Cardiovascular safety of the new estrogen-free contraceptive pill containing 4 mg drospirenone alone in a 24/4 regime.

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Abstract

Background: A new estrogen-free contraceptive has been approved by both the FDA and more than 15 European authorities. It is composed of drospirenone at a dosage of 4 mg in a regimen 24/4. The molecule is known to have anti-gonadotropic, anti-mineralocorticoid, anti-estrogenic, and antiandrogenic properties.

Methods: The purpose of these clinical trials with a new estrogen-free contraceptive was to introduce a method with high efficacy and reducing cardiovascular risks.

Study design: Three European and American multicenter clinical trials have been conducted in more than 2,500 patients and more than 25,000 cycles, not only demonstrating an excellent efficacy (Pearl Index of 0.73) but also investigating possible cardiovascular risks. In the USA study, 422 participants (41.9%) had a risk factor for VTE, while in the European studies, 261 patients (16.6%) had at least one VTE risk factor. Amount of arterial and venous thromboembolic events, hemostasiological data, blood pressure development, and ECG data were evaluated.

Results: No single case of VTE was documented, no changes in hemostasiological parameters were observed, a small decrease in RR in patients with pretreatment values between 130 and 140 and 7 or 85 to 90 mm Hg and no influence on ECG parameters were observed.

Conclusions: The introduction of a new estrogen-free contraceptive with 4 mg of non-micronized drospirenone in a 24/4-day regimen expands contraception options for women as not only a high efficacy could be demonstrated during clinical trials but also a very high cardiovascular safety profile was observed even in women with cardiovascular risk factors.

EudraCT registration numbers: 2010-021787-15 & 2011-002396-42. Clinicaltrials.gov: NCT02269241

Background

Combined hormonal contraceptives (CHC) are widely used, be highly accepted, provide adequate protection, have a low side effect profile, and are associated with additional health benefits.

The main concerns regarding their use are cardiovascular risks – mainly the venous thromboembolism (VTE) risk – which on the one hand, make these preparations unsuitable for women with risk factors, but on the other hand, give rise to justified fears in healthy women [1].

In addition to this limitation, the increased risk of VTE events in healthy COC users is 6–12/10,000 women/year compared to a risk of 2/10,000 women/year in non-users. In the further subdivision, according to the latest dates of the EMA, the risks of the combined preparations with levonorgestrel or norethisterone are 5–7 cases/10,000 women/year, 8–11 cases in the ethinylestradiol-dienogest-containing and 9–12 cases in the combined formulations with the progestogenic desogestrel, gestodene and drospirenone [2].
This development was based on laboratory and epidemiological data suggesting that estrogen is the responsible component in the COC concerning an increased cardiovascular risk and that the progestogens per se (except for medroxyprogesterone acetate and norethisterone) do not increase this risk.

Laboratory data show that ethinylestradiol exerts a pro-coagulator effect due to its metabolism in the liver by increasing the factors responsible for clotting and reducing fibrinolytic factors. Estradiol or estradiol valerate is thought to have a lower influence in the liver than ethinylestradiol [3] due to shorter half-life and faster metabolization. Estrogens alter the dynamic balance of hemostasis by increasing coagulatory factors (e.g., factor VII) and anti-fibrinolytic factors (e.g., PAI-1). The number of D-dimers increases sequentially due to the higher content of fibrin and its degenerate products in the blood. This balance is also influenced by the amount of ethinylestradiol concentration that activates the coagulation and the sort and dose of the progestogen that enables anti-fibrinolytic factors such as PAI-1 [4].

As mentioned above, epidemiological studies have shown that COC increases the risk of VTE by two to four times, depending on the dose of estrogen and the type of progestogen [1, 2]. Progestogens per se do not increase the rate of thrombotic events, except for those with a partial glucocorticoid activity [4, 5].

The aim of the presented studies was to provide information regarding its cardiovascular safety, including women at high risk or with contraindications to the use of COC.

**Methods**

Two prospective, multicentre phase III studies were performed to demonstrate the efficacy and safety of a DRSP only contraceptive pill in Europe and one in the USA.

Study 1 in Europe included 41 centers located in the Czech Republic, Germany, Hungary, Poland, and Romania. Study 2 in Europe was a double-blinded, randomized controlled trial including 88 centers in Austria, Czech Republic, Germany, Hungary, Poland, Romania, Slovakia, and Spain. The studies were performed between July 11, 2011, and January 27, 2014. Data from both studies were used for the analysis of the primary endpoint; the overall PI. Secondary endpoints were PI after correction for additional contraception for sexual activity status, method failure PI, and cumulative pregnancy rate. The first European study was performed between July 11, 2011, and March 18, 2013, and the second European study between August 01, 2012, and January 27, 2014.

In the USA study, the patients were enrolled at 39 trial centers. The study was performed between October 09, 2014, and October 04, 2017.

**Ethics Approval**

For each of the investigational centers, ethical approval was obtained.
Each center’s Institutional Review Board approved the protocol. Women provided written informed consent prior to enrolment. Registration was at clinicaltrials.gov: NCT02269241 for the USA trial and EudraCT registration numbers: 2010-021787-15 & 2011-002396-42 for the European trails.

Study Medication

In both European studies, the study medication was one tablet containing 4 mg non-micronized DRSP per day, via the oral route, with consecutive administration of 24 active pills and four placebo tablets, and no tablet-free interval between two successive cycles. The dosage was determined during phases I and II studies.

Desogestrel 0·075 mg (in a regimen of 28 active pills) was the comparator for safety in Study 2. Randomization to DRSP or desogestrel in a 5:2 ratio was performed by a contract research organization (Scope International AG) using a validated system that automates the random assignment of treatment groups to randomization numbers.

USA trial

Prospective, open-label, single-arm, multicentre trial. Participation included up to thirteen 28-day treatment cycles. Up to eight study visits were scheduled: screening (baseline), dispensation, and cycles 1, 3, 6, 9, and 13. A final follow-up visit was scheduled for 10 or 14 days after cycle 13 or after early discontinuation (EDV). Urine-pregnancy tests were conducted at every study visit. Participants also performed home urine-pregnancy tests at the start of each cycle.

During each cycle, participants swallowed one active tablet containing drospirenone 4 mg for 24 consecutive days, followed by four days placebo.

Study Populations

Inclusion criteria for the European studies were; women of child-bearing potential, at risk of pregnancy, agreeing to use only the study medication for contraception for the duration of the study treatment, aged 18 to 45, with systolic blood pressure (SBP) < 140 mmHg and diastolic blood pressure (DBP) < 90 mmHg.

In Study 1, women could either start the study medication with a break of ≥ 1 day after the administration of another hormonal contraceptive (“starters”) or switch directly from another hormonal contraceptive to the study medication with no interruption in administration (“switchers”). In Study 2, switchers were "direct" (had no break between administration of another oral contraceptive and study drug) or "indirect" (had a break between the administration of another oral contraceptive and study medication of > 2 days and ≤ four months).

USA trial
Sexually active, healthy, non-pregnant women aged ≥ 15 years seeking contraception were eligible for enrolment. Breastfeeding women at least six weeks postpartum could enroll for safety evaluations only. Non-menopausal participants had regular menstrual cycles during the previous six months when not using hormonal contraception or three complete cycles after birth if not breastfeeding. Participants could have prior experience using COCs.

**Statistical Analyses**

In each study, efficacy analyses were performed on the full analysis set (FAS), defined as all subjects who took at least one dose of the study medication and who were not pregnant at entry.

The primary and secondary efficacy endpoints were calculated for each study separately and for both studies pooled, as well as their 95% Confidence Intervals (CI).

**Results**

The contraceptive efficacy of drospirenone 4 mg is supported by phase III clinical trials, which included two European and one USA clinical trials, Archer et al. [6], Palacios et al. [7] and Kimble et al. [8].

The pooled analysis of both European studies showed a total PI of 0.73 [95% CI: 0.3133; 1.4301] (14,329 cycles of drospirenone 4 mg) and an adjusted PI of 0.7898 [95% CI: 0.3410; 1.5562] [7].

In the USA study following results were observed: Among non-breastfeeding women aged ≤ 35 years, there were 17 pregnancies (Pearl index: 4.0 (95% confidence interval [CI], 2.3–6.4, n = 953), of which three were unconfirmed and two were from sites excluded from the main analysis for major breaches of FDA regulations. The Pearl index was 2.9 (95% CI: 1.5–5.1) for confirmed pregnancies among 915 non-breastfeeding women aged ≤ 35 years from sites with no protocol violations [8].

**Cardiovascular Safety**

**Hemostasiological parameters**

Thirty-nine patients taking drospirenone 4 mg (24/4) and 29 patients taking desogestrel 0.075 mg daily as a comparative group, over a continuous period of 9 cycles, were evaluated. The measured hemostasiological parameters were APC resistance, antithrombin III (ATIII), D-dimer, C-reactive protein (CRP), and clotting factors VII and VIII [9].

The clotting factor VII (FVII) baseline value was lower in the drospirenone group (1.12, SD 0.2486) than in the desogestrel group (1.24, SD 0.2607). The FVII averages were comparable between the two groups, but the difference from the starting point- to the end value was with drospirenone 4 mg (difference
The mean C-reactive protein (CRP) baseline value in the drospirenone group (1.14, SD 0.2052) was also lower than in the desogestrel group (1.29, SD 0.2447, p = 0.0069). The changes in the final values were identical (1.10, SD 0.1688) for drospirenone vs. desogestrel (1.13, SD 0.2230). The difference in the mean change from starting value to final value was 0.03 for drospirenone vs. 0.15 for desogestrel (p = 0.0249). A significant D-dimer reduction was observed in the drospirenone group. The baseline values were 264.9 ng/ml and fell to 215.0 ng/ml; while in the group of desogestrel, there was an increase from 201.4 ng/ml to 281.5 ng/ml (see Table 1).

### Table 1
Baseline and endpoint values of hemastosiological parameters.

|                | APC resistance | ATIII | FVII | FVIII | Protein C | D-dimer (ng/ml) |
|----------------|----------------|-------|------|-------|------------|-----------------|
| Baseline       | 2.711          | 0.946 | 1.123| 0.939 | 1.14       | 264.9           |
| Endpoint       | 2.998          | 0.99  | 1.066| 1.012 | 1.108      | 215             |

**Thromboembolic Events**

During the clinical development program of drospirenone 4 mg, there were no reports of venous thromboembolism (VTE). There were also no reports of arterial thromboembolism, myocardial infarcts, strokes, or pulmonary embolisms.

In phase III clinical trials 1, 2, and 3 (Europe and US studies), a significant number of participants with risk factors for VTE have been enrolled. In the US, 422 participants (41.9%) had a risk factor for VTE, while in studies 1 and 2, 116 patients (16.3%) had a risk factor and 145 (16.9%) respectively. See Tables 2 and 3.
Table 2
Patients characteristics of thromboembolic risk factors of the European studies.

|                                | Study 1                  | Study 2                  | Desogestrel   |
|--------------------------------|--------------------------|--------------------------|---------------|
| n (%)                          | Drospirenone (N = 713)   | Drospirenone (N = 858)   | Desogestrel   |
| Age, mean (SD), yr             | 28.7 (7.1)               | 28.9 (7.1)               | 28.9 (7.1)    |
| Age group                      |                          |                          |               |
| ≤ 35 yr                        | 569 (79.8)               | 682 (79.5)               | 259 (78.0)    |
| > 35 yr                        | 144 (20.2)               | 176 (20.5)               | 73 (22.0)     |
| BMI, mean (SD) (kg/m²)         | 23.0 (3.8)               | 23.0 (3.5)               | 22.8 (3.9)    |
| BMI group                      |                          |                          |               |
| < 30                           | 672 (94.2)               | 828 (96.5)               | 316 (95.2)    |
| ≥ 30                           | 41 (5.8)                 | 30 (3.5)                 | 16 (4.8)      |
| BP group (mm Hg)               |                          |                          |               |
| SBP < 130, DBP < 85            | 571 (80.1)               | 727 (84.7)               | 290 (87.3)    |
| SBP ≥ 130, DBP ≥ 85            | 142 (19.9)               | 131 (15.3)               | 42 (12.7)     |
| Presence of ≥ 1 VTE risk factor| 110 (15.4)               | 142 (16.5)               | 59 (17.8)     |
| Current smoker                 | 182 (25.5)               | 237 (27.6)               | 103 (31.0)    |
| Regular menstrual bleeding during the last 6 cycles | 680 (95.4) | 786 (91.6) | 305 (91.9) |
| Prior treatment with sex hormones and modulators of genital system | 455 (63.8) | 704 (82.1) | 288 (86.7) |
| Starters                       | 287 (40.3)               | 417 (48.6)               |               |
Table 3
Patients characteristics of thromboembolic risk factors of the USA study.

| Risk factors                                                                 | N = 1006 |
|------------------------------------------------------------------------------|----------|
| Family history of thromboembolic illness, n (%)                              |          |
| Yes                                                                          | 12 (1.2%)|
| No                                                                           | 993 (98.8%)|
| Missing                                                                      | 1        |
| Evidence of predisposing conditions for a vascular or metabolic disease, n (%)|          |
| Yes                                                                          | 5 (0.5%) |
| No                                                                           | 1001 (99.5%)|
| Current smoker older than 35 years or non-smoker over 40 years old, n (%)   |          |
| Yes                                                                          | 51 (5.1%)|
| No                                                                           | 955 (94.9%)|
| BMI > 30 kg/m², n (%)                                                        |          |
| Yes                                                                          | 353 (35.1%)|
| No                                                                           | 653 (64.9%)|
| Number of VTE risk factors, n (%)                                            |          |
| 0                                                                            | 611 (60.8%)|
| 1                                                                            | 367 (36.5%)|
| 2                                                                            | 27 (2.7%) |
| ≥ 3                                                                          | 0        |
| Missing                                                                      | 1        |

The main risk factors were age > 35 years and BMI > 30. BMI values over 30 were present in 71 patients in Europe and 388 in the USA. There, 188 women had a BMI > 35, and 88 had a BMI > 40.

A further risk factor was smoking. In 26% of the cases, smokers were randomized in the EU and 18% % in the US study.

Afro-American and Hispanic women who per se have a higher thromboembolic represented 35,6 and 22,8% of the population in the USA trial.

These data are consistent with the hemostasiological parameters of drospirenone 4 mg [9]. Therefore, drospirenone 4 mg can be used as a safe contraceptive option, also in women with thromboembolic risk factors, without increasing the venous or arterial thromboembolic risks.

Effects On Mild Hypertension
The administration of drospirenone in combination with estrogens for six months is associated with a slight decrease in systolic (SBP) and diastolic (DBP) blood pressure, compared to levonorgestrel in combined formulations [10]. This small influence on blood pressure was also shown when 3 mg drospirenone was compared with 0.015 mg desogestrel [11]. These results are justified by the anti-mineralocorticoid effect of drospirenone.

In study 1 in Europe, an average decrease of 8 mm Hg in systolic blood pressure (SBP) and 5 mm Hg in diastolic blood pressure (DBP) was observed in participants who had baseline values >SBP 130 mm Hg or >DBP 85 mm Hg (n = 137). In the group with average SBP (< 130 mm Hg) and/or DBP < 85 mm Hg (n = 548), the absolute mean change was 0.00 mm Hg for SBP and DBP (see Table 4).

| Table 4                                                                 |
|------------------------------------------------------------------------|
| Blood pressure development of study 1 in Europe.                        |
|                                                                        |
| **Changes from baseline**                                               |
|                                                                        |
| SBP (mmHg) Mean (SD)                                                   |
| N = 548                                                                |
| 1.77 (10.08)                                                           |
| Med 0.0                                                                |
| DBP (mmHg) Mean (SD)                                                   |
| N = 137                                                                |
| -7.59 (9.19)                                                           |
| Med -8.0                                                               |
|                                                                        |
| DBP (mmHg) Mean (SD)                                                   |
| N = 548                                                                |
| 1.06 (8.20)                                                            |
| Med 0.0                                                                |
| DBP (mmHg) Mean (SD)                                                   |
| N = 137                                                                |
| -4.85 (7.85)                                                           |
| Med -5.0                                                               |

The data in study 2 showed that the women with a baseline value of SBP > 130 mm Hg or DBP > 85 mm Hg (n = 130) had an average decrease of 7.0 mm Hg with drospirenone 4 mg for the systolic value and 5.5 mm Hg for the diastolic value over time. For participants with average SDP (< 130 mm Hg) and DBP < 85 mm Hg, the absolute mean change was 0.00 mm Hg for both parameters.

**Electrocardiogram (ECG)**

The following variables related to ECG were collected for 151 women using DRSP at the day starting with the study medication (visit 1) and after finishing the study (at day 29 + 2 of the last cycle) (visit 2) and 56 women using desogestrel as a control group. These parameters were evaluated: (mean) heart rate, RR, PR, and QRS duration, QT duration, QTcB – Bazett’s correction formula, and QTcF-Fridiricia’s correction formula. These ECGs were centrally evaluated.

At the starting visit summary, mean (SD) QRS duration was comparable between the treatment groups: 90.9 (8.1) ms in the drospirenone and 89.6 (8.3) ms in the desogestrel group. Statistically significant differences in mean (SD) QRS duration between the treatment groups were seen at visit 2: 92.0 (8.4) ms in the drospirenone vs. 88.4 (8.6) ms in the desogestrel group (LS mean difference of 3.58 ms, 90% CI:
1.40; 5.77) and with regard to the mean (SD) change from visit 1 to visit 2: 1.5 (5.4) ms in the drospirenone vs. -1.1 (5.0) ms in the desogestrel group (LS mean difference of 2.55 ms, 90% CI: 1.13; 3.97). Nevertheless, these differences were not significant.

In the drospirenone group, the mean (SD) QT interval changed from 383 (22.1) ms at visit 1 to 390.8 (23.0) ms at visit 2. In the desogestrel group, it changed from 385.3 (19.9) to 384.3 (27.1). No statistically significant differences at both visits were observed between the treatment groups. The mean (SD) QT duration changed by 8.0 (22.0) ms in the drospirenone group and by -0.9 (20.5) ms in the desogestrel group. The LS mean difference of 8.90 ms between the groups was statistically significant (90% 2-sided CI: 3.13; 14.68).

The mean (SD) QTcB interval increased by 0.7 (15.8) ms in the drospirenone group and decreased by -1.5 (20.7) ms in the desogestrel group, and the difference of 2.19 ms between the groups’ changes was not statistically significant (90% 2-sided CI: -2.44; 6.82).

The mean QTcF interval increased by 3.2 (12.3) ms in the drospirenone group and decreased by -1.3 (14.5) ms in the desogestrel group. The difference of 4.55 ms between the groups’ changes was statistically significant (90% 2-sided CI: 1.09; 8.02). However, such change (4.55 ms) is below the threshold of regulatory concern (around 5 ms) given that it is not associated with an increased risk of torsade de pointes according to the Note for Guidance on the Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs [12].

The analysis of categorical QTcF indices demonstrated that in the drospirenone group one woman at visit one and at visit 2 had QTcF > 450 ms and one woman had a QTcF increase of 30 ms-60 ms from baseline at visit 2, whereas none of the women met these criteria in the desogestrel group. There were no women in either treatment group with QTcF > 470 ms or an increase from baseline of the QTcF > 60 ms. None of the drospirenone group women at visit 2 had a heart rate of < 50 bpm while one woman met this criterion in the desogestrel group. Table 5 shows the data.

| Table 5 | ECG data of 151 women before and after 9 cycles of 4 mg drospirenone. |
|---------|-------------------------------------------------------------------|
|         | SBP < 130 and DBP < 85 (mmHg)                                      |
| Changes from baseline | N = 723                                                              |
| SBP (mmHg) | Mean (SD) | −0.3 (10.0)                                             |
| Median | 0.0                                                |
| DBP (mmHg) | Mean (SD) | −0.8 (7.7)                                               |
| Median | 0.0                                                |
|         | SBP ≥ 130 and DBP ≥ 85 (mmHg)                                  |
| Changes from baseline | N = 130                                                              |
| SBP (mmHg) | Mean (SD) | −8.3 (8.6)                                               |
| Median | −7.0                                               |
| DBP (mmHg) | Mean (SD) | −7.2 (8.4)                                               |
| Median | −5.5                                               |
Discussion

No single case of VTE was documented, no changes in hemastosiological parameters were observed, a small decrease in RR in patients with pretreatment values between 130 and 140 and/or 85 to 90 mm Hg and no influence on ECG parameters were observed.

The use of combined contraceptives results in an acceleration of coagulation and fibrinolysis, as demonstrated by Kuhl [13], Winkler [14], and Schindler [15], by increasing various markers of hemostasis and fibrin turnover. This is induced by the action of ethinylestradiol on hepatic and vascular function and documented by the rise of sex hormone-binding globule (SHBG) [15]. Progestogens with pronounced androgenic properties, e.g., levonorgestrel, may counteract estrogen-induced changes in the hepatic synthesis of hematological factors. Other progestogens with antiandrogenic properties or with neutral androgenetic properties may not [15].

DRSP exhibits a different pharmacokinetic profile when administered together with ethynyl estradiol. While the new formulation with 4 mg DRSP contains 33% more active ingredient than a reference combined oral contraceptive (3 mg DRSP + 0·02 mg ethinylestradiol), the extent of systemic exposure at steady-state is about 32% less with the new formulation, without dose correction (AUC₀−₂₄ₜ, ss GMR = 77·81%, 90% CI = 74·64% − 81·12%)[16]. Combined with a reduced Cₘₐₓ, this pharmacokinetic profile of the new formulation may be relevant for similar efficacy and enhanced safety, both characteristics explaining the high efficacy and safety profile found in these clinical trials.

A weakness of the study is the clinical extrapolation on VTE events as 3.333 women-years cases would have been needed to assess the statistical number of events without any hormonal influence and the total observational period of the studies enrolled 1.102 women-years as the primary endpoint was the definition of pearl-index.

Conclusions

The estrogen-free contraceptive containing 4 mg of drospirenone in a 24/4 regimen intake provides effective contraception with a good safety/tolerability profile in a broad group of women, including overweight or obese women and is an option for most women regardless of blood pressure, BMI or thromboembolic risks.

Declarations

Ethics approval and consent to participate

The overall approval for the trial 1 with the leading ethical committee was given the 01.07.2011 by the Ethikkommission des Landes Sachsen-Anhalt, Geschäftsstelle, number 10/0607 EK. The overall approval for the trial 2 with the leading ethical committee was given the 13.07.2012 by the Landesamt für
Gesundheit und Soziales Berlin, Geschäftstelle der Ethik Kommission des Landes Berlin, number 11/0606 EK.

The dates on which the records were first entered in the EudraCT database were between 2010-11-05 and 2011-04-14. The EudraCT is since the 2011-03-22 open and public available. As documented in the submitted protocol of study 1, the date the first subject entered was 2011-07-11. EudraCT registration numbers: 2010-021787-15 & 2011-002396-42. Registration was at Clinicaltrials.gov: NCT02269241 for the USA trial.

All participants consented to participate in the clinical trial.

Consent for publication

All authors have consented for publication.

There is no identifying information in this manuscript.

If identifying images or other personal or clinical details of participants are presented that compromise anonymity, a statement of consent to publish from the patient should be included.

Not Applicable.

Availability of data and material

Clinical trial register: Registration was at clinicaltrials.gov: NCT02269241 for the USA trial and EudraCT registration numbers: 2010-021787-15 & 2011-002396-42 for the European trials.

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Competing interests

Santiago Palacios is a consultant to Pfizer, Amgen, MSD, Gynea, Procare Health, Bayer, Sérélys Shinogi, Exeltis, Abbott, and Gedeon Richter. Enrico Colli and Pedro Antonio Regidor are employees of Exeltis. Santiago Palacios is an editorial member of BMC Women’s Health.

Authors’ contributions

All authors have read and approved the manuscript.

SP and EC were responsible for the practical realization of the study. PAR was responsible for the writing and coordination of the manuscript.

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