CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-010

STATISTICAL REVIEW(S)

JUN 22 1990

NDA #: 20-010

Applicant: Schering-Plough

Name of Drug: Lotrisone Lotion (Clotrimazole 1% /betamethasone dipropionate 0.05%)

Indication: [redacted]

Documents Reviewed: Volume 1.7 of NDA (Technical Section for Statistics)

Introduction

The sponsor has requested approval of lotrisone lotion is indicated for [redacted] The agency has previously agreed that a single study on tinea cruris patients is sufficient to prove the efficacy of Lotrisone lotion for both tinea cruris and tinea corporis. This study, protocol S87-024, will be reviewed here. A separate study of patients with tinea pedis is currently in progress. In addition the Division of Anti-Infective Drug Products has agreed to waive the normal requirements for showing efficacy of a combination drug product (i.e. the demonstration of superiority of the combination over each seperate component); the sponsor is only required to show superiority over placebo.

Study Design

Protocol S87-024 was a three-center, randomized, vehicle controlled study of the effectiveness of Lotrisone lotion in the treatment of moderate to severe tinea cruris.

Patients with a clinical diagnosis of tinea cruris were evaluated by a study investigator who selected a representative area on each patient (designated as the target site) for detailed examination. Patients were included in the study if they received a total symptom score of at least 6 and an erythema score of at least 2 at the target site. The total symptom score was calculated as the sum of seven individual symptom scores which were each scored as follows: 0 (not present), 1 (mild), 2 (moderate) and 3 (severe). The symptoms included erythema, scaling, pruritis, maceration, vesicles, papules, and pustules.

All patients were tested for baseline fungal infection by KOH and culture. Those with positive KOH results were provisionally enrolled in the study pending the outcome of culture results. Only those with positive culture however (and positive KOH) were to be included in the efficacy analysis.

Patients were instructed to apply the medication daily over all affected areas for a period of two weeks and return for follow-up

visits at days 3, 8 and 15. Medication was terminated after two weeks; however, patients were told to return for a final follow-up visit at day 29.

Efficacy was assessed by the individual and total symptom scores at the target site at each return visit. In addition, the patients' overall clinical status and global response to treatment were evaluated at each return visit. Clinical status was scored from 0 (no signs or symptoms present) through 3 (severe). Global response was scored as follows: 1=complete (100% clearing), 2=excellent (75% - <100% clearing), 3=good (50% - < 75% clearing), 4=fair (25% - <50% clearing), 5=poor (<25% clearing) and 6= treatment failure. No one measure or combination of measures was singled out a priori as the primary efficacy measure(s).

Data Analysis

Each of 11 efficacy measures (i.e. 7 symptom scores, total symptom score, percentage change in total symptom score, clinical status and global response) was analyzed at each of the 4 return visits, treatment endpoint, and study endpoint using ANOVA methods. Treatment and study endpoint were defined as the last visit within the treatment interval (days 1-14) and the last visit within the study interval (days 1-29) respectively. The ANOVA models included investigator and treatment main effects and a treatment*investigator interaction.

Fungal eradication as measured by KOH, culture and mycology (positive if either culture or KOH were positive, negative if both culture and KOH were negative) was evaluated using the GSK method of log-linear models; these models included treatment, investigator and treatment*investigator terms.

In addition to the above pooled analyses, each of the three investigator's results were analyzed separately using t-tests for the efficacy variables and Fisher's exact test for fungal eradication.

The above analyses were performed on both the evaluable subset and on all patients included in the safety analysis (intent-to-treat). Data from invalid patient visits (see Patient Review below) were excluded from the analysis of evaluable patients but not from the intent-to-treat analysis.

Patient Review

Overall 65 Lotrisone and 67 vehicle patients were enrolled in the study. Six patients (2 Lotrisone and 4 vehicle) dropped out immediately after the initial visit and were excluded from both the safety and efficacy analysis. An additional 6 patients were excluded from the efficacy analysis only. These included 2 Lotrisone and 3 vehicle patients who had negative baseline cultures and 1 vehicle patient who received an unacceptable concomitant medication. All but one of the 12 excluded subjects were in investigator [redacted] study.

Of those patients included in the efficacy analysis, 7 Lotrisone

and 15 vehicle patients prematurely discontinued the study due to treatment failure and 1 patient in each group was lost to follow up. All of these patients thus had at least 1 visit with missing data. In addition, data from individual visits were excluded from the efficacy analyses if the visit was more than 1 day off schedule or when the patient missed the visit entirely. Eleven day 8 visits (including 5 in Lotrisone patients), 11 day 15 visits (4 in Lotrisone patients) and 18 day 29 visits (6 in Lotrisone patients) were thus excluded. Table 1 summarizes these findings by investigator.

Results of Statistical Analysis

Comparison of demographic and baseline disease characteristics demonstrated no significant differences between the two treatment groups. The baseline means of the individual and total symptom scores differed by no more than .1 between treatment groups.

Three of the symptoms, vesicles, papules and pustules, were sufficiently rare (mean baseline score of <= .5) that the study had limited power to detect differences between treatment groups. The treatment groups were comparable with respect to these measures.

The ANOVA results of the other (=major) efficacy measures are shown in Table 2. With the exception of maceration, all demonstrated significant ($p <= .01$) treatment effects in favor of Lotrisone at all 6 time points. Maceration showed significant treatment effects at day 29 and treatment and study endpoint. Although both Lotrisone and vehicle patients demonstrated clinical improvement, this effect was greater in the Lotrisone patients. For instance at 29 days Lotrisone patients demonstrated a 76% mean reduction in total symptom score and a mean global response of 2.1 compared to a 55% reduction in total symptom score and a mean global response score of 3.3 in vehicle patients.

For all of these efficacy measures however a significant treatment*investigator interaction was observed at at least 1 time point; therefore the sponsor also performed analyses of the individual investigators, using t-tests . For all time points from day 15 on (including treatment and study endpoint) Lotrisone patients numerically outperformed vehicle patients on all major efficacy measures in each of three investigator centers. Dr. [redacted] and Dr. [redacted] centers each demonstrated significant differences at endpoint (as well as various other times) in percent improvement in total symptom score, clinical status and global response ($p < .01$). In [redacted] center the differences in these measures were not statistically significant (at any time point) although the global response score was borderline ($p=.06$) at endpoint.

Log-linear analysis demonstrated that at each time point fungal eradication as measured by mycology was greater in Lotrisone than in vehicle patients. KOH and culture results were generally similar to the mycology results. As with the efficacy measures however, significant treatment*investigator interactions

were observed. Analysis of individual investigators revealed that [redacted] center demonstrated a significantly higher mycological cure rate for Lotrisone patients at all time points. In Dr. Schenefelt's center Lotrisone patients also had a greater cure rate at each time interval but the difference was statistically significant only at day 15. In [redacted] study however mycological cure rates were very low across the board and comparable between the two treatment groups (e.g. 25% for Lotrisone vs 24% for vehicle patients at study endpoint).

The results of the intent-to-treat analysis were generally similar to the efficacy analysis.

Two of 63 (3%) Lotrisone and one of 63 (2%) vehicle patients exhibited an adverse reaction possibly or probably related to treatment. In each case the reaction was dry skin.

Comments

The sponsor's analyses were generally reproducible. The choice of log-linear models for the analysis of fungal eradication is not justified by the sponsor; it seems that a simpler approach such as a Mantel-Haenszel analysis would have been sufficient. Such an approach gives similar results with respect to significant treatment effects and interactions.

The ANOVA models for the individual symptom scores (and for total symptom score) at each time point utilize only the current score; they do not incorporate the baseline score. An analysis of covariance model with the baseline score as the covariate is an alternative approach which does incorporate baseline data. Running this covariance model on the data gave essentially the same results as the applicant's ANOVA models. The sponsor's individual analysis of each investigator using t-tests is problematic. The t-tests performed on the individual and total symptom scores at each time period do not take into account the baseline score. Within some of the centers there were non-trivial differences between treatment groups with respect to the baseline means of particular scores (these differences tended to balance out when the whole study was considered). Since the scores at subsequent times are correlated with the baseline scores the analyses as performed are not valid; therefore I ran analysis of covariance models (one for each investigator) where treatment was the main effect and baseline level the covariate. Additionally, for those measures without a baseline score (e.g. percentage improvement, clinical status and global response) I ran Wilcoxon rank-sum tests since some of these measures are markedly non-normally distributed. The results of these analyses were generally consistent with those of the sponsor.

Summary

The sponsor has in my opinion provided sufficient statistical evidence that Lotrisone lotion is more effective than its vehicle

in the treatment of tinea cruris. The overall study results show a strong and consistent effect favoring Lotrisone lotion . There were investigator*treatment interactions observed; these were due to the smaller magnitude of effect in the group, not a difference in the direction of effect. It would be of interest however to determine what identifiable factors, if any, contributed to the difference in effect observed in this group.

/S/

Paul F Pinsky
Mathematical Statistician

Concur: Dr. Nevius /S/

Dr. Dubey /S/

cc:
Orig.
HFD-520
HFD-520/Mr. Bostwick
HFD-713/Dr. Dubey[File: DRU 1.3.2]
HFD-713/Dr. Nevius
HFD-713/Mr. Pinsky
HFD-344/Dr. Lisook
Chron

This review contains 5 pages and 2 tables.

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Table 1 : Number of Evaluable Subjects by Investigator

Investigator	Enrolled	Evaluable for Safety	Evaluable for Efficacy at Visit Day 3	Day 8	Day 15	Day 29
[redacted]						
Lotrisone	20	20	20	20	20	17
Placebo	22	21	21	21	21	16
	--	--	--	--	--	--
	41	41	41	41	41	33
[redacted]						
Lotrisone	21	21	21	18	18	17
Placebo	21	21	21	18	12	8
	--	--	--	--	--	--
	42	42	42	36	30	25
[redacted]						
Lotrisone	24	22	20	15	14	13
Placebo	24	21	17	10	9	7
	--	--	--	--	--	--
	43	37	37	25	23	20

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Table 2: Significance Levels of Efficacy Measures

	Visit					
	Day 3	Day 8	Day 15	Last Trt	Day 29	Endpoint
Symptom						
Erythema	.002	<.001	.02	.005	.06	<.001
Scaling	.008	.002	.002	<.001	<.001	<.001
Maceration	.82	.61	.11	.02	.02	.003
Pruritis	.002	<.001	.002	<.001	.02	<.001
Total Sign	<.001	<.001	<.001	<.001	.003	<.001
% Improve (Total sign)	<.001	<.001	<.001	<.001	.004	<.001
Clinical Stat	<.001	.001	.001	<.001	.003	<.001
Global Response	<.001	<.001	<.001	<.001	<.001	<.001