interval of -20% to +20%. The DSPIDP analysis is based on 95% CI around the difference. However, the same conclusion is derived regardless of which confidence interval is used in analyzing the data: Terconazole 0.8% vaginal cream is not inferior to Terazole 3. Please also see Dr. Sheryl Dixon's statistical review of this NDA.*

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Table 2. Primary Efficacy Analysis: Therapeutic Cure Rate at Visit 3 (Day 21-30)

Parameter	Generic	Terazol 3g	90% C.I. for Bioequivalence of Generic to Terazol 3g
Per-Protocol Subjects			
Visit 3 (Day 21 -30)	(N=114)	(N=122)	(2.11%, 29.83%) ¹
Therapeutic Cure	83 (73%)	73 (60%)	
Therapeutic Failure	31 (27%)	49 (40%)	
Modified Intent-to-Treat Subjects			
Visit 3 (Day 21 -30)	(N=140)	(N=153)	(6.65%, 26.20%) ¹
Therapeutic Cure	103 (74%)	85 (56%)	
Therapeutic Failure	37 (26%)	68 (43%)	
Unevaluable	3 (2%)	1 (1%)	

Only subjects with therapeutic responses of 'Cure' or 'Failure' were included in confidence interval calculation.
¹ Confidence intervals from Wald's method with Yates' continuity correction.

MO Comment: *The 95% confidence interval for the per-protocol subjects is 0.2% to 25.5% and 2.0% to 28.0% in the modified intent-to-treat subjects. For the efficacy analyses, the sponsor used a last-observation-carried-forward (LOCF) approach for missing efficacy results in the MITT population. In Dr. Dixon's statistical review, she regarded MITT subjects with missing data as failures and therefore her review does not include these subjects as cures. Since the sponsor only used this LOCF approach for a few patients, the efficacy results are not significantly different regardless of which analysis method is used. See Dr. Dixon's statistical review.*

The finding that the sponsor drug was not inferior to the RLD, despite the fact that the two drugs are identical with regard to active ingredient, strength, dosage and route of administration prompted the review team to once again assess other possible sources for the non-inferiority of the ALTANA product. Efficacy was evaluated by center, severity strata and drug lot. None of these parameters were found to be different between the two treatment groups. The same conclusion was reached whether the review team evaluated the outcomes based on the Office of Generic Drugs' definition of successful outcome (signs and symptoms and negative KOH and culture) or our division's definition of success (signs and symptoms and negative culture).

In addition, demographic characteristics such as race, age, weight and height were found to be comparable between the two treatment groups in the MITT and PP population (see section II in Appendix). Likewise, there was no baseline difference in the signs and symptoms (itching; burning/irritation; erythema; edema; excoriation) of vulvovaginal candidiasis present at study entry between the two treatment groups (see section V in Appendix). Given our methodical elimination of other parameters that might explain the findings of non-inferiority of the sponsor drug to the identical RLD it seems reasonable to invoke a statistical explanation for these findings. A 95% confidence interval indicates that there is a 1 in 20 chance of finding that the sponsor drug is not similar to the RLD; the ALTANA study might be representative of that small chance finding.

1.3.3 Safety

The sponsor defined an adverse event (AE) as “any untoward medical occurrence (sign, symptom or laboratory finding), regardless of severity and whether or not attributed to the study medication.” All subjects in the ITT population were monitored for the occurrence of adverse events, which were recorded on the clinical report form and followed until they resolved. Protocol investigators evaluated the AEs with respect to seriousness, severity and relationship to the study medication. A serious adverse event was defined as any adverse experience occurring at any drug dose that resulted in any of the following outcomes: death, an immediately life-threatening illness, an inpatient hospitalization or prolongation of existing hospitalization, a congenital anomaly or birth defect, a persistent or significant disability, or any other important medical event. Worsening signs and symptoms of vulvocandidiasis was considered an adverse event.

The main safety parameter in this study was the incidence of all adverse events occurring within the two treatment groups. Overall, the safety profile of the sponsor (generic) drug was comparable to the RLD (Terazol 3® 3). **Table 3** summarizes the number of subjects reporting treatment-emergent adverse events. Of the 460 ITT subjects, 95 had one or more treatment-emergent AEs regardless of relationship to the study medication: forty-eight (20.8%) subjects treated with Terconazole 0.8% vaginal cream compared to 47 (20.5%) subjects treated with Terazol ® 3 vaginal cream 0.8%. There was no significant statistical difference between the two treatment groups with respect to adverse event occurrence (p=0.895). Most of the AEs were considered mild or moderate in severity. Severe AEs noted during the study were allergic reaction (1 RLD subject), breast pain (1 sponsor drug subject), furunculosis (1 sponsor drug subject), vaginal moniliasis (2 RLD subjects) and vaginitis (1 sponsor drug subject and 1 RLD subject). Vaginitis was the only adverse event that occurred in more than 5% of the subjects in either treatment arm: 3% in the sponsor drug group and 5.2 % in the RLD group.

Table 3. Number of Subjects Reporting Treatment-Emergent Adverse Events

Parameter	Generic (N=231)	Terazol 3® (N=229)	p-value
Adverse event(s) regardless of relationship to study medication	48 (20.8%)	47 (20.5%)	0.895 ¹
Adverse event(s) probably related or related to study medication	4 (1.7%)	6 (2.6%)	0.462 ¹

¹ P-values for treatment comparisons from Cochran-Mantel-Haenszel test for general association, stratified by center.

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The number of subjects reporting treatment-emergent adverse events probably related to the study medication was low, four (1.7%) subjects receiving the sponsor drug and six (2.6%) subjects receiving the RLD. Adverse events considered to be related to the study medication included: allergic reaction (1 sponsor drug subject and 2 RLD subjects), pelvic pain (1 sponsor drug subject), nausea (1 RLD subject), pelvic pain (1 sponsor drug subject), uterine spasm (1 sponsor drug subject), vulvovaginitis (1 sponsor drug subject) and vaginitis (3 RLD subjects). One adverse event was considered severe: allergic vulvovaginitis which occurred in 1 subject receiving the RLD.

One subject experienced an AE that was classified as serious by FDA definition. Subject 643 (sponsor drug group) developed an infected left axilla carbuncle that required a 3 day hospitalization. The patient recovered without sequelae. The event was considered by the investigator to be unrelated to the study medication. A copy of the subject's complete CRF can be found in the Appendix.

No deaths were reported. Two subjects, one from each treatment arm, discontinued due to allergic reactions and two subjects, one from each treatment arm, discontinued due to vaginitis.

In conclusion, the ALTANA study showed that terconazole 0.8% vaginal cream posed no major safety concern for females aged 18 and older being treated for vulvovaginal candidiasis.

1.3.4 Dosing Regimen and Administration

Subjects applied study medication intravaginally once daily for three consecutive days.

1.3.5 Drug-Drug Interactions

Not applicable.

1.3.6 Special Populations

Not applicable.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Terconazole Vaginal Cream 0.8% is a vaginal cream with the active drug terconazole in a vehicle consisting of butylated hydroxyanisole, cetyl alcohol, isopropyl myristate, polysorbate 60, polysorbate 80, propylene glycol, steryl alcohol, and purified water. The product is intended for the treatment of vulvovaginal candidiasis in adults.

2.2 Currently Available Treatment for Indications

There are numerous existing drug products for the treatment of VVC. Many of these are available as generic formulations, a few are available as over the counter products.

2.3 Availability of Proposed Active Ingredient in the United States

Three products with the same active ingredient have been approved in HFD 590. Terconazole vaginal products approved in DSPIDP.

Terconazole Prescription Products Approved in HFD 590			
Drug Name	Terazole-7 0.4% Cream (20 mg)	Terazole-3 80 mg Supp.	Terazole-3 0.8% Cream (40 mg)
Dosing	qhs x 7d	qhs x 3d	qhs x 3d
NDA #	19-579	19-641	19-964
Approval	12-31-87	05-24-88	02-21-91
Sponsor	Ortho to RWJ, J&J	Ortho to RWJ, J&J	Ortho to RWJ, J&J
Availability	Rx	Rx	Rx
Note	240 mg NDA withdrawn while under review.	160 mg dose discontinued due to development of flu-like symptoms in Germany.	

2.4 Important Issues With Pharmacologically Related Products

Terconazole is an azole antifungal agent. Several safety issues that are relevant to the systemically administered azoles are not expected to occur significantly with this topical formulation as the drug is not absorbed systemically.

2.5 Presubmission Regulatory Activity

ALTANA initially filed ANDA — with the OGD for this product and issued a Refuse to Receive Letter (September 03, 2003) since it did not meet DBE's criteria for bioequivalence. The other available option for approval as a generic would have required a 505(j) filing, which would require an additional bioequivalence study that demonstrates bioequivalence to the RLD. According to FDA's Draft Guidance entitled, "Applications covered by Section 505(b)(2)" Generally, an application for a pharmaceutically equivalent drug product must be submitted under section 505(j) of the Act and the proposed product must be shown to be bioequivalent to the reference listed drug (21 CFR 314.101(d)(9)). Applications for proposed drug products where the rate (21 CFR 314.54(b)(2)) and/or extent (21 CFR 314.54(b)(1)) of absorption exceed, or are otherwise different from, the 505(j) standards for bioequivalence compared to a listed drug may be submitted pursuant to section 505(b)(2) of the Act. Such a proposed product may require additional clinical studies to document safety and efficacy at the different rate and extent of delivery. Generally, the differences in rate and extent of absorption should be reflected in the labeling of the 505(b)(2) product. The proposed product does not need to be shown to be clinically *better* than the previously approved product; however, a 505(b)(2) application should not be used as a route of approval for poorly bioavailable generic drug products unable to meet the 505(j) standards for bioequivalence. If the proposed product is a duplicate of an already approved product, it should not be submitted as a 505(b)(2) application (21 CFR 314.101(d)(9))."

Even if the proposed product was a duplicate of an already approved product and should not be submitted as a 505 b2, OGD opined that the candidate formulation was not bioequivalent to the RLD and could not be approved under their threshold for bioequivalence. However, the OGD requested that the sponsor perform additional analyses for the primary outcome, using an alternate timepoint window of day 22- 30, as opposed to the protocol specified visit window. This additional analysis however, still failed to satisfy the bioequivalence threshold and review of the NDA proceeded in HFD 590.

The clinical study submitted with the NDA is different from the proof of efficacy studies submitted to the Division except that the comparator is a drug product with the same active ingredient, the same excipients, strength, route of administration and dose.

2.6 Other Relevant Background Information

The efficacy of terconazole as a treatment for VVC in the original NDA filed by the innovator was reviewed by Dr. Joseph Winfield (NDA 19-579, approved December 87). The studies evaluating the efficacy of terconazole as a 7 day therapy for VVC enrolled 1600 women in 4 controlled studies, from 47 investigative sites. The efficacy from some of these studies is reproduced from Dr. Winfield's reviews shown below:

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Protocol C82—056	0.8% terconazole	0.4 % terconazole	Placebo
Visit 3 outcomes			
Clinical cure	32/49 (65.3%)	37/56 (66.1)	13/59 (22.0)
Micologic cure	27/49 (55.1)	36/56 (64.3)	8/59 (13.6)
Therapeutic cure	27/49 (55.1)	34/56 (60.7)	8/59 (13.6)
Symptom relief			
Day 3	19/49 (38.8)	20/55 (36.4)	10/59 (16.9)
Day 7	34/49 (69.4)	40/55 (72.7)	16/59 (27.1)

Protocol C82—056	0.8% terconazole	0.4 % terconazole	Placebo
Visit 3 outcomes			
Clinical cure	36/47 (76.6%)	30/44 (68.2)	11/43 (25.6)
Mycologic cure	31/47 (66)	30/44 (68.2)	9/43 (20.9)
Therapeutic cure	31/47 (66)	29/44 (63.6)	8/43 (18.6)
Symptom relief			
Day 3	16/46 (34.8)	15/43 (34.9)	7/43 (16.3)
Day 7	33/46 (71.7)	35/43 (81.4)	19/43 (44.2)

Protocol C82—056	0.8% terconazole	0.4 % terconazole	2% miconazole	Placebo
Visit 3 outcomes				
Clinical cure	69.0	59.6	70.0	25.0
Mycologic cure	64.3	57.4	60.0	16.7
Therapeutic cure	59.6	55.3	60.0	16.7
Symptom relief				
Day 3	47.5	38.4	22.5	29.8
Day 7	75	62.5	67.5	40.4

Protocol C82—024	0.8% terconazole	0.4 % terconazole	0.2% miconazole
Visit 3 outcomes			
Clinical cure	75	76.9	73.5
Mycologic cure	68.8	65.9	66.2
Therapeutic cure	65.4	63.7	64.2
Symptom relief			
Day 3	41.0	45.6	40.1
Day 7	77.0	83.3	79.5

In these studies, the therapeutic cure achieved with the RLD varied from 55% to 66%, compared to 13 to 18% with placebo. Of interest is the finding that there appeared to be no convincing dose response between the terconazole formulations, with the 0.2% and the 0.4% formulations showing efficacy rates that were better than the 0.8% formulation, in several of the analyses. The comparison against placebo however, showed consistently better outcomes with the active drug and serves as evidence that terconazole is an active antifungal agent.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

See Dr. Matecka's review.

3.2 Animal Pharmacology/Toxicology

Not applicable.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

One pivotal bioequivalence study is presented (ALT 0347-05-01, initiated October 30, 2001 and completed May 14, 2003) is presented by the sponsor. The review team also reviewed the original NDA for the RLD, to compare the efficacy and safety findings for the RLD in this NDA with the established efficacy in the original submission.

4.2 Tables of Clinical Studies

Not applicable.

4.3 Review Strategy

The single study was reviewed and an attempt was made to understand whether there was a systematic bias that favored the candidate formulation over the RLD. Efficacy was reviewed by center, by investigator, by study formulation etc, and no such factor was found to have explained the findings.

4.4 Data Quality and Integrity

After the Office of Generic Drugs' evaluation of data quality and integrity, the Medical Officer from HFD 590 reviewed a sample of the case report forms and is satisfied with the study's conduct.

4.5 Compliance with Good Clinical Practices

The study was conducted in compliance with GCP. A greater number of patients were excluded from the MITT for protocol violations in the study drug group (91) versus the RLD (67). The review team determined that the addition of these patients in the analysis would not materially alter the conclusions derived.

4.6 Financial Disclosures

Not applicable.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

See Dr. De Los Reyes' review.

5.2 Pharmacodynamics

See Dr. De Los Reyes' review.

5.3 Exposure-Response Relationships

Not applicable.

6 INTEGRATED REVIEW OF EFFICACY

Not applicable. The single study submitted for review is presented above.

7 INTEGRATED REVIEW OF SAFETY

Not applicable. The single study submitted for review is presented above.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Terconazole 0.8% vaginal cream applied once daily for 3 consecutive days was found to be as safe and not inferior to the comparator drug, Terazol 3 vaginal cream 0.8%.

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Therefore the Division has no concerns regarding the candidate drug's dosing regimen and administration.

8.2 Drug-Drug Interactions

The therapeutic effect of Terconazole 0.8% vaginal cream is not affected by oral contraceptive use.

8.3 Special Populations

Not applicable.

8.4 Pediatrics

Pediatric waiver is granted for this vaginal azole, as for most VVC products, because the disease occurs infrequently in children.

8.5 Advisory Committee Meeting

Not applicable.

8.6 Literature Review

Not applicable.

8.7 Postmarketing Risk Management Plan

Not applicable.

8.8 Other Relevant Materials

Not applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

This study was originally designed to fulfill the Office of Generic Drugs'(OGD) requirement for determination of bioequivalence of the candidate drug product, Terconazole 0.8% vaginal cream, to the reference listed drug (RLD), Terazol 3 vaginal cream 0.8%. The OGD refused to receive the application since the pivotal study failed to show bioequivalence of the sponsor drug to the RLD, because the CI around the

difference in proportions of therapeutic cures between the study arms exceeded the pre-set 90% bounds. The primary efficacy parameter was the proportion of therapeutic cures at Visit 3 (Day 21-30). Therapeutic cure was defined as clinical cure plus a mycological cure (negative KOH and culture for *Candida* species). ALTANA performed a study which showed their drug product to be non-inferior to the RLD in terms of therapeutic cure rate (73% vs 60% respectively) in the PP population on Visit 3 (Day 21-30). Likewise, in the MITT population, the therapeutic cure rate for the candidate drug (71%) was non-inferior to the RLD (56%). The safety analysis of the candidate drug was found to be favorable; there was no statistically significant difference between the sponsor drug and the RLD with regard to occurrence of adverse events. These findings confirm that Terconazole 0.8% vaginal cream (ALTANA) is not inferior to Terazol 3 based on HFD-590's CI, -15 to 15%. The table below summarizes the pertinent data.

ALTANA 0347-05-01

EFFICACY		Sponsor Drug	RLD	Difference	95% CI
Visit 3 outcomes (day 21-30)					
PP	Therapeutic cure	83/114 (73%)	73/122 (60%)	13%	(0.2 %, 25.8%)
MITT	Therapeutic cure	100/140 (71%)	86/153 (56%)	15%	(2.0 %, 28.0%)
PP	Clinical cure	96/114 (84%)	90/122 (74%)	10%	(-1.1 %, 21.1 %)
MITT	Clinical cure	116/140 (83%)	107/153 (70%)	13%	(2.8 %, 23.2 %)
PP	Mycological cure	88/114 (77%)	80/122 (66%)	11%	(-1.3 %, 23.3 %)
MITT	Mycological cure	108/140 (77%)	97/153 (63%)	16%	(3.0 %, 25.0%)
SAFETY		Sponsor Drug	RLD	p value	
Any AE		48/231 (20.8%)	47/229 (20.5%)	0.895	
Drug related AE		4/231 (1.7%)	6/229 (2.6%)	0.462	
Severe		3 furunculosis, generalized rash, breast pain, vaginitis	4 allergic reaction, vaginal moniliasis, nausea salivary gland enlargement		

9.2 Recommendation on Regulatory Action

The sponsor has shown that the candidate drug is both safe and efficacious in the treatment of vulvovaginal candidiasis and the Division endorses approval of this application. The review team also finds the proposed label acceptable for product launch.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Not applicable.

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9.3.2 Required Phase 4 Commitments

Not applicable.

9.3.3 Other Phase 4 Requests

Not applicable.

9.4 Labeling Review

We did a side by side review of the paper copy of the proposed drug label and the RLD label and found them to contain the same basic information. The sponsor added a geriatric section to the label which we find acceptable. The sponsor uses generic nomenclature and seeks no trade name.

9.5 Comments to Applicant

There are no additional comments to be sent to the applicant.

10 APPENDICES

10.1 Review of Individual Study Reports

Title of Study

(NDA 21-735) A Multicenter, 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.

Purpose

The purpose of this multicenter, double-blind, randomized parallel-group study was to evaluate the safety and therapeutic equivalence of terconazole 0.8% vaginal cream (ALTANA Inc.) to Terazol® 3 vaginal cream 0.8% (Ortho-McNeil Pharmaceutical Corporation) in the treatment of vulvovaginal candidiasis.

Methods

Subjects who met the inclusion criteria were randomized in a 1:1 ratio to one of two treatment groups and then required to apply either the candidate drug (terconazole 0.8% vaginal cream) or the registered listed drug (RLD) (Terazol® 3) once a day at bedtime for 3 consecutive days. Clinical evaluation of the subjects was done on Visit 2 (Day 8-10) and Visit 3 (Day 21-30).

Inclusion Criteria: the following conditions had to be met:

- females who met the following criteria were eligible for the study: age \geq 18 years old, non-pregnant and non-lactating and either at least two years postmenopausal, surgically sterile or using adequate birth control measures (including abstinence, oral contraceptives, implants, tubal ligation or IUD). The following contraceptive methods were considered unacceptable during the treatment period because of their potential to interact with the study medications: diaphragms, condoms, sponges or spermicide (these methods, when combined with a spermicide, were considered acceptable if used during the untreated follow-up period).
- clinical diagnosis of vulvovaginal candidiasis defined as having a total score of \geq 2 for at least one sign (erythema, edema or excoriation) and \geq 2 for at least one symptom (itching or burning/irritation) of the vagina and /or vulva, rated on a 4-point scale where 0=none, 1=mild, 2=moderate and 3=severe.
- microscopic diagnosis of vulvovaginal candidiasis: confirmed by the presence of hyphae/pseudohyphae and /or budding yeast cells on examination of a KOH mount of a specimen obtained by vaginal mucosa swab.

- Wet smear of vaginal fluid negative for *Trichomonas vaginalis* or clue cells.
- Free of significant clinical disease other than vulvovaginal candidiasis
- able to provide written informed consent
- able to abstain from vaginal intercourse during the 3-day treatment period
- able to use sponsor-provided non-lubricated condoms (for infection prevention) during intercourse at the time of the untreated follow-up period. Use of a condom for contraception during the follow-up period required spermicide use.
- Ability to comply with study requirements with regards to treatment dosing requirements, visit schedule and therapy prohibitions
- Ability to complete the study as specified in the protocol

Exclusion Criteria: the following criteria would exclude a woman from the study

- Pregnancy or lactation
- Presence of abdominal pain or fever
- Significant medical conditions that could compromise participation in the study or place the subject at risk: e.g. immunological deficiencies.
- Vulvovaginal infection associated with pathogens other than *Candida* such as bacterial vaginosis, *Trichomonas vaginalis*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, herpes simplex, or human papilloma virus.
- Cervical intraepithelial neoplasia or cervical cancer on Pap smear obtained at baseline will result in subject removal at Visit 2
- Excessive use of alcohol, drugs or a condition that would compromise protocol compliance

- Hypersensitivity to the imidazole class of drugs or any components of the study medications
- Concomitant use of an antifungal agent or antimicrobial for a systemic, mucocutaneous or skin infection other than vulvovaginal candidiasis
- Previous enrollment in the study
- Use of any vaginal therapeutic, medicated douche or feminine spray within 7 days before entry into the study. Prohibition of intravaginal therapy with an imidazole antifungal within 14 days prior to study entry
- Use of systemic corticosteroid treatment within two months prior to study entry
- Use of any systemic antifungal within one month before study entry or systemic antibiotic during the entire period of study participation
- Use of water douches within 3 days before study entry
- Treatment with terconazole or an investigational drug within 30 days before study entry

Procedures: At baseline evaluation, patients were examined and a vaginal examination was performed. A culture, gram stain, wet mount and KOH of vaginal secretions was taken. Clinical evaluation was conducted on Visit 2 (Day 8-10) and Visit 3 (Day 21-30). See study schedule in **Table 1** below.

Table 1. Study Schedule

Visit Number	1	2	3	
Study Day	Day 1	Day 1-3	Day 8-10	Day 21-30
Informed Consent Obtained	X			
Medical & Medication History	X			
Physical Examination	X			
Urine Pregnancy Test ^a	X			
Signs/Symptoms Assessment	X		X	X
Pap Smear ^b	X			
KOH Microscopy ^c	X		X	X
Wet Smear Microscopy ^d	X			
Specimens for Central Mycology Lab	X		X	X
Specimens for Central Bacteriology Lab ^e	X			
Dispense Study Medication	X			
Apply Study Medication		X		
Retrieve Study Medication			X	
Concomitant Medication Review			X	X
Adverse Events Review			X	X
Investigator's Outcome Question				X

^a If of childbearing potential.

^b If not completed within 12 months prior to enrollment.

^c For *Candida* species.

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^d For *T. vaginalis* and clue cells. ^e For *N. gonorrhoeae* and *C. trachomatis* (DNA probe).

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Subject Populations

Three subject populations were defined in the study: intent-to-treat (ITT), modified intent-to-treat (MITT) and per-protocol (PP). The ITT population consisted of subjects enrolled into the study who received at least one dose of study medication. The MITT population consisted of ITT subjects who met inclusion/exclusion criteria (including a positive baseline fungal culture for *Candida*) and returned for at least one post-baseline visit. The PP population consisted of ITT subjects who met inclusion/exclusion criteria, had a baseline fungal culture for *Candida*, complied with the minimum treatment course (3 consecutive days), had data for all three efficacy variables for 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. The PP population returned to the study site within the specified window for Visit 3 (Day 21-30) or was discontinued from the study due to treatment failure or adverse event having received 3 days of study medication. This group had no protocol violations.

Statistical Analysis

The efficacy analyses were conducted on both the PP and the MITT subject populations.

The primary efficacy parameter was the proportion of subjects with a therapeutic cure at Visit 3 (Day 21-30). The definition of therapeutic cure for this study included a clinical cure plus a mycological cure (negative KOH and culture for *Candida* species).

Definition of outcomes: A subject was considered a clinical cure if the following requirements were met: all signs and symptoms of candidiasis with severity scores of 1 or 2 at the time of protocol entry were absent (score of 0) by the end of treatment; signs and symptoms of candidiasis with severity scores of 3 at protocol entry had scores of 0 or 1 (mild) after treatment, and the investigator confirmed that the subject no longer required therapy for her vulvovaginal candidiasis.

A subject was considered a clinical failure if she had signs and symptoms present at entry that had not cleared as specified in the clinical cure definition and there was evidence that active disease was still present, or the investigator indicated that the subject required additional therapy for vulvovaginal candidiasis.

Secondary efficacy parameters in this study included the number of subjects evaluated as clinical cures at Visit 2 and Visit 3; the number of subjects evaluated as mycological cures at Visit 2 and Visit 3; the clinical signs and symptoms scores at Visit 2 and Visit 3 and the response to the investigator's outcome question at Visit 3. For purposes of this summary the efficacy discussion will focus on results of the primary efficacy parameter between the two treatment groups in the PP and MITT populations. The secondary efficacy parameter results, which support the primary efficacy parameter results, are discussed in section VI of the appendix.

The claim for non-inferiority requires a 95% confidence interval for the difference in the proportions of therapeutic cures between the candidate drug and the RLD at Visit 3 (Day 21-30) contained within the interval of -15% to +15%. The primary analysis in the PP population showed that the therapeutic cure rate was higher for the sponsor drug (73%) than the RLD (60%) at Visit 3 (Day 21-30). Likewise, the sponsor drug showed a higher therapeutic cure rate (71%) in the MITT analysis compared to the reference drug (56%) at Visit 3 (Day 21-30). Thus ALTANA's terconazole 0.8% vaginal cream was found to be not inferior to Terazol @ 3 vaginal cream 0.8% in the PP analysis (95% confidence interval on the difference in therapeutic cure rate: 02.% to 25.8%) and the MITT analysis (95% confidence interval on the difference in therapeutic cure rate: 2.0 % to 28. 0%) at Visit 3 (Day 21-30). Results for mycological, clinical and therapeutic cures are summarized in **Table 2**

Demographic characteristics

Demographic characteristics for the ITT (Table 1), MITT (Table 2) and PP (Table 3) study subjects are summarized below. The ITT population was mostly Caucasian (270/460; 59%). There were 59 (13%) Black subjects; 13(3%) Asian subjects, and 118 (26%) subjects of other races.

Subjects aged in range from 17-82 years. For the ITT population, the two treatment groups were comparable for all demographic characteristics (all $p > 0.05$) except for weight ($p = 0.008$). See **Table 2**. For both the MITT and PP populations, all demographic characteristics were comparable between the two treatment groups (all $p > 0.05$). See **Tables 3 and 4**.

Table 2. Demographic Characteristics for ITT Subjects

Characteristic		Generic (N=231)	Terazol 3% (N=229)	p-value
Race	Caucasian	141 (61%)	129 (56%)	0.264 ¹
	Black	23 (10%)	36 (16%)	
	Asian	8 (3%)	5 (2%)	
	Native American	0 (0%)	0 (0%)	
	Other	59 (26%)	59 (26%)	
Age(years)	Mean \pm Std	36.2 \pm 12.4	37.5 \pm 12.5	0.142 ²
	Min - Max	18 - 82	17 - 76	
Weight(pounds)	Mean \pm Std	154.7 \pm 43.0	157.9 \pm 40.4	0.008 ²
	Min - Max	99.0 - 402.0	100.0 - 328.0	
Height(inches)	Mean \pm Std	64.2 \pm 2.8	64.1 \pm 3.0	0.986 ²
	Min - Max	55.0 - 73.0	52.0 - 72.0	

¹ P-value for treatment comparison from Cochran-Mantel-Haenszel test for general association, adjusted for center.

² P-values for treatment comparisons from Friedman's test with factors of treatment and center.

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Table 3. Demographic Characteristics for MITT Subjects

Characteristic		Generic (N=140)	Terazol 3% (N=153)	p-value
Race	Caucasian	82 (59%)	88 (58%)	0.342 ¹
	Black	12 (9%)	22 (14%)	
	Asian	7 (5%)	4 (3%)	
	Native American	0 (0%)	0 (0%)	
	Other	39 (28%)	39 (25%)	
Age(years)	Mean ± Std	35.9 ± 11.3	37.4 ± 12.3	0.318 ²
	Min - Max	18 - 82	18 - 72	
Weight(pounds)	Mean ± Std	152.2 ± 38.3	157.9 ± 39.9	0.145 ²
	Min - Max	102.0 - 300.0	100.0 - 315.0	
Height(inches)	Mean ± Std	64.1 ± 2.6	63.9 ± 2.9	0.656 ²
	Min - Max	56.0 - 71.0	54.4 - 72.0	

¹ P-value for treatment comparison from Cochran-Mantel-Haenszel test for general association, adjusted for center.

² P-values for treatment comparisons from Friedman's test with factors of treatment and center.

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Table 4. Demographic Characteristics for PP Subjects

Characteristic		Generic (N=114)	Terazol 3% (N=122)	p-value
Race	Caucasian	71 (62%)	73 (60%)	0.508 ¹
	Black	10 (9%)	17 (14%)	
	Asian	5 (4%)	3 (2%)	
	Native American	0 (0%)	0 (0%)	
	Other	28 (25%)	29 (24%)	
Age(years)	Mean ± Std	36.0 ± 11.5	37.4 ± 12.2	0.819 ²
	Min - Max	18 - 82	18 - 72	
Weight(pounds)	Mean ± Std	153.6 ± 39.5	157.5 ± 39.8	0.245 ²
	Min - Max	102.0 - 300.0	100.0 - 315.0	
Height(inches)	Mean ± Std	64.0 ± 2.6	63.9 ± 2.7	0.862 ²
	Min - Max	56.0 - 71.0	54.4 - 72.0	

¹ P-value for treatment comparison from Cochran-Mantel-Haenszel test for general association, adjusted for center.

² P-values for treatment comparisons from Friedman's test with factors of treatment and center.

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Baseline Signs and Symptoms of Vulvovaginal Candidiasis

The two treatment arms of this study were comparable in terms of baseline signs and symptoms (itching; burning/irritation; erythema; edema; excoriation) of vulvovaginal candidiasis. In the MITT population, both the candidate drug and the RLD showed higher baseline ratings for signs and symptoms of itching, burning/irritation and erythema when compared to other symptoms. There were no statistically significant differences at baseline between treatment groups in the MITT population with regard to itching (p=0.975), burning/irritation (p=0.198), erythema (p= 0.988), edema (p= 0.813), excoriation (p=0.635) or total signs and symptoms (p=0.266). See **Table 5**. Likewise, in the PP subjects, there were no statistically significant differences between treatment groups for baseline signs and symptoms with regards to itching, burning/irritation, erythema, excoriation, or total signs and symptoms as shown in **Table 6**.

Table 5. Baseline Evaluation of Clinical Signs and Symptoms of Vulvovaginal Candidiasis for MITT Subjects

Parameter	Category	Generic (N=120)	Terazol 3% (N=153)	p-value
Itching	None	1 (1%)	3 (2%)	0.975 ¹
	Mild	5 (4%)	9 (6%)	
	Moderate	69 (49%)	67 (44%)	
	Severe	65 (45%)	72 (48%)	
Burning/Irritation	Missing	1 (1%)	0 (0%)	0.198 ¹
	None	11 (9%)	3 (2%)	
	Mild	18 (13%)	26 (17%)	
	Moderate	58 (41%)	66 (43%)	
	Severe	52 (37%)	68 (38%)	
Erythema	None	1 (1%)	0 (0%)	0.988 ¹
	Mild	5 (4%)	6 (4%)	
	Moderate	70 (50%)	63 (54%)	
	Severe	63 (45%)	64 (42%)	
Edema	None	8 (5%)	11 (7%)	0.813 ¹
	Mild	42 (30%)	49 (32%)	
	Moderate	55 (40%)	58 (38%)	
	Severe	34 (24%)	35 (23%)	
Excoriation	None	64 (39%)	61 (40%)	0.635 ¹
	Mild	27 (19%)	29 (19%)	
	Moderate	47 (34%)	49 (32%)	
	Severe	12 (9%)	14 (9%)	
Total Signs and Symptoms	Mean ± Std	9.8 ± 3.1	9.8 ± 2.9	0.266 ²
	Min - Max	4 - 16	4 - 16	

¹ P-values for treatment comparisons from Cochran-Mantel-Haenszel row mean score test, adjusted for center.

² P-value for treatment comparison from Friedman's test with factors of treatment and center.

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Table 6. Baseline Evaluation of Clinical Signs and Symptoms of Vulvovaginal Candidiasis for PP Subjects

Parameter	Category	Generic (N=114)	Terazol 3% (N=122)	p-value
Itching	None	1 (1%)	2 (2%)	0.947 ¹
	Mild	3 (3%)	7 (6%)	
	Moderate	52 (46%)	52 (43%)	
	Severe	58 (51%)	61 (50%)	
Burning/Irritation	Missing	1 (1%)	0 (0%)	0.591 ¹
	None	6 (5%)	3 (2%)	
	Mild	14 (12%)	21 (17%)	
	Moderate	48 (42%)	51 (42%)	
	Severe	45 (39%)	47 (39%)	
Erythema	None	1 (1%)	0 (0%)	0.913 ¹
	Mild	6 (4%)	6 (5%)	
	Moderate	53 (46%)	61 (50%)	
	Severe	55 (48%)	55 (45%)	
Edema	None	7 (6%)	7 (6%)	0.650 ¹
	Mild	31 (27%)	35 (31%)	
	Moderate	48 (42%)	46 (38%)	
	Severe	28 (25%)	31 (25%)	
Excoriation	None	39 (34%)	49 (40%)	0.765 ¹
	Mild	25 (22%)	22 (18%)	
	Moderate	40 (35%)	39 (32%)	
	Severe	10 (9%)	12 (10%)	
Total Signs and Symptoms	Mean ± Std	10.1 ± 3.0	9.9 ± 2.9	0.393 ²
	Min - Max	4 - 15	5 - 16	

¹ P-values for treatment comparisons from Cochran-Mantel-Haenszel row mean score test, adjusted for center.

² P-value for treatment comparison from Friedman's test with factors of treatment and center.

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Study protocol violations

Included failure to meet inclusion/exclusion criteria; failure to return for the primary efficacy visit (Visit 3) within the visit window (Day 21-30) [unless discontinued early due to lack of efficacy or because of intolerable adverse events] and using prohibited medications.

Efficacy

Primary Efficacy Analysis: In the primary efficacy analysis of therapeutic cure in the per protocol population at Visit 3 (Day 21-30) the rate of successful outcome was 73% (83/114) in the terconazole 0.8% vaginal cream treated group compared to 60% (73/122) in the Terazol® 3 group (95% CI on the difference in therapeutic cure rate: 0.2% to 25.8%) .

Secondary Efficacy Analysis: The secondary efficacy parameters, conducted at Visit 2 and Visit 3, evaluated the number of subjects with a both a clinical and mycological cure. Subjects meeting criteria for cure were listed as cure regardless of baseline culture results. Subjects with negative baseline cultures were excluded from MITT and PP analyses.

Sponsor Findings of Clinical Cure at Visit 2

The PP population analysis at Visit 2 (Day 8-10) showed that 76% of subjects in the candidate (generic) drug treatment arm and 70% of subjects in the Terazol® 3 treatment arm were considered a clinical cure. The sponsor finds the candidate drug to be clinically equivalent to Terazol® 3 in the PP analysis (90% confidence interval on difference in proportions of clinical cures: -4.08% to 16.30%).

The MITT population analysis at Visit 2 (Day 8-10) showed that 74% of subjects in the candidate drug treatment arm and 69% of subjects in the Terazol® 3 treatment arm were considered a clinical cure. The sponsor finds the candidate drug to be clinically equivalent to Terazol® 3 in the MITT analysis (90% confidence interval on difference in proportions of clinical cures: -3.35% to 15.37%).

Sponsor Findings of Mycological Cure at Visit 2

The PP population analysis at Visit 2 (Day 8-10) showed that 86% of subjects in the candidate drug treatment arm and 74% of subjects in the Terazol® 3 treatment arm were considered a mycological cure. The sponsor finds the candidate drug to be mycologically equivalent to Terazole® 3 in the PP analysis (90 % confidence interval on difference in proportions of mycological cures: 1.71% to 19.68%).

The MITT population analysis at Visit 2 (Day 8-10) showed that 83% of subjects in the candidate drug treatment arm and 74% of subjects in the Terazol® 3 treatment arm were considered a mycological cure. The sponsor finds the candidate drug to be mycologically equivalent to Terazol® 3 in the MITT analysis (90% confidence interval on difference in proportions of mycological cures: 0.46% to 17.21%).

Sponsor Findings of Clinical Cure at Visit 3

The PP population analysis at Visit 3 (Day 21-30) showed that 84% of subjects in the candidate drug treatment arm and 74% of subjects in the Terazol® 3 treatment arm were considered a clinical cure. The sponsor finds the candidate drug to be clinically equivalent to Terazol® 3 in

the PP analysis (90% confidence interval on difference in proportions of clinical cures: 0.96% to 19.92%).

The MITT population analysis at Visit 3 (Day 21-30) showed that 83% of subjects in the candidate drug treatment arm and 70% of subjects in the Terazol ® 3 treatment arm were considered a clinical cure. The sponsor finds the candidate drug to be not inferior to Terazol ® 3 in the MITT analysis (90% confidence interval on difference in proportions of clinical cures: 5.47% to 22.78%).

Sponsor Findings of Mycological Cure at Visit 3

The PP population analysis at Visit 3 (Day 21-30) showed that 77% of subjects in the candidate drug treatment arm and 66% of subjects in the Terazol® 3 treatment arm were considered a mycological cure. The sponsor finds the candidate drug to be not inferior to Terazol® 3 in the PP analysis (90% confidence interval on difference in proportions of mycological cures: 0.64% to 21.51%).

The MITT population analysis at Visit 3 (Day 21-30) showed that 77% of subjects in the candidate drug treatment arm and 63% of subjects in the Terazol ®3 treatment arm were considered a mycological cure. The sponsor finds the candidate drug to be not inferior to Terazol ® 3 in the MITT analysis (90% confidence interval on difference in proportions of mycological cures: 4.42% to 23.05%). Results are summarized in **Table 7**.

MO Comment: The finding of greater clinical cure rate on Visit 3 compared to Visit 2 in the study drug indicates that the earlier efficacy translated into continued benefit in terms of less relapses at Visit 3.

The Division established a 95% confidence interval around the differences in the secondary efficacy analysis of clinical cure rate and mycological cure rate at Visit 2 and 3. Non-inferiority of Terconazole 0.8% vaginal cream to Terazole 3 was established if the 95% confidence interval was contained within the interval of -15% to + 15%. For purposes of this appendix, the data above is reviewed as presented by the sponsor, with a 90% confidence interval. Table 6 below shows both the sponsor's use of a 90% confidence interval to establish bioequivalence of the candidate drug to the RLD and the Division's 95% confidence interval to show non-inferiority. The conclusion is the same regardless of which confidence interval is used in analyzing the data: Terconazole 0.8% vaginal cream is not inferior to Terazole 3. The 95% CI around the difference in the various analyses can be found in Dr. Sheryl Dixon's statistical review of this NDA.

Table 7. Secondary Efficacy Analysis: Clinical Cure Rate and Mycological Cure Rate at Visit 2 and 3.

Parameter	Successful Outcome		OGD	DSPIDP
	Terconazole 0.8% vaginal cream	Terazol ® 3	90% C.I. for Bioequivalence of Terconazole 0.8% vaginal cream to Terazol ® 3 *	95% C.I. for Non-Inferiority of Terconazole 0.8% vaginal cream to Terazol ® 3 **
Per-Protocol Subjects	n (n/N)	n (n/N)		
Visit 2	<i>(N = 114)</i>	<i>(N = 122)</i>		
Clinical cure	87 (76%)	86 (70%)	(-4.08%, 16.30%)	(-6.1%, 18.1%)
Mycological cure	98 (86%)	90 (74%)	(1.71%, 19.69%)	(1.1%, 22.9%)
Visit 3	<i>(N = 114)</i>	<i>(N = 122)</i>		
Clinical cure	96 (84%)	90 (74%)	(0.96%, 19.92%)	(-1.1, 21.1%)
Mycological cure	88 (77%)	80 (66%)	(0.64%, 21.51%)	(-1.3%, 23.3%)
Modified Intent to Treat Subjects*	n (n/N)	n (n/N)		
Visit 2	<i>(N = 140)</i>	<i>(N = 153)</i>		
Clinical cure	103 (74%)	105 (69%)	(-3.35%, 15.37%)	(-6.0%, 16.0%)
Mycological cure	116 (83%)	113 (74%)	0.46%, 17.21%)	(-1.0%, 19.0%)
Visit 3	<i>(N = 140)</i>	<i>(N = 153)</i>		
Clinical cure	116 (83%)	107 (70%)	(5.47%, 22.78%)	(2.8%, 23.2%)
Mycological cure	108 (77%)	97 (63%)	(4.42%, 23.05%)	(3.0%, 25.0%)

n = number of subjects with clinical cure or mycological cure

N = total number of subjects

* Microbiologic outcomes based on a negative KOH

** Microbiologic outcomes based on a negative culture

Only subjects with clinical/mycological responses of "cure" were included in confidence interval calculations.

MO Comment: For the efficacy analyses, the sponsor used a last-observation-carried-forward (LOCF) approach for missing efficacy results in the MITT population. In Dr. Dixon's statistical review, she regarded MITT subjects with missing data as failures and therefore her review does not include these subjects as cures. Since the sponsor only used this LOCF approach for a few patients, the efficacy results are not significantly different regardless of which analysis method is used. For details, see Dr. Dixon's statistical review.

Safety

The overall safety of terconazole 0.8% vaginal cream and Terazol ® 3 were similar. There were no deaths. The more common adverse events in the comparator arm were signs and symptoms

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of vulvovaginal candidiasis. There were no serious systemic adverse events in the study drug treated group. Overall, the study drug is as safe as the reference label drug.

One subject experienced an adverse event that was classified as serious by FDA definition. Subject 643 (sponsor drug group) developed an infected left axilla carbuncle that required a 3 day hospitalization. The patient recovered without sequelae. The event was considered by the investigator to be unrelated to the study medication. A copy of the subject's complete CRF can be found below.

Subject Number: 643 **Initials:** — **Randomized Therapy:** terconazole 0.8% vaginal cream
Dose at Onset of AE: once daily **Exposure Duration at AE Onset:** post-treatment
Study Period: post-treatment **AE Duration:** 3 days **Severity:** severe
Outcome: recovered without sequelae

Subject 643/ — a 47 year-old Hispanic female with a history of type II diabetes mellitus, began study treatment on 03/03/03, completed treatment 2 days later on 03/05/03, and returned for the post-treatment visit on 03/12/03. On — the subject had an infected left axilla carbuncle and saw a surgeon who lanced it and admitted her to the hospital for further treatment. She was given Keflex from 03/24/03 to 03/25/03. While hospitalized she was given Morphine on — , and Unisyn, Percocet, and regular Insulin from 03/25/03 to 03/27/03. She was also given Augmentin from 03/27/03 to 04/05/03, and Vicodin from 03/28/03 to 03/31/03. The subject was released from the hospital on — and recovered without sequelae. The subject completed the study on 03/28/03, but due to the prohibited medication she was excluded from the PP analyses. The event was considered by the investigator to be unrelated to the study medication.

MO comment: While onset of adverse event is temporally related with treatment , the MO concludes that the adverse events is likely to be unrelated to treatment .

10.2 Line by line Labeling Reveiw

We did a side by side paper review of the study drug label and the RLD label and found them to be almost identical. The sponsor added a geriatric section to the label which we find acceptable. The sponsor uses generic nomenclature and seeks no trade name.

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Clinical Review
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REFERENCES

Not applicable.

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/s/

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10/1/04 02:15:32 PM
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