

# Multinational, multicentre, randomised, open-label study evaluating the impact of a 91-day extended regimen combined oral contraceptive, compared with two 28-day traditional combined oral contraceptives, on haemostatic parameters in healthy women

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**ABSTRACT** **Objectives** To evaluate the impact of a 91-day extended regimen combined oral contraceptive (150 µg levonorgestrel [LNG]/30 µg ethinylestradiol [EE] for 84 days, followed by 10 µg EE for seven days [Treatment 1]) compared with two traditional 21/7 regimens (21 days 150 µg LNG/30 µg EE [Treatment 2] or 150 µg desogestrel [DSG]/30 µg EE [Treatment 3], both with seven days' hormone free), on several coagulation factors and thrombin formation markers.

**Methods** Randomised, open-label, parallel-group comparative study involving healthy women (18–40 years). The primary endpoint was change from baseline in prothrombin fragment 1 + 2 (F1 + 2) levels over six months.

**Results** A total of 187 subjects were included in the primary analysis. In all groups, mean F1 + 2 values were elevated after six months of treatment. Changes were comparable between Treatments 1 and 2 (least squares mean change: 170 pmol/L and 158 pmol/L, respectively) but noticeably larger after Treatment 3 (least squares mean change: 592 pmol/L). The haemo-

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static effects of Treatment 1 were comparable to those of Treatment 2 and noninferior to those of Treatment 3 (lower limit of 95% confidence interval  $[-18.3 \text{ pmol/L}] > -130 \text{ pmol/L}$ ).

**Conclusions** The LNG/EE regimens had similar effects on F1 + 2. Noninferiority was demonstrated between extended regimen LNG/EE and DSG/EE.

**KEY WORDS** Coagulation; Combined oral contraceptives; Desogestrel; Haemostatic; Levonorgestrel

## INTRODUCTION

Treatment with combined oral contraceptives (COCs) is associated with an increased risk of venous thromboembolism (VTE) caused by changes in the procoagulant, anticoagulant, and fibrinolytic pathways of blood coagulation<sup>1</sup>. The increase in both procoagulatory and fibrinolytic activity observed during treatment with most COCs indicates a shift of the equilibrium between coagulation and fibrinolysis to a higher level of fibrin turnover. These changes have been attributed to the effects of the oestrogen component, particularly on fibrinogen, factor VII, antithrombin, protein S, plasminogen and tissue plasminogen activator (t-PA). The higher level of fibrin turnover leads to an enhanced formation of prothrombin fragments 1 + 2 (F1 + 2) and D-dimers, as well as thrombin-antithrombin complex and plasmin-antiplasmin complex<sup>2</sup>.

Historically, the link between COCs and VTE has depended on the dose of the oestrogen component (typically supplied as ethinylestradiol [EE]). However, evidence suggests that the incidence of VTE with low-dose COCs varies with the type of progestin and it appears to be up to two-fold lower for pills containing second-generation progestins like levonorgestrel (LNG) than for those releasing third-generation progestins such as desogestrel (DSG) and gestodene<sup>1,3-6</sup>. COCs containing different progestin induce different sensitivities to activated protein C, which may account for the variation in thrombotic risk among COC formulations<sup>7,8</sup>. Women on the lowest combined dose of LNG and EE tend to be less affected by adverse changes in coagulation variables than users of other COC preparations<sup>9</sup>.

The risk of VTE has been reported to be highest in the first months of COC use, as the most dramatic changes in haemostatic indices are observed during the first cycle of exposure<sup>10</sup>. Prolonged duration of COC use does not impact VTE risk, which is immediate,

reversible, noncumulative, and rapidly decreases within three months after stopping<sup>11,12</sup>.

The 91-day extended regimen consists of 150 µg LNG and 30 µg EE for 84 days, followed by seven days of 10 µg of EE in place of placebo or no treatment. This COC is a modification of the traditional 21/7 regimen in which the number of days of combined active tablets administered is increased, resulting in fewer scheduled withdrawal bleeding episodes per year. Certain data suggest that two-thirds of women would choose to have a menstrual period every three months or less<sup>13</sup>; therefore, a regimen associated with fewer withdrawal bleeding episodes may also be favoured by many women. Fewer hormone-free intervals (HFIs) should lead to a reduction in the occurrence of common hormone withdrawal symptoms associated with 21/7 regimens, such as breast tenderness and bloating<sup>14</sup>. Extended regimen COCs may also be used to treat conditions such as endometriosis and dysmenorrhoea<sup>14</sup>. Further, addition of low-dose oestrogen to an extended regimen COC during the HFI improves bleeding profiles while still providing effective prevention of pregnancy<sup>15</sup>.

Although the FDA-approved 91-day COC Seasonique® (Teva Branded Pharmaceutical Products R&D, Inc., Frazer, PA) has been available in the United States since 2006 and in Canada since 2010, no formal study has investigated its effect on haemostatic parameters. To address this need, we initiated a randomised, open-label, parallel-group study to compare the impact of Seasonique® on several coagulation factors and markers of thrombin formation with those of two traditional 21/7-day regimen COCs.

## METHODS

This was a multinational, multicentre, open-label, randomised trial designed to evaluate the haemostatic effects of three COC regimens in women of

child-bearing age. The study was conducted between 23 November 2010 and 2 December 2011, at 22 centres in the United States and three in Italy.

The study was designed to randomise approximately 240 subjects to ensure that approximately 189 would complete six months of treatment. Eligible participants were healthy, premenopausal women aged 18 to 40 years, neither pregnant nor lactating, with a body mass index  $\geq 18$  kg/m<sup>2</sup> and  $< 32$  kg/m<sup>2</sup>. It was required that they should have had one spontaneous menstrual cycle with a duration of 23 to 35 days prior to the screening visit. Participants also agreed to use a non-hormonal, back-up method of contraception (e.g., condom, spermicidal foam, or contraceptive sponge) from the time of consent through the first seven days of study medication use and in situations where two or more tablets in a row were missed. The use of a nonhormonal method of contraception was also required in conjunction with the COC during and seven days after the use of drugs known to interact with COCs. Exclusion criteria included conditions contraindicating the use of COCs; the concomitant use of sex steroids (other hormonal medications, such as L-thyroxine, were allowed); a personal history of or current deep vein thrombosis (DVT), pulmonary embolism, or arterial thromboembolic disease; a genetically determined thrombophilia (including Factor V Leiden mutation, prothrombin mutation, protein C deficiency, protein S deficiency, or antithrombin III

deficiency); a family history of venous thromboembolic event at age 40 or younger in a parent or sibling; and a history of abortion or delivery less than six months before screening.

Subjects who met the eligibility criteria at the screening visit underwent baseline laboratory evaluations. With the exception of urine pregnancy tests, all clinical laboratory evaluations (blood tests, urinalysis, and Pap smear) were performed by ACM Global Central Laboratory (ACM), the central laboratory. ACM provided each site with a copy of the laboratory normal ranges for the study. Those who continued to meet eligibility criteria at the randomisation visit (Visit 2) were then randomly allocated in a 1:1:1 ratio to one of the three open-label treatment groups: the 91-day LNG/EE regimen previously defined (Treatment 1) and two traditional 21/7-day regimen COCs, namely, 21 days' 150 µg LNG/30 µg EE followed by seven days of no treatment (Treatment 2) and 21 days' 150 µg DSG/30 µg EE followed by seven days of no treatment (Treatment 3). In each of the three groups treatment was to last approximately six months. The overall duration of participation for all subjects was approximately eight months, which included a four-to-eight week screening/washout period, four study visits, and a two-week follow-up period (Figure 1).

Participants randomised to Treatment 1 took the first dose on the Sunday following the first day of their menstrual bleeding after the randomisation visit and

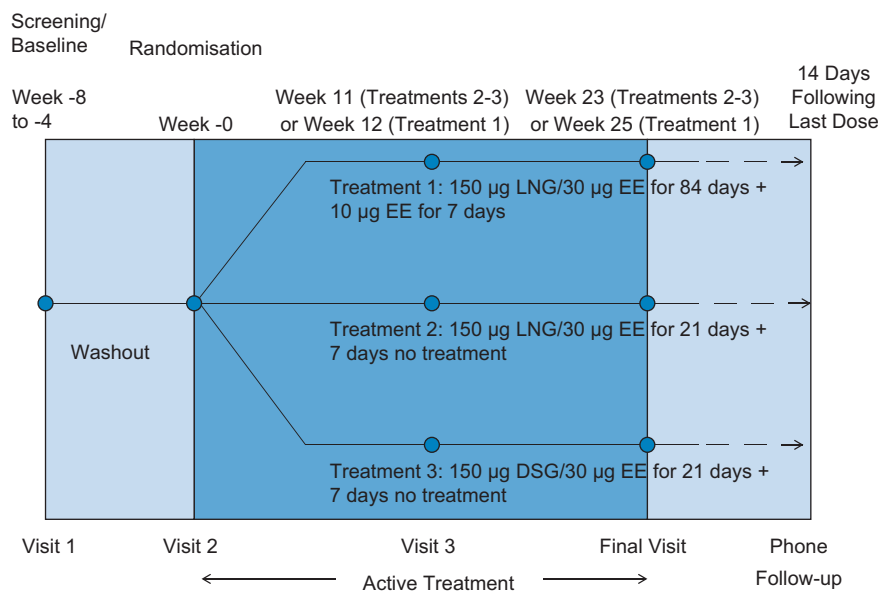


Figure 1 Study design. DSG, desogestrel; EE, ethinylestradiol; LNG, levonorgestrel.

continued taking one tablet daily at approximately the same time for 26 consecutive weeks. Subjects assigned to Treatment 2 or Treatment 3 started taking the COC on the first day of their menses following the randomisation visit and continued to take it daily at approximately the same time for the first 21 days of each 28-day cycle.

### Study endpoints and statistical methods

The primary study endpoint was the change from baseline in prothrombin F1 + 2 levels over the six-month treatment period for the per-protocol (PP) population. The PP population included all participants who had both a baseline and at least one post-baseline measurement of F1 + 2 obtained prior to major protocol violations, if any. Changes from baseline in prothrombin F1 + 2 levels were analysed using a repeated measures analysis of covariance (ANCOVA) with covariate adjustment for baseline, treatment, month, and the treatment by month interaction. Estimated treatment differences and the corresponding 95% confidence intervals (CIs) were calculated. A conclusion of noninferiority would

be reached if the lower limit of the CI for a comparison of interest was greater than  $-130$  pmol/L.

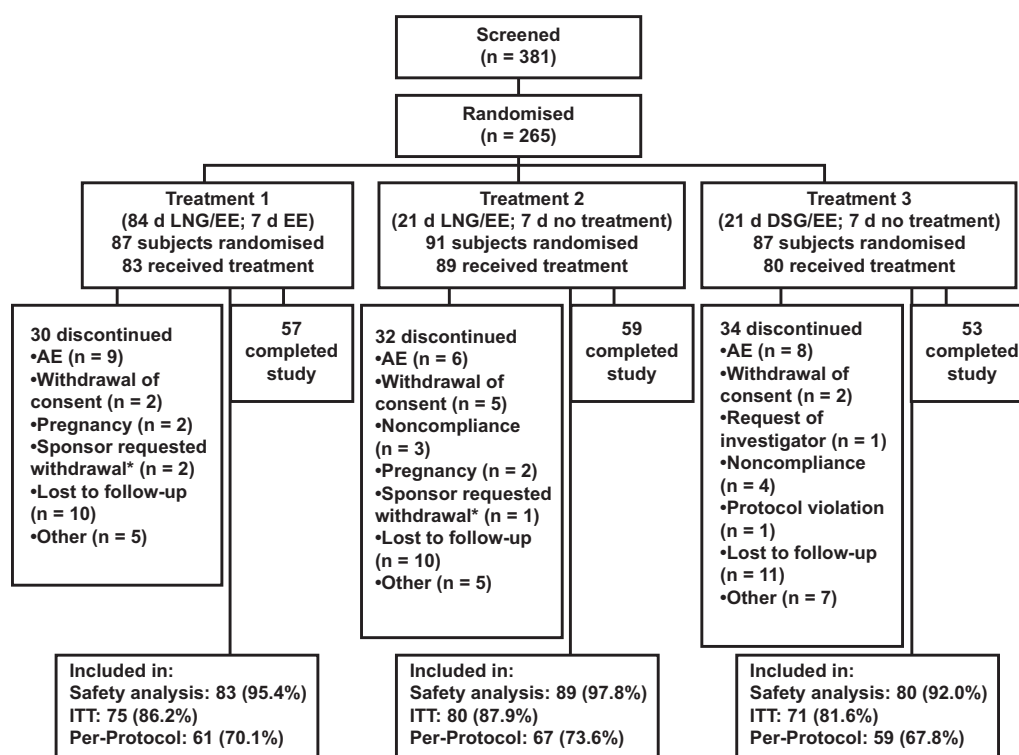
Secondary endpoints were changes in D-dimer, activated partial thromboplastin time (APTT), endogenous thrombin potential (ETP)-based activated protein C (APC) resistance, factor II, factor VII, factor VIII, antithrombin, protein C, free and total protein S, total cortisol, and corticosteroid-binding globulin (CBG) over the six-month treatment period.

Safety endpoints included adverse events (AEs), clinical laboratory tests, and vital signs. AEs were recorded during the study through spontaneous reports by participants or noted by investigators at regularly scheduled visits.

## RESULTS

### Baseline demographic characteristics

Of the 381 women screened, 265 met the inclusion criteria. Of these, 252 took at least one dose of study medication, and 169 completed the study (Figure 2).



**Figure 2** Subject disposition. \*Sponsor requested withdrawal of one woman assigned to Treatment 1 who had participated in another study funded by the sponsor; one woman assigned to Treatment 1 who had elevated D-dimer at the randomisation visit; and one woman assigned to Treatment 2 who exhibited a prothrombin alteration. d, day; DSG, desogestrel; EE, ethinylestradiol; LNG, levonorgestrel; ITT, intent to treat.

The sponsor requested that three women be withdrawn from the study: one on Treatment 1 who had participated in another study funded by the sponsor; one on Treatment 1 who had elevated D-dimer at the randomisation visit; and one on Treatment 2 who exhibited a prothrombin alteration. Four women discontinued their participation after they became pregnant (two on Treatment 1 and two on Treatment 2). The PP population (principal analysis cohort for the primary endpoint) consisted of 187 treated subjects.

There were no major differences in the demographic characteristics between the three treatment groups other than race (Table 1).

At baseline, the mean F1 + 2 levels were within normal range (41–372 pmol/L) for all three treatment groups, although the level was higher in subjects receiving Treatment 2 (207.2 pmol/L) than in those allocated to either Treatment 1 (141.0 pmol/L) or Treatment 3 (147.0 pmol/L), as shown in Table 1.

### Primary endpoint

Each of the three COCs induced an increase in F1 + 2 levels (Figure 3) over the six-month study period.

Changes from baseline in F1 + 2 were moderate and comparable for Treatment 1 (least squares [LS] mean change: 170 pmol/L) and Treatment 2 (LS mean change: 158 pmol/L), but markedly larger for Treatment 3 (LS mean change: 592 pmol/L).

Noninferiority of Treatment 1 to Treatment 3 was demonstrated since the lower limit of the 2-sided 95% CI (− 18.3 pmol/L) was greater than the pre-defined noninferiority bound of − 130 pmol/L. The noninferiority of Treatment 1 to Treatment 2 was not demonstrated (lower limit of 95% CI: − 440 pmol/L), in fact, Treatments 1 and 2 were quite similar in terms of the LS mean change from baseline.

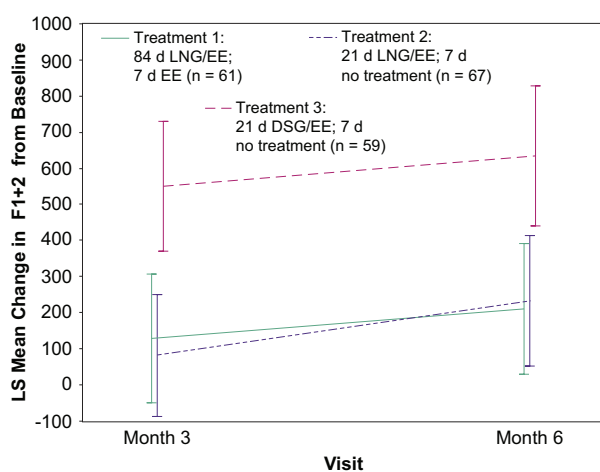
### Secondary endpoints

Secondary endpoints evaluated the haemostatic parameters recommended in the European Medicines Agency's (EMA) *Guideline on Clinical Investigation of Steroid Contraceptives in Women* for assessing the risk of VTE in women using hormonal contraceptives<sup>16</sup>. Treatments 1 and 2 often elicited comparable effects. The response to Treatment 3 at times was the opposite

**Table 1** Demographics and baseline characteristics of the per-protocol population ( $N=187$ ).

Variable	Treatment 1: 84 d LNG/EE; 7 d EE ( $n=61$ )	Treatment 2: 21 d LNG/EE; 7 d no treatment ( $n=67$ )	Treatment 3: 21 d DSG/EE; 7 d no treatment ( $n=59$ )
<i>Race/Ethnicity, n (%)</i>			
Asian	1 (1.6)	5 (7.5)	3 (5.1)
Black or African American	15 (24.6)	10 (14.9)	9 (15.3)
Caucasian	33 (54.1)	34 (50.7)	32 (54.2)
Hispanic	11 (18.0)	17 (25.4)	15 (25.4)
Other	1 (1.6)	1 (1.5)	0 (0)
Height, mean (SD), cm	163.6 (8.4)	164.1 (7.1)	163.8 (6.6)
Age, mean (SD), years	27.3 (5.9)	26.4 (5.9)	26.9 (5.6)
Weight, mean (SD), kg	65.1 (11.6)	64.5 (12.3)	63.9 (10.7)
Body mass index, mean (SD), kg/m <sup>2</sup>	24.3 (3.1)	23.8 (3.6)	23.7 (3.1)
<i>Smoking history</i>			
Current	4 (6.6)	4 (5.0)	1 (1.7)
Former	10 (16.4)	10 (14.9)	7 (11.9)
Never	47 (77.0)	53 (79.1)	51 (86.4)
Diastolic BP, mean (SD), mmHg	70.4 (6.9)	71.0 (7.0)	72.1 (6.9)
<i>Prothrombin fragment 1 + 2, pmol/L</i>			
Mean (SD)	140.95 (63.3)	207.18 (420.0)	146.97 (109.0)
Median (range)	130 (20–445)	134 (44–2987)	119 (45–798)

d, day; LNG, levonorgestrel; EE, ethinylestradiol; DSG, desogestrel; SD, standard deviation; BP, blood pressure.



**Figure 3** Change from baseline in F1 + 2\* at three and six months: per-protocol population. \*Reference range for F1 + 2: 41–372 pmol/L. d, day; DSG, desogestrel; EE, ethinylestradiol; LNG, levonorgestrel; LS, least squares.

of or more pronounced than the response to Treatment 1 (Table 2).

For example, the increase in D-dimer, factor VII, and ETP-based APC resistance, was much greater with DSG/EE than with either LNG/EE regimen. Con-

versely, the levels of free protein S, total protein S, and APTT-based APC resistance were more markedly reduced by DSG/EE than by the LNG/EE regimens.

Whereas sex hormone-binding globulin (SHBG) levels were elevated in all three groups during the study, increases with Treatments 1 and 2 were similar and lower than those with Treatment 3 (Figure 4). All regimens were associated with similar increases in total cortisol (LS mean changes of 217.9 nmol/L with Treatment 1, 262.4 nmol/L with Treatment 2, and 227.7 nmol/L with Treatment 3;  $p =$  not significant [NS] for each comparison) and cortisol-binding globulin (CBG; LS mean changes of 576.3 nmol/L with Treatment 1, 494.3 nmol/L with Treatment 2, and 596.8 nmol/L with Treatment 3;  $p =$  NS for each comparison).

### Safety

Of the 252 subjects included in the safety analysis, 98 (39%) experienced at least one treatment-emergent AE (TEAE). The most commonly reported TEAEs were nausea (7%) and metrorrhagia (6%). Treatment 1 was

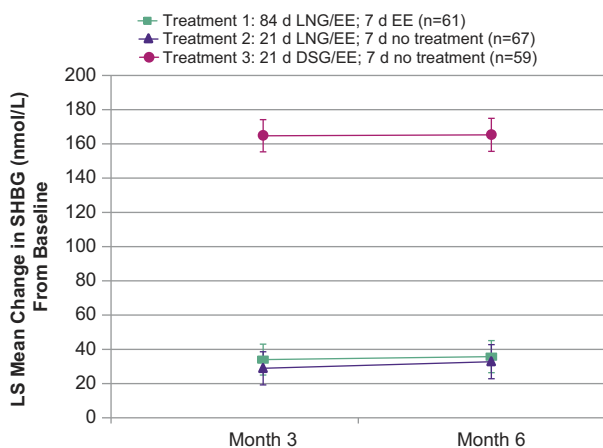
**Table 2** Summary of secondary endpoints: Mean change from baseline in absolute values for selected haemostatic parameters.

Haemostatic parameter	Treatment 1: 84 d LNG/EE; 7 d EE (n = 61)			Treatment 2: 21 d LNG/EE; 7 d no treatment (n = 67)			Treatment 3: 21 d DSG/EE; 7 d no treatment (n = 59)		
	Baseline (Mean)	Overall (Mean)	Change from baseline	Baseline (Mean)	Overall (Mean)	Change from baseline	Baseline (Mean)	Overall (Mean)	Change from baseline
D-dimer (ng/mL)	350.5	415.3	64.8	291.0	379.3	88.3	314.0	482.5	168.5
Factor II (%)	111.2	117.8	6.6	109.9	118.0	8.1	109.9	118.6	8.7
Factor VII (%)	102.9	117.9	15.0	109.6	130.9	21.3	109.9	152.7	42.8*
Factor VIII (%)	101.8	98.3	-3.5	99.8	100.6	0.7	102.1	107.4	5.3 <sup>†</sup>
Protein C activity (%)	117.0	110.3	-6.7	121.6	114.4	-7.2	110.6	111.3	0.74
Protein C antigen (%)	93.8	105.1	11.3	93.6	103.9	10.3	89.5	100.6	11.1
Free protein S (%)	90.2	93.6	3.4	92.2	96.4	4.2	92.1	73.7	-18.4 <sup>‡</sup>
Total protein S (%)	101.0	90.0	-11.0	103.7	90.9	-12.8	98.0	78.5	-19.5 <sup>‡</sup>
Antithrombin (%)	97.8	100.5	2.7	98.3	98.2	-0.13	99.2	98.3	-0.87 <sup>†</sup>
APTT-based APC resistance	2.7	2.6	-0.12	2.7	2.5	-0.14	2.7	2.4	-0.29*
ETP-based APC resistance	1.3	1.7	0.44	1.4	1.7	0.35	1.4	1.9	0.53 <sup>†</sup>

d, day; LNG, levonorgestrel; EE, ethinylestradiol; DSG, desogestrel; APC, activated protein C; APTT, activated partial thromboplastin time; ETP, endogenous thrombin potential.

\* $p < 0.01$  vs. Treatment 1; <sup>†</sup> $p < 0.05$  vs. Treatment 1; <sup>‡</sup> $p < 0.001$  vs. Treatment 1.





**Figure 4** Least squares (LS) mean change from baseline in sex hormone-binding globulin (SHBG; mIU/L): per-protocol population. The overall LS mean changes ( $\pm$  standard error [SE]) in SHBG (nmol/L) from baseline. Treatment 1 and Treatment 2 induced similar changes, 34.87 ( $\pm$  8.40) and 30.85 ( $\pm$  8.08) nmol/L, respectively. For Treatment 3, the LS mean change ( $\pm$  SE) showed a much greater elevation of 165.01 ( $\pm$  8.67) nmol/L ( $p < 0.001$  for Treatment 1 vs. 3). d, day; DSG, desogestrel; EE, ethinylestradiol; LNG, levonorgestrel.

shown to be safe and well tolerated in this study; there were no deaths, no other serious AEs, and no reports of safety concerns. The most commonly reported TEAE in subjects assigned to Treatment 1 was metrorrhagia (13%). Clinical and laboratory AEs observed were consistent with the expected safety profile of the 91-day LNG/EE regimen and those known to be associated with use of other COCs. None of the subjects in any group experienced a VTE.

## DISCUSSION

### Findings and interpretation

This study compared the effects of a 91-day LNG/EE extended regimen (Treatment 1: 84 days' 150  $\mu$ g LNG/30  $\mu$ g EE; seven days' 10  $\mu$ g EE), a traditional 21/7 LNG/EE regimen (Treatment 2: 21 days' 150  $\mu$ g LNG/30  $\mu$ g EE; seven days' no treatment), and a traditional 21/7 DSG/EE regimen (Treatment 3: 21 days' 150  $\mu$ g DSG/30  $\mu$ g EE for 21 days; seven days' no treatment) on several coagulation factors and markers of thrombin formation over six months. Although an increase in F1 + 2 levels was observed for all three regimens, the change from baseline was

considerably larger for the DSG-containing regimen. The haemostatic changes induced by the 91-day LNG/EE regimen (Treatment 1) and the traditional DSG-containing regimen (Treatment 3) were notably different. In contrast, the changes induced by Treatment 1 and the traditional Treatment 2, both of which included LNG/EE, were generally similar. In addition, SHBG levels were elevated in all three groups, although a much greater increase was observed with Treatment 3 (the DSG-containing regimen) compared with the other two groups (Figure 4).

Minor effects on adrenal corticosteroids have been described with COCs<sup>17</sup>. Because the EMA's *Guideline on clinical investigation of steroid contraceptives in women* recommends the assessment of these effects<sup>16</sup>, we have included measures of total cortisol and CBG as secondary endpoints in the present study. All three treatment modalities were associated with a rise in total cortisol and CBG levels but no between-group differences were observed.

### Differences in results and conclusions in relation to other studies

COCs are known to affect certain haemostatic indices<sup>2,18</sup>; however, it is unclear the extent to which these changes reflect the risk of VTE associated with COCs. Guidance provided in 2001 by the Committee for Property Medicinal Products of the EMA advised that although there was no urgency to modify the pattern of COC prescriptions, those containing LNG should be preferred over third-generation regimens for first time users<sup>19</sup>. A recent review by the EMA's Committee for Medicinal Products for Human Use also concluded that the absolute risk for VTE with low-dose combined hormonal contraceptives is small and the risk associated with these agents is lowest for regimens containing LNG, norethisterone, or norgestimate<sup>20</sup>.

A very low incidence of VTE has previously been observed in clinical trials evaluating the 91-day LNG/EE regimen. No thromboembolic events were reported in a one-year study of 1006 women and a long-term extension study involving 320 women<sup>21,22</sup>. Thus, the risk of VTE with extended regimen COCs containing LNG appears to be extremely low.

The findings from the current study are also consistent with previous research comparing traditional and extended COC regimens.<sup>2</sup> For example, Wiegatz *et al.*<sup>2</sup> measured haemostatic parameters in 59 women

treated with either a traditional (21 + 7 days) regimen of 2 mg dienogest and 30 µg EE (DNG/EE) or a 91-day (84 + 7 days) extended regimen with the same daily doses of DNG/EE. The increase in F1 + 2 with the traditional regimen was slight whereas that associated with the extended regimen was somewhat – but not significantly – greater. Similarly, there were no significant between-group differences in the levels of fibrinogen, FVII, and D-Dimer after three and 12 months of treatment<sup>2</sup>. Overall, the changes in the various haemostasis variables observed during treatment with the extended DNG/EE regimen corresponded to those reported for traditional 21/7 COCs<sup>2</sup>.

Among the secondary endpoints in our study, changes in SHBG levels with COCs are of particular interest given that they can be used to measure total oestrogenicity, which may predict VTE risk<sup>23</sup>. Odland and colleagues analysed data retrieved from a non-systematic literature review plus data from EMA application files to investigate the relationship between the risk of VTE with COCs and their impact on SHBG levels<sup>23</sup>. In their study, VTE risk was estimated using an EMA assessment of VTE risk in COC users, which was based on an expert review of published reports. Plotting VTE risk versus the mean SHBG increase observed with specific preparations, the authors observed a relationship between VTE risk and a rise in SHBG levels, and concluded that plasma SHBG levels may be a surrogate marker for VTE risk in users of COCs. Their analysis also revealed that increases in SHBG vary depending on the studies, and, as in our trial, the COC preparations evaluated. Monophasic preparations containing LNG, which were associated with the lowest risk of VTE, caused an average rise in SHBG of around 50%. However, COCs containing other progestins produced much greater increases. The average increase in SHBG associated with COCs was 200–300% for those containing DSG or gestodene, 150% for those including norgestimate, 250–300% for those containing drospirenone or DNG, and 300–400% for cyproterone acetate-based COCs<sup>23</sup>. Although changes in SHBG levels in our study were similar between cyclic and extended LNG/EE regimens, a study comparing continuous 90 µg LNG/20 µg EE versus cyclic 100 µg LNG/20 µg EE reported greater SHBG rises with continuous LNG/EE than with cyclic LNG/EE<sup>24</sup>. The authors hypothesised that the greater changes in SHBG with

the continuous regimen could possibly be explained by the lower total daily dose of LNG.

### Strengths and weaknesses of the study

Strengths of our study included its multinational, multi-centre, and randomised design and the racial diversity of the study population. In addition, we evaluated a large number of haemostatic and hormonal biomarkers – more than those recommended by the EMA – to thoroughly investigate the potential effects of these COCs on coagulation, fibrinolysis, and related VTE risk.

Limitations of the study included a lack of a placebo arm as well as not having a fourth-generation progestin comparator. Moreover, surrogate metabolic markers, such as SHBG, have not yet been definitely established as predictors of thrombosis in women treated with COCs. Consequently, large controlled trials with VTE as an endpoint are needed to objectively determine the clinical relevance of the associations we observed.

### Relevance of the findings: Implications for clinicians and policymakers

Our findings confirm that the effects of COCs on haemostatic biomarkers vary by progestin, with LNG-based COCs causing a less pronounced effect than DSG-based COCs. COC cycle length appears to have little impact on haemostatic biomarkers. Clinicians should consider these findings when prescribing traditional or extended COC regimens for their patients.

### Unanswered questions and future research

The haemostatic biomarkers evaluated in our study are generally thought to be useful surrogate markers of the risk of VTE and other thrombotic events associated with COCs. Nonetheless, these surrogate parameters have not been proven to capture the modifying effect of COCs on thrombotic risk. Additional research is needed to demonstrate the ability of these biomarkers to predict clinical outcomes and to clarify the comparative thrombotic risk of COCs, preferably through large controlled trials.

### CONCLUSIONS

Although the clinical relevance is unclear, the LNG/EE-containing COCs (Treatments 1 and 2) had less



impact on F1 + 2 levels than the DSG/EE-based regimens (Treatment 3) over the six-month treatment period. The 91-day and the 21/7-day LNG/EE regimens had similar effects on F1 + 2 levels. Changes in other haemostatic markers with the 84/7 and 21/7 LNG/EE regimens were similar but were less pronounced than those associated with the DSG-based COC. Thus, the results of this study would suggest that VTE risk for the extended 91-day regimen of LNG/EE, as evaluated by a set of haemostatic markers, is similar to that of the traditional 21/7-day LNG/EE COCs. However, additional studies assessing VTE as an endpoint are needed to confirm the results of our laboratory investigations.

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