Protocol No. CR007129

Comparison of Efficacy and Safety of TriCilest (norgestimate-ethinyl estradiol) and Diane-35 (cyproterone acetate-ethinyl estradiol) in the Treatment of Acne Vulgaris

SYNOPSIS

Name of Sponsor/Company : Janssen-Cilag Taiwan, A Division of Johnson & Johnson Taiwan Ltd.	Individual Study Table Referring to Part of the Dossier :	*(For National Authority Use only)*
Name of Finished Product : TriCilest®	Volume :	
Name of Active Ingredient : Norgestimate-ethinyl estradiol	Page :	
Title of Study: Comparison of Efficacy and Safety of TriCilest (norgestimate-ethinyl estradiol) and Diane-35 (cyproterone acetate-ethinyl estradiol) in the Treatment of Acne Vulgaris		
Investigators: Dr. Shu-Lin Hu, Dr. Chieh-Chen Huang, Dr. Haw-Jeong Lin		
Study Center(s): Cathay General Hospital – Taipei Shin Kong Wu-Ho-Su Memorial Hospital		
Publication: None at present		
Studied period (years): Date of first enrolment: September 17th, 2004 Date of last completed: September 21st, 2005	Phase of development: Local therapeutic study	
Objectives: The objectives of this study were to evaluate the efficacy and safety of TriCilest (norgestimate-ethinyl estradiol) as compared with Diane-35 (cyproterone acetate- ethinyl estradiol) among female patients with moderate acne vulgaris in Taiwan.		
Methodology: Double-blind, randomized 1:1, parallel, active-controlled, multiple center.		

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Number of subjects: Approximately 50 subjects were planned to complete 40 evaluable subjects. At the end of the study, a total 48 subjects were randomized (25 subjects of TriCilest; 23 subjects of Diane-35). All randomized subjects except 3 Diane-35 subjects didn't take any dose of study medication, were included in the ITT/safety population (45 subjects in total). Out of the 45 subjects in the ITT/safety population, 3 TriCilest and 2 Diane-35 treated subjects were furthered considered not evaluable. As a result, there were 40 evaluable subjects, in which 22 subjects were randomly assigned to the TriCilest group and 18 subjects received Diane-35 treatment.
Diagnosis and main criteria for inclusion: Subjects who met the following criteria were allowed to participate in the study: female adults who were 1) of 15 to 49 years old, 2) suffering from moderate acne vulgaris (grade II or III), 3) with 6 to 100 comedones (non-inflammatory lesions), 4) with 10 to 50 inflammatory lesions (papules or pustules), 5) with fewer than 5 nodules, 6) agree to condoms or diaphragm, and spermicide or any other medically approved effective barrier method of contraceptive or a nonhormonal IUD., 7) agree to take as treatment for acne only for the supplied study drug during the three-month treatment phase of the study, 8) documented by an informed consent to participate in the trial on the day before entering the study.
Test product, doses and mode of administration, batch number/exp. date: TriCilest (norgestimate-ethinyl estradiol), 0.18 mg-0.035 mg or 0.215 mg-0.035 mg or 0.25 mg-0.035 mg, oral, E0149, December 2005.
Duration of treatment : Three consecutive menstrual cycles. (Each cycle was 28 days, subjects took one dose of the study drug once at night before bed for the first 21 days of each cycle)
Reference therapy, mode of administration, batch number/exp. date: Diane-35 (cyproterone acetate-ethinyl estradiol), 2 mg-0.035 mg, oral, E0149, December 2005.

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Criteria for evaluation:

Efficacy:
The primary measure of efficacy was change in total lesion count from baseline to the latest available evaluation.

The secondary measures of efficacy were as shown below:
- Change in inflammatory lesion count from baseline to the latest available evaluation
- Change in individual lesion count from baseline to latest available evaluation
- Percentage of subjects showing improvement on the investigator's global assessment
- Subject's end-of-therapy self-assessment

Safety:
Safety profile was evaluated through the following measures:
- Physical tests at screening and last visit
- Adverse events

Additional endpoint:
- Dropout rate after randomization will be compared between treatment groups

Statistical methods:
The primary endpoint, change in inflammatory lesion count, individual lesion counts and total lesion count from baseline to the latest available evaluation between two groups were compared using Analysis of covariance (ANCOVA) incorporating treatment, center as factors and their respective baseline values as covariate.

Secondary efficacy endpoints were analyzed by ANCOVA or Cochran-Mantel-Haenszel test as appropriate. The statistical tests used were two-tailed with α=0.05. In addition to p-values, the summary statistics were also presented for all secondary efficacy endpoints.

Adverse events were reported by treatment groups and by physiological systems as appropriate. Incidence of adverse events between treatments will be analyzed by Cochran-Mantel-Haenszel test. The coding system used was the coding symbols for thesaurus of adverse reaction (COSTART). Changes in physical examinations were displayed for each individual system.

The efficacy evaluation was performed on both the ITT and PPP datasets while the safety evaluations was performed only on the ITT dataset. The primary conclusion will be made for the primary endpoint on the ITT population.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Forty-eight subjects were randomized into this study and 45 of them were included in the ITT population with 25 subjects in the TriCilest group and 20 in the Diane-35 group. Among the ITT population, 5 protocol violators (3 in TriCilest group and 2 in the Diane-35 group) was excluded from the PP population. The primary efficacy conclusion of this study was made based on both of the ITT and PP analysis results for the primary efficacy endpoint.

The primary efficacy variable was the change from baseline to the latest available evaluation in total lesion count. Being an indicator of treatment effect in treating against the acne vulgaris, the primary efficacy result of this study clearly manifested the potency of TriCilest. A reduction (mean±SD) of -43.36±29.98 in total lesion count was observed in ITT population of the TriCilest group with a 95% confidence interval of -52.61 to -33.03 lesions. Comparable results were observed in the Diane-35 group (mean±SD= -34.20±24.16). The mean treatment difference (TriCilest minus Diane-35) was -5.28 with a 95% confidence interval of -20.04 to 9.47 lesions. In PP population, the analysis results are similar, the changes are -46.32±30.45 (95% CI: -56.31 to -34.62) and -35.28±25.26 (95% CI: -50.69 to -26.66) lesions for TriCilest group and Diane-35 group, respectively.

Due to the small sample size and small difference between treatments of this study, the superiority of TriCilest compared to Diane-35 was not evidenced as the upper bound (9.47 for ITT population, 9.45 for PP population) of the 95% C.I. of treatment difference in the ITT population was not greater than 0 and the p-value (0.474 for ITT population, 0.402 for PP population) was greater than the predicted α (0.05). However, both the ITT and the PP analysis results demonstrated the potent effects of the test drug because of the total lesion count (mean±SD: -43.36±29.98 and -46.32±30.45 lesions in ITT and PP populations, respectively) was dropped more than the comparator (mean±SD: -34.20±24.16 and 35.28±25.26 lesions in ITT and PP populations).

All other secondary efficacy variables (change in lesion counts) showed consistent results to the primary efficacy endpoint. The treatment effect of TriCilest group was not statistically significantly different from that of the Diane-35 group.

SAFETY RESULTS:

There were 48 treatment-emergent adverse events (31 in TriCilest, 17 in Diane-35) reported in 26 subjects (18 in TriCilest, 8 in Diane-35; p = 0.018). The most frequently reported adverse event in TriCilest was vaginal hemorrhage (16.0% incidence rate). TriCilest has shown to have significant higher adverse event incidence compared to the Diane-35 group (p=0.020). No adverse events were graded as severe in both groups in event intensity, while, more adverse events in the TriCilest group were graded as moderate compare with which in the Diane-35 group in event intensity (22.6% versus 5.9%). In terms of the adverse event causality, 80.7% versus 76.5% of adverse events were considered to be at least possibly related the study medications for the TriCilest versus Diane-35 group. Five significant adverse events which led to discontinuation of study treatment in 4 subjects were reported in the TriCilest group and 2 of such events occurred in one subject were seen in the Diane-35 group.

Regarding the physical examination results, no new abnormal finding was observed after treatment period in both treatment groups.

TriCilest was shown in this study to be generally well tolerated for subjects with acne vulgaris in the Taiwanese population.

CONCLUSION:

The primary aim of this clinical trial was to study the efficacy and safety of TriCilest given orally once daily compared to Diane-35 once a day for 3 menstrual cycles in subjects suffering from acne vulgaris. Four to five visits, including Screening, Randomization (Baseline, may be on the same day of screening visit) and 3 Evaluation visits, were scheduled for each subject in this study during the 3 cycles of treatment. Efficacy as well as safety profiles were monitored throughout the study.

The conclusion of this study was made based on the primary efficacy analysis results on the ITT and PP populations. The primary endpoint of this study measured the change from baseline to the latest available evaluation on total lesion count. Although the p-value on the comparison of mean treatment effects did not result in a superior outcome for TriCilest against Diane-35, the treatment effect of TriCilest group appears to show slightly better effect than the Diane-35 group. For the ITT population, total lesion count was decreased in the TriCilest group by a mean±SD of -43.36±29.98 (95% confidence interval of -52.61 to -33.03), and it was reduced in the Diane-35 group by a mean±SD of -34.20±24.16 (95% confidence interval of -48.59 to -26.48). Similar results were observed in the PP population, and all these analyses demonstrated the efficacious effects of TriCilest and Diane-35 in alleviating symptoms of acne vulgaris.

Secondary efficacy endpoints were utilized in this study as auxiliaries for efficacy evaluations. Most of the secondary analysis results were consistent to the primary analysis results, in which the potent effects of TriCilest and Diane-35 were evidenced and no treatment group differences were evidenced.

Regarding the AE incidence, a lower percentage of subjects experienced at least one treatment-emergent adverse event was found in the Diane-35 group (40.0%), compared to the TriCilest group (72.0%). The number of adverse event reported in the TriCilest group (31 events) was more than that of the Diane-35 group (17 events). The most frequently reported adverse event was vaginal hemorrhage for the TriCilest group in incidence of 16%. In the Diane-35 group, no single adverse event was reported in more than 2 subjects. 77.4% and 22.6% of the of adverse events reported in the TriCilest group were rated as mild and moderate in severity, compared to 94.1% and 5.9% of the adverse events in the control group which were considered in mild and moderate severity. In terms of the causality, 4 (80.7%) versus 16 (76.5%) adverse events were graded as at least possibly related to the study medications for TriCilest versus Diane-35 group. No serious adverse event was reported in this study in either treatment group. Five adverse events in 4 subjects for the TriCilest group and 2 adverse events in 1 subject for the Diane-35 group resulting in trial treatment discontinuation and were categorized as significant adverse events. No other adverse events incurred trial drug modification in this study.

For physical examination, no subjects had new abnormal finding at the end of study.

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The study was primarily designed to obtain new drug regulatory approval for norgestimate-ethinyl estradiol (TriCilest) in Taiwan through the study design of comparing cyproterone acetate-ethinyl estradiol (Diane-35) in a descriptive manner by at least 40 evaluable subjects. The study results will be served as part of the registration materials for norgestimate-ethinyl estradiol (TriCilest) in the new drug application.
Date of the report: November 17th, 2005

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