

# Superiority of a Combined Contraceptive Containing Drospirenone to a Triphasic Preparation Containing Norgestimate in Acne Treatment

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*This double-blind study compared the efficacy and tolerability of a combined oral contraceptive containing 30 µg ethinyl estradiol and 3 mg drospirenone (EE/DRSP; Yasmin®) with a triphasic preparation containing 35 µg EE and 0.180, 0.215, 0.250 mg norgestimate (EE/NGM; Pramino®, also known as Ortho Tri-Cyclen®) in the treatment of acne vulgaris. The combined presence of antiandrogenic and antimineralocorticoid activities of drospirenone is unique to this novel progestin in that these characteristics most closely resemble those of progesterone. The study was designed to show that EE/DRSP was noninferior or superior to EE/NGM as to the relative decrease from baseline to cycle 6 in percentage of inflammatory and total lesion counts and the investigators' assessment of acne improvement. Other outcomes included subjects' assessment of therapeutic effect, sebum production, and hormone levels.*

*Female subjects were randomized to EE/DRSP (n=568) or EE/NGM (n=586) for 6 treatment cycles, consisting of 21 consecutive days of hormone intake, followed by 7 hormone-free days. The preparation containing EE/DRSP was superior to EE/NGM for reduction in total lesion count (−3.3% in favor of EE/DRSP [95% CI, −6.5 to −0.1; P=.020]) and for*

*investigators' assessment of therapeutic effect on facial acne (+3.6% in favor of EE/DRSP [95% CI, 0.8 to 6.3; P=.006]). The 2 preparations were comparable as to their decreases in inflammatory lesion count. Evaluation of the effect of treatment by subjects was consistent with that of the investigators. Furthermore, both preparations increased the level of sex hormone-binding globulin (SHBG) and decreased the levels of androgens, changes typically associated with acne improvement. Both preparations were well tolerated. In conclusion, owing to the unique pharmacologic activities of drospirenone, the combined oral contraceptive EE/DRSP provides an effective treatment option in female patients with mild to moderate acne.*

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**A**lthough the causes of acne vulgaris are multifactorial, it is well accepted that androgenic hormones play an important role in its pathogenesis.<sup>1</sup> Androgen overproduction or hypersensitivity of the sebaceous glands to normal androgen levels can lead to increased sebum production and acne.<sup>1-3</sup> As such, modulation of androgen levels represents a valid treatment option for acne in women. Evaluating effective therapies for acne is important, considering the potential adverse psychosocial consequences of this skin disease.

Combined oral contraceptives are a highly effective treatment option for acne in women, particularly in those with symptoms of androgenization.<sup>4,7</sup> The beneficial effects of combined oral contraceptives on acne are partly due to their ability to reduce androgen secretion by the ovaries and to increase the levels of sex hormone-binding globulin (SHBG).<sup>1</sup> Moreover, some progestins, such as drospirenone (DRSP), cyproterone acetate, and dienogest, have marked antiandrogenic activity, thereby partially counteracting the effects of endogenous androgens.<sup>8,9</sup>

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DRSP is a novel progestin and an analog of  $17\alpha$ -spironolactone that differs from all other available progestins in that its pharmacologic properties (eg, positive antiminerlocorticoid and progestogenic activities and negative androgenic and glucocorticoid activities) most closely resemble those of progesterone.<sup>8,10</sup> Furthermore, DRSP has antiandrogenic properties through direct actions at the androgen receptor site, which, when combined with ethinyl estradiol (EE) in an oral contraceptive, make it a suitable option in the treatment of acne and other skin-related conditions, in addition to other hyperandrogenic disorders such as hirsutism.<sup>6,11</sup> When included in a combined oral contraceptive preparation, the antiminerlocorticoid activity of DRSP also may compensate for the increased fluid retention and associated weight gain attributed to estrogen. Further, DRSP may help reduce follicular wall edema during the second half of the menstrual cycle, which is partly responsible for the flare-up of inflammatory lesions at this cycle phase.<sup>12</sup> The combination of 30  $\mu$ g EE and 3 mg DRSP (Yasmin<sup>®</sup>) as a contraceptive is well established,<sup>11,13,14</sup> and its effect on acne and seborrhea is comparable with a combined oral contraceptive containing 35  $\mu$ g EE and 2 mg of the antiandrogenic progestin cyproterone acetate.<sup>6</sup>

This multicenter, randomized, double-blind clinical trial was designed to compare the efficacy and tolerability of EE/DRSP with a triphasic preparation containing 35  $\mu$ g EE and norgestimate (NGM) in the treatment of acne vulgaris. To date, this is the largest study designed to investigate the effect of oral contraceptives on acne.

## Materials and Methods

**Study Design**—This was a prospective, double-blind comparative study conducted from May 2000 to September 2001 at 56 investigational centers in Russia (17), Germany (13), Ukraine (12), Czech Republic (9) and Netherlands (5). This study was approved by the appropriate ethics committees or institutional review boards of the participating study centers and was conducted in accordance with the ethical principles of the Declaration of Helsinki (amended in 1996) and the International Conference on Harmonisation (ICH) good clinical practice guidelines. All participants gave written and informed consent before enrollment.

**Patients**—Otherwise healthy female subjects ranging in age from 15 to 40 years without contraindications for combined oral contraceptive use with mild to moderate acne vulgaris were recruited for this study. A subject was eligible if she had 6 to 100 comedones (noninflammatory lesions), 10 to 50 papules or pustules together, and not more than 5 nodules on the

face (inflammatory lesions). Before the baseline observation, washout periods had to be observed for oral contraceptives (Norplant<sup>®</sup> or Mirena<sup>®</sup> [3 cycles]); systemic retinoids or Depo-Provera<sup>®</sup> (6 months); or systemic antiacne agents, such as antibiotics (4 weeks), topical retinoids (4 weeks), and other topical treatments (2 weeks). Other inclusion criteria included normal gynecologic examination and cervical smear within the last 6 months; negative pregnancy test; 3 spontaneous withdrawal bleedings following delivery, abortion, or lactation; and avoidance of comedogenic cosmetics or sunscreens, sex hormone preparations, and antiacne therapy.

Subjects older than 30 years who smoked and those who were pregnant or lactating were excluded from the study. Other exclusion criteria included acne comedonica or nodulocystic/conglobate acne; acne with multiple large nodes, cysts, fistular comedones, or abscessing fistular ducts; previous acne treatment failure with (antiandrogenic) sex hormone preparations given for at least 3 months; and the need for other medication with known acne-inducing effects, such as lithium, vitamin B<sub>1</sub>, or corticoids. All subjects were provided with a nonirritating skin care line (eg, cleansing gel, day cream) for use, as required.

**Treatment**—Subjects were assigned randomly in a 1:1 ratio, according to a computer-generated randomization list, to receive EE/DRSP or a triphasic oral contraceptive containing 35  $\mu$ g EE and increasing doses of NGM (0.180 mg for days 1–7, 0.215 mg for days 8–14, and 0.250 mg for days 15–21 of each cycle)(EE/NGM; Pramino<sup>®</sup>). Subjects received their allocated treatment for 6 cycles; each cycle consisted of once-daily hormone treatment for 21 consecutive days, followed by 7 hormone-free days. Treatment in cycle 1 began on the fifth day after the onset of menstruation, which was considered as day 1 of the treatment cycle.

**Clinical Assessments**—Subjects were evaluated during 9 visits for the following: screening for eligibility, randomization and assessment of dermatologic baseline, treatment assessment on day  $18 \pm 3$  of cycles 1 to 6 and end of study or posttreatment (between days 8–15 after last capsule), or on premature discontinuation. At baseline and at each of the 6 treatment visits, a dermatologist counted acne lesions over the entire face (defined as area bounded by the ears, hairline, and lower margin of the mandibles). The therapeutic effect of treatment on acne and seborrhea was categorized retrospectively by the dermatologist and the subject (by memory recall), as excellent, good, or moderate improvement (collectively referred to as “improved”), and no improvement or aggravation (collectively referred to as “not improved”) at the last treatment visit in cycle 6 or in cases of premature discontinuation.

Sebum production was determined at baseline, cycle 3, and cycle 6 by using a photometry Sebumeter SM810<sup>®</sup> and by calculating the difference between mean sebum content measured initially (after hexane cleansing) and  $2 \pm 0.25$  hours after cleansing on 3 sites on the forehead (right, center, and left, avoiding skin folds and skin around acne lesions). Serum levels of the following hormone parameters were assessed at baseline and at cycle 6 by a central laboratory: total and unbound testosterone (by electrochemoluminescence immunoassay) and androstenedione, dehydroepiandrosterone sulfate (DHEAS), and SHBG (by radioimmunoassay). Assessment of therapeutic efficacy on facial acne and seborrhea was performed at cycle 6 or in case of premature discontinuation by the investigator and the subject. At all study visits, vital signs (blood pressure and heart rate) were measured, and, in addition, subjects reported adverse events (AEs) and any concomitant medication.

Subjects recorded study medication use and bleeding pattern in the daily diary cards. Compliance was assessed by analyzing subject recordings in diary card of tablet intake, along with the return of used, partly used, or unused treatment packs. Vaginal bleeding was assessed by evaluating bleeding records (intensity was rated as none, spotting, light, normal, or heavy) and reported by using 90-day reference periods (RPs). The first RP started on the first day of hormone treatment; the 2 evaluable RPs were 90 days and 78 days, respectively.

*Efficacy Parameters*—Three primary efficacy outcomes were used to assess efficacy: (1) the percentage relative change from baseline to cycle 6 in inflammatory lesion count (papules, pustules, and nodules), (2) the percentage relative change from baseline to cycle 6 in total lesion count (papules, pustules, nodules, and open and closed comedones), and (3) the proportion of subjects who showed improvement of their facial acne according to the investigators' assessment of therapeutic effect.

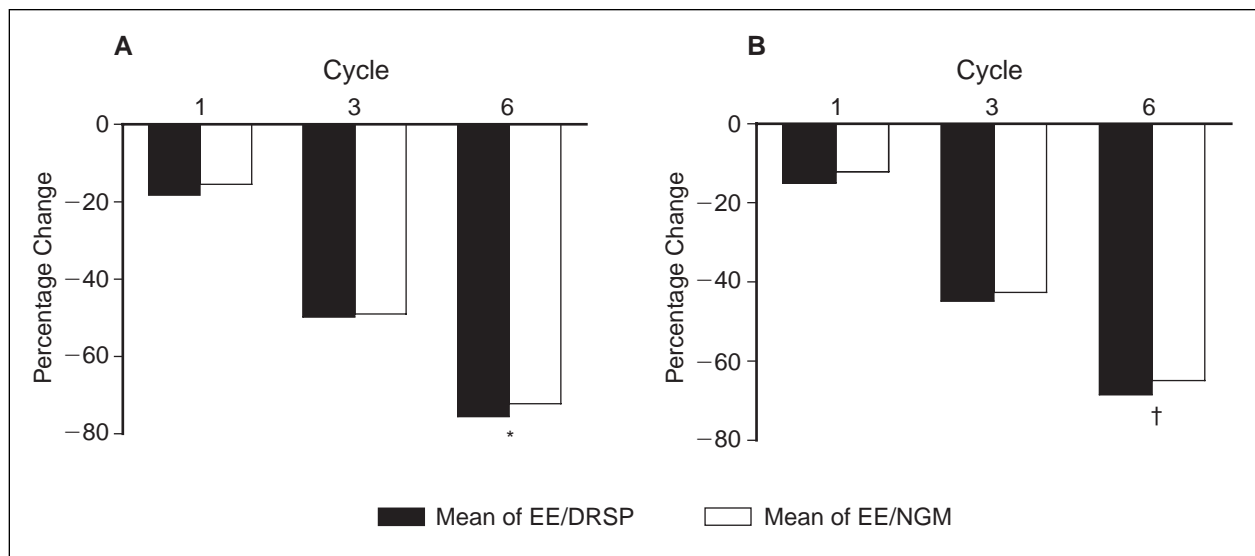
The secondary efficacy variables were subjects' assessment of the therapeutic effect of treatment on facial acne and seborrhea, changes in sebum production, changes in hormone levels, and bleeding record.

*Safety and Tolerability Assessments*—Subjects were given the opportunity to report AEs at each study visit. Vital signs were assessed at each study visit, and physical (including body weight) and gynecologic examinations (including cytologic smears) were performed at screening and at cycle 6. All AEs were coded using the Hoechst Adverse Reactions Terminology System, version 2.3, and classified by the study investigators as to their likely relationship to study medication (ie, none, unlikely, possible, probable, and definite).

*Statistical Analyses*—This study was analyzed according to the ICH of technical requirements for registration of pharmaceuticals for human use E10 guidelines on noninferiority testing.<sup>15</sup> This study tested the hypothesis that EE/DRSP was noninferior to EE/NGM at improving the percentage relative change from baseline to cycle 6 in inflammatory and total lesion counts and the proportion of subjects with acne improvement according to the investigators' assessment, assuming a noninferiority limit of 10% for each primary efficacy variable in favor of EE/NGM using a one-sided *t* test for independent variable at a significance level of  $\alpha = 2.5\%$ . The noninferiority margin of 10% was chosen based on clinical consideration.<sup>4,5</sup> Because the test drug was only considered to be noninferior to reference if all 3 tests were significant, no correction of  $\alpha$  was necessary. Switching from a noninferiority trial to a superiority trial is deemed acceptable at the 5% level if both 95% CIs for the effect of a treatment lie in favor of EE/DRSP.<sup>16</sup>

All randomized subjects who took one dose of study medication or for whom at least one postdose evaluation was available, or both, were included in the full analysis set (FAS). All subjects in the FAS who completed the study without major protocol deviations affecting the primary efficacy variables were included in the per protocol set (PPS). Major protocol deviations included treatment schedule violations (irregular medication intake and violation of timetable for visits), wrong co-medication (potentially acne healing or acne inducing), and major violation of inclusion or exclusion criteria. The PPS was used for the primary analyses of noninferiority, and the FAS was used for the calculation of superiority.<sup>16</sup> Other variables were described using descriptive statistics on the FAS.

*Sample Size Calculations*—Sample size was determined for each of the 3 primary efficacy variables based on the assumption of no treatment difference, a one-sided significance level of 2.5%, and 90% power. The assumed SDs of the relative change in inflammatory and total lesions counts were 40% and 35%, respectively, and the proportion of subjects who improved under active treatment was 88%. For each treatment group, the minimum sample sizes for the primary variables were calculated to be 338 for percentage relative change in inflammatory lesion count, 259 for relative percentage change in total lesion count, and 222 for the proportion of subjects with acne improvement according to the investigators' assessment. For each treatment group, the maximum of the 3 sample sizes ( $n = 338$ ) was selected. If the 3 primary efficacy variables were not correlated, the power of the study would have been 83%.



**Figure 1.** Relative change from baseline in inflammatory lesion count (A) and total lesion count (B) during treatment with 30 µg ethinyl estradiol/3 mg drospirenone (EE/DRSP; n=486) or the triphasic preparation 35 µg ethinyl estradiol/norgestimate (EE/NGM; n=505) in the per protocol set. When analyzed at cycle 6, the effects of EE/DRSP were comparable (\*) or superior (†) to EE/NGM.

However, as these 3 efficacy variables were positively correlated, the power of the study was therefore substantially higher than 83%. Assuming that 65% of the randomized subjects would be included in the PPS, then 520 subjects would need to be randomized to each treatment (1040 subjects in total).

## Results

**Patients**—A total of 1154 subjects were randomized to receive either EE/DRSP (n=568) or EE/NGM (n=586). Of these, 566 subjects assigned to EE/DRSP and 582 subjects assigned to EE/NGM were included in the FAS. The PPS included 486 subjects in the EE/DRSP group and 505 subjects in the EE/NGM group.

There were no relevant differences in demographic and other baseline characteristics of patients in the EE/DRSP and EE/NGM treatment groups (mean ± SD; based on FAS): age (24.2 ± 5.7 vs 23.9 ± 5.9 years), weight (61.1 ± 9.1 vs 61.0 ± 8.7 kg), height (167.5 ± 6.0 vs 167.8 ± 6.0 cm), body mass index (21.7 ± 2.7 vs 21.6 ± 2.7 kg/m<sup>2</sup>), and white race (99.4% vs 99.6%). Similar proportions of subjects in the EE/DRSP and EE/NGM groups had a history of acne (face, 100% in both groups; chest, 33.4% vs 33%; and back, 47.2% vs 44.5%) and seborrhea (88.9% vs 88%).

Premature discontinuation of study medication was reported for 35 (6.2%) subjects in the EE/DRSP group and for 41 (7%) subjects in the EE/NGM group. The main reasons for premature discontinuation of study medication in the EE/DRSP and EE/NGM groups, respectively, were as follows: AEs (18 and 23 subjects), other reasons (9 and 10 subjects);

most of these subjects were lost to follow-up), withdrawal of consent (4 and 4 subjects), protocol deviation (3 and 2 subjects), or lack of efficacy (1 and 2 subjects). Treatment compliance was good in both study groups; during the study, the mean number of tablets taken per cycle ranged from 20.8 to 21.0 in both treatment groups.

**Primary Efficacy Variables**—Inflammatory lesion count decreased with treatment duration in both treatment groups compared with baseline (Figure 1A). The difference for the relative change from baseline to cycle 6 in the mean percentage inflammatory lesion count between the 2 treatment groups (EE/DRSP [−75.5%] vs EE/NGM [−72.2%]) was −3.3% in favor of EE/DRSP (95% CI, −6.6 to 0.1;  $P < .001$ ), thus showing noninferiority to EE/NGM at the 10% level for the relative difference between groups (Table 1).

Total lesion count also decreased with treatment duration in both treatment groups compared with baseline (Figure 1B). As the difference in the FAS for the relative change from baseline to cycle 6 in the mean percentage total lesion count between EE/DRSP (−67.6%) and EE/NGM (−64.3%) was −3.3% in favor of EE/DRSP (95% CI, −6.5 to −0.1;  $P = .020$ ), the superiority of EE/DRSP over EE/NGM was shown for the relative difference between groups (Table 1).

For the investigators' assessment of acne improvement, improvement of facial acne was observed in most subjects treated with EE/DRSP (96.7%) or EE/NGM (93.7%) (Figure 2). The difference in FAS for the investigators' assessment of acne improvement between EE/DRSP (95.6%) and EE/NGM (92.1%)

Table 1.

**Summary of Mean Differences in Lesion Counts and Investigator-Assessed Acne Improvement After 6 Treatment Cycles of EE/DRSP and a Triphasic Preparation of EE/NGM\***

| Efficacy Parameter                               | Data Set | EE/DRSP |                   | EE/NGM |                   | Difference of Means (2-Sided 95% CI) <sup>†</sup> | 1-Sided <i>P</i> for Non-inferiority | 1-Sided <i>P</i> for Superiority |
|--|----------|---------|-------------------|--------|-------------------|---|--------------------------------------|----------------------------------|
|  |          | n       | Mean, % (SD)      | n      | Mean, % (SD)      |   |                                      |                                  |
| Inflammatory lesion count                        | PPS      | 486     | -75.5 (25.6)      | 505    | -72.2 (27.8)      | -3.3 (-6.6 to 0.1)                                | <.001                                | .028                             |
|  | FAS      | 547     | -73.4 (30.2)      | 561    | -71.0 (30.5)      | -2.3 (-5.9 to 1.3)                                | <.001                                | .102                             |
| Total lesion count                               | PPS      | 486     | -68.4 (24.4)      | 505    | -64.9 (26.4)      | -3.5 (-6.7 to -0.3)                               | <.001                                | .016                             |
|  | FAS      | 547     | -67.6 (26.8)      | 561    | -64.3 (26.7)      | -3.3 (-6.5 to -0.1)                               | <.001                                | .020                             |
| Investigator-assessed improvement of facial acne | PPS      | 486     | 96.7 <sup>‡</sup> | 505    | 93.7 <sup>‡</sup> | +3.0 (0.4 to 5.7) <sup>§</sup>                    | <.001                                | .012                             |
|  | FAS      | 551     | 95.6 <sup>‡</sup> | 569    | 92.1 <sup>‡</sup> | +3.6 (0.8 to 6.3) <sup>§</sup>                    | <.001                                | .006                             |

\*EE/DRSP indicates 30 µg ethinyl estradiol/3 mg drospirenone; EE/NGM, 35 µg ethinyl estradiol/0.180, 0.215, 0.250 mg norgestimate; PPS, per protocol set; FAS, full analysis set.

<sup>†</sup>For inflammatory and total lesion counts, a negative value indicates a better effect of EE/DRSP; for improvement of facial acne as assessed by the investigator, a positive value indicates a better effect of EE/DRSP.

<sup>‡</sup>Group proportion.

<sup>§</sup>Difference of proportions.

was +3.6% in favor of EE/DRSP (95% CI, 0.8 to 6.3; *P*=.006), thus again showing the superiority of EE/DRSP over EE/NGM for the relative difference between groups (Table 1).

**Secondary Efficacy Variables**—In general, the results obtained in the PPS were consistent with those obtained in the FAS. For simplicity of data presentation, only the FAS results are presented.

Subjects' assessment of therapeutic effect on facial acne and seborrhea at end of treatment was consistent with that of the investigators'. The proportion of subjects who reported improvement of their facial acne was higher in the EE/DRSP group (93.1%, *n*=550) than in the EE/NGM group (89.1%, *n*=567). In agreement with the high proportion of subjects who rated their facial acne as improved in both treatment groups, the actual numbers of papules, pustules, nodules, and comedones were distinctively lower at cycle 6 than at baseline (Table 2). Sebum production was reduced similarly in both treatment groups at cycle 6 compared with baseline: median sebum production decreased from 137 to 96 µg/cm<sup>2</sup> in the EE/DRSP group and from 141 to 101 µg/cm<sup>2</sup> in the EE/NGM group. As summarized in Table 3, hormone analyses showed that mean levels of androgens decreased while levels of SHBG increased.

Bleeding patterns over the study period were similar between the 2 treatment groups. In both reference periods, more than 94% of subjects who received EE/DRSP or EE/NGM experienced withdrawal bleeding. Both treatments reduced the number of bleeding or spotting days and spotting-only days in reference period 2 compared with reference period 1. From reference period 1 to 2, both treatments reduced to a similar extent the number of bleeding or spotting days (EE/DRSP: [mean±SD] 19.0±6.4 to 14.4±5.2; EE/NGM: 19.8±6.5 to 15.4±5.8) and the number of spotting-only days (EE/DRSP: 5.5±4.7 to 4.0±4.1; EE/NGM: 5.8±4.6 to 4.2±4.2). The mean number of bleeding or spotting episodes also decreased from reference period 1 to 2 by a comparable extent in the EE/DRSP group (4.0±0.7 to 2.7±0.6) and the EE/NGM group (4.0±0.7 to 2.8±0.7).

Good contraceptive reliability was reported for EE/DRSP and EE/NGM. During the 6 treatment cycles, one subject from each group became pregnant: in the EE/DRSP group due to discontinuation of study medication and in the EE/NGM group due to irregular intake of study medication.

**Safety and Tolerability**—Both treatments were generally well tolerated. Treatment-related AEs (possibly, probably, or definitely related to treatment) were

reported in 92 (16.3%) subjects in the EE/DRSP group and in 106 (18.2%) subjects in the EE/NGM group. Signs and symptoms most frequently reported (>2% of subjects affected) as treatment-related AEs (most of which were mild to moderate in intensity) in the EE/DRSP and EE/NGM groups were nausea (4.8% vs 5.5%), headache (3.9% vs 3.6%), breast pain (2.8% vs 2.9%), and abdominal pain (1.4% vs 2.2%). There were no serious treatment-related AEs in the EE/DRSP group. According to the investigator, 2 serious AEs (migraine and fibrocystic breast) possibly related to treatment were reported in 2 subjects in the EE/NGM group.

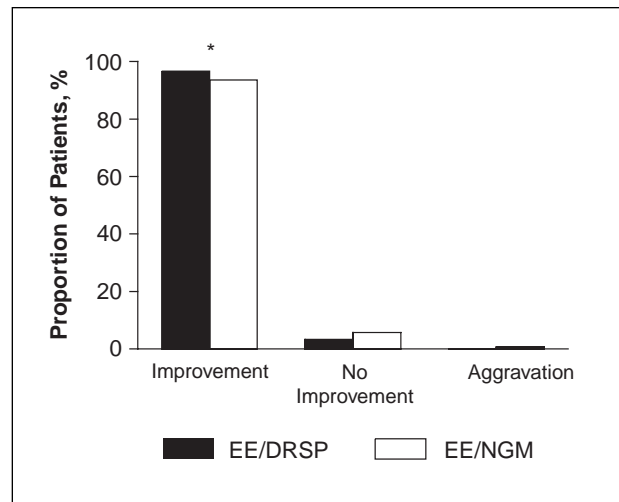
There were no significant changes in any safety parameters throughout the study, including laboratory examinations, physical and gynecologic assessments, or vital signs.

### Comment

In this study of mild to moderate acne, EE/DRSP was shown to be superior to EE/NGM in the reduction of total lesion count and the investigators' assessment of therapeutic effect. However, the 2 preparations were comparable in terms of their positive effects on inflammatory lesion count. Switching study objectives from a noninferiority analysis to a superiority analysis is acceptable because there are no multiplicity issues.<sup>16</sup>

The selection of an appropriate comparator is an important consideration in noninferiority trials; there should be well-controlled data that the comparator is an effective treatment when tested under similar clinical conditions.<sup>15</sup> The efficacy of EE/NGM in the treatment of acne vulgaris was shown in 2 prospective, multicenter, randomized, placebo-controlled studies.<sup>4,5</sup> Compared with placebo, EE/NGM produced significantly greater improvement on all primary efficacy measures (inflammatory lesion count, total lesion count, investigators' assessment) and had more favorable effects on levels of free testosterone and SHBG. The efficacy of EE/NGM in the present investigation, based on the reduction of inflammatory and total lesion counts and the investigators' assessment of therapy, was comparable with that reported previously for this combination.<sup>4,5</sup>

The effects of the combined oral contraceptive EE/DRSP on mild to moderate acne vulgaris observed in this investigation are consistent with those obtained in other studies.<sup>6,11</sup> In one open-label study, the incidence of acne in subjects was substantially reduced compared with baseline after 13 treatment cycles of EE/DRSP (22% to 8%), however, subjects in this study were not selected based on skin condition.<sup>11</sup> In a subsequent trial, 9 cycles of EE/DRSP reduced the mean percentage total acne lesion count compared



**Figure 2.** Investigators' assessment of improvement in facial acne at final examination (cycle 6) after treatment with 30  $\mu$ g ethinyl estradiol/3 mg drospirenone (EE/DRSP; n=486) or the triphasic preparation 35  $\mu$ g ethinyl estradiol/norgestimate (EE/NGM; n=505) in the per protocol set. Excellent, good, or moderate improvement were collectively referred to as "improvement." Asterisk indicates that the effect of EE/DRSP on facial acne was superior to that of EE/NGM.

with baseline by 38% at cycle 6 and by 56% at cycle 9.<sup>6</sup> The proportion of subjects whose acne was rated as improved by the dermatologist after 9 treatment cycles with EE/DRSP in the earlier study (94%, estimated from figure)<sup>6</sup> is comparable with the results of our study (97%).

In this study, both treatments increased the level of SHBG and correspondingly reduced the levels of total testosterone, free testosterone, androstenedione, and DHEAS; these changes usually are associated with decreased sebum production and improvement of acne.<sup>6,17-20</sup> Treatment with EE/DRSP elevated SHBG levels by a greater extent than EE/NGM and was accompanied by a greater reduction in unbound testosterone. However, only marginally greater reductions in total testosterone were observed with the monophasic preparation. Greater reductions in DHEAS levels were observed with EE/DRSP treatment, but both treatments reduced androstenedione levels by a similar extent. Thyroid function was not measured. The overall, more beneficial effect on ovarian and adrenal androgen production, as well as SHBG levels, of EE/DRSP in part may account for its superiority over EE/NGM for reduction in total lesion counts and subjective effects on acne. Furthermore, the changes in hormone levels and improvements in acne observed in this study are in general agreement with previous investigations with EE/DRSP<sup>6</sup> or EE/NGM.<sup>5</sup> Finally, as the antimineralocorticoid activity of drospirenone may reduce follicular wall

Table 2.

### Summary of Effects of EE/DRSP and a Triphasic Preparation EE/NGM on Inflammatory and Total Acne Lesion Counts Over the Entire Face After 6 Treatment Cycles (FAS)\*

| Lesion Type          | EE/DRSP (n=547)    |                   |                           |                     | EE/NGM (n=561)     |                   |                           |                     |
|----------------------|--------------------|-------------------|---------------------------|---------------------|--------------------|-------------------|---------------------------|---------------------|
|                      | Baseline Mean (SD) | Cycle 6 Mean (SD) | Mean Absolute Change (SD) | Mean Change, % (SD) | Baseline Mean (SD) | Cycle 6 Mean (SD) | Mean Absolute Change (SD) | Mean Change, % (SD) |
| <b>Inflammatory</b>  |                    |                   |                           |                     |                    |                   |                           |                     |
| (total)              | 24.4 (11.1)        | 6.0 (6.9)         | -18.4 (11.7)              | -73.4 (30.2)        | 24.2 (11.1)        | 6.5 (6.6)         | -17.9 (11.4)              | -71.0 (30.5)        |
| Papules              | 16.6 (8.7)         | 4.6 (5.0)         | -12.0 (8.9)               | -69.7 (33.1)        | 16.4 (8.7)         | 4.9 (5.3)         | -11.6 (8.8)               | -66.1 (40.3)        |
| Pustules             | 7.3 (6.0)          | 1.4 (2.9)         | -5.9 (5.8)                | -78.6 (45.9)        | 7.2 (6.2)          | 1.5 (2.5)         | -5.8 (5.8)                | -75.2 (46.4)        |
| Nodules              | 0.5 (1.0)          | 0.1 (0.4)         | -0.5 (1.0)                | -93.6 (25.7)        | 0.5 (1.0)          | 0.1 (0.5)         | -0.4 (1.1)                | -82.1 (65.4)        |
| <b>Comedones</b>     |                    |                   |                           |                     |                    |                   |                           |                     |
| Open                 | 18.4 (17.6)        | 6.7 (9.6)         | -12.0 (14.3)              | -59.7 (56.6)        | 17.1 (17.3)        | 6.8 (9.0)         | -10.5 (14.1)              | -50.4 (82.1)        |
| Closed               | 18.1 (13.4)        | 6.4 (7.6)         | -11.8 (13.0)              | -56.1 (62.4)        | 18.2 (13.8)        | 7.0 (7.7)         | -11.2 (12.5)              | -50.9 (77.1)        |
| <b>Total lesions</b> |                    |                   |                           |                     |                    |                   |                           |                     |
|                      | 60.9 (28.5)        | 19.2 (17.0)       | -42.2 (26.8)              | -67.6 (26.8)        | 59.4 (28.7)        | 20.2 (16.4)       | -39.6 (26.2)              | -64.3 (26.7)        |

\*EE/DRSP indicates 30 µg ethinyl estradiol/3 mg drospirenone; EE/NGM, 35 µg ethinyl estradiol/0.180, 0.215, 0.250 mg norgestimate; FAS, full analysis set.

Table 3.

### Summary of Effect of EE/DRSP and a Triphasic Preparation EE/NGM on Androgen and SHBG levels in the FAS After 6 Treatment Cycles\*

| Parameter                    | Visit         | EE/DRSP |              | EE/NGM |              |
|------------------------------|---------------|---------|--------------|--------|--------------|
|                              |               | n       | Mean (SD)    | n      | Mean (SD)    |
| Total testosterone, nmol/L   | Randomization | 304     | 1.7 (0.9)    | 316    | 1.6 (0.8)    |
|                              | Final         | 294     | 1.1 (0.7)    | 305    | 1.1 (0.7)    |
| Testosterone unbound, pmol/L | Randomization | 305     | 5.6 (3.3)    | 316    | 5.2 (2.9)    |
|                              | Final         | 295     | 2.7 (2.2)    | 305    | 3.0 (2.6)    |
| Androstendione, nmol/L       | Randomization | 305     | 6.7 (3.4)    | 316    | 6.3 (3.4)    |
|                              | Final         | 295     | 5.8 (3.2)    | 305    | 5.4 (3.1)    |
| DHEAS, nmol/L                | Randomization | 305     | 6341 (3124)  | 316    | 6216 (2928)  |
|                              | Final         | 294     | 4448 (2561)  | 305    | 4691 (2681)  |
| SHBG, nmol/L                 | Randomization | 305     | 56.7 (39.9)  | 316    | 54.4 (34.7)  |
|                              | Final         | 295     | 170.0 (52.1) | 305    | 132.4 (46.6) |

\*EE/DRSP indicates 30 µg ethinyl estradiol/3 mg drospirenone; EE/NGM, 35 µg ethinyl estradiol/0.180, 0.215, 0.250 mg norgestimate; SHBG, sex hormone-binding globulin; FAS, full analysis set; DHEAS, dehydroepiandrosterone sulfate.

edema during the second half of the menstrual cycle, we expect additional efficacy of EE/DRSP on inflammatory lesions at this cycle phase.

The superior effect of EE/DRSP over EE/NGM on acne, as measured by the reduction of total acne count and the investigators' assessment of therapeutic effect, may be related in part to the unique pharmacologic properties of drospirenone. Drospirenone does not have any androgenic potential.<sup>13,21</sup> In contrast, progestins that are 19-nortestosterone derivatives, such as norgestimate and one of its active metabolites, levonorgestrel, have inherent androgenic potential, though this activity is thought to be minimal at doses used in combined oral contraceptives.<sup>9,22</sup> Nonetheless, this residual androgenic activity may counteract the estrogen-stimulated increases in SHBG levels to some extent, thereby negating some of the positive effects of estrogen on acne.<sup>2</sup>

Both preparations in our study were well tolerated, and the reported AEs are typical for other combined oral contraceptives in similar subject populations.<sup>4,7,11,13</sup> Most AEs were rated as mild or moderate in intensity and generally did not lead to treatment discontinuation. Neither treatment gave rise to any safety concerns. Furthermore, both preparations provided good contraceptive reliability and good cycle control.

In conclusion, the combined oral contraceptive EE/DRSP provides an effective and well-tolerated treatment option in female patients with mild to moderate acne vulgaris. The effects of EE/DRSP on acne were superior to those achieved with EE/NGM for change in total lesion count and the investigators' assessment of therapeutic effect.

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