CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-310

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

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NDA#: 20-310

Applicant: Johnson & Johnson CPI

Name of Drug: Ketoconazole 1% Shampoo

Documents Reviewed: Volumes 1.22, 1.23, 1.25, 1.31 and 1.32.

Indication: Control of itching, flaking and scaling associated with dandruff.

Medical Input: Dr. Ramsey Labib, HFD-520

A. INTRODUCTION

The sponsor submitted results of two placebo-controlled trials and two open supportive trials to establish the safety and efficacy of 1% Ketoconazole shampoo in reducing adherent, loose and total dandruff and itching in subjects with moderate to severe dandruff. The sponsor claims that 1.0% concentration of ketoconazole (formula 1760-156) was appropriate for an OTC formulation and extremly effective and superior to vehicle placebo in reducing dandruff in eight weeks of treatment.

The two placebo-controlled trials (study 16399.41 and 16399.41B) were randomized, double-blind, parallel group studies. Study 16399.41 was single-centered and designed to demonstrate dose-related efficacy of ketoconazole shampoo concentrations (0.3%, 1.0% and 2.0%) compared to vehicle placebo in the treatment of moderate to severe dandruff. Eligible subjects in study 16399.41 were males and females of 18 years age or older, had a total dandruff score (adherent and loose) of 7 or more but with a minimum score of 3 for adherent dandruff, had no active dermatological conditions involving the scalp, had no history of unusual reactions to skin care, not under chronic medications, not pregnant or lactating and no history of atopic dermatitis and/or severe atopic dermatological background. Study 16399.41B was multi-centered and designed to evaluate safety and efficacy of 1.0% ketoconazole only compared to vehicle placebo. Eligible subjects for study 16399.41B were also males and females of 18 years of age or older, but with a total adherent dandruff score of 14 or more.

The two supportive studies (study 16399.41A and 16399.41C) were designed to demonstrate the safety and product performance of ketoconazole 1.0% shampoo. Study 16399.41A was a single-centered, open-label, long-term safety study in subjects previously treated with either vehicle placebo or ketoconazole shampoo (0.3%, 1.0% and 2.0%) in the dose-related study 16399.41. Study 16399.41C was a single-centered, double-blind, parallel group study which evaluated the performance of 1.0% ketoconazole manufactured using two different processes.

The sponsor collected data on efficacy in all four studies. Clinical assessments of efficacy were made as follows: loose, and adherent type dandruff rated on a scale of 0 (no dandruff) to 5 (severe dandruff), and scalp/hair oiliness as "dry", "oily", or "normal". Similarly, itching were rated on a scale of 0 (no itching) to 4 (severe itching). Loose and adherent dandruff were summed to yield total dandruff scores.

The sponsor used two efficacy measurements: global improvement in adherent, loose, and itching from baseline; and percent change in total dandruff score from baseline. It appears global improvement is the primary efficacy parameter and the total score is supportive.

B. EVALUATION

a. Study 16399.41 (Dose-range)

The objective of this study was to evaluate the minimium effective dose of ketoconazole for the treatment of moderate to severe dandruff. 165 subjects were treated: 41 with vehicle placebo, 42 with 0.3%, 41 with 1.0% and 41 with 2.0% ketoconazole shampoo respectively. A total of 159 subjects were evaluable for efficacy analyses. Clinical assessment of dandruff, scalp/hair oiliness and itching were made at baseline prior to randomization and the status of the dandruff condition and its responsiveness to treatment were further evaluated at week 2, 4, 6 and 8 seperately. Evaluable subjects in all four treatment groups were comparable with regard to age, sex, race, height and weight. In my view, the sponsors statistical evaluation (one-way ANOVA model and Pearson's Chi-square test) of these quantitative and qualitative variables between treatment groups were appropriate for this type of data.

There were no significant differences at baseline among evaluable subjects in the four treated groups with respect to adherent and loose dandruff and itching. My analyses confirm the sponsors reported p values (all p's $>=.800$, Table 4A, Appendix A, Vol. 1.22).

Efficacy Analyses: Efficacy analyses were based on changes from baseline in adherent, loose, and total dandruff, and itching. I used Wilcoxons signed rank test and Kruskal-Wallis (a non-parametric analogue to paired T-test and ANOVA) test for within and between treatment comparisons of changes from baseline in efficacy parameters. My analyses confirm the sponsors claim that the reductions from baseline in all three dandruff parameters within all three ketoconazole concentrations (0.3%, 1.0% and 2.0%) and vehicle group were highly significant at week 2 and remained significant thereafter ($p's=.0001$). The differences between treatment groups were significant at week 6, 8 and follow-up period. Comparison between vehicle placebo and 0.3%, 1.0% and 2.0% ($p=.0032$, $p=.0001$ and $p=.0001$ respectively) showed 1.0% and 2.0% were more effective in reducing adherent, loose and total dandruff than vehicle placebo. No statistically significant ($p>.05$) reduction in dandruff

parameters were observed between 1.0% and 2.0% concentrations of ketoconazole. This findings support the sponsors claim that ketoconazole 1.0% is the minimum effective dose for an OTC formulation. The sponsor could have used longitudinal analyses to evaluate trends in improvement in dose and efficacy.

b. Study 16399.41B

The objective of study 16399.41B was to evaluate efficacy and safety of 1.0% ketoconazole shampoo, compared to vehicle placebo in populations from two geographical regions in subjects having moderately severe dandruff. A total of 795 subjects were enrolled in this study: 317 subjects in the vehicle placebo and 478 subjects in the 1.0% ketoconazole shampoo group. Forty five subjects (6%) (15 in the placebo group and 30 in the ketoconazole group) were considered not evaluable for efficacy analyses.

There were no statistically significant differences (all p's $>.05$) between placebo and ketoconazole group with regard to sex, race, age and height. At baseline, no significant differences were observed between the two treatment groups with respect to efficacy variables: total adherent, total loose, total dandruff, hair/scalp oiliness, and itching among randomized and evaluable subjects.

Efficacy Analyses: Efficacy analyses were based on changes from baseline in total adherent dandruff, total loose dandruff, total dandruff, and itching. My analyses agree with the sponsors claim that there is no heterogenity of results between geographic regions, there are statistically significant differences from baseline in all efficacy parameters within treatment groups (all p's $<=.001$). Ketoconazole 1.0% shampoo produced significant ($p=.0001$) reductions in all dandruff parameters and itching than vehicle placebo as early as week two and continued through eight weeks of treatment. Ketoconazole 1.0% shampoo is also statistically more effective than vehicle placebo within geographic region ($p<.001$) and in the overall population ($p=.0001$) in reducing dandruff.

d. Study 16399.41A and 16399.41C (supportive trials)

The objective of study 16399.41A and 16399.41C was to evaluate the long-term safety of ketoconazole 1.0% and product performance. In addition, efficacy data were also evaluated in these two trials. In study 16399.41A, the efficacy were based on changes from baseline in adherent, loose, total dandruff, and itching to month 1, 2, 4, 6, 8, 10, and 12. Clinical assessment were identical to study 16399.41. There were substantial reduction in the efficacy variables from baseline through month 12. In the four-week study 16399.41C (extension of study 16399.41A), ketoconazole 1.0% shampoo was effective regardless of formulation process (lot 0061P and 0022P) and no statistically significant differences were observed

between lots from baseline in adherent, loose or total dandruff or itching.

Adverse Events: The sponsor submitted all adverse experiences reported by subjects treated with study shampoo in the placebo-controlled and supportive trials. Thirty percent (117/356) in ketoconazole 1.0% shampoo and thirty three percent (199/660) in vehicle placebo group reported at least one adverse experince. No statistically significant differences was noted between ketoconazole 1.0% shampoo and vehicle placebo group. The most frequently reported adverse experiences were respiratory tract infection (9%), headache (6%), and sinusitis (4%) in ketoconazole 1.0% shampoo group compared to 11%, 7%, and 4% in vehicle placebo respectively. I find no significant differences between two groups in any reported adverse experiences.

C. CONCLUSION (Which may be conveyed to the sponsor)

Results of the two placebo-controlled trials and two supportive trials demonstrate that:

i. Ketoconazole 1.0% shampoo is more effective than 0.3% ($p=.0001$ vs $p=.0032$) concentration compared to vehicle placebo for the treatment of total dandruff. There is no significant differences between 1.0% and 2.0% concentration ($p=.5531$).

ii. Ketoconazole 1.0% shampoo, applied twice weekly, is statistically more effective ($p=.0001$) in reducing adherent, loose, and total dandruff compared to vehicle placebo over 8 weeks of treatment.

iii. Ketoconazole 1.0% shampoo has an adverse event profile that is statistically similar to vehicle placebo. No statistically significant differences were noted between ketoconazole 1.0% shampoo and vehicle placebo group with regard to most frequently reported adverse experiences nor to total overall adverse events.

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10/7/93

Concur: Dr. Ralph Harkins

Dr. Satya D. Dubey 10-19-93

cc:
orig. NDA-20-310
HFD-520
HFD-520/Ms. R. Cook
HFD-520/Dr. Gavrilovich
HFD-520/Dr. Labib ✓
HFD-713/Dr. Dubey [File: DRU 1.3.2]
HFD-713/Dr. Harkins
HFD-344/Dr. Lisook
This review contains 5 pages.