

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-946**

**STATISTICAL REVIEW(S)**

July 27, 2006

The addendum for this review was entered into DFS by Mohamed Alesh on 7/26/06.

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## **Team Leader note on the Statistical Review for NDA 21,946**

**Background:** The following note is provided as a clarification of statements that appeared in the original statistical review for NDA 21,946; signed in DFS on May 22, 2006. In particular this note refers to Section 1.1 and Section 5.2, titled Conclusions and Recommendations that are reproduced below:

### **1.1 CONCLUSIONS AND RECOMMENDATIONS**

Ketoconazole 2% gel applied once a day for 14 days was significantly different from vehicle in the percentage of seborrheic dermatitis subjects “effectively treated” as assessed after a 14 follow-up period in Study BT1400N01-300-USA. Efficacy of ketoconazole 2% gel over vehicle was supported by post-hoc analyses of seborrheic dermatitis subjects “effectively treated” in Studies BT200-USA-001 and BT200-INT-001.

Section 5.2 was a replication of Section 1.1

#### **Clarification:**

The intent of the term ‘significantly different’ of the first sentence in the conclusions and recommendations is that Ketoconazole 2% gel applied once a day for 14 days was ‘superior’ to its vehicle in the percentage of seborrheic dermatitis subjects “effectively treated”. For this application, in addition to efficacy results of study BT1400N01-300-USA, the sponsor submitted results from two other supportive studies BT200-USA-001 and BT200-INT-001 that were conducted prior to study BT1400N01-300-USA. Each of the supportive studies was conducted to investigate the safety and efficacy of the combination of ketoconazole 2% gel and desonide 0.5% gel against the monads and vehicle. While the contribution of desonide was not established, ketoconazole was superior to the vehicle in each of these supportive studies. As the comparison of ketoconazole against vehicle was not the primary objective of the supportive studies the reviewer referred to the comparison of ketoconazole against vehicle as ‘post-hoc analyses’. It should be noted that the term ‘post-hoc analyses’ was used throughout the review to refer to the comparison of ketoconazole against vehicle in studies BT200-USA-001 and BT200-INT-001.

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Cc:  
Archival NDA  
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/s/

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Mohamed Alesh

7/26/2006 04:24:41 PM

BIOMETRICS

A Clarification note related to the original stat review  
signed in DFS on May 22, 2006



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCES  
OFFICE OF BIOSTATISTICS

## Statistical Review

NDA: 21,946

Drug Name : Ketoconazole USP 2% Topical Gel

Indication: Treatment of Seborrheic Dermatitis

Applicant: Barrier Therapeutics, Inc.

Dates: Electronic submission dated 09/28/2005

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# 1 EXECUTIVE SUMMARY

## 1.1 CONCLUSIONS AND RECOMMENDATIONS

Ketoconazole 2% gel applied once a day for 14 days was significantly different from vehicle in the percentage of seborrheic dermatitis subjects “effectively treated” as assessed after a 14 follow-up period in Study BT1400N01-300-USA. Efficacy of ketoconazole 2% gel over vehicle was supported by post-hoc analyses of seborrheic dermatitis subjects “effectively treated” in Studies BT200-USA-001 and BT200-INT-001.

## 1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

This submission included results from 4 studies in subjects with seborrheic dermatitis. Two of these studies (BT200-USA-001 and BT200-INT-001) were studies the sponsor conducted comparing a combination of ketoconazole 2% and desonide 0.5% gel against its component gels and vehicle. Although these studies demonstrated efficacy of the combination against vehicle they did not demonstrate efficacy of the combination compared to its components. The sponsor provided these studies as supportive evidence of efficacy of ketoconazole 2% gel. The third study BT1400N01-300-USA studied ketoconazole 2% gel versus vehicle. The results of an open-label, non-controlled, long-term safety and efficacy study (BT1400N01-302-USA) will not be discussed in this review. In addition, the results of 5 pharmacology studies will not be discussed.

## 1.3 STATISTICAL ISSUES AND FINDINGS

This reviewer was able to verify the sponsor’s results from data files provided in the submission. The sponsor in the analysis of the percentage of subjects “effectively treated” did not specify the scoring option of the variable (not “effectively treated”=0 or “effectively treated”=1) in the Cochran-Mantel-Haenszel (CMH) test. [Not specifying the SCORES option could allow the sponsor to chose the most favorable one.] The sponsor used the SCORES=TABLE option in the submission which uses the scores 0 and 1 in the calculations. This reviewer verified that the results would be significant using all SCORES options in SAS for the CMH test. The default scoring option in SAS is the SCORES=TABLE option. [The use of the SCORES=MODRIDIT option is common.]

The medical officer expressed interest in comparing the amount of gel taken by subjects. In Study BT1400N01-300-USA, the amount of gel used could not be determined in 18 subjects (9 vehicle and 9 ketoconazole). For subjects on which the amount could be determined, subjects on vehicle used more gel (mean 8.07 grams) than subjects on ketoconazole 2% (mean 6.25 grams). This difference is significant ( $p < 0.01$ ). This difference supports efficacy, the subjects who did not have an active gel used more to treat themselves. In the ketoconazole 2% gel subgroup, “effectively treated” subjects had a mean of 6.24 grams compared to 6.26 grams for not “effectively treated” subjects. In the vehicle gel subgroup, “effectively treated” subjects had a mean of 8.35 grams

compared to 8.02 grams for not “effectively treated” subjects. These differences (“effectively treated” versus not “effectively treated”) within gel subgroups were not significant.

The medical officer noticed that the sponsor defined the Investigator’s Global Assessment of almost clear as “only slight pink color or trace amounts of scaling” in Study BT1400N01-300-USA but did not define it in Studies BT200-INT-001 and BT200-USA-001. This reviewer changed the successfully treated criteria so that the subject had to be completely clear at Day 28 rather than completely clear or almost clear to see if this had a significant impact on the conclusions of these studies. Although there were more ketoconazole patients impacted by this change than vehicle patients, all studies still showed a significant difference between ketoconazole and vehicle favoring ketoconazole in the percentage of patients successfully treated. These new analyses are provided in the statistical analysis discussion of the individual studies.

Although the sponsor’s program did not investigate alternative dosing regimens and the dosing regimen (once a day for 14 days) was chosen originally for the combination product (to lower exposure to topical corticosteroids), this reviewer investigated the dosing data to see whether there was any indication that it was inappropriate. Only one subject on vehicle said they took it twice a day. Only 9 subjects on ketoconazole and 3 subjects on vehicle gel took 20 or more doses of treatment. About 42% of subjects (44% on vehicle, 40% on ketoconazole) took greater than 14 doses of treatment. There is not any strong evidence that once a day dosing is not appropriate.

## **2 INTRODUCTION**

### **2.1 OVERVIEW**

The sponsor had originally studied a combination of ketoconazole 2% gel and desonide 0.5% gel as a combination product for seborrheic dermatitis. These studies (BT200-USA-001 and BT200-INT-001) failed to show efficacy of the combination over its two components but showed efficacy of the combination over vehicle. The sponsor wants to use these two studies as supportive evidence of efficacy of ketoconazole 2% gel. The sponsor has conducted an additional study (BT1400N01-300-USA) to show efficacy of ketoconazole 2% gel over vehicle for this indication.

A ketoconazole 2% cream formulation is approved for seborrheic dermatitis. The recommended dosage for seborrheic dermatitis of that product is twice daily application to the affected area for four weeks or until clinical clearing. **The sponsor’s gel** formulation was studied as a once daily application. The gel formulation does not contain sodium sulfite anhydrous, a sulfate that may cause allergic-type reactions.

#### **2.1.1 COMBINATION STUDIES**

These were randomized, double-blind, vehicle-controlled, multicenter, parallel group studies comparing the combination of ketoconazole 2% gel and desonide 0.5% gel with

ketoconazole 2% gel, desonide 0.5% gel, and vehicle in subjects with moderate to severe seborrheic dermatitis. One was an international study (Belgium and Poland) whereas the other was a U.S. study. There was a 14 day treatment period followed by a 14 day follow-up period.

There was a 2:2:1:1 randomization with the combination and ketoconazole having more subjects. Targeted enrollment was 150 subjects for the combination and ketoconazole and 75 subjects for desonide and vehicle.

To enter the study subjects had to have an investigator assessed baseline score of 2 (moderate) or 3 (severe) for erythema and scaling, at least 1 (mild) for pruritus, and an **investigator's global assessment** of at least 3 (moderate).

The subjects applied treatment once daily to the affected area (scalp hairline, post-auricular area, eyebrows and bridge of nose, naso-labial folds or sternum) for 14 consecutive days.

Clinical assessments of erythema, scaling, and pruritus were made at clinic visits at baseline and days 3, 7, 14 of treatment and day 28 (follow-up). Investigator global assessment was made at baseline and days 7, 14, and 28. The subject recorded the number of doses of medication taken. The tubes of medication were returned and the amount of medication used was calculated.

At each visit the overall severity of the erythema, scaling, and pruritus was evaluated based on a 4-point interval scale, represented as none (0), mild (1), moderate (2), and severe (3). These clinical assessment scores of signs and symptoms were further defined as:

#### Erythema

0= None	No evidence of erythema
1= Mild	Barely perceptible erythema which is faint or patchy, blanches easily to the touch
2= Moderate	Distinct erythema, more difficult to blanch
3 =Severe	Intense (fiery red) erythema, does not blanch

#### Scaling

0=None	No scaling evident on lesions
1=Mild	Barely detectable, scattered, small, flaking scales
2=Moderate	Scales clearly visible and prominent
3=Severe	Coarse, thick scales, with flaking onto clothes or skin

#### Pruritus (Itching)

The investigator asked the subject to rate the severity of itch using the following scale:

0=None	No evidence of pruritus
1=Mild	Present with minimal discomfort
2=Moderate	Appreciable discomfort which interferes with daily activities
3=Severe	Extreme discomfort which prevents the completion of daily activities and may disrupt sleep

The overall severity of the erythema, scaling, and pruritus was determined after examining all of the following areas: scalp hairline, post-auricular area, eyebrows and bridge of nose, naso-labial folds, and sternum. The investigator was asked to verify in the case report form (CRF) that all five areas were examined at each visit.

### Investigator's Global Assessment

At Days 0 (baseline), 7, 14, and 28 the investigator provided a global evaluation to reflect the status of disease severity at the time of evaluation, using the following five-point interval scale:

- 0 Completely clear
- 1 Almost clear
- 2 Mild/pink to red color, or slight scaling
- 3 Moderate/distinct redness or clearly visible scaling
- 4 Severe/severe score in erythema or scaling

A single rating score for each subject was provided. The worst parameter defined the severity.

The primary response evaluation used to assess efficacy was a single binary categorical variable designating each subject as **“effectively treated” at Day 28 with a yes or no answer. “Effectively treated” were those subjects who had Day 28 erythema and scaling assessments of either 0 (none; if the baseline score was 2 or less) or ≤ 1 (mild; if the baseline score was 3). In addition, “effectively treated” subjects had to have an Investigator’s Global Assessment of 1 (almost clear) or less. [Sometimes the sponsor used “successfully treated” rather than “effectively treated” in the study reports.]**

The secondary endpoint used to assess efficacy was the change from baseline in the rating of erythema, scaling, and pruritus at Day 14.

The protocols of these studies stated that study centers with less than 10 subjects per treatment arm will be pooled to form an aggregate of small study centers. Whenever the pooling of these study centers provides an aggregated minimum of 10 subjects per arm, no additional study centers will be added to the aggregate being formed. The process will aggregate the smallest enrollment study center first and proceed to involve the next largest enrollment study center. If there are two or more investigators with the same enrollment, the investigator will be arranged on the list by alphabetizing their last names. The process will terminate when all study centers with a minimum enrollment of less than 10 per treatment arm have been combined. The new set of aggregated study centers

plus the study centers which were not aggregated will be referred to as grouped study centers.

In Study BT200-USA-001, the sponsor changed the pooling strategy in the statistical analysis plan. In that study the pooling was: Study centers requiring pooling will be sorted by recruitment count in descending order. The study centers with the smallest recruitment will be pooled with the largest study center requiring pooling until the aggregate reaches a minimum of 10 patients per arm. At that point, no additional centers will be added and the aggregate becomes a grouped study center. The process will continue with the next largest study center until no study center remains. Fragment study centers, without sufficient companion centers with which to form an aggregate, will be added to grouped study centers already formed in the reverse order of the aggregation, so no grouped study center will have less than 10 patients per treatment arm.

The Breslow-Day test for homogeneity of odds ratios was used to assess consistency of treatment rates across grouped study centers. The analysis was restricted to ITT patients and used an alpha level of 0.10. If the Breslow-Day test was rejected at  $\alpha = 0.10$ , **non-homogeneity would be investigated for “qualitative” or “quantitative” differences.** In either case, if the sponsor deems sufficient cause, the centers in question will not be pooled and an appropriate explanation would be provided.

For the primary efficacy analysis, the Cochran-Mantel-Haenszel (CMH) general association test was used to make the between group tests ( $\alpha = 0.05$ ) described in sections 4.1 and 4.2 of the Statistical Analysis Plan (SAP). [Note: the sponsor did not specify the scoring option for the CMH test.] The Breslow-Day test for homogeneity of the odds-ratio ( $\alpha = 0.10$ ) was to be used to assess the significance of the treatment-by-center interaction. For the secondary efficacy analysis, described in section 4.2.1 of the SAP, tests were to be carried out using the CMH row-mean scores test, stratified by grouped study site. Pair-wise differences between any two treatment groups were significant if both the overall test and the pair-wise test were significant ( $\alpha = 0.05$ ).

## **2.1.2 STUDY BT1400N01-300-USA**

This study was similar to the combination studies with the following exceptions:

This study only compared ketoconazole 2% gel with vehicle.

Study centers with fewer than eight subjects per treatment arm were pooled to form an aggregate of small study centers as described in Section 8.2 of the SAP. The pooling strategy was: Study centers with less than 8 subjects per treatment arm will be pooled to form an aggregate of small study centers. Whenever the pooling of these study centers provides an aggregated minimum of 8 subjects per arm, no additional study centers will be added to the aggregate being formed. The general process for combining of **investigator’s data will be accomplished by taking the investigator with the smallest enrollment and combining it with the investigator with the largest.** If there is a further need to combine data, then the data of the investigator with the second smallest enrollment will be combined with the **investigator’s data which had the second largest**

enrollment, and so on. This process will continue for all investigators who did not have a minimum of 8 subjects per active treatment arm. The new set of aggregated study centers plus the study centers which were not aggregated will be referred to as grouped study centers.

## ***2.2 DATA SOURCES***

The study reports and data for this submission are contained in \\cdsesub1\n21946\N\_000\2005-09-28.

## **3. STATISTICAL EVALUATION**

### ***3.1 EVALUATION OF EFFICACY***

#### **3.1.1 COMBINATION STUDIES**

##### **3.1.1.1 STUDY BT200-USA-001**

There were 459 subjects (154 combination, 152 ketoconazole, 77 desonide, and 76 vehicle) randomized and treated at 18 sites. Overall 21 subjects (5 combination, 7 ketoconazole, 7 desonide, and 2 vehicle) dropped out before trial completion; 16 during the treatment period and 5 during the follow-up period. There was one additional subject in the combination group who was enrolled but never treated. This patient is not included in the ITT population analyses.

The treatment groups were comparable in demographic variables and baseline disease severity.

Center 15 was considered as group center 1; the sponsor pooled sites 5, 7, 8, 16 and 18 into group center 2; pooled sites 2, 6, and 14 into group center 3; pooled sites 12 and 13 into group center 4; pooled sites 9 and 11 into group center 5; pooled sites 1 and 10 into group center 6; and pooled sites 3, 4, and 17 into group center 7. In all there were 7 grouped centers.

Table 1, summarized below, provides the results of the primary efficacy variable for this study. The combination was significantly different from vehicle in the percentage of subjects successfully treated but the study failed in its primary objective to demonstrate that the combination successfully treated a higher percentage than ketoconazole and desonide. [Note that this stratified analysis was really the protocol specified secondary analysis of this variable. The unstratified CMH analysis was the protocol specified primary analysis. The unstratified CMH p-value was 0.0007.]

**Table 1 Summary of Clinical Success (ITT Subjects)**

Clinical success*	Combination (N=154)	Ketoconazole (N=152)	Desonide (N=77)	Vehicle (N=76)	p-value <sup>+</sup>
Yes (n)	34	42	10	5	0.0005
% success (100n/N)	22.1	27.6	13.0	6.6	
95% CI for % success	(15.8, 29.5)	(20.7, 35.5)	( 6.4, 22.6)	( 2.2, 14.7)	
p-value <sup>#</sup>		0.2481	0.0951	0.0031	

\* Clinical success is 'yes' if both erythema and scaling at day 28 are 'none' (0) or 'mild' (1) if the baseline score was severe, and the Global Status at day 28 is 'clear' (0) or 'almost clear' (1) if the baseline score was moderate or severe.

<sup>+</sup> Overall p-value is based on CMH test, stratified by grouped study site.

<sup>#</sup> P-values are for comparisons to the combination group with the two-tailed CMH test stratified by grouped study site.

Source Sponsor's TABLE 11.4.1

These results were confirmed by the reviewer.

If ketoconazole is compared to vehicle in a post-hoc analysis of percentage of patients effectively treated, the Beslow-Day Test for Homogeneity had a p-value of 0.77 indicating the grouped centers gave consistent results. If ketoconazole is compared with vehicle for percentage of subjects effectively treated (27.6% versus 6.6%) in a post-hoc CMH stratified analysis the results are significant (p=0.0002). [The unstratified CMH analysis was the protocol specified primary analysis. The unstratified analysis had an identical p-value of 0.0002.]

**If a patient had to have a Investigator's Global Assessment of completely clear at Day 28 to be considered effectively treated, 33/152 ( 21.7%) ketoconazole patients were effectively treated compared to 4/76 (5.3%) vehicle patients. This difference is significantly different (p=0.0015).**

### 3.1.1.2 STUDY BT200-INT-001

There were 489 subjects (163 combination, 164 ketoconazole, 80 desonide, and 82 vehicle) randomized and treated at 29 sites. Overall 14 subjects (3 combination, 8 ketoconazole, 1 desonide, and 2 vehicle) dropped out before trial completion; 11 during the treatment period and 3 during the follow-up period.

The treatment groups were comparable in demographic variables and baseline disease severity with the exception that the desonide patients had a higher percentage of patients with a baseline investigator global assessment of severe.

The sponsor pooled Belgium sites 01, 04, 05, 06, 07, 08, 09, 10, 12, 13 into Belgium group center 1; Belgium sites 02 and 03 into Belgium group center 2; Poland sites 22, 17, 30, 34, 35, and 36 into Poland group center 1; Poland sites 21, 23, and 33 into Poland group center 2; Poland sites 26, 28, and 29 into Poland group center 3; Poland sites 31, 32, and 38 into Poland group center 4; and Poland sites 24, and 25 into Poland group center 5. In all there were 7 grouped centers. These poolings followed the protocol specified method with the exception that it was done within country and Poland sites 22 and 33 should have been switched in their respective groups. These differences would have negligible impact on the significance level.

Table 2 provides the results of the primary efficacy variable for this study. The combination was significantly different from vehicle in the percentage of subjects successfully treated but the study failed in its primary objective to demonstrate that the combination successfully treated a higher percentage than ketoconazole and desonide. [Note that this stratified analysis was really the protocol specified secondary analysis of this variable. The unstratified CMH p-value was 0.031.]

**Table 2** **Summary of Clinical Success (ITT Subjects)**

Clinical success*	Combination (N=163)	Ketoconazole (N=164)	Desonide (N=80)	Vehicle (N=82)	p-value <sup>†</sup>
Yes (n)	67	60	29	18	0.029
% success (100n/N)	41.1	36.6	36.3	22.0	
95% CI for % success	(33.6, 48.7)	(29.2, 44.0)	( 25.7,46.8)	(13.0, 30.9)	
p-value <sup>#</sup>		0.353	0.442	0.003	

\* Clinical success is 'yes' if both erythema and scaling at day 28 are 'none' (0) or 'mild' (1) if the baseline score was severe, and the Global Status at day 28 is 'clear' (0) or 'almost clear' (1) if the baseline score was moderate or severe.

<sup>†</sup> Overall p-value is based on CMH test, stratified by grouped study site.

<sup>#</sup> P-values are for comparisons to the combination group with the two-tailed CMH test stratified by grouped study site.

If ketoconazole is compared to vehicle in a post-hoc analysis of percentage of patients effectively treated, the Breslow-Day Test for Homogeneity had a p-value of 0.0812 indicating the grouped centers did **not gave consistent enough results [using the sponsor's rule.]** Because the grouping involved many sites, this lack of homogeneity is not attributable to just one site. If the Breslow-Day statistic is calculated from the ungrouped sites, the p-value is 0.56. If ketoconazole is compared with vehicle for percentage of subjects effectively treated (36.6% versus 22.0%) in a post-hoc CMH stratified analysis the results are significant (p=0.021). [The unstratified CMH analysis was the protocol specified primary analysis. The unstratified analysis had a p-value of 0.020.]

Note that the success rates in the international study are all higher than in the US study. The difference in success rates between Ketoconazole and vehicle in the international study is 14.6% and 21% in the US study.

**If a patient had to have an Investigator's Global Assessment of completely clear at Day 28 to be considered effectively treated, 50/164 (30.5%) ketoconazole patients were effectively treated compared to 13/82 (15.8%) vehicle patients. This difference is significantly different (p=0.015).**

### **3.1.2 STUDY BT1400N01-300-USA**

There were 459 (229 Ketoconazole 2%, 230 Vehicle) randomized into the study at 24 sites. Of these 459 subjects, 442(96.3%) completed the study (222 on Ketoconazole and 220 vehicle).

There were a total of 17 subjects (3.7%) (10 vehicle, 7 ketoconazole) who discontinued, and 15 (8 vehicle, 7 ketoconazole) of these subjects discontinued during the treatment period. Reasons for discontinuing the study included subject choice (6 subjects, 1.3%), lost to follow-up (3 subjects, 0.7%), adverse events (five subjects, 1.1%), protocol violation (one subject, 0.2%), treatment failure (one subject, 0.2%), and other (one subject, 0.2%). The reasons for discontinuing were similar across treatment groups. Reasons for discontinuing study participation during the follow-up period included subject choice (one; 0.2%) and other (one; 0.2%). Both subjects were in the vehicle group.

**The sponsor stated that “The most common minor deviations observed in the study were missed applications or application of medication for more than 14 days (231 subjects; 50.3%), followed by out-of-window visits (35 subjects; 7.6%). The most common major deviations were missed applications or application of medication for more than 14 days (36 subjects; 7.8%), followed by out-of-window visits (33 subjects; 7.2%).” The major deviations led to exclusions from the Per Protocol analyses. The most common protocol violations were “other” (5 subjects; 1.1%) and violation of inclusion/exclusion criteria (1 subject; 0.2%). The minor and major deviations, as well as the violations were similar across treatment groups.**

Of the 459 randomized subjects, 272 subjects (59.3%) were male and 187 subjects (40.7%) were female. The mean age was 51.2 years (range: 13.0 to 91.0 years). Four hundred and eight subjects (88.9%) were Caucasian, 24 subjects (5.2%) were African-American, 23 subjects (5.0%) were Hispanic, one subject (0.2%) was Asian, one subject (0.2%) was Native American, and two subjects (0.4%) had other racial identifications. The demographic characteristics were similar across treatment groups (p>0.3).

Baseline dermatological disease factors were similar across treatment groups with respect to duration of current episode, condition of current episode, prior treatment, erythema score, pruritus score, and global evaluation score. The scaling score for the ketoconazole group had a statistically greater percentage of subjects with severe scaling (59/229;

25.8%) than did the vehicle group (40/230; 17.4%) ( $p=0.0267$ ). Overall, the mean duration of the current episode was 77.2 months. A total of 306 subjects (66.7%) had received prior treatment.

The study was conducted as a multicenter study under a common protocol that was intended to be analyzed as a whole. Study centers with fewer than 8 subjects per treatment arm were pooled as described in Section 9.7.1 of the study report and prospectively planned in the statistical analysis plan (Appendix 16.1.8, Section 8.2). Specifically, study centers 11 and 24, 5 and 21, 13 and 16, and 17 and 18 were combined to form grouped centers 27, 28, 29 and 30, respectively. The remaining 16 centers had sufficient subjects per group to be incorporated in the analysis as individual centers. [The sponsor did not specify how tied centers would be handled. Centers 5, 13 and 18 (the largest centers in their pooled group) had 24 patients per group. Any method of handling the tied centers would have negligible impact on the significance level of this study.]

The Breslow-Day test for homogeneity of the odds ratio used to assess the consistency in the effectively treated rate across grouped study centers resulted in a p-value of 0.1033. Although this value for the ITT subjects was greater than the threshold alpha level of 0.10 for statistical significance, a sensitivity analysis was performed to determine the robustness of the treatment effect due to the nearly statistically significant Breslow-Day statistic.

The first step in conducting a sensitivity analysis showed that the extreme grouped study center was center 23. This center was the one when excluded from the homogeneity test provided the largest Breslow-Day p-value of all possible subsets wherein a single grouped center was excluded. Specifically, the Breslow-Day test for the remaining centers with this center excluded had a p-value of 0.4481. Further investigation revealed, however, that this center had the poorest differential treatment response rate showing no effectively treated subjects for the active treatment while the vehicle had 33.3% effectively treated subjects. Elimination of this grouped center from the analysis altered the p-value for the treatment effect from 0.0014 to 0.00016. Clearly, this grouped center does not account for the statistical significance of the entire group when pooled, in fact it hampers the p-value. Furthermore, the differential in success rates for the remaining grouped sites ranged from -8.3% to 37.5% in favor of the active treatment. While grouped study center 23 may represent an outcome which is not entirely consistent with the remaining group study centers, the analysis based on all study centers presents a robust analysis of the treatment effect.

The primary efficacy variable was the proportion of subjects that were effectively treated at Day 28, where effectively treated is defined as **“yes” if erythema and scaling scores** were 0 (none; if the baseline score was 2) or 1 (mild; if the baseline score was 3) and the **Investigator’s Global Assessment score was  $\leq 1$**  (almost clear).

Results from the analysis of effectively treated subjects are presented in Table 3. Overall, there was a significant difference in clinical success across the treatment groups ( $p = 0.0014$ ). Clinical success was observed at Day 28 for 58 ketoconazole subjects (25.3%)

and 32 vehicle gel subjects (13.9%). These results demonstrate that ketoconazole is superior to the vehicle gel in providing effective treatment of seborrheic dermatitis.

**Table 3 Summary of Clinical Success (ITT Subjects)**  
(Study BT400N01-300-USA)

	Ketoconazole	Gel Vehicle	Total
Clinical success*	(N = 229)	(N = 230)	(N = 459)
Yes (n)	58	32	90
% success (100n/N)	(25.3)	(13.9)	(19.6)
95% CI for % success	(19.8, 31.5)	(9.7, 19.1)	(16.1, 23.5)
p-value <sup>#</sup>		0.0014	

\* Clinical success is yes if both erythema and scaling at day 28 are none (=0) [or (=1) if the baseline score was severe], and the Global Assessment score at day 28 is clear (=0) or almost clear (=1).

<sup>#</sup> p-value is based on a two-tailed CMH general association test stratified by grouped study site.  
Source **Sponsor's TABLE 11.4.1**

The difference in success rates between ketoconazole and vehicle is 11.4% in this study which is smaller than the 21% observed in the US study BT200-USA-001 and 14.6% in the international study BT200-INT-001.

Changes from baseline to Day 14 in signs and symptom scores for erythema, scaling and pruritus at Day 14 were the key secondary variables. The mean change in scaling was statistically greater for subjects treated with ketoconazole than for subjects treated with vehicle gel ( means -1.55 and -1.31; respectively; p=0.0022). The changes in erythema and pruritus were not statistically significant for pruritus and erythema (p = 0.1751 and 0.3539, respectively). Because there was a difference at baseline in the severity of scaling, this reviewer analyzed the changes in scaling for subjects with baseline scaling severity of 2 and baseline severity of 3. The difference in mean change of severity of scaling was not significant for subjects with baseline severity of scaling of 2=moderate (-1.25 for vehicle and -1.36 for ketoconazole, p=0.12; the study is not powered for subgroup analyses) but was significant for subjects with baseline severity of scaling of severe=3 (-1.35 for vehicle and -1.91 for keto-conazole, p=0.015).

**If a patient had to have a Investigator's Global Assessment of completely clear at Day 28 to be considered effectively treated, 50/229 (21.8%) ketoconazole patients were effectively treated compared to 31/230 (13.5%) vehicle patients. This difference is significantly different (p=0.019).**

The medical officer asked me to look at the success rates at day 14 when treatment was stopped. Table 4 below provides the frequency table of success or failure at Day 14. The Cochran-Mantel-Haenszel (CMH) test was not significant (p=0.1161 unstratified and 0.0945 stratified by pooled sites). This analysis is a post hoc analysis and should be considered as such but it can provide some useful information.

Table 4 Success at Day 14 by Treatment Group

Treatment	Success at Day 14		
	No	Yes	Total
Gel Vehicle	171 (74%)	59 (26%)	230
Ketoconazole USP 2%	155 (68%)	74 (32%)	229

The following table show the frequencies of successes or failures at Days 14 and 28 for each treatment.

Table 5 Successes at Day 14 and 28 by Treatment Group

Gel Vehicle

Success at 28 Days	Success at Day 14		Total
	No	Yes	
No	162	36	198
Yes	9	23	32
Total	171	59	230

Ketoconazole USP 2%

Success at 28 Days	Success at Day 14		Total
	No	Yes	
No	134	37	171
Yes	21	37	58
Total	155	74	229

Ketoconazole had both more subjects having successes at both Days 14 and 28 and subjects who were successes at Day 28 but who were not successes at Day 14. In the Ketoconazole group, out of the 74 successes at day 14, 37/74 (50%) remained successes at day 28 compared to only 23/59 (39%) in the vehicle group.

**3.1.3. LABELING**

The labeling includes results of the pooled Studies BT200-USA-100, BT200-INT-001, and BT1400N01-300-USA. In addition to claiming statistical significance of the overall success rate, the sponsor claims statistical significance of scaling ( $p < 0.001$ ) and erythema ( $p = 0.045$ ). These significance claims are based on **the sponsor's analysis of changes from baseline at Day 14 with last observation carried forward (LOCF) for scaling and erythema using a Cochran-Mantel-Haenszel (CMH) test stratified by study.** It should be noted that this reviewer could not duplicate the **sponsor's results. Further, this reviewer has the following comments concerning the sponsor's results: (i) Analyses of the pooled data are post-hoc analyses. (ii) The results for erythema are marginally significant ( $p = 0.045$ ). (iii) The corresponding analysis in the individual studies are not significant.** The sponsor reported a p-value of 0.35 for analyzing changes from baseline in erythema using a CMH test with pooled study sites in Study BT1400N1-300-USA with the LOCF approach for imputing missing data. The sponsor did not provide results of similar

analyses for the other studies. Only the pooled analysis is significant. There is thus no replication of significance for the erythema results. Based on these comments, this reviewer recommends that only the study results from Study BT1400N1-300-USA should be included in the label.

### 3.2 EVALUATION OF SAFETY

Table 6 below provides the overall summary of adverse events from the vehicle controlled studies. There were no major differences between ketoconazole and vehicle. Table 7 provides the serious adverse events in these studies.

Table 6 Overall Summary of Adverse Events\*

Number of Subjects	Gel Vehicle		Ketoconazole USP 2%		Total	
	N=388		N=545		N=933	
	n	(%)	n	(%)	n	(%)
Subjects with 1 AE	67	(17.3%)	89	(16.3%)	156	(16.7%)
Subjects with 1 treatment-related** AE	25	(6.4%)	40	(7.3%)	65	(7.0%)
Subjects with 1 serious AE	2	(0.5%)	1	(0.2%)	3	(0.3%)
Subjects with 1 Trt-related** serious AE	0	(0.0%)	0	(0.0%)	0	(0.0%)
Subjects who interrupted/discontinued treatment due to AE	3	(0.8%)	9	(1.7%)	12	(1.3%)
Subjects who discontinued study due to an AE	2	(0.5%)	5	(0.9%)	7	(0.8%)

\*\* Includes events with relationship to study medication of possibly, probably, or certainly related.

\* Integrated results of BT200-USA-001, BT200-INT-001 and BT1400N01-300-USA studies

Source Sponsor's Table 2.7.4.2.1.1.5

Table 7 Overall Summary of Serious Adverse Events\*

Safety Evaluable Subjects			
Ketoconazole USP 2% Topical Gel			
SYSTEM ORGAN CLASS	Gel Vehicle	Ketoconazole USP 2%	Total
Preferred Term	N=388	N=545	N=933
	n (%)	n (%)	n (%)
Any Adverse Event	2 (0.5)	1 (0.2)	3 (0.3)
GASTROINTESTINAL DISORDERS	2 (0.5)	0 (0.0)	2 (0.2)
Pancreatic mass	1 (0.3)	0 (0.0)	1 (0.1)
Small intestinal obstruction nos	1 (0.3)	0 (0.0)	1 (0.1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0 (0.0)	1 (0.2)	1 (0.1)
Femoral neck fracture	0 (0.0)	1 (0.2)	1 (0.1)

Source Sponsor's Table 2.7.4.2.1.1.9

## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 GENDER/AGE/RACE

Summaries of the proportions of effectively treated subjects stratified by age class, gender, and race class for the ITT population are shown in Tables 8, 9 and 10 (taken from sponsor's tables in the summary of clinical efficacy). There were no remarkable findings in these results.

Table 8 Summary of Proportion Successfully Treated by Age Category at Day 28 Intent-to-Treat Subjects Protocols BT200USA01, BT200INT001 and BT400N01-300-USA

Clinical Success* by Age Category	Gel Vehicle (N = 388)	Ketoconazole USP 2% (N = 545)
<= 35 years (N)	108	156
n (Yes)	19	34
% (Yes) (n/N)	(17.6%)	(21.8%)
35 - 49 years (N)	90	151
n (Yes)	12	45
% (Yes) (n/N)	(13.3%)	(29.8%)
49 - 65 years (N)	114	135
n (Yes)	14	46
% (Yes) (n/N)	(12.3%)	(34.1%)
> 65 years (N)	76	103
n (Yes)	10	35
% (Yes) (n/N)	(13.2%)	(34.0%)
> 75 years (N)	16	35
n (Yes)	4	14
% (Yes) (n/N)	(25.0%)	(40.0%)

#### Source Sponsor's Table 14.2.1.3

Table 9 Summary of Proportion Successfully Treated by Gender at Day 28 Intent-to-Treat Subjects Protocols BT200USA01, BT200INT001 and BT400N01-300-USA

Clinical Success* by Gender	Gel Vehicle (N = 388)	Ketoconazole USP 2% (N = 545)
Male (N)	235	335
n (Yes)	34	102
% (Yes) (n/N)	(14.5%)	(30.4%)
Female (N)	153	210
n (Yes)	21	58
% (Yes) (n/N)	(13.7%)	(27.6%)

#### Source Sponsor's Table 14.2.1.4

Table 10 Summary of Proportion Successfully Treated by Race at Day 28  
 Intent-to-Treat Subjects Protocols BT200USA01, BT200INT001 and BT400N01-300-USA

Clinical Success* By Race	Gel Vehicle (N = 388)	Ketoconazole USP 2% (N = 545)
Caucasian (N)	353	481
n (Yes)	51	142
% (Yes) (n/N)	(14.4%)	(29.5%)
African-American (N)	16	32
n (Yes)	1	8
% (Yes) (n/N)	(6.3%)	(25.0%)
Asian (N)	1	3
n (Yes)	0	0
% (Yes) (n/N)	(0.0%)	(0.0%)
Hispanic/Latino (N)	17	25
n (Yes)	3	10
% (Yes) (n/N)	(17.6%)	(40.0%)
Native American (N)	1	0
n (Yes)	0	0
% (Yes) (n/N)	(0.0%)	(0.0%)
Other (N)	0	4
n (Yes)	0	0
% (Yes) (n/N)	(0.0%)	(0.0%)

Source Sponsor's Table 14.2.1.5

#### ***4.2 OTHER SPECIAL/SUBGROUP POPULATIONS***

The proportion of successfully treated subjects at Day 28 (subjects that achieved clinical success) is summarized by baseline Investigator's Global evaluation (ITT population) in Table 11 (taken from sponsor's table in the summary of clinical efficacy). Ketoconazole had a higher percentage of subjects successfully treated in subjects rated either moderate or rated severe by the investigator.

Table 11 Summary of Proportion Successfully Treated by Baseline Global Assessment Score at Day 28 Intent-to-Treat Subjects Protocols BT200USA01, BT200INT001 and BT400N01-300-USA

Clinical Success* by Baseline Global Assessment Score	Gel Vehicle (N = 388)	Ketoconazole USP 2% (N = 545)
3=Moderate (N)	271	358
n (Yes)	40	97
% (Yes) (n/N)	(14.8%)	(27.1%)
4=Severe (N)	117	187
n (Yes)	15	63
% (Yes) (n/N)	(12.8%)	(33.7%)

Source Sponsor's Table 14.2.1.7

## 5 SUMMARY AND CONCLUSIONS

### 5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

Although the sponsor did not specify the SCORES option for calculating the CMH test for the primary efficacy variable, the results were significant using any of the SCORES options.

### 5.2 CONCLUSIONS AND RECOMMENDATIONS

Ketoconazole 2% gel applied once a day for 14 days was significantly different from vehicle in the percentage of seborrheic dermatitis subjects "effectively treated" as assessed after a 14 follow-up period in Study BT1400N01-300-USA. Efficacy of ketoconazole 2% gel over vehicle was also supported by post-hoc analyses of seborrheic dermatitis subjects "effectively treated" in Studies BT200-USA-001 and BT200-INT-001.

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