CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75014

STATISTICAL REVIEW(S)

Statistical Review: ANDA 75-014, Permethrin Creme Rinse, 1%, Alpharma U.S. Pharmaceuticals

Material reviewed: 1. Photocopied material from ANDA 75-014.
2. March 30, 1999 Medical Officer Review by Mary M. Fanning, M.D., Ph.D., Associate Director for Medical Affairs, Office of Generic Drugs.

The issues in this review involve the sponsor's clinical bioequivalence study comparing their product, Alpharma Permethrin Creme Rinse 1%, to the reference listed drug product, NIX® Permethrin Creme Rinse 1% (Warner-Lambert Consumer Health Products). The products are for the treatment of head lice.

Study Design

The experimental design for this bioequivalence study was a parallel group clinical study. 56 subjects were randomized to the NIX® (Reference) group and 55 subjects were randomized to the Alpharma (Test) group.

The two treatments studied were:

Test Product - Alpharma Permethrin Creme Rinse (Lot X805069)

Reference Product - NIX® Permethrin Creme Rinse 1% (Warner-Lambert Consumer Health Products, Lot 7F2424)

Subjects were to be examined at 1, 7, and 14 days post treatment.

Endpoints

Subjects were to be scored at 14 days as

a) Treatment Success = no lice or viable eggs at 7 and 14 days
b) Reinfestation = no lice or viable eggs at 7 days, less than 5 adult lice at 14 days
c) Treatment Failure = live lice at any stage of development at 7 days; any nymphs or more than 5 adult lice at 14 days.

It is not clear how a subject with no lice or viable eggs at day 7 and exactly 5 adult lice at day 14 would be scored.

According to the protocol, primary efficacy of the products was to be based on the percentage of subjects scored as treatment success at day 14. In the final study report, an additional primary endpoint, treatment cure, was proposed. Treatment cure was assessed as the percentage of

subjects scored either as treatment success or as reinfestation at day 14.

Secondary endpoints included pediculicidal activity at day 7, ovicidal activity, and reinfestation rates.

Of these endpoints, all except ovicidal activity were binary measures.

Analysis Populations

The Intent-to-Treat (ITT) analysis population consisted of all subjects who were randomized to treatment, had at least one of the day 7 or day 14 evaluations, and could be scored for the endpoint in question. This is the analysis population reported by the Sponsor.

The medical officer, Dr. Fanning, extracted results for the Efficacy Valid analysis population. This consisted of subjects who completed therapy, were evaluated at each follow-up visit, and met all inclusion and exclusion criteria.

Summary of Sponsor's Statistical Methods

For all binary endpoints, the Sponsor obtained a number of test statistics and p-values using SAS PROC FREQ. These included the Pearson Chi-Square, Cochran-Mantel-Haenszel Chi-Square, Chi-Square with Yates continuity correction, and Fisher's Exact test. All of these test statistics are for testing the statistical hypotheses

$$H_0: p_T = p_R$$

$$H_1: p_T \neq p_R$$

where p_T and p_R are the rates for the Test and Reference products respectively. If we reject H_0 in favor of H_1, as indicated by a p-value less than or equal to 0.05, then we may conclude that p_T and p_R are "definitely different". However, failure to reject H_0 does not necessarily mean that $p_T = p_R$, and rejecting H_0 does not tell us anything about the possible magnitude of the difference $p_T - p_R$. For these reasons, these test statistics are not directly relevant to the question of bioequivalence.

The sponsor reported the p-value for the Cochran-Mantel-Haenszel Chi-Square in their summary report. However, Fleiss (Fleiss, J.L., *Statistical Methods for Rates and Proportions*, second edition, John Wiley & Sons, 1981) states that a continuity correction should be used in Chi-Square statistics for this situation. Also, Chi-Square statistics may not be appropriate for cases where the numbers of successes or failures is very low, as is the case for this study. In the results below, I will report the p-values for the Cochran-Mantel-Haenszel Chi-Square, Chi-Square with Yates continuity correction, and Fisher's exact test.

The sponsor also calculated a 90% confidence interval for the quantity $p_R - p_T$. This differs from the usual convention of considering $p_T - p_R$. However, this is not important so long as the lower allowable limit is equal to minus the upper allowable limit, as is usually the case in generic drug evaluation. The method used to calculate the confidence interval is the Wald method with Yates continuity correction (this is described in Fleiss, *ibid*, formula 2.14, page 29). This confidence interval may be used to test the statistical hypotheses

$$H_0: p_R - p_T < L \text{ or } U < p_R - p_T$$

$$H_1: \quad L \le p_R - p_T \le U$$

at the $\alpha = 0.05$ level of significance. If we reject H_0 in favor of H_1 then we conclude that $p_R - p_T$ lies between L and U, which are the specified allowable limits for $p_R - p_T$ (i.e., L and U are the "goalposts"). Limits of L=-0.2 and U=0.2 have been used in the past for the clinical assessment of biocquivalence for generic drugs.

The Sponsor has also carried out analyses using SAS PROC LOGISTIC in order to make inferences about the odds ratio, $\psi = p_T(1-p_R)/p_R(1-p_T)$ (this is the odds for the Test product relative to the odds for the Reference product). In some circumstances a 90% confidence interval for ψ could be used to test the hypotheses

$$H_0: \psi < l \text{ or } u < \psi$$

$$H_1: \quad l \le \psi \le u$$

for specified "goalposts" l and u. Although, I am not aware of any proposals for odds ratio "goalposts" for clinical bioequivalence studies, the test could be done once l and u are specified.

The Sponsor reported 90% confidence intervals for ψ calculated by the Wald method. For one of the endpoints (Reinfestation), I have also calculated a 90% confidence interval using a method proposed by Cornfield (Cornfield, J. A Statistical Problem Arising From Retrospective Studies, *Proceedings of the Third Berkeley Symposium on Mathematical Statistics and Probability*, pp. 135-148, 1956). This method appears to perform better when there is a zero count.

The secondary endpoint Ovicidal Activity (Hatch Rate) was based on a continuous measure, change-from-baseline in hatch rate of viable eggs collected both pre- and post-treatment. The Sponsor carried out a one way analysis of variance on this measure and obtained point estimates for Test and Reference, as well as a p-value for the null hypothesis that the mean change-from-baseline was the same for Test and Reference. The Sponsor also presented a calculation of a confidence interval for the ratio of the mean changes for Test and Reference. However, the methodology used by the Sponsor is not clear from the submitted printouts. As this was a secondary endpoint, I did not pursue this.

Results: Primary Endpoints

Endpoint: Treatment Success
Analysis Population: ITT

	outcome		
	success	failure	total
Alpharma (T)	46	7	53
NIX (R)	41	13	54

C-M-H Chi-Square p = 0.149
Chi-Square w/cont. corr. p = 0.233
Fisher's exact p = 0.215

$p_R - p_I$ point estimate: -0.109 90% C.I.: -0.250 , 0.033

odds ratio (ψ) point estimate: 2.084 90% Wald C.I.: 0.892 , 4.866

Endpoint: Treatment Cure
Analysis Population: ITT

	outcome		
	cure	no cure	total
Alpharma (T)	46	7	53
NIX (R)	44	10	54

C-M-H Chi-Square p = 0.45
Chi-Square w/cont. corr. p = 0.626
Fisher's exact p = 0.598

$p_R - p_T$ point estimate: -0.053 90% C.I.: -0.188 , 0.081

odds ratio (ψ) point estimate: 1.494 90% Wald C.I.: 0.618 , 3.607

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Endpoint: Treatment Success
Analysis Population: Efficacy Valid

	outcome		
	success	failure	total
Alpharma (T)	44	7	51
NIX (R)	38	13	51

C-M-H Chi-Square p = 0.136
Chi-Square w/cont. corr. p = 0.212
Fisher's exact p = 0.212

$p_R - p_T$ point estimate: -0.118 90% C.I.: -0.265 , 0.030

odds ratio (ψ) point estimate: 2.150 90% Wald C.I.: 0.917 , 5.045

Endpoint: Treatment Cure
Analysis Population: Efficacy Valid

	outcome		
	cure	no cure	total
Alpharma (T)	44	7	51
NIX (R)	41	10	51

C-M-H Chi-Square p = 0.428
Chi-Square w/cont. corr. p = 0.595
Fisher's exact p = 0.596

$p_R - p_T$ point estimate: -0.059 90% C.I.: -0.199 , 0.082

odds ratio (ψ) point estimate: 1.533 90% Wald C.I.: 0.632 , 3.717

Results: Secondary Endpoints

Endpoint: Pediculicidal Activity at Day 7
Analysis Population: ITT

	outcome		
	success	failure	total
Alpharma (T)	48	3	51
NIX (R)	52	3	55

C-M-H Chi-Square p = 0.924
Chi-Square w/cont. corr. p = 0.745
Fisher's exact p = 1.0

$p_R - p_T$ point estimate: 0.004 90% C.I.: -0.089 , 0.098

odds ratio (ψ) point estimate: 0.923 90% Wald C.I.: 0.232 , 3.679

Endpoint: Reinfestation
Analysis Population: ITT

	outcome		
	reinfestation	other	total
Alpharma (T)	0	53	53
NIX (R)	3	51	54

C-M-H Chi-Square p = 0.083
Chi-Square w/cont. corr. p = 0.248
Fisher's exact p = 0.243

$p_R - p_T$ point estimate: 0.056 90% C.I.: -0.014 , 0.126

odds ratio (ψ) point estimate: 0.0 90% Wald C.I.: 0.0 , ∞
90% Cornfield C.I.: 0.0 , 1.723

Endpoint: Ovicidal Activity (Hatch Rate)
Analysis Population: ITT

Test (Alpharma) mean change-from-baseline:	-0.0125
Reference (NIX) mean change-from-baseline:	-0.0181
p-value: 0.0828	

Summary

1. The Sponsor used statistical methods both to assess whether the Test and Reference formulations are "definitely different" and also to assess whether the performance of Test and Reference are within specified allowable limits ("goalposts"). The latter are more relevant to the assessment of bioequivalence.

2. For the primary endpoint Treatment Success, the 90% confidence interval for $p_R - p_T$ does not fall within the usual allowable limits of -0.2 to 0.2, for either the ITT of the Efficacy Valid analysis populations. Treatment Success was the primary endpoint specified in the Sponsor's protocol.

3. For the primary endpoint Treatment Cure, the 90% confidence interval for $p_R - p_T$ falls within the usual allowable limits of -0.2 to 0.2 for both the ITT and the Efficacy Valid analysis populations (although just barely so for the Efficacy Valid analysis population, lower 90% confidence limit = -0.199). Treatment Cure was not specified as an endpoint in the protocol.

4. For the secondary endpoints represented by binary measures - Pediculicidal Activity at Day 7 and Reinfestation - the 90% confidence intervals for $p_R - p_T$ fall within the usual allowable limits of -0.2 to 0.2 for both endpoints (ITT analysis population).

5. For the secondary endpoint represented by a continuous measure - Ovicidal Activity (Hatch Rate) - the p-value for the hypothesis that the mean change-from-baseline is the same for Test and Reference is borderline statistically significant, p=0.0828.

6. For the primary endpoints - Treatment Success and Treatment Cure - the results were more favorable for the Test product (Alpharma). It appears that the 90% confidence interval in the case of Treatment Success did not fall within -0.2 to 0.2 because of the greater Reinfestation rate observed for the Reference product. The secondary endpoints were more mixed. Results were more favorable for Test for Reinfestation, more favorable for Reference for Pediculicidal Activity at Day 7 and for Ovicidal Activity.

/S/

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