Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer HealthCare AG	
Study Number:	91470 (308961)	NCT00307801
Study Phase:	III	
Official Study Title:	A multicenter, double-blind, randomized, parallel-group, placebo-controlled, 7 cycle duration (196 days), phase 3 study of oral estradiol valerate/dienogest tablets for the treatment of dysfunctional uterine bleeding	
Therapeutic Area:	Women's Healthcare	
Test Product		
Name of Test Product:	EV/DNG (Qlaira, BAY86-5027)	
Name of Active Ingredient:	Estradiol valerate (EV), dienogest (DNG)	
Dose and Mode of Administration:	2 days of 3 mg estradiol valerate (EV) SH T00658EA; 5 days of 2 mg EV + 2 mg dienogest (DNG) SH T00658GA; 17 days of 2 mg EV + 3 mg DNG SH T00658M ; 2 days of 1 mg EV SH T00658HA; 2 days of placebo SH T00658P A blister card consists of 28 pills taken orally once a day for 28 days (one cycle). Mode of administration: Oral	
Reference Therapy/Placebo		
Reference Therapy:	Placebo	
Dose and Mode of Administration:	Matching placebo pills administered orally, similarly to test therapy.	
Duration of Treatment:	196 days (7 cycles; each cycle of 28 days).	
Studied period:	**Date of first subjects' first visit:**	16 FEB 2006
	Date of last subjects' last visit:	27 MAY 2008
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	Amendment no. 1 (dated 20 DEC 2005) was applicable for Sweden only and extended the threshold of FSH <40 IU/mL to all study participants to exclude early menopause. Also erythromycin and grapefruit juice were added as prohibited concomitant medications because these medications have an effect on cytochrome CYP 3A4 enzyme activity. Amendment no. 2 (dated 10 JAN 2006) was applicable to the UK only and adjusted the exclusion criterion BMI from >32 to >30 kg/m^2 and excluded all smokers over the age of 35, not only heavy smokers (more than 10 cigarettes per day). Amendment no. 3 (dated 16 JAN 2006) was applicable to Czech	

	Republic only and excluded explicitly subjects with a current diagnosis or history of breast cancer. For subjects ≥45 years of age a non-suspicious mammography had to be obtained within one year before Visit 1. If this was not available, then a non-suspicious mammography must be obtained prior to randomization (Visit 5). Amendment no. 4 (dated 01 FEB 2006) was applicable to Germany only and allowed the use of one or more of the following barrier contraception methods in any combination: • Condoms for use in males, latex or polyurethane • Condoms for use in females • Diaphragm • Cervical cap • Use of spermicide alone was not allowed, however, spermicide could be used in addition to the methods described above to increase the contraceptive efficacy of the barrier method. Amendment no. 5 (dated 04 APR 2006) was applicable to Australia only and excluded all smokers over the age of 35, not only heavy smokers (more than 10 cigarettes per day). Amendment no. 6 (dated 13 JUN 2006) incorporated the revised list of dysfunctional uterine bleeding (DUB) symptoms relating to the primary efficacy variable on the recommendation of the USFDA. According to the FDA's recommendation the definition of the primary efficacy variable including the overall success rate (adding a 50% point estimate) was clarified. Other changes included: • Hospitalizations due to study procedures were not required to be reported as serious adverse events/adverse events (AEs). • Laboratory tests during drug administration that result in clinically significant abnormal values were required to be documented as AEs and were to be repeated until the values returned to baseline levels or to normally acceptable levels. • Handling of dropouts and missing data was changed in order to follow the FDA's recommendations. Amendment no.7 (dated 14 JUN 2007) dealt with problems arising from a possible technical failure of the e-diary. A replacement paper diary was introduced to cover the days of non-retrievable e-diary data. The paper diary was only to be used in emergencies.
Study Centre(s):	The study was conducted in 36 centers in 10 countries: Australia, Czech Republic, Finland, Germany, Hungary, the Netherlands, Poland, Sweden, UK, and Ukraine.
Methodology:	The multicenter, double-blind, randomized, parallel group, placebo-controlled study comprised of the following phases: screening (up to 28 days), a 90-day run-in phase (pre-treatment), 196 days of study drug administration (7 cycles of 28 days each), with no pill-free interval between consecutive cycles, and a 30-day follow-up. Using an e-diary, subjects kept a daily record of menstrual bleeding, number of sanitary protection items used, study drug intake, and pregnancy tests performed. Follicle-stimulating hormone (FSH), prolactin, thyroid stimulating hormone (TSH), luteinizing hormone (LH), sex hormone-binding globulin (SHBG), testosterone, dehydroepiandrosterone (DHEAS) were obtained at screening visit and visit 11 (end of study

	medication or early termination). An endometrial biopsy was done at visit 3 (run-in phase) and visit 11. The subject's overall assessment and investigator's global assessment were done at visit 7 (during study drug administration phase) and visit 11. Psychological general well-being index (PGWBI), McCoy female sexuality questionnaire (MFSQ), EuroQoL (quality of life) 5 dimensional health questionnaire (EQ-5D), and economic evaluation/resource use assessment were evaluated on visit 5 (baseline), visit 7, and visit 11.
Indication/ Main Inclusion Criteria:	Indication: Dysfunctional uterine bleeding (DUB) Main Inclusion Criteria: Women 18 years or older, in general good health, not pregnant or nursing, with a diagnosis of DUB as defined by the presence of at least one of the following symptoms during the run-in phase: • Prolonged bleeding: 2 or more bleeding episodes, each lasting 8 or more days • Frequent bleeding: greater than 5 bleeding episodes, with a minimum of 20 bleeding days overall • Excessive bleeding: 2 or more bleeding episodes each with blood loss volume of 80 mL or more (alkaline hematin method) Women with history of endometrial ablation or dilatation and curettage within 2 months prior to study start were to be excluded. All subjects underwent an endometrial biopsy, unless results were available from a valid endometrial biopsy performed within 6 months of visit 1. The use of steroidal oral contraceptives (OCs), or any drugs that could significantly alter OC metabolism were prohibited during the study.
Study Objectives:	**Primary:** To determine the efficacy and safety of EV/DNG treatment in subjects with dysfunctional uterine bleeding (DUB) as compared to placebo. **Secondary:** • To determine the efficacy of EV/DNG with regard to individual DUB symptoms and menstrual bleeding parameters. • To determine the efficacy of EV/DNG with regard to quality of life and resource use assessment. • To evaluate the effect of EV/DNG on hemoglobin and serum ferritin concentrations.
Evaluation Criteria:	**Efficacy (Primary):** Overall success rate defined by the proportion of subjects with no DUB symptoms during the 90-day efficacy phase. For all enrolled subjects, the absence of DUB symptoms was defined as: • No bleeding episodes lasting more than 7 days and • Not more than 4 bleeding episodes (changed with Amendment no. 6, and • No bleeding episodes with blood loss volume of 80 mL or more In addition, • Not more than 1 bleeding episode increase from baseline and

	• Total number of bleeding days not to exceed 24 days. • No increase from baseline in an individual subject's total number of bleeding days (changed with Amendment no. 6) In addition, for subjects enrolled with specific symptoms, the following criteria had to be met: • For subjects enrolled with prolonged bleeding, the decrease between the maximum duration during run-in phase and the maximum duration during the efficacy phase was to be at least 2 days. • For subjects enrolled with excessive bleeding: (1) the blood loss volume associated with each episode was to be <80 mL and (2) the blood loss volume associated with each bleeding episode was to represent a decrease of at least 50% from the average of the qualifying bleeding episodes, where the qualifying bleeding episodes were those with a blood loss volume 80 mL (per episode) that occurred during the run-in phase. **Efficacy (Secondary):** • Proportion of subjects cured from each individual symptom • Change in blood loss volume for all subjects and for subjects with excessive bleeding • Proportion of subjects cured from prolonged bleeding, excessive bleeding, and frequent bleeding • Menstrual blood loss volume for all subjects participating in the study and subjects with excessive bleeding at Cycle 1, 3, and 7 • Change in number of bleeding days and bleeding episodes • Change in number of sanitary protection items used • Proportion of subjects with improvement in the investigator's global assessment scale on days 84 and 196 • Proportion of subjects with improvement in the subject's overall assessment scale on days 84 and 196 • Change from baseline in quality of life scores on days 84 and 196 • Change from baseline in hemoglobin and serum ferritin concentrations on days 84 and 196 • Change from baseline in hematocrit on days 196 • Change from baseline in psychological general well-being index (PGWBI) score on days 84 and 196 • Change from baseline in McCoy female sexuality questionnaire (MFSQ) score on days 84 and 196 • Change from baseline in Euroqol 5 dimensional (EQ-5D) score on days 84 and 196. • Change from baseline in visual analogue scale (VAS) of the Euroqol 5 dimensional (EQ-5D) score on days 84 and 196 • Resource use assessment by use of a self-administered questionnaire (change in the employment status, days missed from work, productivity while working, regular daily activities, unscheduled outpatient visit at hospital, unscheduled outpatient visit to physician, additional unscheduled procedures, received ambulatory services, no out-of-pocket expenses, and not have any medical treatment) on days 84. and 196 **Safety:** Physical and gynecological examinations, hCG pregnancy tests, Pap

	smear, endometrial biopsy, bleeding pattern, vital signs, clinical laboratory tests, transvaginal ultrasound and AE profile.
Statistical Methods:	**Efficacy (Primary):** Uterine bleeding parameters were analyzed over a 90-day efficacy phase. The primary efficacy variable was analyzed by differences of proportions and their corresponding confidence intervals. Logistic regression models were used to analyze covariates for the primary efficacy variable. **Efficacy (Secondary):** Dichotomous secondary efficacy variables were analyzed by differences of proportions and their corresponding confidence intervals. Continuous secondary efficacy variables were analyzed with an analysis of variance or an analysis of covariance model. **Safety:** Listings of subjects with abnormal findings in physical and gynecological examinations, endometrial biopsies, pregnancy test (home), and transvaginal ultrasound were provided. Safety variables were not analyzed; descriptive statistics were provided by treatment group and visit for body weight, systolic and diastolic blood pressure, and heart rate. Treatment groups were compared with respect to the change from baseline to end of study with analysis of covariance (ANCOVA).
Number of Subjects:	Planned: 180 subjects were to be randomized (120 for EV/DNG and 60 for placebo). Analyzed: 231 subjects were (149 for EV/DNG and 82 for placebo) and considered as intent-to-treat (ITT) population, 226 (145 for EV/DNG and 81 for placebo) were in safety analysis set (SAF), and 89 (55 for EV/DNG and 34 for placebo) were in the per-protocol set (PPS).

Study Results

Results Summary — Subject Disposition and Baseline

Out of 575 screened subjects, 344 subjects were classified as "screening failures". Study medication was administered to 145 subjects in the EV/DNG group and 81 subjects in the placebo group. Study medication was completed by 109 subjects in the EV/DNG group and 62 subjects in the placebo group.

A subject was included in the PPS for analysis if she met all the inclusion/exclusion criteria, did not take any prohibited medication, had at least 75% overall study drug compliance, had no major protocol violations, and completed 7 treatment cycles. A subject who took at least one dose of study medication was included in the safety analysis set. A total of 226 (97.8%) subjects were included in the safety analysis set: 145 (97.3%) subjects in the EV/DNG group and 81 (98.8%) subjects in the placebo group.

The mean age of the subjects of the ITT was 39.5 ± 6.6 years in the EV/DNG group and 38.5 ± 7.5 years in the placebo group. The mean body mass index of the subjects of ITT was 24.55 ± 3.49 kg/m^2 in the EV/DNG group and 25.68 ± 3.01 kg/m^2 in the placebo group. The subject population was well balanced for all demographic and baseline characteristics between the two treatment groups throughout the study course. Reported DUB symptoms at baseline were predominantly excessive bleeding with more than 90% in the two treatment

groups, prolonged bleeding in more than 12%, and prolonged and excessive bleeding in more than 10% of the subjects of the 2 treatment groups.

Results Summary — Efficacy

The primary variable was the overall success rate defined by the number of subjects with the absence of any DUB symptom and who met all the relevant criteria for success during the 90-day efficacy assessment phase, as compared to the number of subjects having at least one qualifying DUB symptom during the run-in phase.

The overall success rate showed a statistically significant benefit in the subjects receiving EV/DNG than in the subjects receiving placebo ($p<0.0001$). The ratio of the overall success within the EV/DNG group (responder and symptomatic non-responder, without non-responders due to missing values) was 0.4074. The 95% confidence interval was 0.3138 - 0.5062. The ratio of the overall success within the placebo group (responder and symptomatic non-responder, without non-responders due to missing values) was 0.0161. The 95% confidence interval was 0.0004 – 0.0866.

The secondary efficacy variables mostly support the clinical benefit of EV/DNG over placebo in the treatment of subjects with dysfunctional uterine bleeding.

Treatment with EV/DNG was superior to placebo in the therapy of excessive bleeding in this study. The point estimates for the proportion of cured subjects who enrolled with excessive bleeding are 41.18% (CI:31.52% - 51.36%) in the EV/DNG group, and 1.69% (CI: 0.04% - 9.09%) in the placebo group. The difference was statistically significant with $p<0.0001$. For the subjects who enrolled with prolonged bleeding, 35% of subjects in the EV/DNG group and 10% of subjects in the placebo group were cured. This difference was not statistically significant. The treatment effect on subjects with frequent bleeding cannot be evaluated as no subjects with this symptom as defined in the protocol of this study were included.

The decrease in menstrual blood loss volume from baseline to the efficacy phase1 was a 458.4 ml ± 409.63 in the EV/DNG group subjects and 93.2 ml ± 267.98 in the placebo group. The difference between the adjusted means (-372.69) was statistically significant ($p<0.0001$ by rank ANCOVA, the 95% confidence interval was between the limits of -489.91 and -255.47).

In the subgroup of subjects with excessive bleeding, the mean decrease from baseline to the efficacy phase was 480.6 ml ± 410.62 in the EV/DNG group subjects. The decrease was 94.17 ml ± 270.17 in the placebo group subjects. The difference between the adjusted means (-391.06) was statistically significant ($p<0.0001$ by rank analysis of variance (ANOVA), the 95% confidence interval was between the limits of -510.18 and -271.94).

The mean decrease from baseline to the efficacy phase in the total number of bleeding days was 5.13 ± 9.72, range: -62 to 13 days in the EV/DNG group and 3.08 ± 7.89, range: -45 to 10 days in the placebo group. The difference between the adjusted means (-2.08) was statistically significant ($p = 0.0186$ by rank ANCOVA).

The mean decrease from baseline to the efficacy phase in the total number of bleeding episodes was 0.35 ± 1.088 in the EV/DNG group and 0.38 ± 0.739 in the placebo group. The difference between the adjusted means (0.012) was not statistically significant ($p = 0.5095$) by rank ANCOVA.

The change from baseline (90 days run-in phase) to the efficacy phase was a decrease in the

total sanitary protection products by 38.43 ± 30.00 in the EV/DNG group subjects and 16.52 ± 32.17 in the placebo group subjects. This change was statistically significant. The p-value from ANCOVA with terms for treatment and center, and baseline as covariates was p<0.0001 with confidence intervals from -30.451 to -14.026.

The difference between treatment groups was statistically significant for the model-estimated mean changes from baseline in hematocrit concentrations at treatment day 196 (1.513% for EV/DNG and -0.046% for placebo; p=0.0049 by ANCOVA).

Statistically significant differences between treatment groups were present at treatment day 196 in the model-estimated mean changes from baseline for ferritin (8.624 for EV/DNG and 0.441 for placebo) (p=0.0017, by rank ANOVA).

For hemoglobin, a statistically significant difference between treatment groups in the model estimated mean changes from baseline (0.697 g/dL for EV/DNG and 0.053 g/dL for placebo) existed at treatment day 196 only (p<0.0001 by rank ANCOVA).

The difference in the proportions of investigators who noted an improvement in the ITT subjects' condition was statistically significantly higher in the EV/DNG group than in the placebo group at both treatment day 84 (83.85% and 39.4%, respectively) and treatment day 196 (84.7% and 39.5%, respectively) (p<0001 at both time-points).

Similarly, the difference in the proportions of subjects who noted an improvement in their condition was statistically significantly higher in the EV/DNG group than in the placebo group at both treatment day 84 (72.4% and 52.9%, respectively) and treatment day 196 (77.9% and 45.1%, respectively) (p=0.008 at treatment day 84, p<0001 at treatment day 196).

The impact of DUB on health-related QoL and resource use was investigated at baseline, Day 84, and Day 196. At baseline subjects of both groups showed high scores in all QoL instruments, with values in the range of a healthy population. Over the course of treatment only small changes were observed. In this study, the placebo arm showed a trend towards slight improvement over time while women under active treatment remained more or less stable.

Results Summary — Safety

No deaths occurred in the course of this study. A total of 6 non-fatal SAEs were reported for 4 of 226 subjects (1.8%), two subjects from the EV/DNG and the placebo group each. The relationship to study drug for two SAEs ductal carcinoma in situ [breast] and chronic cholecystitis) from EV/DNG-treated subjects were assessed as "possible" by the investigator. All other SAEs were assessed as being not or unlikely related to the study drug. Two pregnancies occurred during the course of the study in placebo-treated subjects. In one subject, an intrauterine death was diagnosed. Both cases were terminated with induced abortion.

A total of 465 AEs were reported in 145 (64.2%) subjects during the study course. The frequency of AEs was slightly higher in the EV/DNG group. As generally known from clinical trials the high grade of observation and number of visits has an impact on the frequency of reported AEs.

The most frequently reported AEs were headache (14.5% of the EV/DNG-treated subjects, 14.8% of the placebo-treated subjects), nasopharyngitis (8.3% vs 4.9%, respectively), breast tenderness (4.1% vs 3.7%), metrorrhagia (5.5% vs 1.2%), nausea (4.8% vs 2.5%) and decreased serum ferritin (2.1% vs 7.4%).

The AEs were classified as being treatment-related (possible/probable/definite) for 59 subjects (40.7%) from the EV/DNG group compared to 16 subjects (19.8%) from the placebo group. The most frequent treatment-related AEs were headache for 14 subjects (9.7%) from the EV/DNG group and 6 subjects (7.4%) from the placebo group, metrorrhagia (8 [5.5%] vs 1 [1.2%], respectively), breast pain (8 [5.5%] vs 0 [0.0%]), breast tenderness (5 [3.4%] vs 2 [2.5%]), and nausea (6 [4.1%] vs 0 [0.0%]).

The AEs were classified as being conduct-related (possible/probable/definite) for 18 subjects (12.4%) from the EV/DNG group compared to 4 subjects (4.9%) from the placebo group and showed a comparable pattern as the treatment-related AEs.

Nineteen subjects had AEs which led to discontinuation of the study drug. The most frequent reasons for discontinuation of the study medication each occurred twice in this study and were the following: headache, migraine, nausea, decreased libido, altered mood, and dysmenorrhea. The majority of the AEs leading to discontinuation were rated as treatment-related by the investigators.

The outcome of AEs for the majority of subjects was resolved/resolving by the end of the study, for a total of 118 subjects (52.2%) with 78 subjects (53.8%) from the EV/DNG group and 40 subjects (49.4%) from the placebo group. Two subjects from the EV/DNG group recovered with residual effects (headache, back pain) as well as one subject from the placebo group (chloasma). The outcome of not recovered/not resolved was obtained for a total of 22 subjects (9.7%), with 13 subjects (9.0%) from the EV/DNG group and 9 subjects (11.1%) from the placebo group.

Clinical laboratory evaluations including vital signs were generally within the normal range and gave no reasons for any safety concerns; individual deviations were not determined to be clinically significant. Six AEs of increased blood pressure were reported in this treatment group compared to one AE in the under placebo.

Three EV/DNG and one placebo treated subjects were diagnosed with an abnormal Pap smear at the end of treatment visit which were reported as AEs. Abnormal values resulted in the call for a repeat of the examination after 3 months. Subjects were followed up until resolution or information available about recovery process at the time of report writing was documented in the trial master file.

Conclusion(s)

In this study, the superiority of EV/DNG versus placebo with regard to the efficacy in the treatment of heavy and prolonged bleeding without organic cause has been demonstrated. The effect on frequency of bleeding could not be evaluated due to the underrepresentation of this condition in the study population. Based on the study results, the study drug was safe and well tolerated.

Publication(s):	Fraser IS, Jensen J, Schaefers M, Mellinger U, Parke S, Serrani M. Normalization of blood loss in women with heavy menstrual bleeding treated with an oral contraceptive containing estradiol valerate/dienogest. Contraception. 2012 Aug;86(2):96-101. Epub 2012 Jan 10. PMID: 22240178 Fraser IS, Parke S, Mellinger U, Machlitt A, Serrani M, Jensen J. Effective treatment of heavy and/or prolonged menstrual bleeding without organic cause: pooled analysis of two multinational, randomised, double-blind, placebo-controlled trials of oestradiol valerate and dienogest. Eur J Contracept Reprod Health Care. 2011

	Aug;16(4):258-69. PMID:21774563 Fraser IS, Römer T, Parke S, Zeun S, Mellinger U, Machlitt A, Jensen JT. Effective treatment of heavy and/or prolonged menstrual bleeding with an oral contraceptive containing estradiol valerate and dienogest: a randomized, double-blind Phase III trial. Hum Reprod. 2011 Oct;26(10):2698-708. Epub 2011 Jul 21. PMID: 21784734 Wasiak R, Filonenko A, Vanness DJ, Wittrup-Jensen KU, Stull DE, Siak S, Fraser I. Impact of estradiol-valerate/dienogest on work productivity and activities of daily living in European and Australian women with heavy menstrual bleeding. Int J Womens Health. 2012;4:271-8. doi: 10.2147/IJWH.S31740. Epub 2012 Jul 12. PMID: 22927764 Fraser IS, Zeun S, Parke S, Wilke B, Junge W, Serrani M. Improving the objective quality of large-scale clinical trials for women with heavy menstrual bleeding: experience from 2 multi-center, randomized trials. Reprod Sci. 2013 Jul;20(7):745-54. doi: 10.1177/1933719113477492. Epub 2013 Feb 25. PMID: 23439617		
Date Created or Date Last Updated:	26 Aug 2013	**Date of Clinical Study Report:**	19 MAR 2009

Investigational Site List

Marketing Authorization Holder in Germany	
Name	Bayer Vital GmbH
Postal Address	D -51368 Leverkusen, Germany
Sponsor in Germany	
Legal Entity Name	Bayer HealthCare AG
Postal Address	D -51368 Leverkusen, Germany

List of Investigational Sites

No	Facility Name	Street	ZIP Code	City	Country
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2	Private Practice Dr. Ian Fraser	328-336 Liverpool Road Ashfield, NSW 2131	NSW 2131	Ashfield	AUSTRALIA
3	Center for Clinical& Basic Research	CCBR Pardubice Masarykovo namesti 2667 Pardubice 2667 Czech Republic	2667	Pardubice	CZECH REPUBLIC
4	Gynekologicka ambulance Vanda Horejsi, MD	Matice skolske 104/7	37001	Ceske Budejovice	CZECH REPUBLIC
5	Gynekologicko-poradnicka ambulance Dr. Hlavackova	Gynokologicka ambulance Zeyerova 2442 39701 Pisek Czech Republic	39701	Pisek	CZECH REPUBLIC

6	Lekarsky dum Praha 7 a.s.Gynekologicka ambulance Dr. Jenicek	Gynekologicka ambulance Janovskeho 993/48	170 00	Praha 7	CZECH REPUBLIC
7	Adenova Lääkärikeskus Oy	Länsituulentie 10 A 3. krs.	02100	Espoo	FINLAND
8	Koskiklinikka	Hatanpaanvaltatie 1	33100	Tampere	FINLAND
9	Terveystalo Lahti	Aleksanterinkatu 13	15110	Lahti	FINLAND
10	Ylioppilaiden terveydenhoitosäätiö, Turku	Kirkkotie 13	20540	Turku	FINLAND
11	ClinPharm International GmbH	&Co KG Studienzentrum Schaeferstrasse 61	01067	Dresden	GERMANY
12	emovis GmbH	Wilmersdorfer Str. 79	10629	Berlin	GERMANY
13	Praxis Hr. Dr. K. Greven	Pfarrstr. 47	30459	Hannover	GERMANY
14	Praxis Hr. Dr. S. Schönian	Rappenwörthstr. 48	76287	Rheinstetten	GERMANY
15	Praxis Hr. Dr. U. Kohoutek	Diakonissenstrasse 1	76199	Karlsruhe	GERMANY
16	Borsod-Abauj-Zemplen County Hospital	Szentpeteri kapu 76. 3501 Miskolc	3501	Miskolc	HUNGARY
17	Selya Janos Hospital	Selye Janos Korhaz Gynecology Szechenyi u. 2 Komarom 2921	2921	Komarom	HUNGARY
18	University of Semmelweis	Faculty of General Medicine Department of Obstetrics and Gynecology Ulloi ut 78/A Budapest 1082	1082	Budapest	HUNGARY

19	Medisch Spectrum Twente, Locatie Ariensplein	Ariensplein 1 7511 JX Enschedde	7511 JX	Enschede	NETHERLANDS
20	Menox BV	Menox BV Toernooiveld 220 Mercator 1 Nijmegen 6525 EC	6525 EC	Nijmegen	NETHERLANDS
21	PreCare Trial & Recruitment	PreCare Trial & Recruitment Geleenbeeklaan90 Geleen 6166 GR	6166	Geleen	NETHERLANDS
22	CSK MSWiA	ul. Woloska 137 Warszawa 02-507 Poland	02-507	Warszawa	POLAND
23	Instytut Centrum Zdrowia Matki Polki	Klinika Ginekologii Operacyjnej i Endoskopowej ul. Rzgowska 281/289 Lodz 93-338 Poland	93-338	Lodz	POLAND
24	Poliklinika Ginekologiczna-Poloznicza	ul Zamenhofa 19	15-435	Bialystok	POLAND
25	SPSK nr 1	I Katedra i Klinika Ginekologii AM w Lublinie ul. Staszica 16 Lublin 20-081	20-081	Lublin	POLAND
26	Szpital Kliniczny nr 3	ul. Polna 33 Poznan 60-525 Poland	60-525	Poznan	POLAND
27	Akademiska Sjukhuset	Kvinnokliniken Akademiska sjukhuset SE-751 85 Uppsala	SE-751 85	Uppsala	SWEDEN

28	Karolinska Universitetssjukhuset Huddinge	Karolinska Universitetssjukhuset, Huddinge Kvinnokliniken K63	141 86	Stockholm	SWEDEN
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31	Instr. of Pediatrics, Obstetrics & Gynecology	AMS of Ukraine Dept. of Endocrine Gynecology 22, Reitarskaya ul.	01034	Kiev	UKRAINE
32	Kyiv Medical Academy of Postdyploma Education	Geroev Stalingrada 16	04210	Kiev	UKRAINE
33	Lviv Regional Center Perinatal Center	G. Vashington ul. 6		Lviv	UKRAINE
34	Bridge House Medical Centre	Bridge House Medical Centre MBChB, MRCGP, RCGP 11 Ladybridge Road Cheadle Hulme	SK8 5LL	Cheadle	UNITED KINGDOM
35	Luton & Dunstable Hospital	Lewsey Road Luton, Bedfordshire LU4 0DZ	LU4 0DZ	Luton	UNITED KINGDOM
36	MeDiNova Research	MeDiNova Ltd North London Clinical Studies Centre Mount Vernon Hospital Rickmansworth Road Northwood HA6 2RN	HA6 2RN	Northwood	UNITED KINGDOM

Product Identification Information

Product Type	Drug
US Brand/Trade Name(s)	Natazia
Brand/Trade Name(s) ex-US	Qlaira, Klaira, Qlair, Qlairista
Generic Name	Estradiol valerate, Dienogest
Main Product Company Code	BAY86-5027
Other Company Code(s)	SH T 00658 ID
Chemical Description	Estra–1,3,5(10)–triene–3,17β–diol–17–valerate (WHO) 19-Norpregna-4,9-diene-21-nitrile, 17-hydroxy-3-oxo-17α-Cyanomethyl-17β-hydroxy-estra-4,9-dien-3-one (CAS)
Other Product Aliases	Estradiol 17–valerate Estradiol 17β–valerate Estra–1,3,5(10)–triene–3,17–diol (17β), 17–pentanoate 1,3,5(10)–Estratriene–3,17β–diol–17–valerate ZK 5104 17α-Hydroxy-3-oxo-19-norpregna-4,9-diene-21-nitrile (IUPAC) 17β-Hydroxy-3-oxo-19-nor-17α-pregna-4,9-diene-21-nitrile (17α)-17-Hydroxy-3-oxo-19-norpregna-4,9-diene-21-nitrile ZK00037659 FS-10101-N

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