STUDY SYNOPSIS

Sponsor: ESTETRA SRL **Product**: Estetrol **Active ingredient:** Estetrol	**INDIVIDUAL STUDY TABULAR FORMAT** **Referring to Part XX of the dossier** **Volume:** **Page:**	**(For National Authority Use only)**

Title of study:

A randomized, open-label, multicenter, dose-finding study to evaluate cycle control of 15 mg or 20 mg estetrol combined with either 150 µg levonorgestrel or 3 mg drospirenone, compared to a combined oral contraceptive containing estradiol valerate and dienogest

Investigators and study centers:

The coordinating investigator was Principal Investigator: [redacted], Helsinki, Finland. There were 10 sites in Finland.

Publications:

- Apter D, Zimmerman Y, Beekman L, Mawet M, Maillard C, Foidart JM, Coelingh Bennink HJT. Bleeding pattern and cycle control with estetrol-containing combined oral contraceptives: results from a phase II, randomised, dose-finding study (FIESTA). Contraception. 2016;94(4):366-73. DOI: 10.1016/j.contraception.2016.04.015.
- Apter D, Zimmerman Y, Beekman L, Mawet M, Maillard C, Foidart JM, Coelingh Bennink HJT. Estetrol combined with drospirenone: an oral contraceptive with high acceptability, user satisfaction, well-being and favourable body weight control. Eur J Contracept Reprod Health Care. 2017;22(4):260-267. DOI: 10.1080/13625187.2017.1336532.

Clinical Phase: IIb

Study duration and dates:

The recruitment period was approximately 6.5 months (October 2010 to March 2011) and the study period was 12 months (September 2010 to September 2011) (first subject first visit: 06 September 2010 to last subject last visit: 14 September 2011).

Objectives:

The *primary objective* of the study was to assess vaginal bleeding patterns (cycle control) of 15 mg and 20 mg estetrol (E4) combined with either 150 µg levonorgestrel (LNG) or 3 mg drospirenone (DRSP) during a 24:4 treatment regimen.

The *secondary objectives* of the study were to assess:

- Ovulation inhibition.
- The effect on sex hormone-binding globulin (SHBG) (as added in amendment no. 1).
- Pregnancy rate.
- Health, satisfaction, and body weight.
- Return of menstruation after treatment with E4-LNG or E4-DRSP combined oral contraceptive (COC).
- General safety and acceptability.

Methodology:

A randomized, open-label, multicenter, dose-finding study with subjects assigned to 1 of 5 treatment groups. Stratification was performed based on use of hormonal contraceptive method prior to study participation (starter vs switcher) and site. Subjects received the study medication for a period of 6 consecutive treatment cycles.

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Number of subjects (total and for each treatment):

Planned: 425 subjects, 85 per treatment group

Total treated: 389 (396 randomized, 7 did not start treatment)

- 78 on Qlaira® (1/2/3 mg estradiol valerate [E2V] and 0/2/3 mg dienogest [DNG]).
- 77 on 20 mg E4/150 µg LNG.
- 75 on 20 mg E4/3 mg DRSP.
- 80 on 15 mg E4/150 µg LNG (added after amendment no. 1).
- 79 on 15 mg E4/3 mg DRSP (added after amendment no. 1).

Diagnosis and main criteria for inclusion:

Subjects were included in the study if they met all of the following inclusion criteria:

1. Women aged 18-35 years (inclusive) at the time of screening who were willing to use a COC for 6 subsequent cycles.
2. Good physical and mental health as judged by the investigator determined by medical history, physical examination, clinical laboratory, and vital signs.
3. Regular menstrual cycle (24-35 days) prior to screening.
4. Body mass index (BMI) between ≥18 and ≤30 kg/m^2.
5. Willing to give informed consent in writing.

In addition, key exclusion criteria included (full details can be found in the body of the report):

1. Previous use of any hormonal contraceptive method during the last 3 months prior to randomization (exclusion criterion only applicable for women who were not using a hormonal contraceptive method at the time of screening).
2. Previous use of progestin-only contraceptive methods (e.g. minipill, implant, or intrauterine device) during the last 3 months or during the last 6 months for depot progestin preparations or an injectable hormonal method of contraception (e.g. Depo-Provera®).
3. Use of phytoestrogens.
4. No spontaneous menstruation has occurred following a delivery or abortion.
5. Status post-partum or post-abortion within a period of 2 months before screening.
6. Pregnancy during accurate hormonal contraceptive use in the past.
7. An abnormal cervical smear within 1 year before study start.
8. Untreated chlamydia infection.
9. Known or suspected breast cancer or a history of breast cancer.
10. Any clinically relevant abnormality following review of medical history, laboratory results and physical/gynecological examination at screening as judged by the investigator.
11. Contraindications for contraceptive steroids.
12. Use of 1 or more of the following medications:
    - Antihypertensive drugs.
    - Present use or use within 2 months prior to the start of the study medication of the following drugs: phenytoin, barbiturates, primidone, carbamazepine, oxcarbazepine, topiramate, felbamate, rifampicin, nelfinavir, ritonavir, griseofulvin, ketoconazole, sex steroids (other than pre-and post-

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treatment contraceptive method), and herbal remedies containing *Hypericum perforatum* (St John's Wort).

13. Administration of any other investigational drug within 2 months prior to screening.

Test product, dose and mode of administration, batch number:

The test product was 15 or 20 mg E4 combined with either 150 µg LNG or 3 mg DRSP supplied as tablets, administered orally as 2 separate tablets.

Treatment groups:

- 20 mg E4 combined with 150 µg LNG.
- 20 mg E4 combined with 3 mg DRSP.
- 15 mg E4 combined with 150 µg LNG (added by amendment no. 1).
- 15 mg E4 combined with 3 mg DRSP (added by amendment no. 1).

A single treatment cycle (28 days) consisted of:

- Days 1-24: 1 tablet E4 and 1 tablet of LNG or DRSP per day.
- Days 25-28: 2 placebo tablets per day.

Test product was supplied in blister packs with 24 active tablets and 4 placebo tablets. Batch numbers used were H0962A for 20 mg E4 and H0998 for 15 mg E4 with H0821 and H0997 for the matching placebo; H0961A for DRSP and H0844 for LNG with H0821 and H0997 for the matching placebo for both DRSP and LNG.

Reference therapy:

The reference therapy was Qlaira (1/2/3 mg E2V with 0/2/3 mg DNG; the composition of the tablets was variable throughout the cycle) supplied as tablets in the commercial packaging, administered orally.

A single treatment cycle (28 days) consisted of:

- Days 1-26: 1 tablet of Qlaira per day.
- Days 27-28: 1 placebo tablet per day.

The reference product was supplied in blister packs with 26 active tablets and 2 placebo tablets. The batch number was WED8DP.

Duration of treatment:

6 treatment cycles of 28 days each (regimen 24:4 for the test products and 26:2 for the reference therapy).

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Criteria for evaluation:

Primary parameter:

- Cycle control was evaluated on the basis of vaginal bleeding patterns and tablet intake as recorded daily by subjects using study diaries.

Secondary parameters:

- Ovulation inhibition was assessed by measurement of pregnanediol glucuronide in first void urine, collected weekly during the first 4 treatment cycles (cycle days 7, 14, 21, and 28).
- The effect on SHBG was assessed by measurement of SHBG in blood samples collected at screening (baseline, visit 1), during treatment (visit 6), and at the end of the treatment (visit 7) (as added in amendment no. 1).
- Pregnancy rate was assessed from the occurrence of in-treatment pregnancies.
- Subject satisfaction and health-related effects were assessed by a Patient Reported Outcome Questionnaire (self-administered questionnaire).
- Body weight was measured during each study visit.
- Return of menstruation after study treatment was determined at the follow-up contact (only for women who were not continuing with a new hormonal contraceptive method at the end of the study treatment, e.g. women with a pregnancy wish).
- Acceptability was assessed by analysis of discontinuation rates and reasons for discontinuations.
- Safety data was obtained by determination of routine laboratory parameters, vital signs and cervical smear, by performing physical, gynecological and breast examinations, and by monitoring adverse events (AEs).

Statistical methods:

Efficacy analysis: The study was exploratory and its aim was to gather information that would help decide which regimen should be selected for final Phase III development. As the study was descriptive, no comparative analyses were performed, but 2-sided 95% confidence intervals (CIs) were calculated (binomial method) per treatment group and cycle for all primary and secondary bleeding endpoints. These comparisons were made between the rates of occurrence for each endpoint for all 4 combination treatment arms using Qlaira as the reference group. Due to the exploratory nature, the primary analysis was done on the per protocol (PP) population. Corresponding analyses were also conducted for the intent-to-treat (ITT) population. All secondary analyses were performed using a modified PP (mPP) or ITT (mITT) population.

Safety analysis: The safety analysis was performed for the all-subjects-treated (AST) population. For the analysis of safety data, only tabulations and frequencies were presented. Values outside the reference ranges were flagged in the individual data listings. Safety laboratory data and vital signs were summarized using descriptive statistics. In addition, the calculations were performed for the absolute and relative changes from baseline.

Demographic and baseline characteristics:

All subjects in this study were female. The mean age in the AST population was 24.1 years (range: 18-35 years). All but 2 subjects were Caucasian. Subjects had a mean height of 166.4 cm (range: 151-188 cm), a mean weight of 62.9 kg (range: 44.0-95.0 kg), and a mean BMI of 22.7 kg/m^2 (range: 17.6-30.8 kg/m^2). In general, demographic and baseline characteristics were balanced across treatment groups, with the exception of smoking habits. The proportion of current smokers varied between 10.7% in the

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20 mg E4/DRSP group and 24.7% in the 20 mg E4/LNG group.

Efficacy results:

The aim of the protocol was to find a regimen with at most 20% absence of withdrawal bleeding and/or at most 20% unscheduled intracyclic bleeding. The 15 mg E4/DRSP group and the 20 mg E4/LNG group are the only 2 groups that met both these criteria both in treatment cycle 6:

- Absence of withdrawal bleeding occurred in <20% of subjects in all E4 treatment groups throughout the study and in a much lower proportion than in the Qlaira group (with 27.1% of subjects in treatment cycle 6) in the PP population. The percentage of subjects who did not have withdrawal bleeding was very low in the E4/DRSP groups in the primary analysis cycles (2, 3, and 6): no more than 2 subjects (<4%) had the absence of withdrawal bleeding in any treatment cycle throughout the study. In contrast, between 14.0-18.5% of subjects in the E4/LNG groups and 27.1% of subjects in the Qlaira group reported the absence of withdrawal bleeding in treatment cycle 6.
- Unscheduled intracyclic bleeding was highest in the Qlaira and 15 mg E4/LNG groups, and generally lowest in the E4/DRSP groups in the PP population. In treatment cycle 6, unscheduled bleeding was only reported by <20% of subjects in the 20 mg E4/LNG group (18.9% of subjects) and in the 15 mg E4/DRSP group (16.9% of subjects). Unscheduled bleeding was reported by >20% of subjects in all treatment groups in all other treatment cycles except 1 (treatment cycle 4 for 20 mg E4/DRSP).
- The incidence of subjects with unscheduled bleeding/spotting was generally lower in the E4/DRSP groups across the primary cycles in the PP population than in the other treatment groups. By treatment cycle 6, the 15 mg E4/DRSP group had the lowest incidence of all groups (33.8% compared to 47.8% in the Qlaira group) resulting in a difference of 13.9% fewer subjects with unscheduled bleeding/spotting than in the Qlaira group (95% CI: 30.51, 2.68). The incidence of unscheduled bleeding/spotting was 41.5% in the 20 mg E4/LNG group and 48.3% in the 15 mg E4/LNG group in treatment cycle 6 in the PP population.
- The maximum intensity of unscheduled bleeding/spotting per cycle increased over time with Qlaira (i.e. there was an increase in the proportion of women with heavier bleeding), decreased over time with 20 mg E4/LNG and 20 mg E4/DRSP groups (i.e. there was an increase in the proportion of women with lighter bleeding or spotting), and stayed generally the same with minor fluctuations in the 15 mg E4/LNG and 15 mg E4/DRSP groups.
- Unscheduled bleeding on a given cycle day occurred most frequently in the Qlaira and the 15 mg E4/LNG groups in all cycles after treatment cycle 1 (up to 16% of subjects had unscheduled bleeding on several consecutive days in treatment cycle 6) and was least frequent in the 15 mg E4/DRSP group (up to 3% of subjects had unscheduled bleeding on several consecutive days in treatment cycle 6). From treatment cycles 2 through 6 the proportion of subjects with unscheduled bleeding on a given day was greater in the second half of the unscheduled bleeding period (from day 15 to day 24) particularly in the Qlaira and the 15 mg E4/LNG groups: in treatment cycle 6, unscheduled bleeding between days 12 and 24 was reported by ≤15% of subjects on 2 or more days in the Qlaira group, ≤14% of subjects on 2 or more days in the 15 mg E4/LNG group, ≤11% of subjects on 2 or more days in the 20 mg E4/DRSP group, ≤9% of subjects on 2 or more days in the 20 mg E4/LNG group, and ≤3% of subjects on 2 or more days in the 15 mg E4/DRSP group.
- When analyzed by stratification groups, the occurrence of unscheduled bleeding by cycle day was higher in all treatment groups in starters than in switchers in the first 5 treatment cycles, but had dropped to a similar level as for switchers by treatment cycle 6. In general, the occurrence of

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unscheduled bleeding by cycle day in switchers was low in all treatment cycles.

- The incidence of unscheduled bleeding/spotting by cycle day was also lowest in both the E4/DRSP groups across all cycles. From 12-34% of subjects in the E4/DRSP groups and from 16-46% of subjects in the other treatment groups in the PP population had unscheduled bleeding or spotting during the first treatment cycle, which then decreased notably by treatment cycle 2 and remained lower in subsequent cycles in the E4/DRSP groups and the 20 mg E4/LNG group. By treatment cycles 5 and 6, the occurrence of unscheduled bleeding/spotting on any cycle day was lowest in the 15 mg E4/DRSP group (3-8% on most days compared to 9-19% on most days in the other E4 groups and 10-27% in the Qlaira group in treatment cycle 6).
- Overall, a lower incidence of subjects with unscheduled bleeding/spotting in the primary cycles was observed for 8 of the 12 comparisons to Qlaira in any of the E4 treatment groups: for DRSP groups E4 was lower in 5 of the 6 comparisons to Qlaira and for LNG comparisons E4 was lower in 3 of the 6 comparisons to Qlaira.
- All E4 groups showed a decrease in the mean number of days with unscheduled bleeding/spotting during the course of the study whereas it remained relatively constant in the Qlaira group. In treatment cycle 1, the mean number of days of unscheduled bleeding/spotting in the PP population was between 6.5 days in the Qlaira group and 7.4 days in the 20 mg E4/DRSP group. But by treatment cycle 6, the mean number of days of unscheduled bleeding/spotting had decreased to as low as 3.7 days in the 15 mg E4/DRSP group, was between 4.4 days and 5.4 days in the other E4 groups, and was highest in the Qlaira group (6.0 days).
- The ability of all E4 dose groups to suppress ovulation was demonstrated by the lack of ovulation (by measurement of pregnanediol glucuronide in urine samples collected during the first 4 cycles) and pregnancies in all 389 subjects treated.
- In the starter subjects with available data, mean SHBG levels in the mPP population decreased after screening in the LNG-containing groups (from between 58.2 and 62.7 nmol/L at screening to between 31.6 and 34.7 nmol/L at treatment cycle 6/EOS) and increased in all other groups (from between 54.0 and 64.9 nmol/L at screening to between 83.4 and 92.0 nmol/L at treatment cycle 6/EOS).
- Across all subjects, mean SHBG levels during treatment were lowest in the E4/LNG groups in the mPP population at both treatment cycles 4 and 6/EOS (mean levels between 28.9 and 36.9 nmol/L) and higher in the Qlaira and the E4/DRSP groups (mean levels between 87.5 and 106.4 nmol/L).
- In those subjects who did not start on a new hormonal contraceptive after the end of the study, return of menstruation was not in any way disrupted in subjects taking E4. After stopping use of E4/LNG, E4/DRSP, or Qlaira, all but 4 subjects had a return of spontaneous menstruation within the first 2 months, 2 subjects (15 mg E4/LNG) had a spontaneous menstruation within 2-4 months, and 2 subjects (15 mg E4/LNG) became pregnant within the first cycle after study medication (confirming return of fertility).
- There was an initial decline in satisfaction or health-related quality of life during the first 3 cycles, which improved again to no change between visits in the majority of subjects by treatment cycles 4-6 in all treatment groups. Generally, the Qlaira and DRSP-containing groups had a higher proportion of subjects who reported an improvement (better or much better) at treatment cycle 6 compared to the previous visit (treatment cycle 4) than the LNG-containing groups.
  - For questions 1 (general feeling), 2a (mood), 2b (sexual life), and 2d (overall effect), the majority of subjects in any treatment group reported no change compared to the previous visit (>70% of subjects) at treatment cycle 6. The Qlaira and DRSP-containing groups had higher percentages of

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subjects who felt better or much better in treatment cycle 6 (between 10-19%) than in the LNG-containing groups (between 1-14%). Consistent with this, the percentage of subjects who reported worse for these questions was usually higher in the LNG-containing groups (8-16%) than the other 3 groups (4-10%).

- When asked about the effect of the study medication on premenstrual complaints (question 2c), 59.6% of subjects overall reported no change at treatment cycle 6 compared to the previous visit, and a considerable proportion of subjects in all treatment groups reported better or much better (30.7% overall), with the largest proportion in the 20 mg E4/DRSP group (32.9%) and the smallest proportion in the 15 mg E4/LNG group (27.0%). The small proportion of subjects in the 15 mg E4/LNG group who reported better or much better is due to a much larger proportion of subjects reporting worse or much worse premenstrual complaints (20.3%) than in any of the other groups (2.7-11.1%).
- When asked how satisfied subjects were with their study medication (question 3), >50% of subjects in any treatment group reported being satisfied or very satisfied at treatment cycle 6, with the largest proportion in the 15 mg E4/DRSP group (73.1%). A smaller percentage of subjects (12-14%) in the Qlaira and DRSP-containing groups than in the LNG-containing groups (18-23%) reported being dissatisfied or very dissatisfied.
- When asked if they would consider using the study medication they had been using during that cycle (question 4), a larger proportion of subjects in the Qlaira and DRSP-containing groups answered yes (36-42%) than in the LNG-containing groups (21%).

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Safety results:

The incidence of treatment-emergent adverse events (TE-AEs) was similar in the Qlaira, the 2 E4/LNG groups, and the 20 mg E4/DRSP group (between 71.8% and 80.0% of subjects), and was slightly lower in the 15 mg E4/DRSP group (64.6%), as seen in the table below.

Between 23.1% and 45.5% of subjects across the treatment groups reported a drug-related TE-AE and the majority of subjects reported mild or moderate TE-AEs. There were no deaths and only 1 serious AE (SAE) not considered related to treatment (Qlaira group). There were no in-treatment pregnancies reported during the study.

Type of TE-AE	**Number (%) of subjects (AST population)**				
	Qlaira N=78	**20 mg E4/ 150 µg LNG N=77**	**20 mg E4/ 3 mg DRSP N=75**	**15 mg E4/ 150 µg LNG N=80**	**15 mg E4/ 3 mg DRSP N=79**
TE-AEs	56 (71.8)	57 (74.0)	60 (80.0)	60 (75.0)	51 (64.6)
Deaths	0	0	0	0	0
SAE	1 (1.3)	0	0	0	0
TE-AEs leading to withdrawal [a]	4 (5.1)	12 (15.6)	8 (10.7)	10 (12.5)	5 (6.3)
TE-AEs of known severe intensity	3 (3.9)	2 (2.6)	2 (2.7)	1 (1.3)	3 (3.8)
Drug-related TE-AEs	18 (23.1)	35 (45.5)	31 (41.3)	28 (35.0)	20 (25.3)
Pregnancy	0	0	0	0	0

Source: Table 12.5.8.0

AST = all-subjects-treated; DRSP = drospirenone; E4 = estetrol; LNG = levonorgestrel; N = number of subjects in the AST population; SAE = serious adverse event; TE-AE = treatment-emergent adverse event.

[a] In addition to these 39 subjects who had a TE-AE leading to withdrawal, 2 further subjects were reported as discontinuing the study due to a pre-treatment event.

The most commonly affected SOCs were Infections and infestations and Skin and subcutaneous tissue disorders. The 2 most commonly reported TE-AEs and drug-related TE-AEs were headache and acne, both of which appear to have a dose-related increase in incidence.

Headache reported as a TE-AE (overall and drug-related) was more frequent in both the 20 mg E4 groups (overall: 16.9% in 20 mg E4/LNG and 25.3% in 20 mg E4/DRSP) than in the 15 mg E4 groups (overall: 10.0% in 15 mg E4/LNG and 7.6% in 15 mg E4/DRSP); overall the incidence of headache was lowest in the 15 mg E4/DRSP group. The overall incidence of headache reported as a TE-AE with Qlaira (16.7%) was similar to the 20 mg E4 groups.

Acne reported as a TE-AE (overall and drug-related) was more frequent in the LNG groups (overall: 26.0% in 20 mg E4/LNG and 15.0% in the 15 mg E4/LNG) compared to the DRSP groups of same E4 doses (overall: 14.7% in 20 mg E4/DRSP and 7.6% in 15 mg E4/DRSP), and the 15 mg E4/LNG group was comparable to the 20 mg E4/DRSP group. The 15 mg E4/DRSP regimen caused the least amount of acne reported as a TE-AE: the incidence of acne reported as a drug-related TE-AE was lowest with the 15 mg E4/DRSP regimen (5.1% of subjects) and highest in the 20 mg E4/LNG group (23.4% of subjects), with 9.0% in the Qlaira group.

The only other TE-AE that showed a noticeable difference between treatment groups was breast tenderness, which was reported as a drug-related TE-AE by 6 (8.0%) subjects in the 20 mg E4/DRSP group compared to only 0 or 1 subject in all other treatment groups.

Severe TE-AEs were reported by between 1.3% and 3.9% of subjects in any treatment group. All but 1 of the severe TE-AEs were reported by only 1 subject in any group; dysmenorrhea was reported as severe in 2 subjects in the 20 mg E4/LNG group.

There were no apparent dose- or drug-related trends for changes in any of the hematology, biochemistry, or urinalysis assessments, physical examination or vital signs, or the breast and transvaginal ultrasound examinations.

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The mean endometrial thickness decreased in all treatment groups to a similar degree after 6 cycles of treatment with study medication. Overall, the mean thickness across all treatment groups decreased from 4.32 mm at baseline (visit 1) to 3.12 mm at treatment cycle 6/EOS (visit 7).

The Qlaira group and the 15 mg E4/DRSP group had the highest acceptability among all treatment groups, as they had the lowest proportion of subjects who discontinued treatment (10.3% of the Qlaira group and 8.9% of the 15 mg E4/DRSP group); this was in contrast to 29.9% of subjects in the 20 mg E4/LNG group, 25.0% of subjects in the 15 mg E4/LNG group, and 20.0% subjects in the 20 mg E4/DRSP group. In addition, no subjects in either the Qlaira group or the 15 mg E4/DRSP group discontinued the study due to vaginal bleeding. An assessment of acceptability in the subgroups of starters and switchers showed that, based on the incidence of discontinuation due to AEs, acceptability was similar among all starter treatment groups whereas among switchers it was highest in the Qlaira group and the 15 mg E4/DRSP group.

Conclusions:

The 15 mg E4/3 mg DRSP regimen seems to provide the optimal benefit/risk ratio among the E4 treatment groups. It met the aim of the study to have at most 20% absence of withdrawal bleeding and/or at most 20% unscheduled intracyclic bleeding. This group showed the lowest incidence of unscheduled intracyclic bleeding at treatment cycle 6 (16.9% of subjects), less than 4% of subjects with an absence of withdrawal bleeding (3.5% at treatment cycle 6), small changes in the levels of SHBG, and the least amount of acne reported as a TE-AE. In addition, while the proportion of subjects in the PP population with spotting relative to those with bleeding remained fairly constant over time (fluctuating within a range of 10% of subjects) in most groups, and relative to the proportion of subjects with unscheduled bleeding, the proportion of subjects with unscheduled spotting increased and the proportion of subjects with unscheduled bleeding decreased by >10% of subjects by treatment cycle 6 in 15 mg E4/DRSP group.

Thus, this study provides solid information on how the combination of E4 with either DRSP or LNG acts in terms of efficacy and safety. All E4/DRSP and E4/LNG combinations perform better than Qlaira in terms of cycle control. The 15 mg E4/3 mg DRSP regimen has the most favorable properties and seems the preferred combination for further Phase III clinical development.

Date of final report:

3 October 2012 (Version 1.0)

Date of synopsis:

14 June 2022 (Version 2.0 for Disclosure and Transparency)