CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-307

Statistical Review(s)

STATISTICAL REVIEW AND EVALUATION

Medical Division: **Division of Derm. & Dental Drug Products (DDDDP HFD-540)**
Biometrics Division: **Division of Biometrics III (HFD-725)**

NDA NUMBER:	21-307
SERIAL NUMBER:	000/RS
DATE RECEIVED BY CENTER:	10/05/01
DRUG NAME:	Lotrimin Ultra (Butenafine HCl 1%)
INDICATION:	Tinea corporis
SPONSOR:	Schering-Plough
DOCUMENTS REVIEWED:	Volume 1 (Phase 4 protocol)
STATISTICAL REVIEWER:	Kathleen Fritsch, Ph.D. (HFD-725)
STATISTICAL TEAM LEADER:	Mohamed Alosh, Ph.D. (HFD-725)
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CLINICAL REVIEWER:	Joseph Porres, M.D., Ph.D. (HFD-540)
PROJECT MANAGER:	Frank Cross (HFD-540)
DATE REVIEW COMPLETED:	11/28/01

I. Introduction and Background

The Agency issued an approvable letter for butenafine HCl 1% on July 27, 2001. In the letter the Agency requested the following:

> Also, you should propose a protocol to satisfy a Post Marketing Commitment to evaluate the safety and efficacy of tinea corporis in the 12 year old and under pediatric population, especially since the dermatophyte species responsible may vary from adults.

In this resubmission, the sponsor has submitted a protocol to evaluate the efficacy and safety of butenafine HCl 1% in the treatment of tinea corporis in pediatric patients aged 2 to 12. This study is randomized, double-blind, vehicle-controlled, and multi-center. Approximately 100 pediatric subjects will be randomized in a 1:1 ratio to butenafine or vehicle. Subjects will apply study cream to tinea corporis lesions once daily for 14 days. Subjects will be evaluated on Day 1, and at Weeks 2, 4, and 8.

The primary efficacy endpoint is effective treatment at Week 8, defined as conversion to negative mycology (negative microscopy and culture) with an Investigator's Global Assessment (IGA) of 0 or 1 (cleared, no signs present or minimal signs present). The secondary efficacy endpoints are

- complete cure at Week 8 (negative mycology and IGA = 0)
- IGA at Week 8.

Additional analyses will be conducted for the cure rates at each visit (effective treatment, mycological cure, complete cure), and for the total signs score (sum of the scores for erythema, scaling, vesiculation, maceration, and papules each rated on a 4 point scale (0 = none to 3 = severe)).

Reviewer Comment: Mycological sampling is only planned for Day 1 and Week 8, so calculation of cure rates at Weeks 2 and 4 is not possible. Refer to the clinical review regarding the use of clinical cure rather than effective treatment as the primary efficacy endpoint.

The primary analysis population (MITT) is defined as all subjects randomized with positive dermatophyte culture at baseline and at least one post-baseline assessment. Missing data will be imputed with LOCF. If an evaluation from Week 2 or 4 occurs after the evaluation window (Day 14-16 for Week 2, and Day 26-30 for Week 4), then the observation will be considered missing for that visit (but may still be carried forward to later visits if necessary.)

Reviewer Comment: The MITT population should be defined as all randomized subjects with positive dermatophyte culture at baseline, and should include subjects without post-baseline assessments. A per protocol population should also be defined in the protocol and analyzed as a secondary analysis.

Missing data in the MITT should be imputed two ways. In the first case, subjects who drop out before the final evaluation should be imputed as failures (even if they were considered a success at an earlier visit). In the second case, LOCF should be used to carry forward the result from the subject's last visit (either a success or a failure).

Effective treatment, mycological cure, and complete cure will be analyzed with Cochran-Mantel-Haenszel tests, stratified on center. To assess treatment by center interactions, the Week 8 cure rates will be summarized by center and reviewed for evidence of inhomogeneity across centers. The IGA and total signs scores will also be analyzed with Cochran-Mantel-Haenszel tests. Centers with fewer than 8 subjects per treatment arm per center "will be combined as needed" for analysis.

Sample size calculations were based on the effective treatment rates observed in adults from previous studies (80% for active, 15% for vehicle). The computed sample size of 15 subjects per treatment has been increased to 35 per arm, to allow for differences in cure rates in adults and children. To allow for a 30% delayed exclusion rate, 100 subjects will be randomized.

Reviewer Comment: Refer to the clinical review regarding the definition of the primary endpoint. The sample size should be recalculated using treatment effect estimates for complete cure. The sponsor should also provide more details about how the treatment effect estimates have been obtained to support the adequacy of the calculations.

II. Biostatistics Comments (May be portrayed to sponsor)

1. The MITT population should be defined as all randomized subjects with positive dermatophyte culture at baseline, and should include subjects without post-baseline assessments. Missing data in the MITT population should be imputed two ways. In the first case, subjects who drop out before the final evaluation should be imputed as failures (even if they were considered a success at an earlier visit). In the second case, LOCF should be used to carry forward the result from the subject's last visit (either a success or a failure).

2. A per protocol population should also be defined in the protocol in addition to the MITT population and analyzed as a secondary analysis.

3. Refer to the clinical comments regarding the definition of the primary endpoint. The sample size should be recalculated using treatment effect estimates for complete cure. The sponsor should also provide more details about how the treatment effect estimates have been obtained to support the adequacy of the calculations.

/S/ 11/28/01

/S/ 11/30/01

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Date: May 18, 2001

Addendum to the Statistical Review of March 6, 2001

NDA:	#21-307
Drug Name:	Butenafine HCL 1% Cream
Applicant:	Shering-Plough HealthCare Products
Indication:	Athlete's Foot (Tinea Pedis)
Documents Reviewed:	Sponsor's Briefing Document of March 14, 2001, Sponsor's submission of additional information of May 3, 2001
References:	Statistical Review of November 24, 1995 (Statistical reviewer: Valeria Freidlin, Ph.D.) Statistical Review of November 21, 1997 (Statistical reviewer: Steve Thomson, M.Sc.)
Medical Officer:	Joseph Porres, M.D., Ph.D.
Biostatistics reviewer:	M. Atiar Rahman, Ph.D.

1. Background

Butenafine was originally approved as a prescription drug for the treatment of athlete's foot for both twice a day application for 1 week (1-week dosing regimen), and once a day application for 4 weeks (4-week dosing regimen). In this NDA the sponsor requested a switch of butenafine from prescription to OTC for 1-week dosing regimen only. After reviewing the sponsor's submission, the Division held a teleconference with the sponsor on February 27, 2001. In that teleconference, the Division expressed the following with regard to the OTC switch (see the minutes of the teleconference of February 27, 2001).

"The Agency is most comfortable with either (a) A 4-week dosing regimen for athletes' foot between the toes or (b) Both a 4-week dosing and a 1-week dosing for athletes' foot between the toes along with a patient package insert that could explain the two dosing regimens and expectations."

The sponsor retained their request for 1-week dosing regimen only for the OTC switch and requested a meeting with the Division to discuss this issue. The sponsor submitted a briefing document in March 14, 2001 for this meeting. The briefing document contained alternative (post-hoc) analysis in addition to the original analysis in support of their claim that the 1-week and 4-week dosing regimens have similar treatment effectiveness. This alternative analysis was based on efficacy data of four (4) old studies: #101-001, #010-002, #010-014, and #010-015 originally conducted for the prescription drug application. Henceforth, this review will refer to these studies as Studies #001, #002, #014, and #015. These studies were double-blind, randomized trials with two treatment arms (active, and vehicle). The sponsor did not submit any new study for this OTC switch application. The protocols for Studies #001 and #002 were identical, and the protocols for Studies #014 and #015 were also identical. The designs of these studies were as follows:

Study #001 and #002: These two studies recruited non-onychomycosis subjects only. Subjects were treated once a day for 4 weeks with a follow-up of 4 weeks (treatment + follow-up duration = 8 weeks). Primary efficacy measurement for comparing the active and vehicle was made at the Week 8 visit (end of follow-up). The clinical efficacy endpoints were three: "mycological cure",

"mycological/clinical cure", and "effective treatment". Mycological cure was defined as both negative KOH and negative culture. Mycological/clinical cure was defined as mycological cure and investigator's global assessment of clear (100% improvement). Effective treatment was defined as mycological cure along with a global assessment of at least 80% reduction in signs and symptoms.

Study #014 and #015: These two studies recruited both onychomycosis and non-onychomycosis subjects. Subjects were treated twice a day for 1 week with a follow-up of 5 weeks (treatment + follow-up duration = 6 weeks). Primary efficacy measurement for comparing the active and vehicle was made at Week 6 visit (end of follow-up). The clinical efficacy endpoints were three: "mycological cure", "mycological/clinical cure", and "effective treatment". Mycological cure was defined as both negative KOH and negative culture. Mycological/clinical cure was defined as mycological cure and investigator's global assessment of clears (100% improvement). Effective treatment was defined as mycological cure along with a global assessment of at least 90% reduction in signs and symptoms.

Thus, there were differences in study patient populations and definitions of the "effective treatment" efficacy endpoint between the 4-week dosing regimen studies (#001 and #002) versus the 1-week dosing regimen studies (#014 and #015).

This addendum to the statistical review examines the sponsor's claim of similarity in the effectiveness of 1-week versus 4-week dosing regimens for the OTC switch. This examination (i.e. synthesis) of similarity of treatment effectiveness of 1-week and 4-week dosing regimens is based on the "collective evidences" derived from the results of Studies #001, #002, #014, and #015. These studies have already been reviewed individually (see Statistical Review of November 24, 1995 for Studies #001 and #002, and statistical review of November 21, 1997 for Studies #014 and #015). This reviewer's analysis extracted data set from the above statistical reviews and not from the sponsor's briefing package. The reason for this is that the sponsor's analysis in this briefing package contained several post-hoc changes, whereas this reviewer's goal is to obtain results on minimizing bias due to such post-hoc changes.

2. Sponsor's alternative analysis and reviewer's comments/concerns

The sponsor argued that because of the differences in patient populations and in the definitions of the "effective treatment" endpoint the results between the two dosing regimens were not comparable. Therefore, the sponsor proposed retrospectively to analyze only non-onychomycosis subjects with an alternative definition of the "effective treatment" endpoint. The sponsor's proposed new definition of the "effective treatment" is negative mycology along with no sign or symptom score greater than 1 and the total of all signs and symptoms equal to or less than 2. This definition was used in studies of a similar class of drug called "Terbinafine". The sponsor claimed that the use of this definition of the "effective treatment" endpoint and restricting the analysis to non-onychomycosis subjects would make the 1-week versus 4-week dosing regimens comparable.

The sponsor also proposed new rules for imputation of missing values. According to the new rules a study visit which is more than three days late was considered not evaluable. For late visits, the response of the subject from the previous visit was carried forward. The outcome at the late visit was carried forward, if necessary, to the next visit. The last subject visit was included in the endpoint analysis, whether late or not.

Table 1 (attached) gives the summary of the sponsor's new results. The results are only for the active treatment arm, ignoring the vehicle arm and the randomization between the active and the vehicle arms of the studies. Statistically this is inappropriate and the results could be confounded with other effects. These results may not reflect the results of the true treatment effects of the 1-week and 4-week dosing regimens. In addition, the sponsor made a number of new changes in getting these re-analysis (new analysis) results. These were the use of the new definition of the "effective treatment", new imputation rules, and excluding subjects with onychomycosis from studies #014 and #015. Furthermore the between-study variations were ignored in their 1-week versus 4-week dosing regimens comparisons. Also, any sub-group analysis, unless it is prospectively designed with proper randomization (i.e. stratification) and multiplicity adjustments, is statistically flawed. Any unplanned sub-group analysis is likely to produce spurious sub-grouping results. For example, the International Study of Infract Survival-2 (ISIS-2) investigators recognized the problems associated with performing sub-group comparisons. They illustrated the point by demonstrating that treatment effectiveness seemed to differ by astrological sign; for patients born under Gemini or Libra there was a slightly adverse effect of aspirin on mortality, while for patients born under other signs, the p-value was less than 0.00001. [Reference: ISIS-2 Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17, 187 cases of suspected acute myocardial infraction: ISIS-2. *Lancet* 1988; 349-360].

With all the above flaws, the sponsor's claimed that for the non-onychomycosis subjects the effectiveness of 1-week and 4-week dosing regimens were similar.

3. Reviewer's analysis

In order to examine the sponsor's claim, any additional analysis with minimum possible post-hoc changes is likely to be more meaningful. Therefore, the reviewer performed additional analysis using the original definition of the "effective treatment" but excluding onychomycosis subjects from Studies #014 and #015. Also, on the advice of the clinical team the reviewer analyzed only two efficacy endpoints: "effective treatment" and "mycological/clinical cure". As mentioned earlier, data for this analysis was extracted from the two statistical reviews of November 24, 1995 and November 21, 1997.

This reviewer performed two types of analyses. The first type obtained effect sizes (active treatment response rate "minus" vehicle response rate) for the 1-week and 4-week dosing regimens, respectively. The second type compared the similarity of the effect sizes for 1-week versus 4-week dosing regimens across studies. Table 2 (attached) shows effect sizes (along with 95% confidence interval and p-values) for 4-week dosing regimen separately for Studies #001 and #002 and pooled. For the pooled results of this table (and subsequent tables), 99% confidence interval was reported to account for multiplicity due to unplanned subgroup analysis, post-hoc data pooling, and also for the fact that the trial randomization was not stratified by the sub-group of interest. Furthermore, similarity comparisons (1-week versus 4-week dosing regimens) were made across studies, whereas the general practice is to make such a comparison within the trial.

The pooling was done by using the random effect model proposed by DerSimonian and Laird. [Reference: DerSimonian, Rebecca and Laird, Nan, Meta-Analysis in Clinical Trials, *Controlled Clinical Trials 7:177-188,1986.*] This method takes into account both within and between study variations. Table 2 indicates that 4-week dosing regimen effect size for non-onychomycosis subjects

were fairly consistent across Studies #001 and #002. Estimates and 95% confidence intervals were as follows (Table 2a):

Table 2a (Reviewer's Table): Effect Sizes for Non-Onychomycosis Subjects for 4-Week Dosing Regimen

Extracted from Tables 2 (Attached)

Endpoint	Study	Effect size (Active minus vehicle)	95% Confidence interval
Effective Treatment	#001	37%	(19% , 56%)
	#002	43%	(20% , 62%)
	#001 and #002 Pooled	40%	(23% , 56%)*
Mycological/Clinical Cure	#001	21%	(3% , 41%)
	#002	18%	(-4% , 40%)
	#001 and #002 Pooled	19%	(4% , 34%)*

*For pooled analysis a 99% confidence interval on effect size is reported.

Table 3 (attached) shows results for the 1-week dosing regimen, seperately for Studies #014 and #015, and pooled. The results are also split by onychomycosis and non- onychomycosis sub-groups. As the randomization for these trials were not stratified by this disease factor (onychomycosis), the claimed results for non-onychomycosis subjects may be subject to bias. The effect sizes appeared to be larger in Study #015 versus #014, by 16 percent for the "effective treatment" endpoint and 18 percent for the "mycological cure" endpoint. This indicates between study variability in the effect size. Pooled estimates and 95% confidence intervals for non-onychomycosis subjects are as follows (Table 3a):

Table 3a (Reviewer's Table): Effect Sizes for Non-Onychomycosis Subjects for 4-Week Dosing Regimen

Extracted from Tables 3 (Attached)

Endpoint	Study	Effect size (Active minus vehicle)	95% Confidence interval
Effective Treatment	#014	35%	(19% , 54%)
	#015	51%	(34% , 67%)
	#014 and #015 Pooled	43%	(23% , 63%)*
Mycological/Clinical Cure	#014	10%	(-2% , 29%)
	#015	28%	(13% , 46%)
	#014 and #015 Pooled	19%	(4% , 41%)*

*For pooled analysis a 99% confidence interval on effect size is reported.

Table 4 presents 1-week versus 4-week dosing regimen comparisons with respect to the "effective treatment" and the "mycological/clinical cure" endpoints for non-onychomycosis sub-groups. The purpose of this comparison is to validate the sponsor's claim of similarity in effectiveness of the two dosing regimens. Comparisons were made several ways: Study #014 versus Study #001, Study #014 versus Study #002, Study #015 versus Study #001, Study #015 versus Study #002, and pooled Studies #014 and #015 versus pooled Studies #001 and #002.

Table 4 shows the non-inferiority margin estimates given by the absolute value of the lower confidence bound on the 1-week versus the 4-week dosing regimen differences in efficacy. These estimates ranges from 11% to 33% for the "effective treatment" and from 11% to 30% for the "mycological/clinical cure" endpoints. The pooled study gives non-inferiority margin estimates of 22% for the "effective treatment" and 27% for the "mycological/clinical cure" endpoints. Therefore, 3 out of 4 cases non-inferiority margins of the "effective treatment" calculated from the individual studies are 20% or greater. The worst case is 33% for the Study #014 versus #002 comparison. Similarly 2 out of 4 cases the non-inferiority margin of the "mycological/clinical cure" calculated from the individual studies are greater than 20%. The worst case is 30% for the Study #014 versus #001 comparison. Also the the non-inferiority margin of both the "effective treatment" and the "mycological/clinical cure" calculated from the pooled studies were greater than 20%.

Since the statistical review data was slightly different from the sponsor's data, this reviewer also performed a separate set of similar analysis using data from the sponsor's old submission (Submission volumes of NDA 20-524, 1995 and 1996). This data set has the original definition of the "effective treatment", The analysis was done after excluding the onychomicosis subjects. Table 5 shows the results. Table 5 shows that the non-inferiority margin, ranges from 17% to 34% for the "effective treatment" and 9% to 24% for the "mycological/clinical cure". The pooled study gives non-inferiority estimates of 29% for the "effective treatment" and 20% for the "mycological/clinical cure". Therefore, 3 out of 4 cases non-inferiority margins of the "effective treatment" calculated from the individual studies are greater than 20%. Similarly 2 out of 4 cases the non-inferiority margins of the "mycological/clinical cure" calculated from the individual studies are greater than 20%. Also the the non-inferiority margin of both the "effective treatment" and the "mycological/clinical cure" calculated from the pooled studies are greater than 20%.

Table 4a shows a comparitive summary of the non-inferiority margins calculated from the statistical review data and sponsor's data.

Table 4a (Reviewer's Table): Non-Inferiority Margins Estimates for the 1-Week Versus 4-Week Dosing Regimen Comparison for Non-Onychomycosis Subjects Using the Statistical Review Data and Sponsor's Data

Extracted from Tables 4 and 5 (Attached)

Endpoint	Data set	Non-inferiority margin using data from the statistical review	Non-inferiority margin using data from the sponsor's submission
Effective Treatment	Study #014 vs. Study #001	26	34
	Study #014 vs. Study #002	33	40
	Study #015 vs. Study #001	11	17
	Study #015 vs. Study #002	18	23
	Studies #014 + #015 vs. Study #001 + #002	22	30
Mycological/ Clinical Cure	Study #014 vs. Study #001	30	24
	Study #014 vs. Study #002	24	22
	Study #015 vs. Study #001	14	11
	Study #015 vs. Study #002	12	9
	Studies #014 + #015 vs. Study #001 + #002	27	20

Note: The above non-inferiority margin estimates are the lower 95% confidence bounds on the 1-week versus the 4-week Dosing regimen differences for the single study comparisons and lower 99% confidence bounds for the pooled study comparisons.

4. Conclusion

The lower confidence bounds for the 1-week versus 4-week dosing regimen difference in efficacy endpoints gave non-inferiority margin estimates which were generally 20% or greater based on the single study comparisons or pooled data. Therefore, this reviewer concludes that there is no substantial evidence to support the sponsor's claim that the 1-week and the 2-week treatment regimens were similar in efficacy.

/S/ 5/23/01

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Table 1 (Sponsor's Table)*
Percentages of Subjects and 95% Confidence Interval with Treatment Success in Active Arm in Non-Onychomycosis subjects

*Data extracted from the sponsor's Table 2S, page 2 of 14, in the briefing package

Endpoint	Week	#001	#002	#014	#015
Mycological cure	1	32%	40%	50%	49%
	2	64 (51, 77)	70 (56, 84)	56 (43, 69)	67 (54, 81)
	4	89	90	--	--
	6	--	--	85 (76, 95)	76 (64, 88)
	8	83 (73, 93)	88 (77, 98)	--	--
Mycological/Clinical cure	1	2%	0%	4%	0%
	2	8	0	0	7
	4	21 (10, 32)	18 (6, 29)	--	--
	6	--	--	17 (7, 27)	35 (21, 48)
	8	32 (20, 45)	28 (14,41)	--	--
Effective treatment	1	9%	0%	17%	15%
	2	28 (16,40)	15 (4, 26)	25 (14, 36)	44 (30, 58)
	4	21 (10, 32)	18 (6, 29)	--	--
	6	--	--	56 (43, 69)	60 (46, 74)
	8	62 (49, 75)	68 (53,82)	--	--

Table 2 (Reviewer's Table)*
Summary of Results for 4-Week Dosing Regimen
Studies #001 and #002
(Data sets extracted from statistics review of November 24, 1995)

* Data sets used from statistics review of November 24, 1995, pages 9, 10, 16 and 17

		Treatment Group				
Endpoint	Study	Active	Vehicle	Difference	95% Conf. Int.	P-value
Effective Treatment	#001	29/53 (54.7%)	9/52 (17.3%)	37.4%	(19.4, 56.4)	<0.0001
	#002	25/40 (62.5%)	8/40 (20.0%)	42.5%	(19.9, 61.8)	0.0002
	#001 and #002 Pooled	54/93 (58.1%)	17/92 (18.5%)	39.6%[1]	(22.8, 56.3[1])	<0.0001
Mycological/Clinical cure	#001	17/53 (32.1%)	6/52 (11.5%)	20.5%	(3.1, 40.8)	0.0172
	#002	11/40 (27.6%)	4/40 (10.0%)	17.5%	(-4.3, 39.5)	0.0834
	#001 and #002 Pooled	28/93 (30.1%)	10/92 (10.9%)	19.2%[1]	(4.4, 33.9[1])	0.0004

Note: In these two studies subjects with onychomycosis were not recruited.
[1]99% confidence interval, using the Random effect model. (DerSimonian, Rebecca and Laird, Nan, Meta-Analysis in Clinical Trials, *Controlled Clinical Trials 7:177-188,1986.*)

Table 3 (Reviewer's Table)*
Summary of Results for 1-Week Dosing Regimen Sub-Grouping by Presence and Absence of Onychomycosis
Studies #014 and #015
(Data sets extracted from statistics review of November 21, 1997)

*Data extracted from statistics review of November 21, 1997, pages 9 and 18

			Treatment Group				
Endpoint	Sub-Group	Study	Active	Vehicle	Difference	95% Conf. Int.	P-value
Effective Treatment	Without Onychomycosis	#014	17/48 (35.4%)	0/54 (0.0%)	35.4%	(19.2, 53.9)	<0.0001
		#015	31/54 (57.4%)	4/61 (6.6%)	50.9%	(34.1, 67.0)	<0.0001
		#014 and #015 Pooled	48/102 (47.1%)	4/115 (3.5%)	42.9%[1]	(23.0, 62.7[1])	<0.0001
	With Onychomycosis	#014	25/72 (34.7%)	4/71 (5.6%)	29.1%	(15.1, 45.7)	<0.0001
		#015	22/77 (28.6%)	9/70 (12.9%)	15.7%	(0.5, 32.5)	0.0256
		#014 and #015 Pooled	47/149 (31.5%)	13/141 (9.2%)	22.5%[1]	(5.3, 39.8[1])	<0.001
	All subjects	#014	42/120 (35.0%)	4/125 (3.2%)	31.8%	(21.4, 43.5)	<0.0001
		#015	53/131 (40.5%)	13/131 (9.9%)	30.5%	(19.2, 42.00)	<0.0001
		#014 and #015 Pooled	95/251 (37.8%)	17/256 (6.6%)	31.2%[1]	(22.5, 40.0[1])	<0.0001

Note: Subgroup analysis is after the fact exploratory analysis, not pre-specified in the protocol.
[1]99% confidence interval, using the Random effect model. (DerSimonian, Rebecca and Laird, Nan, Meta-Analysis in Clinical Trials, *Controlled Clinical Trials 7:177-188,1986.*)

Table 3 (Reviewer's Table)* Continued
Summary of Results for 1-Week Dosing Regimen Sub-Grouping by Presence and Absence of Onychomycosis
Studies #014 and #015
(Data sets extracted from statistics review of November 21, 1997)

*Data extracted from statistics review of November 21, 1997, pages 9 and 18

			Treatment Group				
Endpoint	Sub-Group	Study	Active	Vehicle	Difference	95% Conf. Int.	P-value
Mycological/ Clinical cure	Without Onychomycosis	#014	5/48 (10.4%)	0/54 (0.0%)	10.4%	(-2.4, 29.1)	0.0206
		#015	16/54 (29.6%)	1/61 (1.6%)	28.0%	(12.9, 46.0)	<0.0001
		#014 and #015 Pooled	21/102 (20.6%)	1/115 (0.9%)	19.0%[1]	(4.0, 41.1[1])	<0.0001
	With Onychomycosis	#014	6/72 (8.3%)	1/71 (1.4%)	6.9%	(0.0, 22.5)	0.1158
		#015	9/77 (11.7%)	0/70 (0.0%)	11.7%	(1.6, 25.9)	0.0033
		#014 and #015 Pooled	15/149 (10.1%)	1/141 (0.7%)	9.2%[1]	(2.7, 15.8[1])	0.0004
	All subjects	#014	11/120 (9.2%)	1/125 (0.8%)	8.37%	(1.1, 18.3)	0.0023
		#015	25/131 (19.1%)	1/131 (0.8%)	18.3%	(9.9, 28.1)	<0.0001
		#014 and #015 Pooled	36/251 (14.3%)	2/256 (0.8%)	13.1%[1]	(0.3, 25.9[1])	<0.0001

Note: Subgroup analysis is after the fact exploratory analysis, not pre-specified in the protocol.
[1]99% confidence interval, using the Random effect model. (DerSimonian, Rebecca and Laird, Nan, Meta-Analysis in Clinical Trials, *Controlled Clinical Trials 7:177-188,1986.*)

Table 4 (Reviewer's Table)*
Comparisons of 1-Week Dosing Regimen Versus 4-Week Dosing Regimen
in Non-Onychomycosis Subjects
(Data sets extracted from statistics review of November 24, 1995 and November 21, 1997)

*Data extracted from the following sources:
"Effective treatment" Statistics review of NDA 20-524 / 1S, November 24, 1995, Table 3, page 10 and Table 7, page 17 for Studies #001 and #002
Statistics review of NDA 20-524 / Se2-001, November 21, 1997, Table 8a, page 9 and Table 18a, page18 for Studies #014 and #015
"Mycological/ Clinical Cure" Statistics review of NDA 20-524, November 24, 1995, Table 2a, page 9 and Table 6a, page 16 for Studies #001 and #002
Statistics review of NDA 20-524 / Se2-001, November 21, 1997, Table 8a, page 9 and Table 18a, page18 for Studies #014 and #015

		1-Week Dosing Regimen			4-Week Dosing Regimen					
Endpoint	Data set	Active	Vehicle	Diff.	Active	Vehicle	Diff.	Regimen Diff.[1]	95% Conf. Int.	P-value
Effective Treatment	Study #014 vs. Study #001	17/48 (35%)	0/54 (0%)	35%	29/53 (55%)	9/52 (17%)	38%	-2.0%	(-26.0, 17.4)	0.348
	Study #014 vs. Study #002	17/48 (35%)	0/54 (0%)	35%	25/40 (63%)	8/40 (20%)	43%	-7.1%	(-33.1, 14.3)	0.218
	Study #015 vs. Study #001	31/54 (57%)	4/61 (7%)	50%	29/53 (55%)	9/52 (17%)	38%	13.4%	(-11.3, 33.5)	0.166
	Study #015 vs. Study #002	31/54 (57%)	4/61 (7%)	50%	25/40 (63%)	8/40 (20%)	43%	8.4%	(-18.2, 29.4)	0.324
	Studies #014 + #015 vs. Study #001 + #002	48/102 (47%)	4/115 (3%)	44%	54/93 (58%)	17/92 (18%)	40%	4.0%	(-22.0, 30.0[2])	0.368
Mycological/ Clinical Cure	Study #014 vs. Study #001	5/48 (10%)	0/54 (0%)	10%	17/53 (32%)	6/52 (12%)	20%	-10.0%	(-29.7, 5.3)	0.086
	Study #014 vs. Study #002	5/48 (10%)	0/54 (0%)	10%	11/40 (28%)	4/40 (10%)	18%	-7.1%	(-24.2, 13.1)	0.279
	Study #015 vs. Study #001	16/54 (30%)	1/61 (2%)	28%	17/53 (32%)	6/52 (12%)	20%	7.5%	(-14.4, 25.2)	0.296
	Study #015 vs. Study #002	16/54 (30%)	1/61 (2%)	28%	11/40 (28%)	4/40 (10%)	18%	12.0%	(-12.1, 29.4)	0.214
	Studies #014 + #015 vs. Study #001 + #002	21/102 (21%)	1/115 (1%)	20%	28/93 (30%)	10/92 (11%)	19%	0.48%	(-26.5, 27.5[2])	0.469

[1]Diff. = {(Active of 1-Week dosing regimen – Vehicle of 1-Week dosing regimen) - (Active of 4-Week dosing regimen – Vehicle of 4-Week dosing regimen)}
[2] 99% confidence interval. Standard error derived from the Random effect model. (DerSimonian, Rebecca and Laird, Nan, Meta-Analysis in Clinical Trials, *Controlled Clinical Trials 7:177-188,1986.*)

Table 5 (Reviewer's Table)*
Comparisons of 1-Week Dosing Regimen Versus 4-Week Dosing Regimen in Non-Onychomycosis Subjects (Data sets extracted from Sponsor's submission)

*Data extracted from the following sources:
"Effective treatment" NDA 21-307, September 29, 2000, Sponsor's Table 4, Vol. 1.6, page 10 025, for Studies #001 and #002 (both active and vehicle). [This sponsor's table extracted data from NDA #20-524, submitted in 1995][1]
NDA 20-524, November 15, 1996, Sponsor's Table 18e, Vol.10.2, Page 0 0144, for study #014 (both active and vehicle).
NDA 20-524, November 15, 1996, Sponsor's Table 18e, Vol.10.9, Page 0 0140, for study #015 (both active and vehicle).
"Mycological/clinical cure" NDA 21-307, September 29, 2000, Sponsor's Table 2, Vol. 1.6, page 10 072, for Studies #001, #002, #014 and #015 (active only). [This sponsor's table extracted data from NDA #20-524, submitted in 1995] [1]
NDA 21-307, September 29, 2000, Sponsor's Table 3, Vol. 1.6, page 10 076, for Studies #001, #002, #014 and #015 (vehicle only). [This sponsor's table extracted data from NDA #20-524, submitted in 1995] [1]

		1-Week Dosing Regimen			4-Week Dosing Regimen					
Endpoint	Data set	Active	Vehicle	Diff.	Active	Vehicle	Diff.	Regimen Diff.[2]	95% Conf. Int.	P-value
Effective Treatment	Study #014 vs. Study #001	17/48 (35%)	1/56 (2%)	33%	36/53 (68%)	13/52 (25%)	43%	-10%	(-34,11)	0.15
	Study #014 vs. Study #002	17/48 (35%)	1/56 (2%)	33%	28/40 (70%)	9/40 (23%)	47%	-14%	(-40, 8)	0.09
	Study #015 vs. Study #001	31/55 (56%)	4/66 (6%)	50%	36/53 (68%)	13/52 (25%)	43%	7%	(-17, 28)	0.33
	Study #015 vs. Study #002	31/55 (56%)	4/66 (6%)	50%	28/40 (70%)	9/40 (23%)	47%	3%	(-23, 25)	0.48
	Studies #014 + #015 vs. Study #001 + #002	48/103 (47%)	5/122 (4%)	43%	64/93 (69%)	22/92 (24%)	45%	-2%	(-30, 25[3])	0.39
Mycological/ Clinical Cure	Study #014 vs. Study #001	8/48 (17%)	0/56 (0%)	17%	17/53 (32%)	6/52 (12%)	20%	-3%	(-24, 13)	0.26
	Study #014 vs. Study #002	8/48 (17%)	0/56 (0%)	17%	12/40 (30%)	4/40 (10%)	20%	-3%	(-22, 18)	0.50
	Study #015 vs. Study #001	19/55 (35%)	2/66 (3%)	32%	17/53 (32%)	6/52 (12%)	20%	12%	(-11, 29)	0.19
	Study #015 vs. Study #002	19/55 (35%)	2/66 (3%)	32%	12/40 (30%)	4/40 (10%)	20%	12%	(-9, 34)	0.08
	Studies #014 + #015 vs. Study #001 + #002	27/103 (26%)	2/122 (2%)	24%	29/93 (31%)	10/92 (11%)	20%	4%	(-20, 28[3])	0.29

[1] In all tables extracted from Vol. 1.6, the sponsor provided only the percentages of subjects with treatment success ("effective treatment" and "mycological/clinical cure"). This reviewer calculated the number of subjects with treatment success (numerator) from the total number of subjects in each treatment group (denominator) using these percentages of treatment success as numerator = denominator x percentage of treatment success.
[2] Diff. = {(Active of 1-Week dosing regimen – Vehicle of 1-Week dosing regimen) - (Active of 4-Week dosing regimen – Vehicle of 4-Week dosing regimen)}
[3] 99% confidence interval. Standard error derived from the Random effect model. (DerSimonian, Rebecca and Laird, Nan, Meta-Analysis in Clinical Trials, *Controlled Clinical Trials 7:177-188,1986.*)

Statistical Review and Evaluation

NDA #:	21-307
Drug Name:	Butenafine HCL 1% Cream
Applicant:	Shering-Plough HealthCare Products
Indication:	Athlete's Foot (Tinea Pedis), Jock Itch (Tinea Cruris), and Ringworm (Tinea Corporis)
Documents Reviewed:	Vol. 1 and 6 of the sponsor's submission, dated 9/28/2000
Medical Officer:	Joseph Porres, M.D., Ph.D.
Biostatistics reviewer:	M. Atiar Rahman, Ph.D.

1. Background

Butenafine was approved as a prescription drug for the treatment of athlete's foot (Tinea Pedis), jock itch (Tinea Cruris), and ringworm (Tinea Corporis) under three separate NDAs with three different treatment regimens. Under NDA #20-524 butenafine was approved for once a day application for 4 weeks (Treatment Regimen 1) for the treatment of athlet's foot, under NDA 20-524/Supplement 001 butenafine was approved for twice a day application for 1 week (Treatment Regimen 2) also for the treatment of athlet's foot, and under NDA #20-663 butenafine was approved for once a day application for 2 weeks (Treatment Regimen 3) for the treatment of jock itch, and ringworm. In this NDA the sponsor is requesting an approval of switch of butenafine from prescription to over the counter (OTC) status, for twice a day application for 1 week for the treatment of athlet's foot, once a day application for 2 weeks for the treatment of jock itch, and ringworm. Since the requested OTC treatment regimen for the treatment of jock itch is the same as that of prescription drug, there was no further statistical analysis needed. However, since there were two treatment regimens in the prescription drug for the treatment of athlete's foot and the sponsor is requesting only one of them for OTC treatment, there was a concern of treatment comparability of the two treatment regimens. The Medical Officer requested statistical analysis of sponsor's data dealing with comparability of Treatment Regimen 1 and Treatment Regimen 2 for the treatment of athlet's foot.

2. Design and Sample Size

In the sponsor's analysis, data for the treatment of athlet's foot were taken from studies #PDC 010-001 (001) and #PDC010-002 (002), included in NDA 20-524 (Treatment Regimen 1), and studies #PDC 010-014 (014) and #PDC 010-015 (015), included in NDA 20-524/Suppiment 001 (Treatment Regimen 2). The study protocols for studies #001 and #002 were similar and those for studies #014 and #015 were similar. Among the exclusion criteria, patients with concurrent onychomycosis were excluded from studies #001 and #002, but were included in studies #014 and #015. The number of subjects enrolled for these studies were as follows:

Study 001: Enrolled=150, MITT=105 (53 in Butenafine and 52 in Vehicle)
Study 002: Enrolled=119, MITT=80 (40 in Butenafine and 40 in Vehicle)
Study 014: Enrolled=451, MITT=247 (121 in Butenafine and 126 in Vehicle)
Study 015: Enrolled=402, MITT=271 (132 in Butenafine and 139 in Vehicle)

The primary endpoints for studies #001 and #002 were,

i) Mycological cure: Negative KOH and negative culture
ii) Effective treatment: Mycological cure, and Investigator Global Assessment of clear or excellent
iii) Overall cure: Mycological cure and clinical cure.

In addition to these three primary endpoints, studies #014 and #015 had one additional primary endpoint namely, Mycological/Clinical cure (Target 0 cure) defined as mycological cure and target lesion Total Signs and Symptoms score equal to zero. This was considered as a secondary endpoint in studies 001 and 002.

3. Sponsor's Analysis

The sponsor stated that for the comparison of efficacy measures across studies, a selection of common measure was required. The sponsor argued, since the effective treatment and overall cure depended on the investigator's assessment and investigators rating scale were different[1] in the two treatment regimens, effective treatment as well as overall cure could not be used for unbiased comparison of treatment success. The sponsor further argued that since mycological cure was defined similarly for all 4 studies and all studies included assessment of the same set of 6 signs and symptoms[2] with ordinal scale differed slightly only at their upper ends, mycological cure and mycological/clinical cure should be the appropriate endpoints for the comparison of two treatment regimens. Further to make the 4 study populations comparable the sponsor excluded all subjects with concurrent onychomycosis from studies 014 and 015 (Treatment Regimen 2). There were 57.9% and 55.4% of subjects in with concurrent onychomycosis in studies 014 and 015, respectively.

The sponsor performed two types of analyses to show that the observed difference in mycological cure, as well as mycological/clinical cure for the treatment of athlete's foot between the two treatment regimens was within the range that could be expected of 2 replications of a single treatment regimen.

In the first analysis, which is of descriptive nature, the sponsor compared the variation of percentage of subjects with mycological cure in the active arm of the two studies in Treatment Regimen 2 with that of the two treatment regimens at Week 2. The sponsor's calculated treatment success rates and the corresponding 95% confidence intervals are given in Table 1.

[1] "Excellent" as 80% to 99% improvement in clinical signs and symptoms for Treatment Regimen 1 and 90% to 99% improvement for Treatment Regimen 2.
[2] 1) Cracking/fissures, 2) Erythema, 3)Scaling, 4) Maceration, 5)Pruritis, and 6) Burning/stinging

Table 1: Percentage of Patients with Treatment Success in Active Arm
(Sponsor's Table)

Variable	Week	Study 001	Study 002	Study 14	Study 15
Mycological Cure	1	32.1	40.0	52.1	49.1
	2	66.0 [52-79]*{27}**	72.5 [56-85]*{29}**	54.2 [40-69]*{29}**	69.1 [55-81]*{26}**
	4	90.6	87.5	--	--
	6	--	--	85.4 [72-94]*{22}**	76.4 [63-87]*{24}**
	8	83.0 [70-92]*{22}**	87.5 [73-96]*{23}**	--	--
Mycological Cure/ Clinical cure	1	1.9	0.0	4.2	0.0
	2	7.5	0.0	0.0	9.1
	4	24.5 [14-39]*{25}**	22.5 [11-38]*{27}**	--	--
	6	--	--	16.7 [8-30]{22}	34.5 [22-49]*{27}**
	8	32.1 [20-46]*{26}**	30.0 [17-47]*{30}**	--	--

*Numbers in the square brackets represent 95% confidence interval
** Numbers in the curly bracket represents the width of the 95% confidence interval (calculated by the reviewer)

From Table 1 we have the following differences in mycological cure rates between studies within a treatment regimen as well as between two treatment regimens at week 2.

Table 2: Differences in Mycological Cure Rates Between Studies within a Treatment Regimen and Between Two Treatment Regimens at week 2

Study 001 Regimen 1	Study 002 Regimen 1	Difference	Study 014 Regimen 2	Study 015 Regimen 2	Difference	Studies 001 and 002 Regimen 1	Studies 014 and 015 Regimen 2	Difference
66.0%	72.5%	6.5%	54.2%	69.1%	14.9%	69.25%	61.80%	7.6%

The sponsor argued that the difference of percentage of subjects with mycological cure between the two regimens (7.6%) was less than that between two studies in the Treatment Regimen 2 i.e. between studies 014 and 015 (14.9%). This value (14.9%) was also less than the width of the 95% confidence intervals on the estimate of percentage of subjects with mycological cure in each study as given in Table 1 (26% to 29%). Based on these two pieces of information the sponsor concluded that the observed difference between the two treatment regimens was within the range that could be expected of two replications of a single treatment regimen.

In the second analysis the sponsor performed a Chi-square test to test the null hypothesis of no difference in the percentages of subjects with mycological cure in the active arm among 4 studies in two treatment regimens. The calculated p-value was 0.490. In sponsor's Chi-square test they included only 196 total subjects from 4 studies with 40 to 55 patients from each study. The sponsor did not specify their selection criterion of these subjects and the exact number of subjects included in each study for analysis. They also did not mention the time point of the Chi-square test.

The sponsor repeated similar analysis to compare the percentages of subjects with mycological/clinical cure in Treatment Regimen 1 at week 8 (End of the follow up period for Treatment Regimen 1) with percentages of subjects with mycological/clinical cure in Treatment Regimen 2 at week 6 (End of the follow up period for Treatment Regimen 2). The sponsor also drew similar conclusion as was drawn for mycological cure, i.e. the observed difference in mycological/clinical cure between the two treatment regimens was within the range that could be expected of 2 replications of a single treatment regimen.

The sponsor made graphical comparisons of mycological cure rate profiles and separately for mycological/clinical cure rate profiles of the 4 studies from two treatment regimens. These graphs (Figure 1 – Figure 2) are shown in the appendix. The sponsor made further graphical comparison of mycological/clinical cure rates profiles of studies 014 and 015 with that of 3 other studies of a similar compound terbinafine 1%. . These graphs (Figure 3 – Figure 4) are also shown in the appendix. Terbinafine is used for the treatment of athlete's foot. The sponsor believed that the comparison of results from these 3 studies were relevant to the discussion of butenafine results because of the similarity of study design, study populations and close relationship of the drug entities. The first of these two studies were twice a day application for 1 week and the third study was once a day for 4 weeks. These graphs showed that the percentage of subjects with mycological/clinical cure at Week 6 ranged from 17% to 38%. The sponsor concluded that both the lower and upper ends of the range were represented by one of the butenafine studies and one of the terbinafine studies (see Figure 3).

Reviewer's comments:

1) *It should be noted that in study 014 about 55% of the enrolled subjects entered the MITT phase compared to about 70% in other studies. The patient population in study 014 seems to have different characteristic than the other three studies.*
2) *The sponsor's justification of choosing the endpoint for comparison (Mycological cure, and Mycological/Clinical cure) and the time point of comparisons are questionable. At week two treatment period of studies 014 and 015 were completed whereas the treatment of studies 001 and 002 were ongoing. It should be noted that the evaluation time point (end of follow up period) for Treatment Regimen 1 was Week 8 and that for Treatment Regimen 2 was Week 6.*
3) *Through the descriptive method and Chi-square test the sponsor intended to show equivalency of the four studies. To show equivalency the sponsor should have used proper statistical method involving the confidence interval and equivalence margins acceptable by the Division. It should be noted that for equivalence test the data of both new and reference treatment usually come from the same trial. In this case data for Treatment Regimen 1 and Treatment Regimen 2 came from different studies. Hence, the result should be interpreted carefully. Also this is a post-hoc analysis. The sample size was not calculated for such comparison.*
4) *For the purpose of comparability of study population in Treatment Regimen 1 and Treatment Regimen 2, the sponsor, in their analysis, excluded patients with concurrent onychomycosis from studies 014 and 015. This violets the MITT principle. A similar analysis using the MITT population should have been done and compare the results. It should be noted that at baseline 57.9% of the subjects in Study 014 and 55.4% of the subjects in Study 015 had concurrent onychomycosis. Therefore, in their analysis the sponsor excluded more than 50% of the MITT subjects from studies 014 and 015.*
5) *In sponsor's Chi-square test they included only 196 total subjects from 4 studies with 40 to 55 patients from each study. They did not specify their selection criterion of these subjects. The sponsor also did not mention about the time point of the Chi-square test.*

4. Reviewer's analysis

In a Clinical/Biostatistics meeting on 1/23/01, the comparability of two treatment regimens for the treatment of athlete's foot was discussed. It was suggested that a non-inferiority test of Treatment Regimen 2 for "Effective Treatment" at the end of follow up period[3] should be conducted in reference

[3] Week 8 for Regimen 1 and Week 6 for Regimen 2

to Treatment Regimen 1. However, it was difficult to conclude non-inferiority as no non-inferiority margin (delta) was specified. So instead, it was recommended to set the 95% confidence interval on the difference of percentage of subjects with effective treatment between the two treatment regimens and indicate the non-inferiority margin needed to establish non-inferiority. Data for this analysis were taken from the Statistical review report of NDA 20-524/1S (Review date 11/24/1995) and Statistical review report of NDA 20-524 (6S)/SE2-001 (Review date 11/21/1997). The reviewer's calculations are based on the MITT population specified in the above mentioned statistical review report.

4.1 Estimation of Non-Inferiority Margin for the Comparison of Effective Treatment

This reviewer constructed the 95% confidence intervals on the differences of percentage of subjects with effective treatment in active arm between Regimen 2 and Regimen 1 for the following five comparisons, 1) Study 001 vs. Study 014, 2) Study 001 vs. Study 015, 3) Study 002 vs. Study 014, 4) Study 002 vs. Study 015, and 5) combined data of Studies 001 and 002 vs. combined data of Studies 014 and 015. For each comparison the non-inferiority margin was chosen to be the absolute values of the 95% lower confidence limits (C.L.).

Following table shows the estimated 95% confidence intervals and the corresponding non-inferiority margins for 5 comparisons,

Table 3: Estimated 95% Confidence Intervals and Non-Inferiority Margins for Effective Treatment

	Comparison	% of Subjects with Effective Treatment			95% C.I		Non-Inferiority
		Regimen 1	Regimen 2	Difference % .	Lower	Upper	Margin
1	Study 001 vs. Study 14	54	35	-19	- 36	-4	36
2	Study 001 vs. Study 15	54	40	- 14	- 30	2	30
3	Study 002 vs. Study 14	70	35	- 35	- 53	-18	53
4	Study 002 vs. Study 15	70	40	-30	- 48	-12	48
5	Studies 001 and 002 vs. Studies 14 and15	61	38	- 23	- 35	-12	35

The results in Table 3 show that to establish non-inferiority of Treatment Regimen 2 compared to Treatment Regimen 1 by using Study 001 against Study 014 one needs a non-inferiority margin of at least 36%. Similarly, to establish non-inferiority of Treatment regimen 2 compared to Treatment Regimen 1 by using Study 001 against Study 015 one needs a non-inferiority margin of at least 30%. The non-inferiority margins for the comparisons of study 002 with studies 014 and 015 have similar interpretation. Comparison 5 shows that to establish non-inferiority of Treatment Regimen 2 compared to Treatment Regimen 1 using the combined data from studies 001 and 002 with the combined data of 014 and 015 one needs a non-inferiority margin of at least 35%. It should be noted that the non-inferiority margin calculated from the combined studies has all data from Treatment Regimen 1 and Treatment Regimen 2. It needs a clinical judgment to check the appropriateness of the non-inferiority margin to establish non-inferiority. However, these margins are much wider than what was used in the Division in the past.

It should be noted that for non-inferiority test the data of both new and reference treatment usually come from the same trial. In this case data for Treatment Regimen 1 and Treatment Regimen 2 came from different studies. Hence, the result should be interpreted very carefully. Also this is a post-hoc analysis. The sample size was not calculated for such comparison.

4.2 Additional Analysis

Following a discussion with the Medical Officer this reviewer performed additional analysis for "Overall Cure", and "Target 0 Cure", similar to that for the effective treatment.

Overall Cure (Mycological Cure and Clinical Cure)

Tables 4 and 5 show the estimated 95% confidence intervals and the corresponding non-inferiority margins for overall cure and target 0 cure, respectively.

Table 4: Estimated 95% Confidence Intervals and Non-Inferiority Margins for Overall Cure

	Comparison	% of Subjects with Effective Treatment Regimen 1	Regimen 2	Difference %	95% C.I. Lower	Upper	Non-Inferiority Margin
1	Study 001 vs. Study 14	21	8	-13	- 23	-2	23
2	Study 001 vs. Study 15	21	20	-1	- 14	12	14
3	Study 002 vs. Study 14	23	8	-15	- 26	-3	26
4	Study 002 vs. Study 15	23	20	-3	- 17	11	17
5	Studies 001 and 002 vs. Studies 14 and15	22	14	-8	- 16	1	16

Target 0 cure (Mycological cure and Total Score (Signs/Symptoms) = 0)

Table 5: Estimated 95% Confidence Intervals and Non-Inferiority Margins for Target 0 Cure

	Comparison	% of Subjects with Effective Treatment Regimen 1	Regimen 2	Difference %	95% C.I. Lower	Upper	Non-Inferiority Margin
1	Study 001 vs. Study 14	32	16	-17	- 29	-3	29
2	Study 001 vs. Study 15	32	23	-9	- 23	4	23
3	Study 002 vs. Study 14	28	16	-12	- 26	2	26
4	Study 002 vs. Study 15	28	23	-5	- 20	10	20
5	Studies 001 and 002 vs. Studies 14 and15	30	20	-11	- 21	-1	21

5. Summary/Conclusion

Butenafine was approved as a prescription drug for the treatment of athlete's foot, jock itch, and ringworm. It was approved for once a day application for 2 weeks for the treatment of jock itch and ringworm and was also approved for the treatment of athlete's foot for two different treatment regimens (1) once a day application for 4 weeks (Treatment Regimen 1) and (2) twice a day application for 1 week (Treatment Regimen 2). In this application the sponsor is requesting an approval of switch of butenafine from prescription to over the counter (OTC) status, for once a day application for 2 weeks for the treatment of jock itch and ringworm, and twice a day application for 1 week for the treatment of athlete's foot. Since there were two treatment regimens in the prescription drug for the treatment of athlete's foot and the sponsor is requesting only one of them for OTC treatment, there was a concern of treatment comparability of two the treatment regimens. The Medical

Officer requested to review the sponsor's data for the comparability of Treatment Regimen 1 and Treatment Regimen 2 for the treatment of athlete's foot.

The sponsor performed two types of analyses. In the first analysis, which is of descriptive nature, the sponsor compared the variation of percentage of subjects with mycological cure in the active arm of the two studies in Treatment Regimen 2 with that of the two treatment regimens at Week 2. In the second analysis the sponsor performed a Chi-square test to compare the percentages of subjects with mycological/clinical cure in the 4 studies from the two treatment regimens. The sponsor concluded that the observed difference in mycological cure, as well as mycological/clinical cure for the treatment of athlete's foot between the two treatment regimens was within the range that could be expected of 2 replications of a single treatment regimen.

The Medical team suggested to test the non-inferiority of Treatment Regimen 2 in reference to Treatment Regimen 1. However, it was difficult to conclude non-inferiority as no non-inferiority margin (delta) was specified. So instead, it was recommended to set the 95% confidence interval and indicated the non-inferiority margin needed to establish non-inferiority.

Table 3 shows the results of this analysis. The results show that to establish non-inferiority of Treatment Regimen 2 compared to Treatment Regimen 1 by using Study 001 against Study 014 one needs a non-inferiority margin of at least 36%, and by using Study 001 against Study 015 one needs a non-inferiority margin of at least 30%. The non-inferiority margins for the comparisons of study 002 with studies 014 and 015 have similar interpretation. Finally, to establish non-inferiority of Treatment Regimen 2 compared to Treatment Regimen 1 using the combined data from studies 001 and 002 and combined data of 014 and 015 one needs a non-inferiority margin of at least 35%. It needs a clinical judgment to check the appropriateness of the non-inferiority margin to establish non-inferiority. However, these margins are much wider than what was used in the Division in the past.

It should be noted that for non-inferiority test the data of both new and reference treatment usually come from the same trial. In this case data for Treatment Regimen 1 and Treatment Regimen 2 came from different studies. Hence, the result should be interpreted very carefully. Also this is a post-hoc analysis. The sample size was not calculated for such comparison.

/S/ 3/6/01

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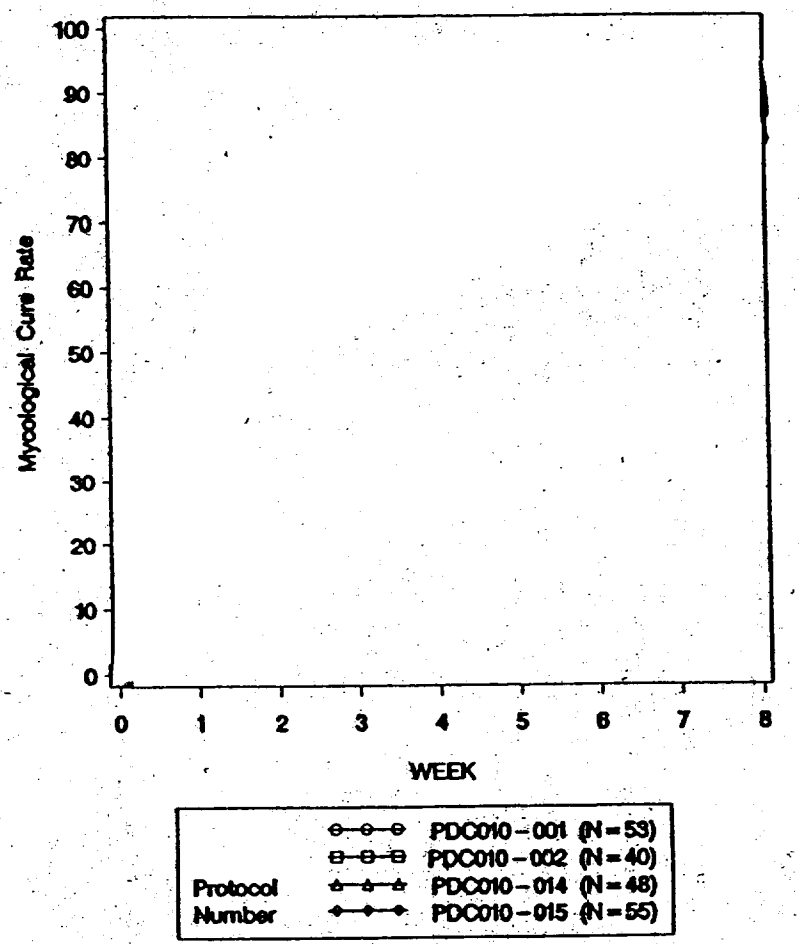
HFD-725/ Dr. Alosh
HFD-725/ Dr. Rahman
HFD-700/ Dr. Anello

This review contains 13 pages.

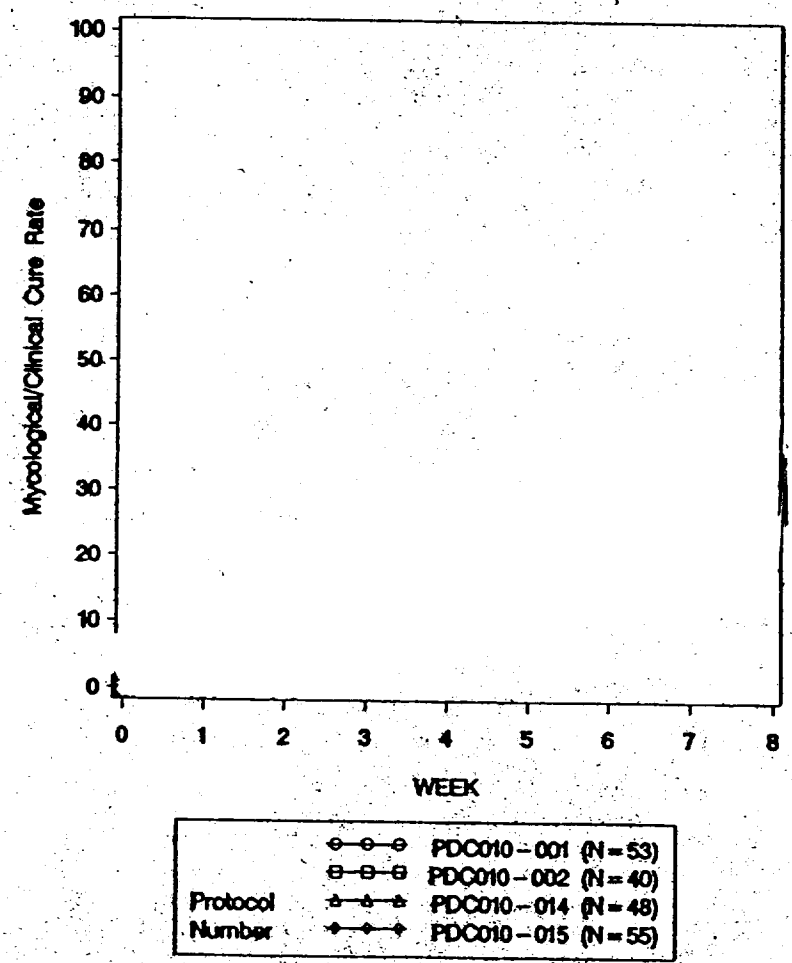
Appendix

Figure 1: Proportion (%) of Patients with Mycological Cure vs. Weeks After Initiation of Treatment, Active Treatment Only [1]



[1]Source: Sponsor's submission, dated 9/28/2000, vol. 1, page 3 127

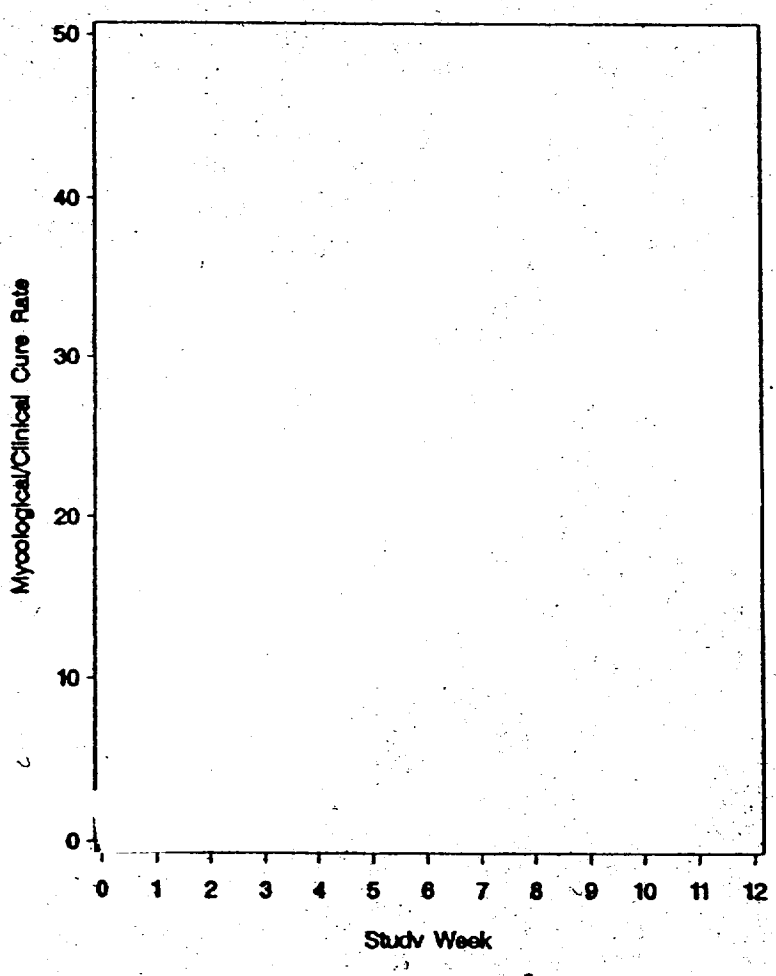
Figure 2: Proportion (%) of Patients with Mycological/Clinical Cure vs. Weeks After Initiation of Treatment, Active Treatment Only [1]



[1]Source: Sponsor's submission, dated 9/28/2000, vol. 1, page 3 128

Figure 3: Proportion (%) of Patients with Mycological/Clinical Cure vs. Weeks After Initiation of Treatment, 1-week bid Treatment Regimens, Butenafine and Terbinafine

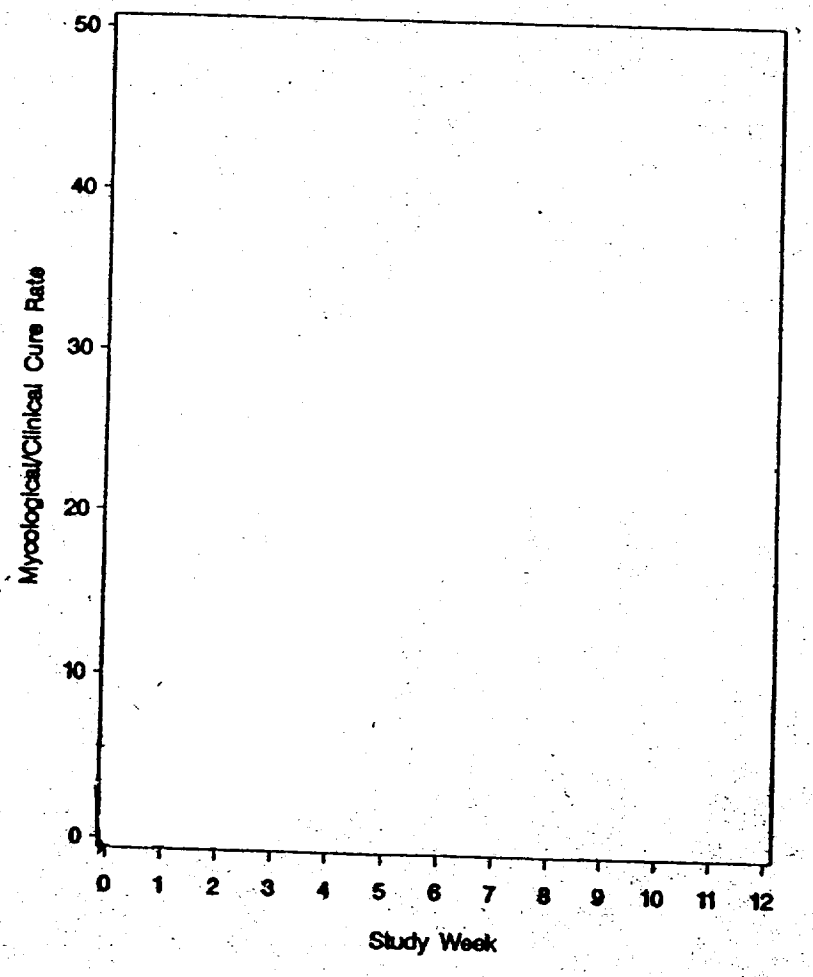
Key: 1= PDC010-014, butenafine 1%, 1 week bid
2= PDC010-015, butenafine 1%, 1 week bid
3= 2-1, terbinafine 1%, 1 week bid
4= 2-2, terbinafine 1%, 1 week bid
5= 2508-01, terbinafine 1%, 1 week bid



[1]Source: Sponsor's submission, dated 9/28/2000, vol. 1, page 3 134

Figure 4: Proportion (%) of Patients with Mycological/Clinical Cure vs. Weeks After Initiation of Treatment, All Treatment Regimens, Butenafine and Terbinafine[1]

Key: 1= PDC010-014, butenafine 1%, 1 week bid
2= PDC010-015, butenafine 1%, 1 week bid
3= 2-1, terbinafine 1%, 1 week bid
4= 2-2, terbinafine 1%, 1 week bid
5= 2508-01, terbinafine 1%, 1 week bid
6= PDC010-001, butenafine 1%, 4 weeks qd
7= PDC010-002, butenafine 1%, 4 weeks qd
8= 2508-01, terbinafine 1%, 4 weeks bid



[1]Source: Sponsor's submission, dated 9/28/2000, vol. 1, page 3 135