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General Section

Hemostatic effects of two desogestrel-containing combined oral contraceptive regimens: a multinational, multicenter, randomized, open-label study

K. Peters[1], N. Gordon[2], N. Ricciotti[3], J. Hsieh[4], B. Howard[5], H. Weiss[6]

[1] Praxis for Gynecology, Obstetrics and Clinical Research, Hamburg (Germany)
[2] Maccabi-health Service, Haifa (Israel); [3] Teva Branded Pharmaceutical Products, R&D, Inc., Frazer, PA (USA)
[4] Teva Branded Pharmaceutical Products, R&D, Inc., Chester, PA (USA)
[5] Teva Global Medical Affairs, Frazer PA (USA); [6] Teva Global Medical Affairs, Petach Tikva (Israel)

Summary

Purpose of investigation: To compare the effects of desogestrel (DSG) 150 mcg/ethinyl estradiol (EE) 20 mcg for 21 days followed by either seven days of EE ten mcg (21/7-active) or no treatment (DSG/EE+no Tx) on hemostatic markers. *Materials and Methods:* This was a randomized, multicenter, open-label study that enrolled healthy premenopausal women. Non-inferiority of 21/7-active to DSG/EE+no Tx was determined if the upper limit of the two-sided 95% CI of the mean treatment difference in prothrombin fragment 1+2 (F1+2) over 24 weeks between groups was < 130 pmol/L. *Results:* 246 subjects (n=125, 21/7-active; n=121, DSG/EE+no Tx) comprised the primary analysis. Mean F1+2 levels increased in both 21/7-active and DSG/EE+no Tx regimens (least square [LS] mean changes +45 pmol/L and +56.8 pmol/L, respectively). LS mean treatment difference was -11.8 pmol/L (95% CI: -54.8, 31.2). *Conclusion:* The effect of adding EE ten mcg to the seven-day hormone-free interval of DSG/EE on F1+2 levels was non-inferior to traditional DSG/EE.

Key words: Combined oral contraception; Hemostasis; Coagulation; Desogestrel.

Introduction

Historically, the increased risk of venous thromboembolism (VTE) with use of combined oral contraceptives (COCs) was attributed to the high estrogen dose in COCs [1]. Estrogen is associated with increases in procoagulant and fibrinolytic activity, resulting in greater fibrin turnover [2,3]. This prothrombotic activity is supported by COC-induced increases in prothrombin fragment 1+2 (F1+2), D-dimer, plasminogen, and plasmin-antiplasmin complex, and decreases in tissue plasminogen activator [2, 3]. As the estrogen dose in COCs has decreased over time, observational studies have suggested differences in VTE risk among low-dose COCs (20-30 mcg ethinyl estradiol [EE]) combined with different synthetic progestins, with elevated risk among third- and fourth-generation progestins compared with second-generation progestins (eg, levonorgestrel) [4-8]. These COCs have been shown to induce variable changes in sensitivities to activated protein C (APC) and alterations in the anticoagulant protein S [2,9-11].

Adding low-dose estrogen during the traditional hormone-free interval (HFI) may improve efficacy and tolerability by increasing ovarian suppression and improving hormone withdrawal symptoms and cycle control [12-16]. One such COC regimen contains desogestrel (DSG) 150 mcg and EE 20 mcg for 21 days, followed by EE ten mcg for seven days (21/7-active regimen). The efficacy and safety of the 21/7-active regimen in pregnancy prevention were demonstrated in a previous six-month, phase 3 study [17].

The European Medicines Agency (EMA) recommends that all novel steroid contraceptives should be evaluated for the pharmacological effects of therapy on various potential markers of VTE risk, preferably in comparison to a comparator with an established VTE risk profile [18]. While effects of traditional 21/7-day dosing regimens containing DSG on hemostatic variables have been previously reported [9, 11, 19], it is currently unknown what effect, if any, adding low-dose estrogen during the HFI will have on these parameters.

Metabolic profiles in phase 2 study of two 21/7 oral contraceptive regimens (±7 hormone-free days). *F. Baro, H. Weiss, K. Peters, N. Ricciotti. Presented at ACOG, April 26-30, 2014, Chicago, IL (USA). Obstet. Gynecol., 2014, 123(5 suppl 1), 104S.*

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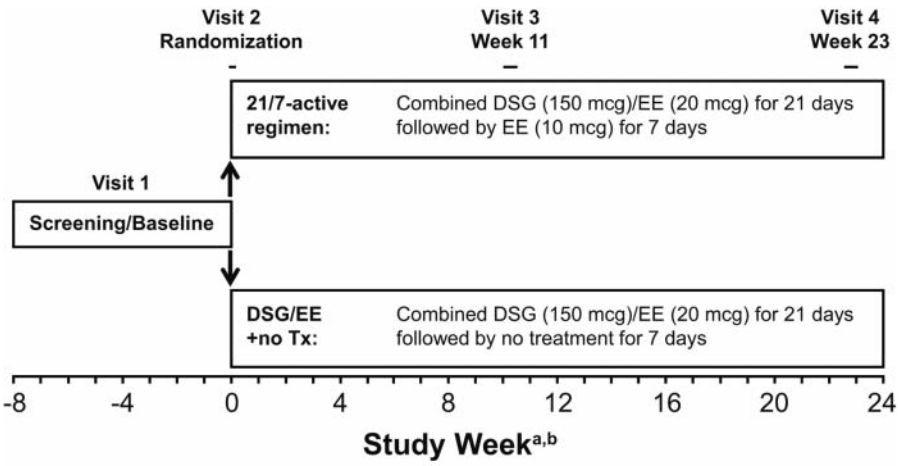

Figure 1. — Study flow diagram. [a] Fasting blood samples were obtained at Visits 2, 3, and 4 for determination of hemostatic parameters. [b] A final telephone contact was performed approximately 14 days after the last dose for all subjects who took at least one dose of study medication.

Therefore, the objective of this study was to compare the treatment effect on various hemostatic and coagulation markers of the following two DSG-containing COCs: 1) 21 days of DSG/EE with seven days of EE; and 2) 21 days of DSG/EE with seven days of no treatment.

Materials and Methods

Study design and population

This randomized, multicenter, multinational, open-label trial was conducted at 21 European centers and five Israeli centers from October 25, 2011, until September 13, 2012 (ClinicalTrials.gov identifier: NCT01388491). The study protocol was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline as currently amended and was approved by an Institutional Review Board at each study site. Written informed consent was obtained from each patient before any study procedures were performed.

Eligible subjects included premenopausal women aged 18-40 years with a body mass index (BMI) ≥ 18 and ≤ 30 kg/m^2 and regular menstrual cycles, with one spontaneous cycle occurring prior to or concurrent with the screening period. Subjects with any condition contraindicating COC use (eg, thromboembolic disorders or known or suspected clotting disorders, cerebrovascular or coronary artery disease, diabetes mellitus, uncontrolled or untreated hypertension) were excluded, as were women with a history of VTE, arterial thromboembolism, or a family history of VTE at age ≤ 40. Women who were pregnant, breastfeeding within two months before screening, postpartum or post-abortion for $\leq$ two months before screening, smokers ≥ 35 years of age, or using concomitant sex hormones (estrogens, progestins, androgens) were also excluded. Participants at risk of pregnancy must have been willing to use an effective method of non-hormonal contraception throughout the last dose of study drug.

Study design and procedures

The study consisted of a screening period of approximately four to eight weeks, a 24-week open-label treatment period with scheduled laboratory assessments, and a posttreatment period of approximately two weeks (Figure 1). Women meeting eligibility criteria at screening underwent baseline laboratory evaluations. At Visit 2, eligible participants were randomized to receive treatment in a 1:1 ratio using an interactive response allocation system at each site. Treatment 1 consisted of combined DSG 150 mcg/EE 20 mcg for 21 days followed by EE ten mcg for seven days (21/7-active regimen). Treatment 2 consisted of combined DSG 150 mcg/EE 20 mcg for 21 days followed by no treatment for seven days (DSG/EE+no Tx). Women assigned to the 21/7-active regimen were instructed to take one pill daily starting on the first day of menses following the randomization visit (first-day start) or on the first Sunday following the first day of menses (Sunday start). Women randomized to DSG/EE+no Tx were instructed to begin treatment using first-day start (per product label) for the first 21 days of each 28-day cycle, with a seven-day period in each 28-day cycle when the participants did not take any pills. All participants were instructed to take each pill at approximately the same time each day. Adherence with study drug was assessed by telephone calls to participants during each seven-day EE or no-pill interval, along with pill counts at scheduled study visits.

Efficacy assessments

The primary efficacy measure was the mean change from baseline in F1+2 levels in the per-protocol (PP) population over the 24-week treatment period. The PP population was defined as all randomized women who received at least one dose of study drug and completed both baseline and ≥ 1 postbaseline measurements of F1+2 before experiencing any major protocol violations. Secondary assessments included D-dimer, activated partial thromboplastin time (aPTT)-based APC resistance, antithrombin, protein C, total protein S, and sex hormone–binding globulin (SHBG). All clinical laboratory tests were performed by a central laboratory, with the exception of urine pregnancy tests, which were performed locally. For hemostatic laboratory tests, the subjects were instructed to fast and refrain from moderate to vigorous exercise prior to the sample collection. Investigators were directed to collect blood samples for hemostatic laboratory parameters at approximately the same time of day as the first collection. Safety was assessed by recording adverse events (AEs), clinical laboratory test results, bleeding and spotting, and vital signs. The safety population was defined as all randomized women who took $\geq$ one dose of study drug.

Statistical analysis

The study was designed to enroll approximately 240 women to ensure that 126 women (63/group) would be included in the efficacy analysis, which would achieve a power of 80% for the primary assessment. The mean change from baseline in F1+2 levels over 24 weeks was analyzed using a repeated measures analysis of covariance (ANCOVA) adjusted for baseline, treatment, visit,

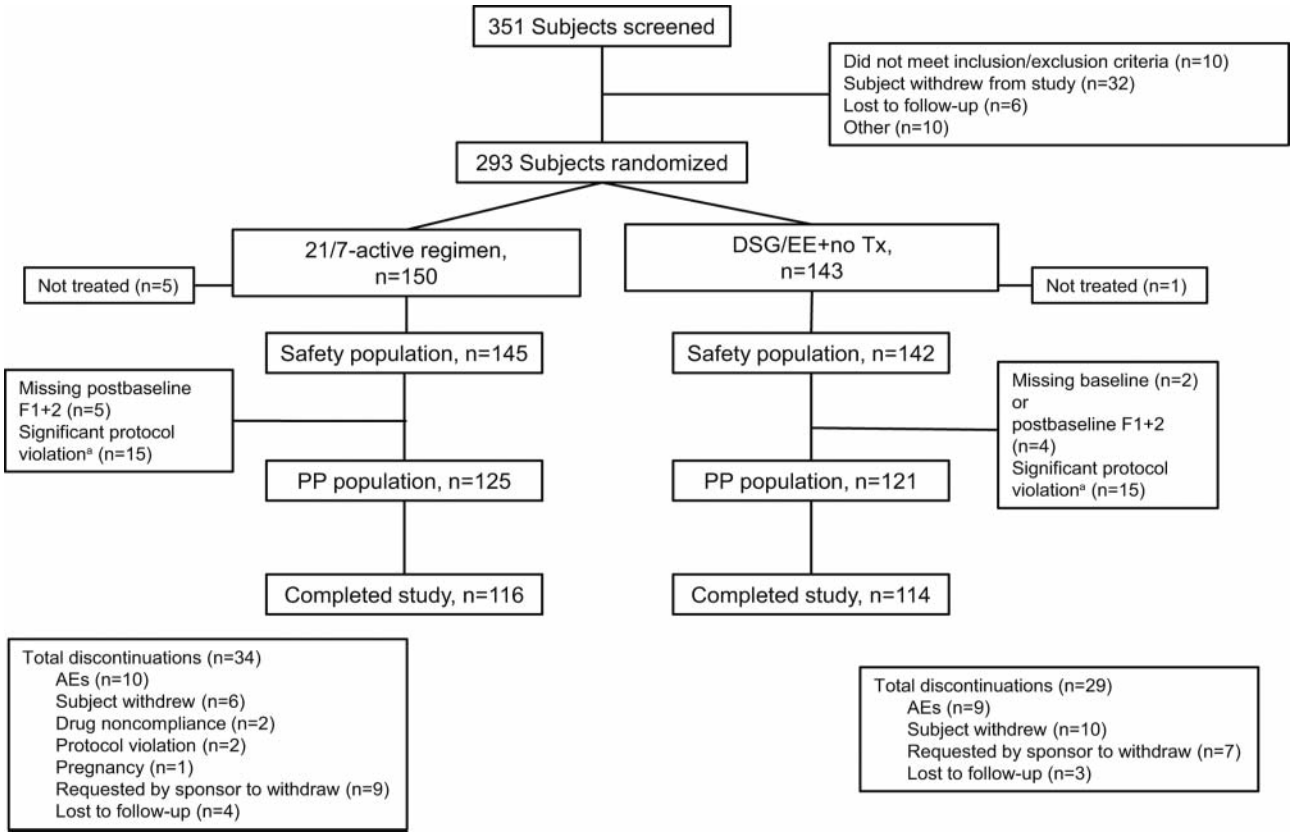

Figure 2. — Subject disposition by treatment group. [a] Significant protocol violations did not always result in study discontinuation. Subjects with significant protocol violations were included in the PP analyses until the protocol violation occurred.

and treatment-by-visit interaction. Based on a previous analysis of hemostatic variables in women treated with third-generation COCs [2], non-inferiority of the 21/7-active regimen to DSG/EE+no Tx would be demonstrated if the upper limit of the two-sided 95% confidence interval (CI) of the difference in mean change between treatments (21/7-active regimen – DSG/EE+no Tx) was < 130 pmol/L. Assuming a mean increase of 200 pmol/L in prothrombin F1+2 over six months for the active control and assuming a standard deviation of 300, preserving 33% of the effect of the active control results in a non-inferiority margin of 130. Secondary hemostatic endpoints were also analyzed as previously described using repeated measures. Safety assessments were summarized using descriptive statistics.

Results

Of the 351 women screened, 293 were enrolled, and a total of 230 completed the study (Figure 2). There was one withdrawal due to pregnancy in the 21/7-active group. The safety population included 287 subjects (n=145, 21/7-active; n=142, DSG/EE+no Tx), and of these, 246 women (n=125, 21/7-active; n=121, DSG/EE+no Tx) were included in the PP analysis. Demographic and baseline characteristics were generally comparable between treatment groups; 33% (95/287) of women were classified as current smokers (Table 1). Mean baseline F1+2 levels were within

Table 1. — *Demographics and baseline characteristics.*

	21/7-active regimen (n=145)	DSG/EE+ no Tx (n=142)
Age, years, mean±SD	26.4 ± 5.0	27.0 ± 5.3
Weight, kg, mean±SD	61.6 ± 10.4	60.1 ± 9.4
Height, cm, mean±SD	164.1 ± 6.0	163.7 ± 5.8
BMI, kg/m^2, mean±SD	22.9 ± 3.6	22.4 ± 3.1
Race, n (%)		
White	140 (97)	136 (96)
Black	1 (< 1)	1 (< 1)
Asian	0	1 (< 1)
American Indian or Alaskan Native	0	1 (< 1)
Other	4 (3)	3 (2)
Hormone contraceptive history, n (%)		
Prior user	102 (70)	99 (70)
New starter	43 (30)	43 (30)
Smoking history, n (%)		
Never	88 (61)	81 (57)
Former	9 (6)	14 (10)
Current	48 (33)	47 (33)
F1+2, pmol/L		
Mean ± SD	206.8±256.5	213±266.3
Median (range)	136 (20, 1200)	134 (20, 1200)

BMI: body mass index; DSG: desogestrel; EE: ethinyl estradiol; SD: standard deviation; Tx: treatment.

Table 2. — *Effect of treatment on hemostatic parameters in PP population from baseline over 24 weeks.*

	21/7-active regimen (n=125)		DSG/EE+no Tx (n=121)		
Parameter (normal range)	Baseline mean ± SE	LS mean change ± SEM	Baseline mean ± SE	LS mean change ± SEM	LS mean difference (95% CI)
F1+2 (pmol/L) (41-372 pmol/L)	n=125 206.8 ± 22.9	n=125 45.0 ± 15.2	n=121 213 ± 24.2	n=121 56.8 ± 15.6	-11.8 (-54.8, 31.2)
D-dimer (mcg/L) (0-729 mcg/L)	n=119 233.5 ± 10.2	n=118 16.4 ± 10.3	n=116 218.8 ± 6.7	n=114 13.4 ± 10.5	3.0 (-26.0, 31.9)
aPTT-based APC-R (2.00-3.36)	n=124 2.7 ± 0.05	n=124 -0.3 ± 0.02	n=120 2.8 ± 0.05	n=120 -0.4 ± 0.02	0.1 (0.0, 0.14)
Antithrombin (%) (75%-130%)	n=124 101.8 ± 1.3	n=124 -1.6 ± 1.2	n=121 100.9 ± 1.2	n=121 -3.2 ± 1.2	1.6 (-1.7, 4.9)
Protein C (activity [%]) (70%-180%)	n=124 110.9 ± 2.4	n=124 16.3 ± 1.9	n=121 112.4 ± 2.8	n=121 13.0 ± 1.9	3.2 (-2.1, 8.6)
Protein S (total antigen [%]) (50%-147%)	n=124 85.0 ± 1.4	n=124 -11.4 ± 1.1	n=121 83.7 ± 1.5	n=121 -6.6 ± 1.1	-4.8 (-7.9, -1.8)
SHBG (nmol/L) (28-146 nmol/L)	n=125 76.7 ± 5.4	n=125 163.4 ± 7.3	n=120 73.8 ± 3.4	n=120 149.1 ± 7.5	14.3 (-6.3, 34.8)

APC-R: activated protein C resistance; aPTT: activated partial thromboplastin time; DSG: desogestrel; EE: ethinyl estradiol; LS: least squares; PP: per protocol; SE: standard error; SEM: standard error of the mean; SHBG: sex hormone-binding globulin; TX: treatment.

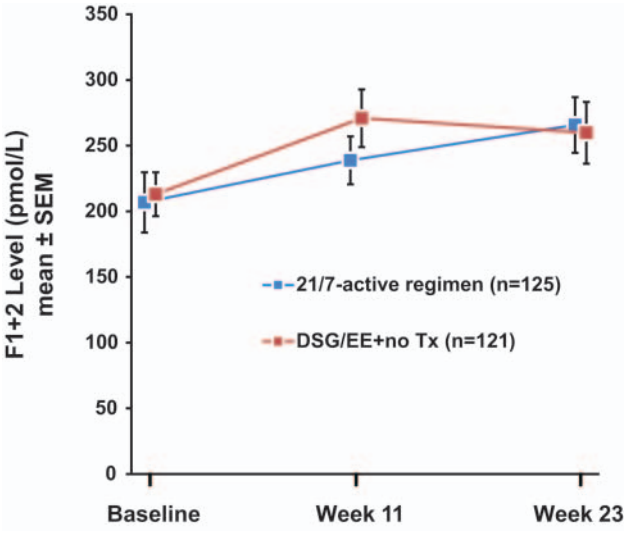

Figure 3. — Effect of treatment on F1+2 levels. No statistically significant differences between treatment groups were observed. (The points are offset slightly for clarity).

normal range (41-372 pmol/L) for both groups. Of the participants who received treatment, 82% (119/145) were ≥ 80% adherent for the 21/7-active regimen and 73% (104/142) were ≥ 80% adherent for DSG/EE+no Tx.

Primary efficacy

Over 24 weeks of treatment, the mean change in F1+2 levels from baseline in the PP population increased in both the 21/7-active regimen and DSG/EE+no Tx (least square [LS] mean changes of +45.0 pmol/L and +56.8 pmol/L, respectively), with mean values remaining within normal range.

Table 3. — *TEAEs occurring in ≥ 5% of subjects in either treatment group.*

	21/7-active regimen (n=145)	DSG/EE+ no Tx (n=142)
Subjects with ≥ 1 TEAE, n (%)	97 (67)	80 (56)
Metrorrhagia	50 (34)	28 (20)
Alpha globulin increased	11 (8)	8 (6)
Prothrombin level increased	8 (6)	7 (5)
Headache	9 (6)	16 (11)
Dysmenorrhea	4 (3)	7 (5)

DSG: desogestrel; EE: ethinyl estradiol;
TEAE: treatment-emergent adverse event; Tx: treatment.

The LS mean difference between treatments was -11.8 pmol/L (95% CI: -54.8, 31.2) (Table 2), demonstrating non-inferiority of the 21/7-active regimen to DSG/EE+no Tx, as the predefined upper limit of the two-sided 95% CI was < 130 pmol. Specific mean F1+2 levels assessed at week 11 and week 23 are reported for each group (Figure 3).

Secondary efficacy

Secondary hemostatic efficacy variables increased or decreased in the same direction for both treatment groups (Table 2) over the 24-week treatment period, with mean values remaining within normal range. Mean D-dimer values increased similarly in both treatment groups. Increases in APC resistance, as assessed by reductions in the aPTT-based APC resistance test, were observed in both treatment groups, with greater decreases in DSG/EE+no Tx compared with the 21/7-active regimen. Anticoagulatory protein C activity increased in both groups, while total protein S and antithrombin values decreased in both groups. While

the decrease in protein S was greater in those receiving the 21/7-active regimen compared with DSG/EE+no Tx, the values remained within normal range.

There were also notable, yet comparable, increases in the endocrine marker SHBG for both groups over the 24-week treatment period; mean values were above the upper limit of normal compared with baseline values (212% and 202% for 21/7-active and DSG/EE+no Tx, respectively).

Safety

The majority of subjects in the safety analysis set completed at least five cycles of treatment. Treatment-emergent AEs (TEAEs) were reported in 67% (97/145) of subjects who received the 21/7-active regimen and 56% (80/142) of subjects who received DSG/EE+no Tx (Table 3). Most AEs were mild or moderate in severity (54% [78/145] mild and 12% [18/145] moderate for 21/7-active and 35% [49/142] mild and 19% [27/142] moderate for DSG/EE+no Tx). The most frequently reported TEAEs were metrorrhagia (34% for 21/7-active; 20% for DSG/EE+no Tx) and headache (6% for 21/7-active; 11% for DSG/EE+no Tx). There were no deaths or thromboembolic events during the study. One serious AE (appendicitis) occurred in DSG/EE+no Tx but was not considered related to treatment by the study investigator. Discontinuations due to AEs occurred in ten subjects in the 21/7-active regimen and in nine subjects in DSG/EE+no Tx. The most frequent reasons for withdrawals due to AEs were metrorrhagia (n=3, 21/7-active), weight increased (n=2 each, 21/7-active and DSG/EE+no Tx), nausea (n=1, 21/7-active; n=2, DSG/EE+no Tx), and acne (n=2, 21/7-active). There were no clinically meaningful trends in mean changes from baseline for any laboratory variable or vital sign. Mean numbers of bleeding or spotting days (withdrawal or breakthrough bleeding) during cycle 1 were comparable between treatment groups (12.7 days, 21/7-active; 11.2 days, DSG/EE+no Tx) and were stable and comparable in subsequent cycles in both groups (approximately five to six days).

Discussion

COC use can alter a wide variety of biological markers involved in procoagulatory, anticoagulatory, and fibrinolytic pathways [2, 9-11,18]. The present study was designed to investigate the effects of the 21/7-active regimen with those of 21/7 DSG/EE+no Tx on various markers of hemostasis and coagulation. Increases in F1+2 levels over the 24-week treatment period occurred in both groups (+45.0 pmol/L, 21/7-active regimen; +56.8 pmol/L, DSG/EE+no Tx); the increase in the 21/7-active regimen was found to be similar to the increase in DSG/EE+no Tx (primary endpoint). Secondary hemostatic measures increased or decreased in the same direction for both treatment groups, with no clear emergent patterns between the groups.

In general, the alterations in hemostatic markers reported in this analysis are in line with those of previously conducted smaller analyses of COCs containing third-generation progestins, including DSG [8, 9, 11, 19]. Significant reductions in protein S have been reported with DSG-containing COCs [8, 9, 11]. Based on the APC resistance test used, protein S has been shown to correspond with APC resistance among various COCs [11].

In addition to alterations in hemostatic markers from the present analysis, large increases (> 200%) in SHBG levels were noted with both the 21/7-active regimen and DSG/EE+no Tx. SHBG levels provide an assessment of the total estrogenicity associated with COCs and may be an additional surrogate marker for VTE risk [20, 21]. Although not associated with increased VTE risk among non-hormonal contraceptive users [22], observational studies have shown associations between increasing SHBG levels and increasing VTE risk among various COCs, and increased APC resistance [20, 21]. Odlind *et al.* reported a 200%-300% increase in SHBG levels among users of COCs containing DSG or another third-generation progestin, gestodene [20].

The most common AEs reported (metrorrhagia, headache, dysmenorrhea) were generally consistent with the known safety profiles of other COCs, with the exception of the rate of metrorrhagia, which was somewhat higher than the rate of metrorrhagia from a previous large study of a DSG-containing COC [23]. This may, however, be a result of the study duration being < one year and the relatively small number of subjects.

Both DSG regimens were well-tolerated in the present study; there were no deaths or VTEs. Studies have linked both estrogen and progestin components of COCs to the increased VTE risk associated with their use [4-8]. Although the risk with current COCs is low (between five and 12 cases/10,000 COC users) [24], COCs containing third-generation progestins, including DSG, are associated with approximately twice the VTE risk than those containing the second-generation progestin levonorgestrel [4, 5, 7, 8]. Since 2005, regulatory authorities have required clinical programs for COCs to investigate their treatment effects on biologic variables that may be related to VTE risk, including those studied in this analysis [18]. In 2014, the EMA completed a review of the VTE risk associated with combined hormonal contraceptives, including third- and fourth-generation COCs. The agency concluded that overall VTE risk for all combined hormonal contraceptives is small and benefits of their use in preventing unwanted pregnancy continue to outweigh risks [24].

The 21/7-active COC is a regimen that contains EE ten mcg during the traditional seven-day HFI. Adding low-dose EE during the HFI is thought to enhance ovulation suppression, providing less risk of escape ovulation and improved tolerability [12, 16]. Ovulation inhibition data

from a randomized, open-label study demonstrated similar effective hormonal suppression with the 21/7-active regimen to that of two commercially available regimens including a 21/7 and extended-COC regimen with a shortened HFI (24/4) [25]. Common symptoms, including headache, have been reported among COC users during the traditional HFI [16]. The reported rate of headache in the present analysis was less in the 21/7-active group (6%) than in the DSG/EE+no Tx group (11%); however, additional prospective analyses are required to better evaluate the effects of the 21/7-active regimen on tolerability.

This large, multicenter, randomized non-inferiority study assessed the effects of two DSG-containing COC regimens on a variety of hemostatic measures and SHBG. Although these biomarkers are thought to be related to VTE risk in women treated with COCs, there are no validated surrogate markers that can predict VTE outcomes in COC users [26], which is a limitation of the study. The lack of a placebo and/or comparator arm containing a different progestin could also be considered a limitation to the present analysis and inclusion would have added insight; however, this study's goal was to examine the effect of the added estrogen component in the 21/7-active regimen. Additional influences of circadian and seasonal variations on hemostatic variables [27, 28] were not specifically addressed in the current study design, although blood samples were collected at approximately the same time of day from each subject to help decrease the within-subject variability. Of note, 33% of participants in each treatment group were current smokers, and smoke exposure can also induce alterations in hemostasis through various mechanisms leading to a prothrombotic state [29]. Finally, because of COCs' vast impact on the coagulation-fibrinolysis cascade, there is therefore a need to further examine the complex associations between COCs and VTE risk, including during large, randomized trials that contain both hemostatic markers and clinical VTE endpoints.

Conclusion

The change in F1+2 levels over 24 weeks of treatment with DSG/EE for 21 days, followed by low-dose EE for seven days, was non-inferior to that of DSG/EE for 21 days, followed by a seven-day HFI. Additional changes in several other hemostatic variables occurred in both treatment groups, with no clear emergent trends between groups. Both treatments were generally safe and well-tolerated in a population of healthy, reproductive-age women. Based on these results, which used surrogate endpoints, no greater VTE risk would be expected with use of the novel DSG/EE regimen compared with the traditional 21/7 dosing regimen. Further analysis of VTE outcomes associated with use of the 21/7-active regimen is needed to support these findings.

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Address reprint requests to:
K. PETERS, M.D.
Praxis for Gynecology
Obstetrics and Clinical Research
Berner Heerweg 157
22159 Hamburg (Germany)
e-mail: klaus@dr-peters.net