

# A Combined Oral Contraceptive Containing 3-mg Drospirenone/20- $\mu$ g Ethinyl Estradiol in the Treatment of Acne Vulgaris: A Randomized, Double-blind, Placebo-Controlled Study Evaluating Lesion Counts and Participant Self-assessment

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*This study compared the efficacy of a low-dose combined oral contraceptive (COC) containing 3-mg drospirenone and 20- $\mu$ g ethinyl estradiol (3-mg DRSP/20- $\mu$ g EE) administered in a 24-day active*

*pill/4-day inert pill (24/4) regimen and placebo in women with moderate acne vulgaris during 6 treatment cycles. A total of 534 participants were randomized and dispensed study medication (n=266 [3-mg DRSP/20- $\mu$ g EE 24/4 regimen COC group]; n=268 [placebo group]). Women of reproductive age were eligible for inclusion in the study. Treatment with the 3-mg DRSP/20- $\mu$ g EE 24/4 regimen COC was associated with a greater reduction from baseline to end point in individual lesion counts (papules, pustules, open and closed comedones) compared with placebo. The mean nodule count remained essentially constant throughout the study and was low in both treatment groups. There was a significantly higher probability that a participant had an improved assessment on the investigator's overall improvement rating scale (odds ratio [OR], 4.02; 95% CI [confidence interval], 2.29–7.31; P<.0001) and participant's overall self-assessment rating scale (OR, 2.82; 95% CI, 1.60–5.13; P=.0005) in the 3-mg DRSP/20- $\mu$ g EE 24/4 regimen COC group than in the placebo group. The COC 3-mg DRSP/20- $\mu$ g EE 24/4 regimen is a suitable option for women with moderate acne vulgaris who require contraception.*

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Acne vulgaris is a common skin problem that may be associated with poor self-esteem. Although it is prevalent among adolescents, many women develop acne.<sup>1</sup> It now is recognized that androgen-stimulated sebum production is one of the key factors in the development of acne vulgaris.<sup>2</sup> Hormonal therapies comprising ethinyl estradiol (EE) for the treatment of acne are designed to augment sex hormone-binding globulin (SHBG) and thereby reduce free testosterone levels<sup>3-5</sup> in addition to lowering serum androgen levels by inhibiting ovulation.<sup>6</sup> However, these favorable effects of EE may be negated by the inclusion of androgenic progestins, particularly 19-nortestosterone derivatives.<sup>7</sup>

A combined oral contraceptive (COC) formulation containing 3-mg drospirenone (DRSP), a progestin with antimineralocorticoid and antiandrogenic properties,<sup>8</sup> in combination with 20- $\mu$ g EE (3-mg DRSP/20- $\mu$ g EE) has been approved in the United States as a contraceptive and recently as a treatment of moderate acne vulgaris. The formulation, consisting of 24 days of active pills and 4 days of inert pills (24/4 regimen), has proven contraceptive efficacy, a good safety profile, and a favorable bleeding pattern, and also is approved for the treatment of the emotional and physical symptoms associated with premenstrual dysphoric disorder.<sup>7,9-11</sup>

The aim of this large, multicenter, randomized, double-blind, placebo-controlled US study was to assess the efficacy and safety of 3-mg DRSP/20- $\mu$ g EE in the 24/4 regimen for the treatment of moderate acne vulgaris during 6 treatment cycles. We report results of the secondary efficacy variables here.

## Methods

**Design**—Detailed methodology of this study has been reported elsewhere.<sup>12</sup>

**Efficacy Evaluations**—The primary and secondary efficacy analyses were based on an amended full analysis set, which consisted of women with more than 20 inflammatory lesions and 20 noninflammatory lesions. The original inclusion criterion was amended in the early course of the study based on the request of the US Food and Drug Administration to change the indication from mild to moderate acne vulgaris to moderate acne vulgaris. Primary efficacy evaluations have been reported elsewhere.<sup>12</sup>

The secondary efficacy variables included mean change from baseline to end point (visit 5 [cycle 6]) data with missing values replaced using the last observation carried forward procedure) in individual lesion counts for papules, pustules, nodules, and open and closed comedones, as well as the proportion of participants who showed improvement on a 6-point investigator's overall improvement rating

scale ranging from 1 (clear skin with complete clearance of acne lesions) to 6 (deterioration with worsening acne symptoms) and a 5-point participant's overall self-assessment rating scale ranging from 1 (excellent improvement) to 5 (worse). In addition, a subgroup of participants had serum hormone levels analyzed at baseline and end point.

**Safety Evaluations**—Details of the safety analyses of this study have been described elsewhere.<sup>12</sup>

**Assessments**—Facial acne lesion counts were performed by the investigators at screening and at treatment cycles 1, 3, and 6. Both the investigator's overall improvement and the participant's overall self-assessment ratings were obtained at end point.

In a subgroup of 40 women, serum hormone levels were evaluated at baseline and end point. Hormone assessments (total and free testosterone, dehydroepiandrosterone sulfate [DHEAS], androstenedione, SHBG serum levels) were performed at a central laboratory. Samples were obtained as scheduled, stored at  $-18^{\circ}\text{C}$ , and analyzed at the end of the study.

**Statistical Analyses**—Details of the statistical analyses of this study have been described elsewhere.<sup>12</sup>

## Results

**Participants**—A total of 534 participants were randomized and dispensed medication and were part of the full analysis set ( $n=266$  [3-mg DRSP/20- $\mu$ g EE 24/4 regimen COC group];  $n=268$  [placebo group]). The amended full analysis set consisted of 458 participants ( $n=228$  [3-mg DRSP/20- $\mu$ g EE 24/4 regimen COC group];  $n=230$  [placebo group]) with moderate acne vulgaris (Figure 1). In all, 155 participants prematurely discontinued from the study. The most common reasons for premature discontinuation from the study in the 3-mg DRSP/20- $\mu$ g EE group were adverse events (17/266 [6.4%]), lost to follow-up with no further information available (16/266 [6.0%]), withdrawal of consent (17/266 [6.4%]), and other (16/266 [6.0%]). In the placebo group, the most common reasons for premature discontinuation were adverse events (13/268 [4.9%]), lost to follow-up with no further information available (22/268 [8.2%]), withdrawal of consent (15/268 [5.6%]), and other (20/268 [7.5%]).

**Efficacy Evaluations**—The 3-mg DRSP/20- $\mu$ g EE 24/4 regimen COC reduced individual lesion counts from baseline to end point for both inflammatory (papules and pustules) and noninflammatory (open and closed comedones) acne lesions. The adjusted mean change from baseline to end point in all lesion counts was consistently higher in the 3-mg DRSP/20- $\mu$ g EE 24/4 regimen COC group compared with the placebo group (Figure 2). The mean



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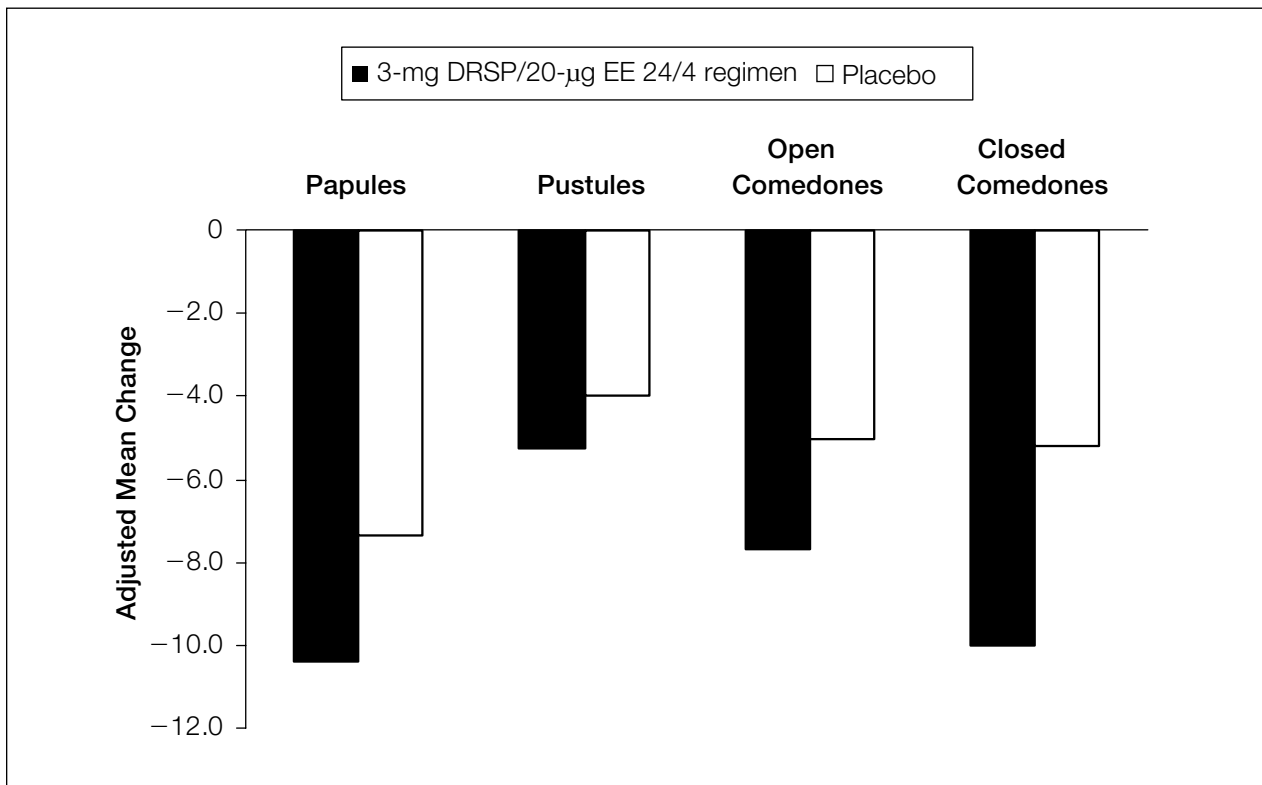
**Figure 1.** Flowchart of study participants. The number of participants who did not meet amended criteria includes participants who discontinued. A criterion for participants in the amended full analysis set was a minimum of 40 lesions, including 20 inflammatory and 20 noninflammatory lesions, in order to include only women with moderate acne vulgaris. The number of participants who discontinued treatment includes participants who did not meet amended criteria. Reasons for discontinuation classified as other include closure of enrollment, randomization error, sponsor decision, study drug noncompliance, participant moved/moving, and visit noncompliance. Reprinted from *Contraception*, Copyright 2008, with permission from Elsevier.<sup>12</sup>

nodule count remained essentially constant throughout the study and was low in both treatment groups.

From treatment cycle 3 to end point, the reduction in all inflammatory (papules, pustules, and nodules) and noninflammatory (open and closed

comedones) lesion counts was more pronounced in the 3-mg DRSP/20- $\mu$ g EE 24/4 regimen COC group than in the placebo group (Figures 3 and 4).

In addition, the odds ratio (OR) of participants having an improved assessment on the investigator's



**Figure 2.** Adjusted mean change from baseline to end point (visit 5 [cycle 6] data with missing values replaced using the last observation carried forward procedure) in lesion counts (papules, pustules, open and closed comedones)(amended full analysis set). *P* values show the difference between the 3-mg drospirenone (DRSP)/20-µg ethinyl estradiol (EE) 24-day active pill/4-day inert pill (24/4 regimen) combined oral contraceptive and placebo treatment groups (papules, *P* = .0002; pustules, *P* = .0119; open comedones, *P* = .0693; closed comedones, *P* = .0002). The rank analysis of variance for open comedones yielded *P* = .0012, as normality was rejected at an  $\alpha$  level of .05.

overall improvement rating scale was significantly greater with the 3-mg DRSP/20-µg EE 24/4 regimen COC (OR, 4.02; 95% CI [confidence interval], 2.29–7.31; *P* < .0001) compared with the placebo (Figure 5). Similarly, the OR of a participant rating her skin appearance on the participant's overall self-assessment rating scale as improved at end point was 2.82 (95% CI, 1.60–5.13; *P* = .0005) with the 3-mg DRSP/20-µg EE 24/4 regimen COC compared with the placebo (Figure 5).

The mean change in hormone levels by treatment from baseline to end point are presented in the Table. Between treatment groups, mean change from baseline to end point in serum hormone levels showed a statistically significant decrease in free testosterone levels (*P* = .0024) and a statistically significant increase in SHBG levels (*P* = .0022) in the 3-mg DRSP/20-µg EE 24/4 regimen COC group compared with the placebo group. There were no statistically significant changes between treatment groups in total testosterone, DHEAS, or androstenedione levels.

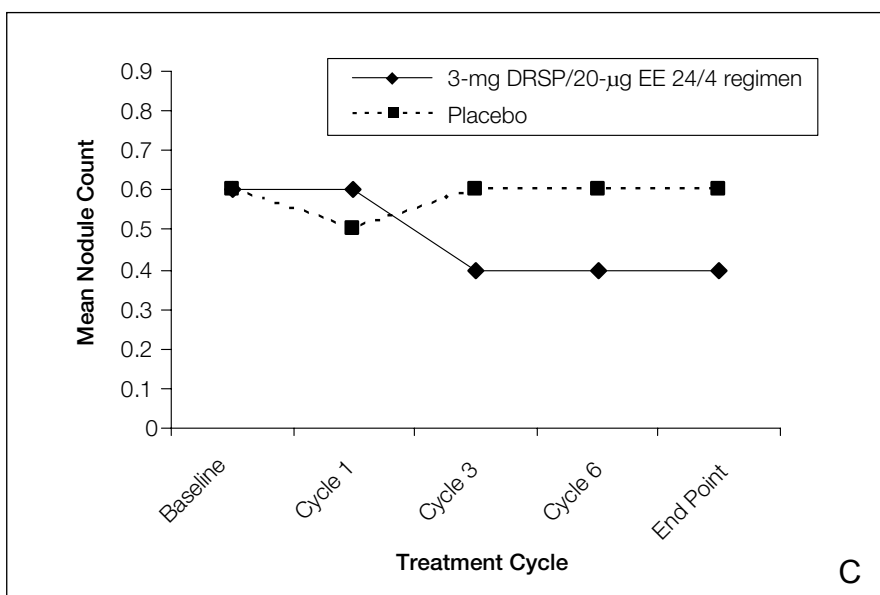
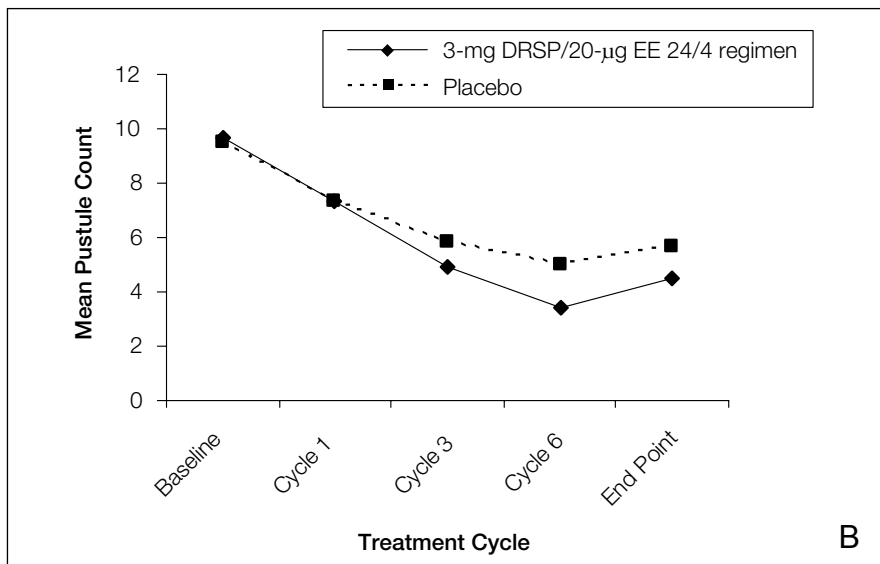
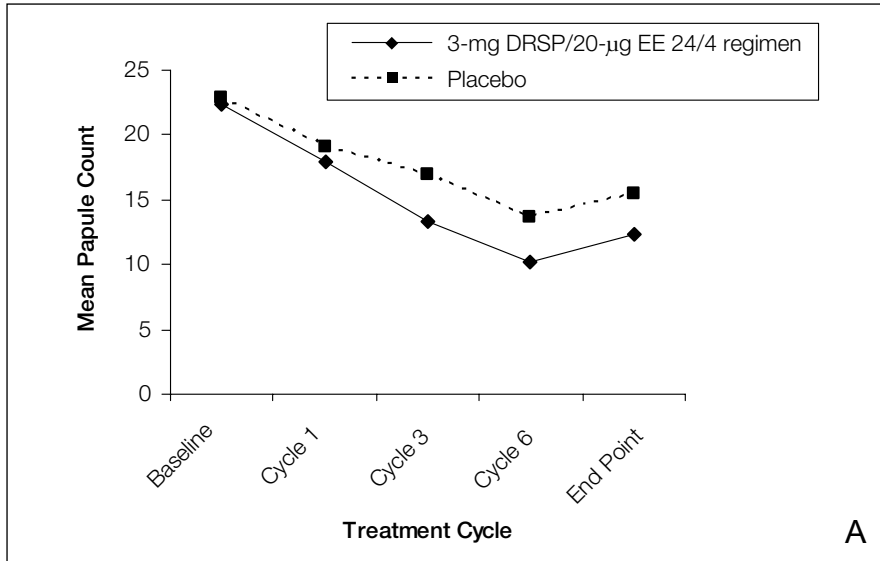
Results of the primary efficacy end points assessed in this study have been reported elsewhere.<sup>12</sup>

### Comment

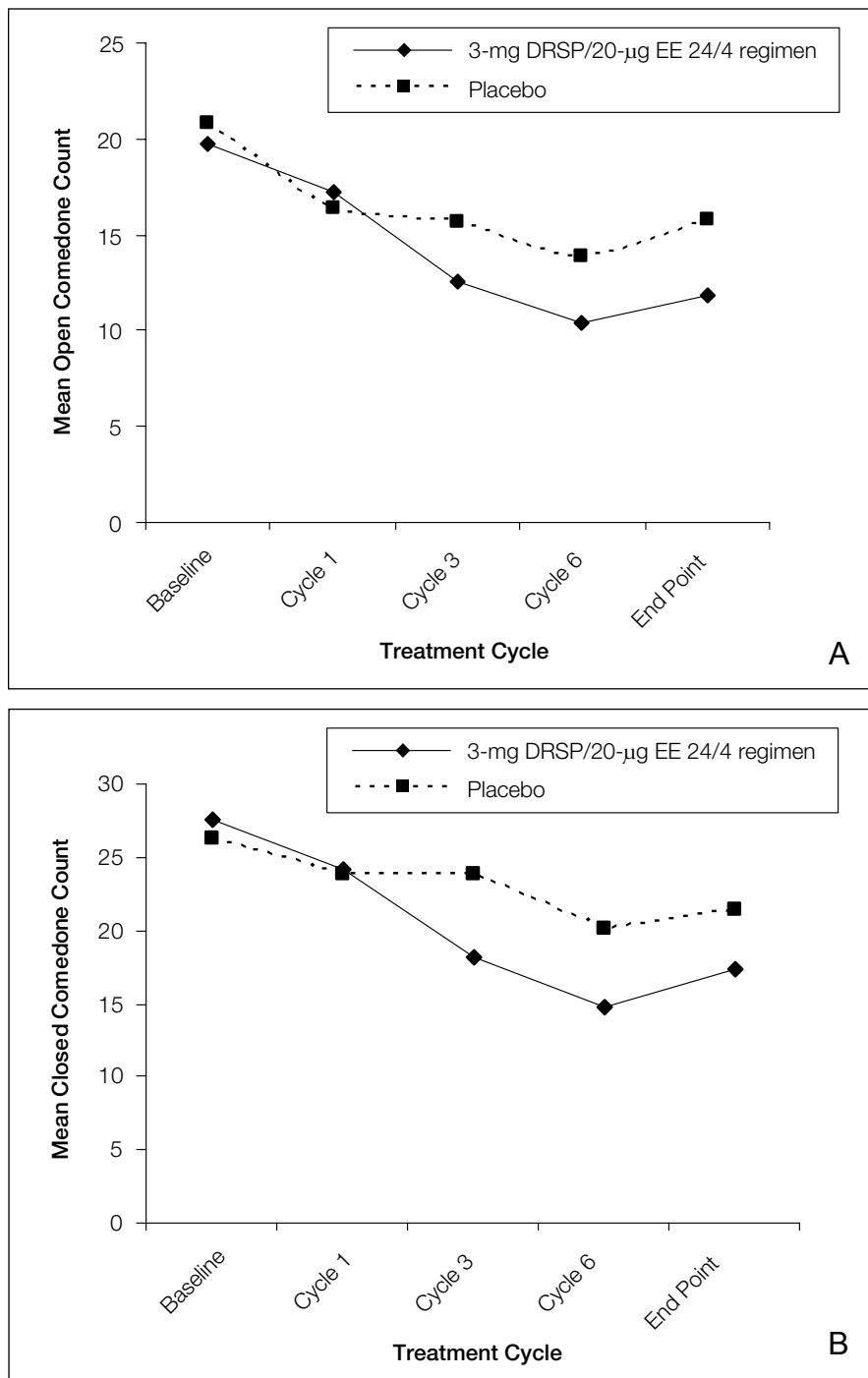
The results of this study showed that the novel COC comprising 3-mg DRSP/20-µg EE in a 24/4 regimen reduced acne lesion counts, partly reflecting the positive effects of EE on SHBG levels, the direct antiandrogenic properties of DRSP, and the reduction in free testosterone and androstenedione serum levels resulting from the inhibition of ovulation. Moreover, these changes were associated with meaningful clinical benefit as rated by both the investigators and participants. Results of the primary efficacy and safety end points assessed in this study have been described elsewhere.<sup>12</sup>

The mean nodule count remained essentially constant throughout the study and was low in both treatment groups. Because the aim of the study was to evaluate moderate acne, not severe acne, there were too few nodules to make any conclusions.

The favorable effects of the 3-mg DRSP/20-µg EE 24/4 regimen COC on acne are due to its antiandrogenic properties. Prior studies with other COCs also have shown a significantly greater reduction in acne lesion counts with active



**Figure 3.** Mean inflammatory lesion counts in the 3-mg drospirenone (DRSP)/20-µg ethinyl estradiol (EE) 24-day active pill/4-day inert pill (24/4 regimen) combined oral contraceptive and placebo treatment groups at baseline; treatment cycles 1, 3, and 6; and end point for papules (A), pustules (B), and nodules (C) (amended full analysis set). End point is treatment cycle 6 data with missing values replaced using the last observation carried forward procedure.

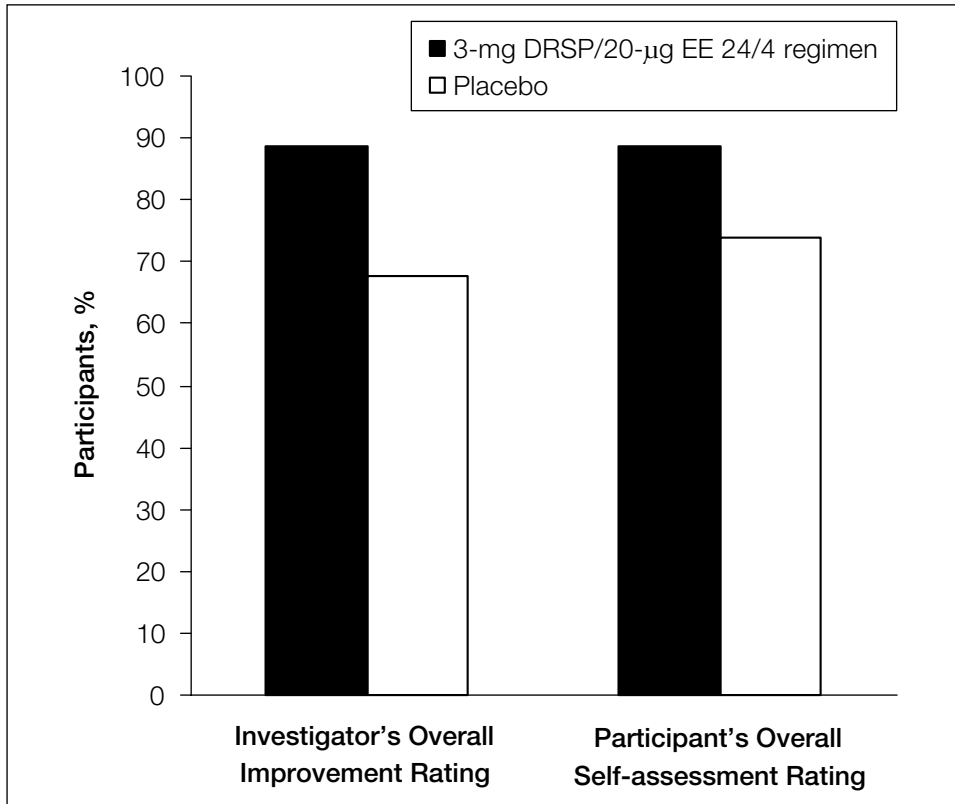


**Figure 4.** Mean noninflammatory lesion counts in the 3-mg drospirenone (DRSP)/20-µg ethinyl estradiol (EE) 24-day active pill/4-day inert pill (24/4 regimen) combined oral contraceptive and placebo treatment groups at baseline; treatment cycles 1, 3, and 6; and end point for open comedones (A) and closed comedones (B) (amended full analysis set). End point is treatment cycle 6 data with missing values replaced using the last observation carried forward procedure.

treatment compared with placebo ( $P < .05$ ).<sup>6,13,14</sup> The beneficial effects of these COCs on acne are due to their estrogen components, which, at best, counteract androgenic activity. The 3-mg DRSP/20-µg EE 24/4 regimen is the only low-dose COC available in the United States comprising a progestin with antiandrogenic properties. Moreover, the shortened hormone-free interval and 30-hour half-life of the 3-mg DRSP/20-µg EE 24/4 regimen COC results in continuous antimineralocorticoid

and antiandrogenic activities and reduced endogenous estradiol fluctuations throughout the treatment cycle.

Despite the high drop-out rate observed during the study, only a small proportion of participants discontinued study treatment because of adverse events (6.4% [17/266], 3-mg DRSP/20-µg EE 24/4 regimen COC group; 4.9% [13/268], placebo group). Other reasons for early discontinuations included withdrawal of consent and lost to follow-up.



**Figure 5.** Proportion of participants who had an improved assessment on the investigator's overall improvement and participant's overall self-assessment rating scales at end point (amended full analysis set). *P* values show the difference between the 3-mg drospirenone (DRSP)/20-µg ethinyl estradiol (EE) 24-day active pill/4-day inert pill (24/4 regimen) combined oral contraceptive and placebo treatment groups (investigator's overall improvement, *P* < .0001; participant's overall self-assessment, *P* = .0005).

### Mean Change in Serum Hormone Levels by Treatment From Baseline to End Point<sup>a</sup>

Treatment	Hormone	Baseline		End Point		<i>P</i> Value <sup>b</sup>
		<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)	
DRSP/EE ( <i>n</i> = 18)	Total testosterone	18	53.3 (21.7)	13	-16.0 (28.1)	.0625
	Free testosterone	18	1.4 (0.7)	13	-0.8 (0.6)	.0004
	DHEAS	18	195.8 (104.5)	13	-29.1 (81.72)	.2238
	Androstenedione	18	2.1 (0.9)	13	-0.4 (0.6)	.0298
	SHBG	18	45.6 (18.7)	13	114.8 (106.0)	.0021
Placebo ( <i>n</i> = 18)	Total testosterone	17	47.9 (18.6)	13	-5.8 (20.3)	.3197
	Free testosterone	17	1.6 (0.8)	13	0.2 (1.0)	.5764
	DHEAS	17	188.4 (94.2)	13	9.6 (54.4)	.5362
	Androstenedione	17	2.0 (0.8)	13	0.0 (1.0)	.8937
	SHBG	17	34.6 (12.1)	13	-0.2 (7.7)	.9434

Abbreviations: SD, standard deviation; DRSP, 3-mg drospirenone; EE, 20-µg ethinyl estradiol; DHEAS, dehydroepiandrosterone sulfate; SHBG, sex hormone-binding globulin.

<sup>a</sup>Baseline evaluations were performed at visit 2; end point was visit 5 (treatment cycle 6); data with missing values were replaced using the last observation carried forward procedure. No on-treatment data available for 4 participants in the 3-mg DRSP/20-µg EE 24/4 regimen combined oral contraceptive group and 3 participants in the placebo group.

<sup>b</sup>*P* value from a paired *t* test for a within-treatment comparison of means at baseline (visit 2) and treatment cycle 6 (or the early termination visit).

Similar to the present study, a placebo response has been observed in prior COC studies,<sup>6,14-16</sup> which could be attributed to several factors, including participants avoiding the use of comedogenic skin care products, as advised by the study protocol; increased attention to skin hygiene; and spontaneous improvement due to the fluctuating clinical course of the disease.

This study showed an increase in SHBG serum levels, with a simultaneous decline in free testosterone and androstenedione serum levels, as seen in prior COC studies.<sup>1,17,18</sup>

### Conclusion

Participants treated with the 3-mg DRSP/20- $\mu$ g EE 24/4 regimen had significantly greater decline in acne lesion counts than those treated with the placebo ( $P < .05$ ). In addition, the 3-mg DRSP/20- $\mu$ g EE 24/4 regimen COC significantly lowered serum levels of free testosterone ( $P = .0004$ ) and androstenedione ( $P = .0298$ ) and significantly increased SHBG levels ( $P = .0021$ ), with no significant changes in total testosterone or DHEAS levels. The 3-mg DRSP/20- $\mu$ g EE 24/4 regimen COC was considered an effective treatment of moderate acne vulgaris by investigators and participants.

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