CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-408

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

Medical Division: Division of Dermatologic/Dental Drug Products (DDDDP, HFD-540)
Biometrics Division: Division of Biometrics III (HFD-725)

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NDA NO.:	21-408
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DATE RECEIVED:	12/17/01, 02/08/02, 4/11/02, 4/15/02, and 6/11/02
DRUG NAME:	Mentax TC (butenafine HCl) Cream 1%
INDICATION:	Tinea versicolor
ROUTE OF ADMINISTRATION:	Topically once daily for 7 days
SPONSOR:	Bertek Pharmaceuticals, Inc.
DOCUMENTS REVIEWED:	Volumes 1, 15-21 submitted on 12/14/01; SAS data sets on 2/8/02; correspondence submitted on 4/10/02, 4/12/02 and 6/11/02
Related INDs, NDAs:	IND 60,471; NDA 20,524; NDA 20,633
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1. EXECUTIVE SUMMARY

1.1 Conclusion and Recommendations

Two pivotal trials (studies PDC 010-0 33 and PDC 010-036, denoted as studies 33 and 36) were submitted in support of the efficacy claim of Mentax TC Cream (butenafine) 1%, in the treatment of tinea versicolor for 7 days. The efficacy claim is supported for each of these pivotal trials in terms of the percentage of subjects achieving effective treatment.

Safety results from studies PDC 010-033, PDC 010-036, PDC 501-005 and PDC 501-006, denoted as studies 33, 36, 05 and 06, based on the incidence of adverse events are compared between Mentax TC and vehicle groups. From statistical point of view, the safety profile of Mentax TC Cream is similar to that of vehicle cream. Whether or not the safety data from studies 05 and 06 should be included in the labeling is a clinical issue, as the indication and dosing differed from those in the pivotal trials.

1.2 Overview of the Clinical Program and Studies Reviewed

The study drug product is Mentax TC 1% Cream (butenafine), which is designed for a topical use once daily for 7 days in the treatment of tinea versicolor. Result from pivotal trials 33 and 36 as well as safety results from studies 05 and 06 were submitted in support of the efficacy and safety claim of Mentax TC Cream.

The two pivotal trials were conducted in US during September 1999 – November 2000. Total of 129 and 217 subjects were enrolled from 5 and 8 centers, respectively, for studies 33 and 36. The enrolled subjects were randomized in an allocation ratio of 2:1 to Mentax TC and vehicle groups. This resulted in 86 and 43 subjects in Mentax TC and vehicle groups, respectively, for study 33; while 143 and 74 subjects for study 36. The time point for efficacy assessment was Day 49.

Studies 05 and 06 were conducted in US during June 1997 – August 1998 for the treatment of tinea pedis. Four treatment arms (combination drug, butenafine alone, betamethosone alone, and vehicle) were included for each study. The drug administration was twice daily for 10 days. The Sponsor submitted safety data from butenafine alone (i.e. Mentax TC) and vehicle arms in the current NDA. Total of 397 and 405 subjects in Mentax TC and vehicle group, respectively, are included.

1.3 Principal Findings

Efficacy Evaluation for Studies 33 and 36

The demographic and baseline characteristics of the enrolled patients were:

- Between 12 and 76 years of age with about 95% and 94% of subjects were between 17 – 64 years for studies 33 and 36, respectively.
- About 52% and 54% of subjects are males in studies 33 and 36, respectively.
- About 67% and 82% of subjects are Caucasians in studies 33 and 36, respectively.
- The mean total signs/symptoms score of disease severity at baseline was about 5.0 and 4.4 in the respective study.

The endpoints used for efficacy evaluation at Day 49 are:

Primary: percentage of subjects achieved effective treatment, where effective treatment is defined as negative mycology plus total sign/symptom score of ≤ 1, with scaling score of 0.
Secondary:

- Percentage of subjects with negative mycology
- Percentage of subjects with complete cure, where complete cure is defined as negative mycology plus total signs/symptoms score of 0.

➢ Overall Efficacy:

The intent-to-treat (ITT) analysis with the last observation carried forward (LOCF) method for treating missing data showed the superiority of Mentax TC Cream to vehicle in the percentage of subjects achieving effective treatment at Day 49 (p-value = 0.0176 and 0.0033 for studies 33 and 36, respectively).

For negative mycology rate and complete cure rate at Day 49, Mentax TC Cream is superior to its vehicle for each study (i.e. p-value = 0.001 and 0.0110 for study 33; p-value < 0.001 and 0.0021 for study 36). The efficacy results are presented in the table below.

Pivotal Study	Efficacy endpoints at Day 49	Mentax TC	Vehicle	p-value
33	**Primary:**			
	Effective Treatment rate[1]	37/86 (43%)	10/43 (23%)	0.0176
	Secondary:			
	Negative mycology rate	44/86 (51%)	10/43 (23%)	0.0010
	Complete cure rate[2]	34/86 (40%)	8/43 (19%)	0.0110
36	**Primary:**			
	Effective Treatment rate[1]	77/143 (54%)	25/74 (34%)	0.0033
	Secondary:			
	Negative mycology rate	87/143 (61%)	25/74 (34%)	< 0.001
	Complete cure rate[2]	74/143 (52%)	23/74 (31%)	0.0021

[1]The definition of "effective treatment" is the Agency's recommendation: negative mycology + total sign/symptom score ≤ 1 + scaling score of 0.
[2]Complete cure is defined as negative mycology + total signs/symptoms score of 0.

It should be noted that 27% (=23/86) and 30% (=13/43) of subjects in Mentax TC and vehicle groups, respectively, used less than 14.0 grams or 2-gram/day of study medication for study 33; compared to 35% (=50/143) and 35% (=26/74) for Mentax TC and vehicle in study 36. It is not clear whether use of lower amount of study medication implies less disease severity. An analyses excluding these subjects showed the superiority of Mentax TC to its vehicle in effective treatment rate (p-value = 0.0163 and 0.0020 for studies 33 and 36, respectively).

Safety Assessment

From statistical point of view, the safety profile of Mentax TC Cream is similar to that of vehicle cream in terms of the incidence of adverse events.

- The incidence rates of adverse events were 9.4% vs. 13% for Mentax TC vs. vehicle based on studies 33 and 36 combined (once daily for 7 days); compared to 22.4% vs. 21.7% for studies 05 and 06 combined (twice daily for 10 days).
- The treatment-related adverse event rate was 2.2% vs. 0.9% for Mentax TC vs. vehicle based on studies 33 and 36 combined and 1.5% vs. 1.2% based on studies 05 and 06.

It should be noted, however, that studies 05 and 06 are for different indication and have different dosing. It is a matter of clinical judgement whether the labeling should include safety data from studies 05 and 06.

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2. STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1. Introduction and Background

Mentax® (butenafine HCl 1%) was originally approved in 1996 under NDA 20-524 and NDA 20-633 and is currently marketed in the US. The drug is labeled for the indication of interdigital tinea pedis, tinea cruris, and tinea corporis. The approved treatment regimen was twice daily for 7 days or once daily for 4 weeks for interdigital tinea pedis; and once daily for 14 days for tinea corporis and tinea cruris. As an efficacy supplement to NDA 20-524 (SE1-005), two Phase 3 clinical trials (PDC 010-031 and PDC 010-032, denoted as studies 31 and 32) were conducted and resulted in the approval of the currently marketed formulation (dated 6/7/2001) for the indication of tinea versicolor. The dosing for tinea versicolor was once daily for 14 days.

The Sponsor's proposed drug product in the current NDA submission (NDA 21-408) is a new formulation of butenafine HCl 1% Cream, called Mentax TC 1% Cream. According to the Sponsor, it differs from the currently marketed formulation by the addition of polyolprepolymer-2 and propylene glycol and by the use of trolamine instead of diethanolamine — The drug product Mentax TC 1% Cream is designed as a topical use once daily for 7 days in the treatment of tinea versicolor.

Seven studies were completed and submitted in the statistical section of the current NDA to support the drug application of Mentax TC Cream. They are:

- two Phase 3 pivotal trials (studies 33 and 36),
- 21-day cumulative irritation study (protocol PDC 010-037),
- repeated insult patch test study (protocol PDC 010-038),
- human phototoxicity test study (protocol PDC 010-047),
- human photoallergy repeated insult patch test study (PDC 010-048),
- single-center, open-label absorption study (PDC 010-046).

Additionally, the summary of efficacy results from studies 31 and 32 (under NDA 20-524/SE1-005, once daily for 14 days) as well as the safety data from studies 05 and 06 are included.

This statistical review will primarily address the efficacy and safety of Mentax TC Cream. Consequently, two Phase 3 pivotal trials 33 and 36 are reviewed. It should be noted that studies 05 and 06 included treatment with Mentax TC Cream despite the different indication. According to the Sponsor, it was an agreement with the Agency that safety data from studies 05 and 06 is submitted. Therefore, safety results from these studies are summarized in the review.

Table 1 presents an overview of studies 33, 36, 05 and 06. For studies 33 and 36, two treatment arms were included in each trial. The primary objective was to demonstrate the superiority of Mentax TC Cream to its vehicle. It should be noted that only study protocol 36 was submitted for the Agency's review, but not study 33. The Sponsor indicated that study 33 was originally designed as a Phase 2 trial, but was amended later to increase enrollment to power the study due to an unexpectedly large patient enrollment. Studies 05 and 06 were two Phase 3 clinical trials for the indication of tinea pedis. However, only safety data from butenafine and vehicle groups are included in this review, results from other groups are not reported.

Table 1. Overview of the Four Trials

Study	Study conducted Country (date)	Patients inclusion	Treatment arms, n	Comments on treatments
Pivotal Trials				
33	US (9/99 – 12/99)	Patients aged 12 and above; and had tinea versicolor	Butenafine: 86 Vehicle: 43	Treatment was once daily for 7 days
36	US (7/00 – 11/00)	Patients aged 12 and above; and had tinea versicolor	Butenafine: 143 Vehicle: 74	Treatment was once daily for 7 days
Trials for Safety Assessment				
05	US (6/97 – 3/98)	Patients aged 12 and above; and had tinea pedis	Butenafine/betamethosone: 196 Butenafine: 197 betamethosone: 197 Vehicle: 201	Treatment was twice daily for 10 days
06	US (7/97 – 8/98)	Patients aged 12 and above; and had tinea pedis	Butenafine/betamethosone: 206 Butenafine: 200 Betamethosone: 206 Vehicle: 204	Treatment was twice daily for 10 days

2.2 Data Analyzed and Sources

The data summary in this review is based on the Sponsor's NDA submission and electronic SAS data sets submitted on 12/14/01, 2/8/02, 4/10/02, 4/12/02 and 6/11/02.

2.3 Statistical Evaluation of Evidence on Efficacy/Safety

Results of the efficacy and safety for the pivotal trials 33 and 36 are evaluated in this section.

2.3.1. Efficacy Review of Studies 33 and 36

Study Design

Two studies were identically designed as randomized, double-blind, vehicle-controlled, parallel-group and multicenter (i.e. 5 and 8 centers for studies 33 and 36, respectively), and were conducted in US during September 1999 – November 2000. The objective was to show the superiority of Mentax TC Cream (butenafine) to its vehicle in the treatment of tinea versicolor once daily for 7 days.

A total of 201 subjects were pre-planned and 217 patients were actually enrolled in study 36. According to the Sponsor, study 33 was originally designed as a Phase 2 trial and 72 subjects were pre-planned. But they increased the enrollment to 130 subjects, due to an unexpectedly large enrollment (per amendment dated 11/16/99). According to the protocol, the sample size 130 would detect a treatment difference of 30% cure rate between Mentax TC and vehicle creams with power of 81%. A total of 129 subjects were actually participated in study 33.

The enrolled subjects were 12 years of age or older, had total signs/symptoms score of at least 3 and were clinically diagnosed having tinea versicolor and confirmed positively by mycology. They were randomized in a ratio of 2:1 to Mentax TC and vehicle treatments. This resulted in 86 and 43 subjects in Mentax and vehicle groups, respectively, for study 33; compared to 143 and

74 subjects for study 36. According to the Sponsor, the randomization procedure was done based on computer-generated numbers using Mathematica prior to subject enrollment. The detailed randomization procedure is presented in Appendix A. The studies were conducted in a double-blind fashion, as the appearance of the drug medications (active or vehicle) was the same, and were dispensed in identically packaged 30-gram tubes.

Endpoints Specified in the Protocols and Submission:
For efficacy evaluation, the following endpoints were specified in the Sponsor's protocols:

- Primary: Percentage of subjects with effective treatment at Day 49, where effective treatment was defined as negative mycology plus total sign/symptom score (i.e. sum of scores for erythema, scaling and pruritus) ≤ 1 for all lesions.
- Secondary:
  - Percentage of subjects with negative mycology at Day 49.
  - Percentage of subjects with complete cure at Day 49, where complete cure was defined as negative mycology plus total signs/symptoms score of 0 for all lesions.

Subjects were evaluated clinically for the severity of signs and symptoms of tinea versicolor and mycology for the presence of hyphae at Day 1 (Baseline), Days 8, 28 and 49. According to the Sponsor, mycological confirmation of tinea versicolor was accomplished by microscopic examination of skin scrapings taken from a tinea versicolor lesion. The signs and symptoms score was graded based on all lesions, which include all lesions identified at baseline and new lesions emergent during the treatment phase of the study. The degree of severity for each of three signs and symptoms of tinea versicolor (i.e. erythema, scaling, and pruritus) was based on the following 4-point scale:

Score	Severity	Erythema	Scaling	Pruritus
0	Absent	Absent	Absent	Absent
1	Mild	Barely perceptible, pinkish color present	Powdery scaling observable only upon scratching the skin	At least occasionally present but not bothersome to subject
2	Moderate	Distinctive pink or light red color present	Powdery scaling observable without scratching the skin	Present and bothersome some of the time
3	Severe	Deep red color present	Marked presence of coarser (flaky) scaling	Present and so bothersome the subject thinks about it much of the time

The Sponsor also included several confirmatory efficacy endpoints. They were:

- Effective treatment rate at Days 8 and 28
- Negative mycology rate at Days 8 and 28
- Complete cure rate at Days 8 and 28
- Effective clinical response rate at Days 8, 28, and 49, where effective clinical response is defined as total signs/symptoms score ≤ 1.
- Mean change in total signs/symptoms score at Days 8, 28, and 49
- Percent change from baseline in total signs/symptoms score at Days 8, 28, and 49.

Sponsor's safety parameter was the incidence, severity and relationship of adverse events for each treatment group.

Population Analyzed in the Protocols and Submission:
Two populations were analyzed for efficacy:

- Intent-to-treat (ITT) population: defined as all randomized subjects with confirmed tinea versicolor who were dispensed study medication. Their primary analysis was based on such population.
- Per-Protocol (PP) population: a subject was excluded from PP population if:
  1. failure to meet all inclusion/exclusion criteria
  2. failure to apply at least 3 doses to all lesions noted at baseline or emergent during the treatment period
  3. use of disallowed medication at any time during the entire study period
  4. end-of-study visit < 42 days or > 56 days after Day 1
  5. application of > 7 doses of study medication

The details of inclusion/exclusion for the ITT and PP populations are presented in efficacy results section.

For handling missing values in the efficacy evaluation, the last observation carried forward (LOCF) method was proposed for both populations.

Sponsor's safety population included all subjects who were dispensed study medication (active or vehicle) and subsequently provided information either at a post-baseline visit or by another route such as telephone contact.

Statistical Analysis Plan Specified in the Protocols:

- Study 36:
  - Cochran-Mantel-Haenszel (CMH) test adjusting for center was proposed to analyze the primary and the secondary efficacy endpoints.
  - Analysis of covariance (ANCOVA) with the terms of center and baseline data was proposed to analyze the change of signs/symptoms score from baseline.
- Study 33:
  - No pre-specified statistical methods were included in the original protocol (dated 8/17/99). However, CMH test adjusting for center and ANCOVA method were used in the Sponsor's current NDA submission.

Comparison Criteria:
The primary comparison was Mentax TC Cream against its vehicle cream. The criterion for superiority evaluation was that p-value < 0.05.

Multiplicity Issues:
No multiplicity adjustment is needed as one primary efficacy endpoint was specified in the protocols.

Reviewer's Comments on Studies 33 and 36:

1. Sponsor's study 33 was conducted during 9/99 – 12/99. According to the Sponsor, it was originally planned as a Phase 2 trial, but later was submitted as one of the two pivotal trials. No statistical analysis methods were pre-specified in the study protocol (dated 8/17/99). The final version of protocol with statistical analysis methods was dated 2/10/00. Furthermore, Sponsor's additional randomization codes were generated on 9/22/99 and 10/18/99. However, Sponsor's protocol amendment of increasing enrollment was dated 11/16/99.

   The Agency made a request on 6/10/02 to the Sponsor to clarify why the date of amendment follows the dates of generating the additional randomization codes and whether any interim analyses were done to extend the study enrollment. The Sponsor's response was received on 6/11/02 via fax. After reviewing the Sponsor's submission, the comments are:
   - Although the protocol amendment date (i.e. 11/16/99) followed the dates of generating additional randomization codes (i.e. 9/22/99 and 10/18/99), it is not likely that interim analyses were done to extend the study enrollment since:
     - Treatment duration was 7 days and the endpoint for efficacy assessment was Day 49 (i.e. 42-day post-treatment).
     - The first patient was enrolled on 9/3/99 and the last patient was enrolled on 11/9/99.
   - The statistical analysis methods used in study 33 are the same as those the Agency recommended for studies 31 and 32 (per NDA 20,524/SE1-005), which resulted in the approval of Mentax for the indication of tinea versicolor in 2001. The same analysis methods were pre-specified for study 36.
   - The p-values for efficacy results in study 33, while significant still, are larger than those of study 36, which were pre-planned.

2. At the pre-NDA meeting dated 5/21/01, the Agency made a comment concerning the Sponsor's efficacy endpoints. That is, the sign/symptom score for scaling should be 0 for effective treatment and complete cure, unless confirmatory cultures are performed. Following a discussion with the clinical reviewer, the efficacy endpoints for an anti-fungal drug product are:
   - Primary: Percentage of subjects with effective treatment at Day 49
   - Secondary:
     - Percentage of subjects with negative mycology at Day 49
     - Percentage of subjects with complete cure at Day 49

   Both effective treatment and complete cure must have scaling score of 0 at Day 49.

It should be noted that the Sponsor's primary efficacy endpoint pre-specified in the protocols did not require the scaling score of 0. As the results based on both definitions are similar, this review reports results of effective treatment using the Agency's recommendation.

Furthermore, this statistical review will focus on the primary and the secondary efficacy endpoints stated above. Results of other confirmatory efficacy endpoints are not reported.

3. Sponsor's randomization document for study 33 suggests that center G5 (Houston, Texas) was not pre-planned and was added during the course of the trial (per Appendix A). The impact of center G5 on the efficacy results will be commented in the efficacy results section.

Efficacy Results for Studies 33 and 36:

1. Patient Disposition and Baseline Characteristics

To evaluate the comparability between treatments for studies 33 and 36, Table 2 and Table B.1 of the Appendix present the patient disposition and baseline demographics/characteristics, respectively.

Generally, treatment groups were comparable with respect to the ITT and safety populations within each trial. A higher rate of subjects was included in PP population for Mentax TC group in study 33, but was for vehicle group in study 36. However, the difference is not statistically significant. For the treatment distribution by center, the results are presented in Table B.2 of the Appendix. No significant discrepancies are indicated.

For patient demographics and baseline characteristics, generally no outstanding discrepancies between treatments are identified within each study. A difference between Mentax TC and vehicle groups in the race distribution is observed in study 36 (i.e. p-value = 0.0298). Mentax TC group had no patients who were categorized in "other" race, as compared to 5% in vehicle group. As the numbers of subjects are small for races other than Caucasian, it is difficult to make formal statistical comparison between the two treatment groups. It should be noted that treatments were comparable if the race distribution is categorized as Caucasian vs. non-Caucasian (p-value = 0.1685 based on Cochran-Mantel-Haenszel chi-square test).

Despite the treatments were comparable in the age distribution (i.e. p-value = 0.4640 and 0.3276 for studies 33 and 36), a difference between treatments in the mean age is indicated in study 36 (p-value = 0.0442 and 0.0106 based on analysis of variance method and Wilcoxon rank sum test, respectively). Vehicle group had a higher mean age than Mentax TC group (i.e. 35.6 vs. 31.7 years). The age effect on the efficacy results will be commented in the primary efficacy endpoint section.

Table 2. Patient Disposition: Studies 33 and 36

	Study 33		Study 36	
	Mentax TC n(%)	**Vehicle n(%)**	**Mentax TC n(%)**	**Vehicle n(%)**
Randomized	86	43	143	74
ITT population	86 (100%)	43 (100%)	143 (100%)	74 (100%)
Per-Protocol population	78 (91%)	36 (84%)	125 (87%)	69 (93%)
< 3 doses for new lesions	1 (1%)	0	2 (1%)	0
< 3 or > 7 doses	1 (1%)	2 (5%)	0	0
Discontinued study	2 (2%)	1 (2%)	8 (6%)	3 (4%)
End-of-study visit at <42/ >56 days	2 (2%)	2 (5%)	3 (2%)	0
No post-baseline visits	2(2%)	2 (5%)	4 (3%)	1 (1%)
Used excluded medication	0	0	1 (1%)	1 (1%)
Safety Population	84 (98%)	41 (95%)	139 (97%)	73 (99%)
No post-baseline visits	2 (2%)	2 (5%)	4 (3%)	1 (1%)

Source: Sponsor's NDA submission (page 6225, Volume 17; page 6801, Volume 18)

2. Primary Efficacy Endpoint

Overall Analysis:
Efficacy results from studies 33 and 36 in the percentage of subjects with effective treatment of all lesions at Day 49 are presented in Table 3. The summary of Table 3 is:

- Analyses based on ITT and PP populations are generally consistent.
- Mentax TC cream is significantly superior to its vehicle based on ITT analysis (p-value ≤ 0.0176).

It should be noted that Mentax TC is numerically better than its vehicle in study 33 based on PP analysis, but not statistically significant (p-value = 0.1006). The non-significant result could be due to

1. Number of subjects in PP population is not powered enough.
2. A relatively lower percentage of subjects in vehicle group were included in PP population (i.e. 36-subject/84%), as compared to Mentax TC group (i.e. 78-subject/91%). With the same number of subjects achieving effective treatment in vehicle group, this results in a relatively higher effective treatment rate for vehicle arm.

Table 3: Number (%) of Subjects with Effective Treatment at Day 49 – Studies 33 and 36

SUTDY 33	Endpoint *	Mentax TC (n=86)	Vehicle (n=43)	p-value[1]
ITT analysis	Effective treatment	37 (43%)	10 (23%)	0.0176
PP analysis	Effective treatment	34/78 (44%)	10/36 (28%)	0.1006
SUTDY 36	**Endpoint ***	**Mentax TC (n=143)**	**Vehicle (n=74)**	**p-value[1]**
ITT analysis	Effective treatment	77 (54%)	25 (34%)	0.0033
PP analysis	Effective treatment	73/125 (58%)	24/69 (35%)	0.0019

Source: Sponsor's NDA submission (pages 6258, 6272, Volume 17; pages 6836, 6853, Volume 18).
* Effective treatment is defined as negative mycology + total sign/symptom scores ≤ 1 + scaling score of 0.
[1] p-value is the comparison between Mentax and vehicle groups, and is based on Cochran-Mantel-Haenszel test adjusting for center.

Discussion:

1. Although Mentax TC is superior to its vehicle in terms of effective treatment rate for study 33, it should be noted that the homogeneity assessment of response rate across center is significant (p-value = 0.0121). Efficacy results by center are examined. They are presented in Table B.3 of the Appendix:
   - Efficacy results are generally consistent for centers G1, G3, and G4, but not for center G2 (i.e. opposite efficacy results, 0 vs. 33% for Mentax vs. vehicle) and center G5 (i.e. a relatively lower response rate than the other three centers, 11% vs. 0 for Mentax vs. vehicle).

   The non-homogeneity outcome across center in study 33 is primarily due to center G2, as it had opposite efficacy results compared to other centers (Table B.4 of the Appendix). Following the examination of patients' drug usage, demographic and baseline characteristics for center G2 as compared to other centers, no significant difference is indicated. Efficacy results excluding center G2 show the superiority of Mentax TC to its vehicle (p-value = 0.0023, Table B.4 of the Appendix).

Also, it should be noted that center G5 had weaker efficacy results as compared to centers G1, G3 and G4, consequently, it does not affect the overall efficacy conclusion.

2. There was a difference between treatments with respect to mean age in study 36 (p-value = 0.0442 and 0.0106 based on analysis of variance method and Wilcoxon rank sum test). The impact of the age effect on efficacy results is examined based on the following analyses:
   (a) logistic regression to study the relationship between response rate and age
   (b) effective treatment rate over age groups of 12-16, 17-30, 31-64 and > 64
   (c) effective treatment rate over pediatric (< 17 years of age) and adult (≥ 17 years of age) groups

   No significant difference due to age is indicated from the analyses.

Subgroup Analysis:
Subgroup efficacy results by age (i.e. pediatric vs. adult), gender, race (i.e. Caucasian vs. non-Caucasian) and baseline total signs/symptoms score are examined. The results are presented in Table B.5 of the Appendix. It should be noted that studies were not designed to test efficacy within subgroups. The treatment effect of Mentax TC Cream was generally similar across subgroups. The efficacy of Mentax TC is statistically superior to its vehicle in adult, male and Caucasian groups in both studies (p-value ≤ 0.0336).

3. Secondary Efficacy Endpoints

The secondary efficacy endpoints evaluated at Day 49 included:
- Percentage of subjects with negative mycology
- Percentage of subjects with complete cure

The results of the secondary efficacy endpoints are presented in Table 4 for studies 33 and 36.

Table 4: Results of the Secondary Efficacy Endpoints at Day 49 – Studies 33 and 36

SUTDY 33	Analysis	Mentax TC (n=86)	Vehicle (n=43)	p-value[1]
Number (%) of subjects with negative mycology	ITT PP	44 (51%) 40/78 (51%)	10 (23%) 10/36 (28%)	0.0010 0.0129
Number (%) of subjects with complete cure	ITT PP	34 (40%) 31/78 (40%)	8 (19%) 8/36 (22%)	0.0110 0.0587
STUDY 36	**Analysis**	**Mentax TC (n=143)**	**Vehicle (n=74)**	**p-value[1]**
Number (%) of subjects with negative mycology	ITT PP	87 (61%) 81/125 (65%)	25 (34%) 24/69 (35%)	< 0.001 < 0.001
Number (%) of subjects with complete cure	ITT PP	74 (52%) 70/125 (56%)	23 (31%) 22/69 (32%)	0.0021 0.0014

Source: Sponsor's NDA submission (pages 6258, 6272, Volume 17; pages 6836, 6853, Volume 18).
[1] p-value is the comparison between Mentax TC and vehicle groups, and is based on Cochran-Mantel-Haenszel test adjusting for center.

Both studies show the superiority of Mentax TC cream over its vehicle regardless of populations analyzed (i.e. ITT or PP). The ITT analysis demonstrates that Mentax TC cream is significantly better than its vehicle with respect to negative mycology rate (i.e. p-value = 0.0010 and < 0.001 for studies 33 and 36, respectively) as well as complete cure rate (i.e. p-value = 0.0110 and 0.0021, respectively).

Results of subgroup analysis by age (i.e. pediatric vs. adult), gender, race (i.e. Caucasian vs. non-Caucasian) and baseline total sign/symptom score are summarized in Table B.6 of the Appendix. The results generally show that Mentax TC is better than vehicle over subgroups. Mentax TC is statistically superior to its vehicle for adult, male and Caucasian groups with respective to negative mycology rate and complete cure rate.

4. Discontinuation and Missing Values Handling

For each of studies 33 and 36, the discontinuation rate ranged between 2% and 6% over treatment groups (per Table 2). The treatment arms were comparable within each study in terms of study discontinuation rate.

Sponsor's ITT analysis treated missing values at Day 49 based on the last observation carried forward (LOCF) method. To study the impact of imputation method on the efficacy results, the missing value pattern for Mentax TC and vehicle groups is examined. The results are presented in Table 5:

- Treatments are comparable with respect to the proportion of subjects with missing data at each time point. The missing data rates at Day 49 are small. Consequently, it is not expected to have a significant impact on the efficacy results due to methods of missing data handling.

Table 5. Missing Value Pattern over Time Points (Reviewer's Summary)

	Study 33			Stud 36		
Day	Mentax TC (n=86)	Vehicle (n=43)	p-value*	Mentax TC (n=143)	Vehicle (n=74)	p-value*
8	3 (3.5%)	2 (4.7%)	0.7480	9 (6.3%)	3 (4.1%)	0.4948
28	6 (7%)	7 (16%)	0.0993	13 (9%)	5 (6.8%)	0.5554
49	3 (3.5%)	3 (7%)	0.3770	11 (7.7%)	4 (5.4%)	0.5299

Source: Summary is based on the Sponsor's electronic SAS data sets (files: demo.xpt, leseval.xpt).
* p-value is reviewer's analysis and based on Cochran-Mantel-Haenszel test adjusting for center.

5. Efficacy over Time

Efficacy results over various time points (i.e. Days 8, 28 and 49) are presented in Table B.7 of the Appendix to observe the efficacy trend. It should be noted that the primary time point for efficacy evaluation is Day 49.

Generally, the response rates of Mentax TC are non-decreasing over time with similar rates at Days 28 and 49. Mentax TC is better than its vehicle over time. Results in study 36 showed that Mentax TC is statistically superior to vehicle with respect to all response rates at Days 28 and 49. For study 33, Mentax TC is statistically better than vehicle at Day 49.

2.3.2 Safety Review of Studies 33 and 36

The Sponsor's safety population included all subjects who were dispensed study medication (active or vehicle) and subsequently provided information either at a post-baseline visit or by another route such as telephone contact. This included 125 and 212 subjects in studies 33 and 36, respectively (per Table 2). Results of safety assessment based on the amount of drug exposure, incidence rates of adverse events, and serious adverse events for Mentax TC and vehicle

treatments are presented in Tables 6-8. It should be noted that p-value is provided in the comments (shown below) for indication purpose only, as studies were not designed to test safety.

Drug Exposure:
The results in Table 6 show that treatment groups are generally comparable with respect to the percentage of subjects who took 7 doses of drug (i.e. one dose daily for 7 days). Mentax TC group may have a numerically higher mean drug exposure as compared to its vehicle (i.e. 29.3 grams vs. 25.1 grams for Mentax vs. vehicle in study 33; and 20.6 grams vs. 18.7 grams in study 36). However, the difference in the mean drug exposure is not statistically significant (p-value = 0.2747 and 0.3413 for studies 33 and 36, respectively).

Incidence of Adverse Events:
Results for the incidence of adverse events are summarized in Tables 7-8. The safety profile of Mentax TC is generally similar to that of vehicle group, as:

- The incidence rate of adverse events is generally comparable between Mentax TC and vehicle groups within each study (i.e. 7.1% vs. 7.3% for Mentax TC vs. vehicle in study 33 and 10.8% vs. 16.4% in study 36, Table 7).
- Most events were mild to moderate in intensity and were post-treatment (i.e. after Day 7).
- The treatment-related adverse event rate is small for each study (i.e. 1% vs. 0 for Mentax TC vs. vehicle in study 33 and 3% vs. 1.4% in study 36, Table 7).
- One subject in Mentax TC group (< 1%) withdrew prematurely due to an adverse event.
- Treatments are comparable with respect to the incidence rate over various types of adverse event (Table 8). Relatively higher percentages of subjects had adverse events of infections and infestations (i.e. 4.8% vs. 5% for Mentax TC vs. vehicle in study 33 and 6% vs. 9.6% in study 36, Table 8). However, they were not treatment-related.

Table 6: Amount of Drug Exposure – Studies 33 and 36

Drug Exposure	Study 33		Study 36		Studies 33 and 36 combined	
	Mentax TC n=84	Vehicle n=41	Mentax TC n=139	Vehicle n=73	Mentax TC n=223	Vehicle n=114
Drug Usage, number (%)						
# subjects took 7 doses	75 (89%)	36 (88%)	123 (88%)	68 (93%)	198 (89%)	104 (91%)
# subjects took 6 doses	8 (10%)	3 (7%)	12 (9%)	5 (7%)	20 (9%)	8 (7%)
# subjects took 5 doses	0	0	2 (1%)	0	2 (<1%)	0
# subjects took 2 doses	0	0	1 (<1%)	0	1 (<1%)	0
# subjects took 8 doses	1 (1%)	0	0	0	1 (<1%)	0
# subjects took 10 doses	0	2 (5%)	0	0	0	2 (2%)
# subjects took 14 doses	0	0	1 (<1%)	0	1 (<1%)	0
Average Drug Usage, grams						
Mean (s.d.)	29.3 (20.0)	25.1 (19.9)	20.6 (14.1)	18.7 (14.2)	23.9 (17.1)	21.0 (16.7)
Range	1.6 – 87.6	0.0 – 79.5	0.0 – 56.8	0.0 – 57.1	0.0 – 87.6	0.0 – 79.5

Source: Sponsor's NDA submission (pages 6236-6237, 6289, Volume 17; pages 6813, 6871, Volume 18; and page 7962, Volume 21).

Table 7: Overall Incidence of Adverse Events: Studies 33 and 36

Events	Study 33		Study 36		Studies 33 and 36	
	Mentax TC n=84	Vehicle n=41	Mentax TC n=139	Vehicle n=73	Mentax TC n=223	Vehicle n=114
Subjects with at least one AE	6 (7.1%)	3 (7.3%)	15 (10.8%)	12 (16.4%)	21 (9.4%)	15 (13%)
Total of AEs	7	3	18	18	25	21
Adverse events by intensity*						
Mild	1	1	3	5	4	6
Moderate	6	2	13	8	19	10
Severe	0	0	2	2	2	2
Application site reaction AEs						
Number of subjects	0	0	4 (3%)	1 (1.4%)	4 (1.8%)	1 (0.9%)
Number of events	0	0	5	1	5	1
Treatment-related AEs						
Number of subjects	1 (1%)	0	4 (3%)	1 (1.4%)	5 (2.2%)	1 (0.9%)
Number of events	1	0	5	1	6	1
Event by intensity:						
Mild	1	0	2	1	3	1
Moderate	0	0	2	0	2	0
Severe	0	0	1	0	1	0
On-treatment adverse events+:						
Number of subjects	1 (1%)	0	5 (3.6%)	4 (5.5%)	6 (2.7%)	4 (3.5%)
Number of events	1	0	6	4	7	4
Post-treatment adverse events+:						
Number of subjects	5 (6%)	3 (7.3%)	11 (8%)	11 (15%)	16 (7.2%)	14 (12.3%)
Number of events	6	3	12	14	18	17
Premature withdrawal due to AE	0	0	1 (0.7%)	0	1 (0.4%)	0
Serious adverse events	0	0	0	1 (1.4%)	0	1 (0.9%)
Deaths	0	0	0	0	0	0

Source: Sponsor's NDA submission (pages 6283-6288, Volume 17; pages 6864-6869, Volume 18; pages 7943-7961, Volume 21).
* For AE intensity, only the most severe adverse event per patient was counted.
+ On-treatment refers to Treatment Days 1-7. Post-treatment refers to after Treatment Day 7.

Table 8: Summary of Adverse Events: Studies 33 and 36

Adverse Events	Study 33		Study 36	
	Mentax TC n=84	Vehicle n=41	Mentax TC n=139	Vehicle n=73
Subjects had at least one adverse events	6 (7.1%)	3 (7.3%)	15 (10.8%)	12 (16.4%)
Number of Adverse events	7	3	18	18
All events (# of events/# of subjects(%))				
Gastrointestinal disorders	2/2 (2.4%)	0	0	2/2 (2.7%)
General disorders and application site	0	0	3/2 (1.4%)	2/2 (2.7%)
Infections and infestations	4/4 (4.8%)	2/2 (5%)	8/8 (6%)	8/7 (9.6%)
Injury and poisoning	0	0	1/1 (0.7%)	0
Musculoskeletal, connective tissue/ bone	0	0	1/1 (0.7%)	0
Nervous system disorders	1/1 (1.2%)	0	2/2 (1.4%)	5/2 (2.7%)
Renal and urinary disorders	0	0	1/1 (0.7%)	0
Respiratory thoracic/mediastinal disorders	0	1/1 (2.4%)	0	0
Skin and subcutaneous tissue disorders	0	0	2/2 (1.4%)	1/1 (1.4%)
Treatment-related AEs (# of events/# of subjects(%))				
General disorders and application site	0	0	3/2 (1.4%)	0
Nervous system disorders	1/1 (1.2%)	0	0	0
Skin and subcutaneous tissue disorders	0	0	2/2 (1.4%)	1/1 (1.4%)

Source: Sponsor's NDA submission (pages 6283-6284, Volume 17; pages 6864-6865, Volume 18; page 7945, Volume 21).

2.4 Findings in Special/Subgroup Populations

No significant discrepancies in efficacy results are indicated across subgroup for studies 33 and 36 (see Section 2.3.1 for details).

2.5 Statistical and Technical Issues

Following a discussion with the clinical reviewer, there might be an issue about drug accountability although the difference in mean drug usage between treatments is not statistically significant within each study (i.e. p-value = 0.2747 and 0.3413 for studies 33 and 36, Section 2.3.2). As the Sponsor did not have data concerning the percentage of body area involved the disease; less drug usage might imply less disease severity. To investigate the impact of this issue on the efficacy results, data on patient's drug usage are examined.

Twenty-three (27%) and 13 (30%) subjects in Mentax TC and vehicle groups, respectively, used less than 14.0 grams or 2-gram/day of study medication for study 33; while 50 (35%) and 26 (35%) subjects were in Mentax TC and vehicle arm for study 06. It should be noted that the cutoff point of drug usage 14.0 grams or 2-gram/day is per the clinical reviewer's judgement. The details about subjects who used less than 14.0 grams or 2-gram/day are listed in Table B.8 of the Appendix.

Among the subjects who used less amount of study drug, the effective treatment rate is 48% (=11/23) vs. 31% (=4/13) for Mentax vs. vehicle in study 33 and 64% (=32/50) vs. 54% (=14/26) for study 36. Per the clinical reviewer's request, an analysis is performed excluding subjects who used less than 14 grams of study drug. For study 33, 63 and 30 subjects are included for analysis in Mentax TC and vehicle group, respectively. Ninety-three and 48 subjects are in Mentax TC and vehicle group for study 36. The efficacy results are presented in Table B.9 of the Appendix. The impact of drug accountability on the efficacy results is not pronounced as:

- Mentax TC is superior to its vehicle with respect to effective treatment rate for each study (i.e. p-value = 0.0163 and 0.0020 for studies 33 and 36, respectively). No non-homogeneity response rate across center is observed.
- Mentax TC is superior to its vehicle with respect to negative mycology rate and complete cure rate in each of the two studies.

2.6 Evaluation of Safety from Other Trials (Studies 05 and 06)

Sponsor submitted safety results from studies 05 and 06 to support the safety claim of Mentax TC drug application. It should be noted that the two studies were for the indication of tinea pedis and the dosing regimen was twice daily for 10 days. However, according to the Sponsor, safety data submission was in an agreement with the Agency at the pre-NDA meeting (dated 5/21/01).

Study Design and Endpoints

Both studies were conducted in US during June 1997 – August 1998. They were randomized, double-blind, vehicle-controlled, and multicenter phase 3 trials. Studies were designed to evaluate the safety and efficacy of a combination drug product, butenafine HCl 1%/betamethasone dipropionate 0.064%, in the treatment of tinea pedis. Four treatment arms

were included in each study: combination drug – butenafine/betamethosone, butenafine alone (i.e. Mentax TC cream), betamethosone alone, and vehicle.

The drug usage was twice daily for 10 days. The objectives for efficacy evaluation in the studies were:

Summary of Safety Results:

A total of 397 and 405 subjects were in butenafine (i.e. Mentax TC) and vehicle groups, respectively. Safety results for studies 05 and 06 combined based on the incidence of adverse events are presented in Tables 9-10. The safety profile for Mentax TC is generally similar to that for vehicle, as:

- The adverse event incidence rates are comparable between Mentax TC and vehicle groups (i.e. 22.4% vs. 21.7%, Table 9). It should be noted that incidence rates are higher than those in studies 33 and 36 (i.e. 9.4% vs. 13%, Table 7). The higher adverse event rate could be due to that more frequent dosing (i.e. twice daily) and longer treatment duration (i.e. 10 days) were administered in studies 05 and 06. However, studies are comparable in terms of treatment-related adverse event rates (i.e. 2.2% vs. 0.9% in pivotal trials, as compared to 1.5% vs. 1.2% in studies 05 and 06 combined).
- Most adverse events were mild to moderate in severity (i.e. 94% vs. 93% for Mentax TC vs. vehicle).
- The overall and treatment-related incidence rates are generally comparable between treatments over various types of adverse events (Table 10). Higher percentages of subjects had adverse events related to infections/infestations and nervous system disorders (i.e. 8.3% vs. 6.4% for Mentax TC vs. vehicle groups for infections/infestations, and 4.3% vs. 4.4% for nervous system disorders). However, the events related to infections/infestations were not treatment-related. On the other hand, among the events of nervous system disorders, two and one event in Mentax TC (0.5%) and vehicle (0.2%) group, respectively, were judged to be treatment-related. No significant difference between treatments is indicated.

Table 9: Incidence of Adverse Events: Studies 05 and 06 Combined

Events	Mentax TC n=397	Vehicle n=405
Subjects with at least one adverse event	89 (22.4%)	88 (21.7%)
Total adverse events	126	134
All adverse events by intensity, # of events		
Mild	72	78
Moderate	46	47
Severe	8	9
Application site reaction AEs		
Number of subjects	8 (2.0%)	3 (0.7%)
Total number of events	10	9
Treatment-related adverse event		
Number of subjects	6 (1.5%)	5 (1.2%)
Total number of events	9	11
Treatment-related AEs by intensity*, # of events		
Mild	3	2
Moderate	3	6
Severe	3	2
On-treatment adverse events+		
Number of subjects	42 (10.6%)	34 (8.4%)
Total number of events	54	47
Post-treatment adverse events+		
Number of subjects	57 (14.4%)	63 (15.6%)
Total number of events	72	87
Premature withdrawal due to AE	1 (0.3%)	3 (0.7%)
Serious adverse events	1 (0.3%)	1 (0.2%)
Deaths	0	0

Source: Sponsor's NDA submission (pages 8009-8044, Volume 21).
* For AE intensity, only the most severe adverse event per patient was counted.
+ On-treatment refers to Treatment Days 1-10. Post-treatment refers to after Treatment Day 10.

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Table 10: Summary of Adverse Events: Studies 05 and 06 Combined

Events	Mentax TC Cream n=397	Vehicle Cream n=405
All adverse events		
Number of subjects	89 (22.4%)	88 (21.7%)
Total number of events	126	134
All adverse events, # of events/# of subjects(%)		
Blood and lymphatic system disorders	5/3 (0.8%)	15/8 (2.0%)
Cardiac disorders	3/2 (0.5%)	1/1 (0.2%)
Gastrointestinal disorders	10/8 (2.0%)	7/6 (1.5%)
General disorders/application site condition	11/10 (2.5%)	7/6 (1.5%)
Immune system disorders	6/6 (1.5%)	4/4 (1.0%)
Infections and infestations	37/33 (8.3%)	28/26 (6.4%)
Injury and poisoning	1/1 (0.3%)	7/7 (1.7%)
Investigations	9/8 (2.0%)	6/6 (1.5%)
Metabolism and nutrition disorders	3/3 (0.8%)	6/6 (1.5%)
Musculoskeletal, connective tissue/bone disorders	2/2 (0.5%)	4/4 (1.0%)
Neoplasms benign and malignant	2/2 (0.5%)	2/2 (0.5%)
Nervous system disorders	21/17 (4.3%)	22/18 (4.4%)
Pregnancy, puerperium and perinatal condition	1/1 (0.3%)	0
Psychiatric disorders	1/1 (0.3%)	0
Renal and urinary disorders	1/1 (0.3%)	3/3 (0.7%)
Reproductive system and breast disorders	2/2 (0.5%)	1/1 (0.2%)
Respiratory, thoracic/mediastinal disorders	4/4 (1.0%)	8/7 (1.7%)
Skin & subcutaneous tissue disorders	6/6 (1.5%)	12/8 (2.0%)
Vascular disorders	1/1 (0.3%)	1/1 (0.2%)
Treatment-related adverse events		
Number of subjects	6 (1.5%)	5 (1.2%)
Total number of events	9	11
Treatment-related AEs, # of events/# of subjects(%)		
Blood and lymphatic system disorders	0	2/2 (0.5%)
Cardiac disorders	1/1 (0.3%)	1/1 (0.2%)
Gastrointestinal disorders	1/1 (0.3%)	0
General disorders/application site condition	2/1 (0.3%)	1/1 (0.2%)
Nervous system disorders	2/2 (0.5%)	1/1 (0.2%)
Psychiatric disorders	1/1 (0.3%)	0
Skin & subcutaneous tissue disorders	2/2 (0.5%)	6/3 (0.7%)

Source: Sponsor's NDA submission (pages 8016-8017 and 8009-8044, Volume 21)

2.7 Conclusions and Recommendations

The Sponsor in this submission presented results from two pivotal studies (studies 33 and 36) and two Phase 3 studies (studies 05 and 06) in support of the efficacy and safety claim of Mentax TC Cream for the treatment of tinea versicolor. The cream was administered topically on the affected area following normal bathing routine once daily for 7 days. The efficacy results at Day 49 based on the ITT population with the last observation carried forward (LOCF) method for handling missing data are summarized in Table E.1.

Efficacy:

➢ Overall Efficacy:

The pivotal trials 33 and 36 demonstrates that Mentax TC Cream is superior to its vehicle with respect to:

- Primary: Percentage of subjects with effective treatment at Day 49 (p-value ≤ 0.0176).
- Secondary:
  - Percentage of subjects with negative mycology at Day 49 (p-value ≤ 0.0010).

° Percentage of subjects achieving complete cure at Day 49 (p-value ≤ 0.0110).

Table E.1: Summary of Efficacy Results

Pivotal Study	Efficacy endpoints	Mentax TC number/n (%)	Vehicle number/n (%)	Comparison
Study 33	**Primary:**			
	Effective Treatment rate[1]	37/86 (43%)	10/43 (23%)	0.0176
	Secondary:			
	Negative mycology rate	44/86 (51%)	10/43 (23%)	0.0010
	Complete cure rate[2]	34/86 (40%)	8/43 (19%)	0.0110
Study 36	**Primary:**			
	Effective Treatment rate[1]	77/143 (54%)	25/74 (34%)	0.0033
	Secondary:			
	Negative mycology rate	87/143 (61%)	25/74 (34%)	< 0.001
	Complete cure rate[2]	74/143 (52%)	23/74 (31%)	0.0021

[1] Effective treatment is defined as negative mycology + total sign/symptom score ≤ 1+ scaling score of 0.
[2] Complete cure is defined as negative mycology + total sign/symptom score of 0.

➢ It should be noted that 27% (=23/86) and 30% (=13/43) of subjects in Mentax TC and vehicle groups, respectively, used less than 14.0 grams or 2-gram/day of study medication for study 33; compared to 35% (=50/143) and 35% (=26/74) for Mentax TC and vehicle in study 36. It is not clear whether use of lower amount of study medication implies less disease severity. An analyses excluding these subjects showed the superiority of Mentax TC to its vehicle in effective treatment rate (p-value = 0.0163 and 0.0020 for studies 33 and 36).

Safety: (Studies 33, 36, 05 and 06)
From statistical point of view, the safety profile of Mentax TC Cream is similar to that of vehicle cream in terms of the incidence of adverse events.

➢ Studies 33 and 36:
- Mentax TC group had a numerically higher mean drug exposure as compared to its vehicle. However, the difference is not statistically significant.
- The incidence rate of adverse events is generally comparable between Mentax TC and vehicle groups within each study (i.e. 7.1% vs. 7.3% for Mentax TC vs. vehicle in study 33 and 10.8% vs. 16.4% in study 36). No significant difference is indicated.
- Most events were mild to moderate in intensity and were post-treatment.
- The treatment-related adverse event rate is small for each study (i.e. 1% vs. 0 for Mentax TC vs. vehicle in study 33 and 3% vs. 1.4% in study 36).
- Less than 1% of subjects in Mentax TC arm withdrew prematurely due to an adverse event.
- Relatively higher percentages of subjects had adverse events of infections and infestations (i.e. 4.8% vs. 5% for Mentax TC vs. vehicle in study 33, and 6% vs. 9.6% in study 36). However, they were not treatment-related.

➢ Studies 05 and 06 combined:
- The incidence rates are comparable between Mentax TC and vehicle groups (i.e. 22.4% vs. 21.7%). It should be noted that incidence rates are higher than those in pivotal trials (i.e. 9.4% vs. 13%). This could be due to that more frequent dosing and longer treatment duration

were administered (i.e. twice daily for 10 days vs. once daily for 7 days). The treatment-related adverse event rates were 1.5% vs. 1.2% for Mentax vs. vehicle.

- Most adverse events were mild to moderate in intensity (i.e. 94% vs. 93% of events for Mentax TC vs. vehicle).
- Higher percentages of subjects had adverse events related to infections/infestations and nervous system disorders (i.e. 8.3% vs. 6.4% for Mentax TC vs. vehicle groups for infections/infestations, and 4.3% vs. 4.4% for nervous system disorders). However, the events related to infections/infestations were not treatment-related. On the other hand, among the events of nervous system disorders, two and one event in Mentax TC (0.5%) and vehicle (0.2%) group, respectively, were judged to be treatment-related. No outstanding difference between treatments is indicated.

It should be noted, however, that safety results from studies 05 and 06 were for different indication and used different drug dosing regimen. It is a matter of clinical judgement whether the labeling should include safety data from studies 05 and 06.

Shiowjen Lee, Ph.D.
Mathematical Statistician, Biometrics III

Concur: Mohamed Alosh, Ph.D.
Team Leader, Biometrics III

cc:
Archival: NDA 21-408/N-000
HFD-540/Div. File
HFD-540/Dr. Wilkin
HFD-540/Dr. Walker
HFD-540/Dr. Carr
HFD-540/Mr. Cross
HFD-710/Dr. Anello
HFD-725/Dr. Huque
HFD-725/Dr. Alosh
HFD-725/Dr. Lee

This review contains 33 pages (1 cover page, 1 page of table of contents, 3 pages of executive summary, 17 pages of text and 11 pages of Appendix).

APPENDIX A

Randomization Procedure

Study 33 (conducted in US during September 1999 – December 1999):

Five centers (i.e. labeled as G1 – G5) were included in study 33. According to the Sponsor, the randomization codes for each center were prepared based on computer-generated numbers (Mathematica) prior to patient enrollment. Treatment assignment was in blocks of three with a 2:1 ratio to butenafine and vehicle and was done in a sequential order of patient enrollment within each center.

As indicated by the Sponsor, the trial was originally designed as Phase 2 and 72 subjects were pre-planned (protocol dated 8/17/99). That is, eighteen codes were prepared on 8/25/99 for each of four centers G1 – G4. However, the Sponsor on 9/22/99 generated 36 additional randomization codes for centers G1 – G4 and 27 codes for an additional center G5. Another 9 codes were generated on 10/18/99 for center G4. Later an amendment dated 11/16/99 was issued in which patient enrollment was increased to 130 subjects to ensure 81% power. As the date of protocol amendment related to the increase of study enrollment was followed by the dates of generating the additional randomization codes, the Agency made a request to the Sponsor on 6/10/02 for clarification (See Appendix A.1). The Sponsor's response was received via fax on 6/11/02. After reviewing the Sponsor's submission, the comments are:

- Although the protocol amendment date (i.e. 11/16/99) followed the dates of generating additional randomization codes (i.e. 9/22/99 and 10/18/99), it is not likely that interim analyses were done to extend the study enrollment since:
  - Treatment duration was 7 days and the endpoint for efficacy assessment was Day 49 (i.e. 42-day post-treatment).
  - The first patient was enrolled on 9/3/99 and the last patient was enrolled on 11/9/99.
- The statistical analysis methods used in study 33 are the same as those the Agency recommended for studies 31 and 32 (per NDA 20,524/SE1-005), which resulted in the approval of Mentax for the indication of tinea versicolor in 2001. The same analysis methods were pre-specified for study 36.
- The p-values for efficacy results in study 33, while significant still, are larger than those of study 36, which were pre-planned.

Study 36 (conducted in US during July 2000 – November 2000):

Eight centers were in study 36 (i.e. labeled as B1 – B8). According to the Sponsor, a total of 201 subjects were pre-planned. Therefore, 27 randomization codes were generated for each center based on Mathematica computer program (dated 6/19/00) prior to subject enrollment. The first patient was enrolled on 7/24/00 (per documentation in the Sponsor's NDA submission, pages 7010-7035, Volume 18). The enrolled patients were randomized in a ratio of 2:1 to butenafine and vehicle, respectively. The treatment assignment was done in a sequential order of patient enrollment within each center.

As 27 randomization codes were generated for each center, some centers (i.e. B3, B6, B7, and B8) run out of codes during the course of the trial. Consequently, additional randomization codes

were generated for each of the four centers (B3, B6, B7 and B8). No discrepancies are indicated following the examination of the generation dates and subject enrollment dates (pages 7022-7035, Volume18).

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Appendix A.1

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: June 10, 2002 Number of Pages (including cover sheet) – 1

TO: Charity Schuller, Pharm.D., Senior Associate, Regulatory Affairs
COMPANY: Bertek Pharmaceuticals, Inc.
FAX #: 919-993-5910

MESSAGE: For your NDA 21-408, Mentax-TC (butenafine HCl cream,) Cream, 1%, we have the following informational request from the Biostatistical Reviewer:

It is not clear from the Sponsor's submission whether study PDC 010-033 was originally designed as a Phase 2 or Phase 3 trial. According to the protocol dated 8/17/1999, sample size calculation for this study was based on estimated response rates of 60% and 30% for active and placebo, respectively, leading to an estimated sample size of 72 patients to ensure 53% power. Following the original 72 randomization codes generated on 8/25/1999 for centers G1-G4, the Sponsor on 9/22/1999 generated 36 additional codes for centers G1-G4 and 27 codes for an additional center G5. Also, another 9 codes were generated on 10/18/1999 for center G4. Later an amendment dated 11/16/1999 was issued in which patient enrollment was increased to 130 subjects to ensure 81% power. Please clarify:

1. The justification for having the date of amendment following the dates of generating the additional randomization codes related to the increase of the study enrollment.

2. Whether the extension of study enrollment was based on any interim analysis for the data. In such case, please provide details about the number of interim analyses and number of patients completing the trial at each interim analysis.

Thank you.

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APPENDIX B

Table B.1: Patient Demographics and Baseline Characteristics: Studies 33 and 36 – ITT Population

STUDY 33	Mentax TC (n=86)	Vehicle (n=43)	p-value
Age (years)			
Mean (s.d.)	36.0 (13.5)	34.6 (13.3)	0.5672*
Range	12 – 64	14 – 75	
Distribution, n(%)			
12 – 16	4 (5%)	2 (5%)	0.4640
17 – 30	30 (35%)	18 (42%)	
31 – 64	52 (61%)	22 (51%)	
above 64	0	1 (2%)	
Gender, n (%)			
Male	46 (53.5%)	21 (49%)	0.7093
Female	40 (46.5%)	22 (51%)	
Race, n (%)			0.4088
White	61 (71%)	26 (61%)	
Black	6 (7%)	5 (12%)	
Asian	0	1 (2%)	
Hispanic	18 (21%)	10 (23%)	
Others	1 (1%)	1 (2%)	
Signs/symptoms severity, mean (s.d.)	4.90 (1.41)	5.00 (1.70)	0.7114

STUDY 36	Mentax TC (n=143)	Vehicle (n=74)	p-value
Age (years)			
Mean (s.d.)	31.7 (12.7)	35.6 (14.2)	0.0442*
Range	13 – 76	14 – 75	
Distribution, n(%)			
12 – 16	7 (5%)	3 (4%)	0.3276
17 – 30	70 (49%)	29 (39%)	
31 – 64	65 (46%)	40 (54%)	
above 64	1 (0.7%)	2 (3%)	
Gender, n (%)			1.0000
Male	77 (54%)	40 (54%)	
Female	66 (46%)	34 (46%)	
Race, n (%)			0.0298
White	121 (85%)	57 (77%)	
Black	9 (6%)	8 (11%)	
Asian	3 (2%)	0	
Hispanic	10 (7%)	5 (7%)	
Others	0	4 (5%)	
Signs/symptoms severity, mean (s.d.)	4.45 (1.33)	4.35 (1.22)	0.6043

Source: Summary is based on the Sponsor's NDA submission (page 6227, Volume 17; page 6803, Volume 18) and electronic SAS data set (file: demo.xpt).
*p-value is obtained by the reviewer and is based on analysis of variance.

Table B.2: Patient Enrollment and Treatment by Center

Study 33/Center	Mentax TC	Vehicle	Total
G1. Tashjian – California	17	8	25
G2. Ling – Georgia	12	6	18
G3. Rodriguez – Florida	18	9	27
G4. Stough – Arkansas	21	11	32
G5. Bruce – Texas	18	9	27
Total	86	43	129

Study 36/Center	Mentax TC	Vehicle	Total
B1. Pariser – Virginia	16	8	24
B2. Butterwick – California	12	7	19
B3. Whiting – Texas	20	11	31
B4. Horwitz – Florida	10	5	15
B5. Jaratt – Texas	18	9	27
B6. Jones – Texas	22	12	34
B7. Savin – Connecticut	23	11	34
B8. Shavin – Georgia	22	11	33
Total	143	74	217

Source: Sponsor's NDA submission (page 6250, Volume 17; page 6828, Volume 18)

Table B.3: Patient Effective Treatment* Rate by Center
ITT Population

Study 33/Center	Sample size (Mentax, vehicle)	Mentax TC (n=86)	Vehicle (n=43)
G1. Tashjian – California	(17, 8)	11 (65%)	3 (38%)
G2. Ling – Georgia	(12, 6)	0	2 (33%)
G3. Rodriguez – Florida	(18, 9)	10 (56%)	3 (33%)
G4. Stough – Arkansas	(21, 11)	14 (67%)	2 (18%)
G5. Bruce – Texas	(18, 9)	2 (11%)	0
Total	(86, 43)	37 (43%)	10 (23%)

Study 36/Center	Sample size (Mentax, vehicle)	Mentax TC (n=143)	Vehicle (n=74)
B1. Pariser – Virginia	(16, 8)	9 (56%)	3 (38%)
B2. Butterwick – California	(12, 7)	2 (17%)	2 (29%)
B3. Whiting – Texas	(20, 11)	4 (20%)	3 (27%)
B4. Horwitz – Florida	(10, 5)	4 (40%)	1 (20%)
B5. Jaratt – Texas	(18, 9)	12 (67%)	3 (33%)
B6. Jones – Texas	(22, 12)	17 (77%)	7 (58%)
B7. Savin – Connecticut	(23, 11)	10 (43%)	2 (18%)
B8. Shavin – Georgia	(22, 11)	19 (86%)	4 (36%)
Total	(143, 74)	77 (54%)	25 (34%)

Source: Sponsor's NDA submission (page 6259, Volume 17; page 6837, Volume 18).
*Effective treatment is defined as negative mycology + total sign/symptom score ≤ 1 + scaling score of 0.

Table B.4: Sensitivity Analysis on Patient Effective Treatment Rate by Excluding One Study Site at a Time (Reviewer's Analysis): Study 33

Center Exclusion	# patients in analysis (Mentax, vehicle)	Mentax TC n(%)	Vehicle N(%)	p-value[1]	B-D test[2]
G1	(69, 35)	26 (38%)	7 (20%)	0.0436	0.0056
G2	(74, 37)	37 (50%)	8 (22%)	0.0023	0.6817
G3	(68, 34)	27 (40%)	7 (21%)	0.0333	0.0047
G4	(65, 32)	23 (35%)	8 (25%)	0.2706	0.0379
G5	(68, 34)	35 (51%)	10 (29%)	0.0295	0.0073
Overall	(74, 43)	37 (43%)	10 (23%)	0.0176	0.0121

Source: Sponsor's SAS data set (files: leseval.xpt).
[1]p-value is the comparison between Mentax TC and vehicle and is based on Cochran-Mantel-Haenszel test adjusting for center.
[2]B-D test is Breslow-Day test for homogeneity of responses across center.

Table B.5: Patient Effective Treatment Rate by Demographics: ITT Population

Study	Study 33			Study 36		
Subgroup	**Mentax TC (n=86)**	**Vehicle (n=43)**	**p-value***	**Mentax TC (n=143)**	**Vehicle (n=74)**	**p-value***
Age						
Pediatric (< 17)	2/4 (50%)	1/2 (50%)	0.8084	4/7 (57%)	2/3 (67%)	0.1573
Adult (≥ 17)	35/82 (43%)	9/41 (22%)	0.0173	73/136 (54%)	23/71 (32%)	0.0032
Gender						
Male	19/46 (41%)	3/21 (14%)	0.0336	33/77 (43%)	8/40 (20%)	0.0076
Female	18/40 (45%)	7/22 (32%)	0.1257	44/66 (67%)	17/34 (50%)	0.1145
Race						
Caucasian	26/61 (43%)	6/26 (23%)	0.0318	66/121 (55%)	20/57 (35%)	0.0057
Non-Caucasian	11/25 (44%)	4/17 (24%)	0.4789	11/22 (50%)	5/17 (29%)	0.2697
Total baseline Signs/symptoms						
3	5/19 (26%)	5/13 (38%)	0.7414	22/41 (54%)	11/24 (46%)	0.6042
4	5/17 (29%)	0/5	0.1489	25/43 (58%)	6/17 (35%)	0.0569
5	8/14 (57%)	1/6 (17%)	0.0152	18/31 (58%)	5/20 (25%)	0.0413
6	18/30 (60%)	2/11 (18%)	0.0172	4/13 (31%)	3/10 (30%)	0.6537
≥ 7	1/6 (17%)	2/8 (25%)	0.6581	8/15 (53%)	0/3	0.3261

Source: Sponsor's NDA submissions (pages 6266-6271, Volume 17; pages 6847-6852, Volume 18) and electronic SAS data sets (files: demo.xpt, leseval.xpt).
* Reviewer's analysis based on Cochran-Mantel-Haenszel test adjusting for center. P-value is for indication purpose only, otherwise, a multiplicity adjustment would need to be made.

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Table B.6: Secondary Efficacy Endpoints by Demographics: ITT Population

Number(%) of subjects with negative mycology						
Study	**Study 33**			**Study 36**		
Subgroup	**Mentax TC (n=86)**	**Vehicle (n=43)**	**p-value***	**Mentax TC (n=143)**	**Vehicle (n=74)**	**p-value***
Age						
Pediatric (< 17)	3/4 (75%)	1/2 (50%)	0.3173	5/7 (71%)	2/3 (67%)	0.1573
Adult (≥ 17)	41/82 (50%)	9/41 (22%)	0.0016	82/136 (60%)	23/71 (32%)	< 0.001
Gender						
Male	23/46 (50%)	3/21 (14%)	0.0085	39/77 (51%)	8/40 (20%)	< 0.001
Female	21/40 (53%)	7/22 (32%)	0.0242	48/66 (73%)	17/34 (50%)	0.0288
Race						
Caucasian	31/61 (51%)	6/26 (23%)	0.0047	71/121 (59%)	20/57 (35%)	0.0012
Non-Caucasian	13/25 (52%)	4/17 (24%)	0.1887	16/22 (73%)	5/17 (29%)	0.0270
Total baseline Signs/symptoms						
3	7/19 (37%)	5/13 (38%)	0.9341	25/41 (61%)	11/24 (46%)	0.3025
4	6/17 (35%)	0/5	0.0990	28/43 (65%)	6/17 (35%)	0.0246
5	9/14 (64%)	1/6 (17%)	0.0053	20/31 (65%)	5/20 (25%)	0.0115
6	21/30 (70%)	2/11 (18%)	0.0022	6/13 (46%)	3/10 (30%)	0.4533
≥ 7	1/6 (17%)	2/8 (25%)	0.6581	8/15 (53%)	0/3	0.3261

Number(%) of subjects with complete cure						
Study	**Study 33**			**Study 36**		
Subgroup	**Mentax TC (n=86)**	**Vehicle (n=43)**	**p-value***	**Mentax TC (n=143)**	**Vehicle (n=74)**	**p-value***
Age						
Pediatric (< 17)	2/4 (50%)	1/2 (50%)	0.8084	4/7 (57%)	2/3 (67%)	0.1573
Adult (≥ 17)	32/82 (39%)	7/41 (17%)	0.0106	70/136 (51%)	21/71 (30%)	0.0020
Gender						
Male	17/46 (37%)	2/21 (10%)	0.0220	32/77 (42%)	7/40 (18%)	0.0036
Female	17/40 (43%)	6/22 (27%)	0.1162	42/66 (64%)	16/34 (47%)	0.0993
Race						
Caucasian	25/61 (41%)	4/26 (15%)	0.0081	64/121 (53%)	20/57 (35%)	0.0104
Non-Caucasian	9/25 (36%)	4/17 (24%)	0.4789	10/22 (45%)	3/17 (18%)	0.0558
Total baseline Signs/symptoms						
3	4/19 (21%)	3/13 (23%)	0.8680	22/41 (54%)	9/24 (38%)	0.2136
4	4/17 (24%)	0/5	0.2059	24/43 (56%)	6/17 (35%)	0.0839
5	7/14 (50%)	1/6 (17%)	0.0316	18/31 (58%)	5/20 (25%)	0.0413
6	18/30 (60%)	2/11 (18%)	0.0172	4/13 (31%)	3/10 (30%)	0.6537
≥ 7	1/6 (17%)	2/8 (25%)	0.6581	6/15 (40%)	0/3	0.4533

Source: Sponsor's NDA submissions (pages 6266-6271, Volume 17; pages 6847-6852, Volume 18) and electronic SAS data sets (files: demo.xpt, lesevel.xpt).
*Reviewer's analysis based on Cochran-Mantel-Haenszel test adjusting for center. P-value is for indication purpose only, otherwise, a multiplicity adjustment would need to be made.

Table B.7: Patient Response Rates over Time[@] – Studies 33 and 36

Number (%) of responders in pivotal trials (based on all randomized subjects)

Response Category	Day	Study 33		Study 36	
		Mentax TC (n=86)	Vehicle (n=43)	Mentax TC (n=143)	Vehicle (n=74)
Effective Treatment[1]	8*	17 (20%)	3 (7%)	53 (37%)	20 (27%)
	28[©]	35 (41%)	12 (28%)	79 (55%)[+]	24 (32%)
	49[©]	37 (43%)[+]	10 (23%)	77 (54%)[+]	25 (34%)
Complete Cure[2]	8*	12 (14%)	3 (7%)	41 (29%)	15 (20%)
	28[©]	24 (28%)	12 (28%)	77 (54%)[+]	22 (30%)
	49[©]	34 (40%)[+]	8 (19%)	74 (52%)[+]	23 (31%)
Negative Mycology	8*	29 (34%)	11 (26%)	69 (48%)	29 (39%)
	28[©]	52 (60%)[+]	15 (35%)	95 (66%)[+]	26 (35%)
	49[©]	44 (51%)[+]	10 (23%)	87 (61%)[+]	25 (34%)

Source: Sponsor's NDA submission (page 6258, Volume 17; page 6836, Volume 18).
[@]The purpose is for efficacy trend. It should be noted that the primary time point for efficacy evaluation is Day 49.
* End of treatment.
[©] Post-treatment visit. Day 49 is the primary time point for efficacy evaluation.
[+] Statistically superior to vehicle (p-value < 0.05).
[1] Negative mycology + total sign/symptom score ≤ 1 + scaling score of 0.
[2] Negative mycology + total sign/symptom score of 0.

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Table B.9: Efficacy Results Excluding Subjects Who Used Less than 14.0 grams Drug Medication: Studies 33 and 36 (Reviewer's Analysis)

		Number and percentage of responders			
Study	Response Category	Mentax TC	Vehicle	Comparison[1]	Homogeneity[2]
33	Effective treatment*	26/63 (41%)	6/30 (20%)	0.0163	0.9167
	Negative mycology	31/63 (49%)	6/30 (20%)	0.0013	0.9910
	Complete cure	24/63 (38%)	5/30 (17%)	0.0133	0.6884
36	Effective treatment*	45/93 (48%)	11/48 (23%)	0.0020	0.7240
	Negative mycology	51/93 (55%)	11/48 (23%)	< 0.001	0.7941
	Complete cure	43/93 (46%)	10/48 (21%)	0.0015	0.7530

Source: Sponsor's SAS data sets submission (files: lesevel.xpt, and drugacct.xpt).
*Effective treatment is defined as negative mycology + total sign/symptom scores ≤ 1 + scaling score of 0.
[1]p-value is based on Cochran-Mantel-Haenszel test adjusting for center.
[2]p-value is based on Breslow-Day test for homogeneity of responses across center.

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