

CLINICAL REVIEW

Application Type NDA
Application Number 22-252
Priority or Standard Standard

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Division / Office Division of Reproductive and Urologic
Products (DRUP) / Office of Drug
Evaluation III (ODE III)

Reviewer Name Gerald Willett M.D.
Review Completion Date April 28, 2010

Established Name Estradiol valerate / Dienogest (EV/DNG)
Trade Name To be determined
Therapeutic Class Combination oral contraceptive
Applicant Bayer HealthCare Pharmaceuticals Inc.

Formulation Oral tablets
Dosing Regimen - Days 1-2 (3.0 mg EV)
Cycle Days (dose) Days 3-7 (2.0 mg EV + 2.0 mg DNG)
Days 8-24 (2.0 mg EV + 3.0 mg DNG)
Days 25-26 (1.0 mg EV)
Days 27-28 (placebo)

Indication Contraception (primary)
Heavy and/or prolonged menstrual
bleeding (secondary)

Intended Population Women of childbearing age

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List of Abbreviations and Definitions

ADR	Adverse drug reaction
AE	Adverse event
ANCOVA	Analysis of covariance
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
CBG	Cortisol-binding globulin
CI	Confidence interval
COC	Combination oral contraceptive
CHMP	Committee for Medicinal Products for Human Use
Climodien 1/2	Menopausal hormone therapy consisting of 1 mg EV / 2 mg DNG (once daily use)
Climodien 2/2	Menopausal hormone therapy consisting of 2 mg EV / 2 mg DNG (once daily use)
CRF	Case report form
DHEA-S	Dehydroepiandrosterone sulfate
DNG	Dienogest
DRUP	Division of Reproductive and Urologic Products
DUB	Dysfunctional uterine bleeding
ECG	Electrocardiogram
EE	Ethinyl estradiol
EMA	European Agency for the Evaluation of Medicinal Products
EOS	End of study
EV	Estradiol valerate
EV/DNG	Estradiol valerate / dienogest (to-be marketed product) = Cycle days 1-2 (3.0 mg EV) Cycle days 3-7 (2.0 mg EV + 2.0 mg DNG) Cycle days 8-24 (2.0 mg EV + 3.0 mg DNG) Cycle days 25-26 (1.0 mg EV) Cycle days 27-28 (placebo)
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
GGT	Gamma glutamyltransferase
HbA1c	Hemoglobin A1c
hCG	Human chorionic gonadotropin
HDL	High-density lipoprotein
HMB	Heavy menstrual bleeding
HT	Hormone therapy
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IND	Investigational new drug
IRB	Institutional review board
ISE	Integrated summary of efficacy
ISS	Integrated summary of safety
IUD	Intrauterine device
IUS	Intrauterine system
LDL	Low-density lipoprotein
LH	Luteinizing hormone
LNG	Levonorgestrel

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LNG IUS	Levonorgestrel-releasing intrauterine system
LOCF	Last observation carried forward
NSAID	Non-steroidal anti-inflammatory drug
MBL	Menstrual blood loss
MedDRA	Medical Dictionary for Drug Regulatory Activities
MFSQ	McCoy Female Sexuality Questionnaire
Microgynon	Monophasic COC with 0.03 mg EE / 0.15 mg LNG (1 per day x 21, then 7 placebo)
MI	Myocardial infarction
Miranova	Monophasic COC with 0.02 mg EE / 0.10 mg LNG (1 per day x 21, then 7 placebo)
NDA	New drug application
ODE III	Office of Drug Evaluation III
OGTT	Oral glucose tolerance test
PBAC	Pictorial Blood Loss Assessment Chart
PGWBI	Psychological General Well-Being Index
PI	Pearl Index
PID	Patient identification number
PPS	Per-protocol analysis set
PSUR	Periodic Safety Update Report
SAE	Serious adverse event
SD	Standard deviation
SH D 593 B (Miranova)	Monophasic COC with 0.02 mg EE / 0.10 mg LNG (1 per day x 21, then 7 placebo)
SH T00658ID	To be marketed 4-Phasic product (estradiol valerate and dienogest); EV/DNG
SHBG	Sex hormone-binding globulin
SOC	System organ class
Triquilar	<u>3-Phasic COC</u> Cycle days 1-6 (0.03 mg EE / 0.05 mg LNG) Cycle days 7-11 (0.04 mg EE / 0.075 mg LNG) Cycle days 12-21 (0.03 mg EE / 0.125 mg LNG) Cycle days 22-28 (placebo)
TSH	Thyroid stimulating hormone
TVU	Transvaginal ultrasound
Valette	Monophasic COC with 0.03 mg EE / 2.0 mg DNG (1 per day x 21, then 7 placebo)
VLDL	Very low-density lipoprotein
VTE	Venous thromboembolism
WHO	World Health Organization
WY	Women years

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval is recommended for the Applicant's proposed primary indication for EV/DNG, that of "Prevention of pregnancy in women of reproductive age."



1.2 Risk Benefit Assessment

Contraception

The risk benefit assessment is favorable for the primary indication of contraception. There is no evidence in the extensive safety database submitted in this NDA that the use of EV/DNG by women will result in any new safety problem or will result in an increased incidence of any known combined oral contraceptive (COC)-related adverse event compared to similar COCs. The benefit of this product is comparable to other approved COCs. Table A presents the key contraceptive efficacy data calculated by the FDA biostatistician (Dr. Fang) from the 2 pivotal Phase 3 contraceptive trials (Studies 306660 - Europe and 304742 – US/Canada) that had contraception as a primary endpoint. The primary difference between these results and the Applicant's results is that DRUP has recently considered "during treatment" pregnancies to include only those occurring within 7 days (rather than 14 days) after study drug treatment. Therefore only 5 pregnancies were felt to qualify as "during treatment" in Study 304742 and only 9 pregnancies were felt to qualify as "during treatment" in Study 306660. The Applicant's results that included 14 days post treatment identified 6 pregnancies in Study 304742 and 10 pregnancies in Study 306660.

Table A: Contraceptive Efficacy Data from the Pivotal Phase 3 Studies (Based on Pregnancies that Occurred During Cycles 1 to 13 Including 7 Days after Treatment in Subjects 18 to 35 Years of Age)

Study	Cycles *	Pregnancies	Pearl Index _u	Upper 95% CI	KMLT **
306660	11,274	9	1.04	1.97	0.0099
304742	3,969	5	1.64	3.82	0.0157

CI = confidence interval; u = unadjusted

* = The number of cycles = those in which back-up contraception was not used

** = Kaplan Meier life table estimate of contraceptive failure rate at the end of one year

Source: Integrated summary of efficacy; tables 4, 5 & 6 pages 825-827 of 909 and submission #13 (Jan 28, 2010) which provided the number of cycles

The Applicant also submitted a large Phase 3 (active comparator) trial that

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obtained pregnancy information from 1,335 cycles with no use of back-up contraception, but which did not specify contraception as a primary endpoint. The EV/DNG arm of this study (Study 304004), which had 399 subjects receiving medication, had no “during treatment” pregnancies reported.

Heavy and/or Prolonged Menstrual Bleeding

[REDACTED] (b) (4)

The determination of a responder in the 2 Phase 3 trials (Studies 308961 – Europe/Australia and 308960 – US/Canada) for this secondary bleeding indication required the absence of DUB symptoms in a 90-day efficacy period, defined as:

- No bleeding episodes lasting more than 7 days and
- No more than 4 bleeding episodes and
- No bleeding episodes with blood loss volume of 80 mL or more

In addition there could be:

- No 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 patient’s total number of bleeding days

In addition, for patients enrolled with specific symptoms, the following criteria had to be met:

- If patients enrolled with prolonged bleeding, the decrease between the maximum duration during the run-in phase and the maximum duration during the efficacy phase should be at least 2 days
- If patients enrolled with excessive bleeding: (1) the blood loss volume associated with each episode should be < 80 mL and (2) the blood loss volume associated with each bleeding episode should represent a decrease of at least 50% from the average of the qualifying bleeding episodes, where the qualifying bleeding episodes are those with a blood loss volume \geq 80 mL (per episode) that occurred during the run-in phase

The Applicant was also asked by DRUP to set a point estimate for a treatment effect that would be considered clinically meaningful. The Applicant proposed that a 50% responder rate would be required for efficacy success in the two Phase 3 pivotal studies. This responder rate was not based on data from focus group analyses of women with heavy and/or prolonged bleeding; however, the

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for postmarketing risk evaluation or mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

A postmarketing surveillance study is recommended as a requirement because the progestin in this product (dienogest) is a new molecular entity.

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The proposal by the Applicant to incorporate the US market into the International Active Surveillance Study of Women Taking EV/DNG (INAS-EV) is acceptable. However, some of the details concerning the US component to the study may need to be clarified with the Applicant.

For additional details on the INAS-EV study, see Section 7.3.5

2 Introduction and Regulatory Background

2.1 Product Information

EV/DNG represents a new combination oral contraceptive product in the U.S. in regard to utilizing a) estradiol valerate in an oral form, b) a new progestin called dienogest and c) a 4-phasic active drug regimen. The Applicant has conducted a drug development program that was designed to study the product for the primary indication of contraception and also for a secondary indication of dysfunctional uterine bleeding in women without organic pathology. The term dysfunctional uterine bleeding (DUB) in general refers to uterine bleeding without evidence of pathology, such as endometrial polyps, fibroids, or uterine neoplasia. DUB has been made more specific in this NDA application (b) (4)

The Applicant has received drug approval in Europe for the proposed EV/DNG product submitted for approval in NDA 22-252. Initial approval for this product as a contraceptive was in November, 2008 and marketing began in 2009. Marketing of oral estradiol valerate combined with dienogest in a menopausal therapy product (e.g., Climodien 2/2) has been carried out in Europe since 2001. Marketing of a combination oral contraceptive that contains ethinyl estradiol and dienogest (e.g., Valette) has been carried out in Europe since 1995.

In this review the term **EV/DNG** alone or **final EV/DNG regimen** refers to the to-be-marked product that is the subject of this review. The term **developmental EV/DNG regimen** refers to a product that contains either different individual drug doses or different cycle day dosing.

2.2 Currently Available Treatments for Proposed Indications

There are numerous combination oral contraceptives approved in the U.S. that are either biphasic or triphasic in their hormonal dosage amounts during a 28 day pill cycle. EV/DNG, if approved, will represent the first 4-phasic active drug regimen. EV/DNG also contains a progestin, dienogest, which represents a new molecular entity in the U.S. market. The estrogenic component of EV/DNG, estradiol valerate, is approved as an injectable formulation in the U.S. but this

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product will be the first oral preparation of estradiol valerate in this country.

Historically, class labeling of COCs used to contain a section devoted to non-contraceptive health benefits. Evidence supporting these benefits was generally derived from the medical literature, not from separate studies of each COC product. For example, in the Ortho Tri-Cyclen Lo label, the beneficial effects on menses included increased menstrual cycle regularity, decreased blood loss, decreased incidence of iron deficiency anemia and decreased incidence of dysmenorrhea. These benefits are not included in recent COC labeling.

This is the first application for a combination oral contraceptive for a labeled secondary indication of heavy and/or prolonged menstrual bleeding.

Other medical treatments approved for “bleeding” in women include the following:

- Norlutin® (norethindrone) 10-20 mg (daily for cycle days 5-23) for menstrual irregularity and functional uterine bleeding [No longer marketed]
- Norlutate® (norethindrone acetate) 2.5-10 mg (daily for cycle days 5-23) for menstrual irregularity and functional uterine bleeding [No longer marketed]
- Aygestin® (norethindrone acetate) 2.5-10 mg for 5-10 days to produce secretory transformation of an endometrium (to treat abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology)
- Provera® (medroxyprogesterone acetate) 5-10 mg for 5-10 days (to treat abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer)
- Mirena® (levonorgestrel-releasing intrauterine system) for up to 5 years of use (to treat heavy menstrual bleeding in women who choose to use intrauterine contraception as their method of contraception)
- Lysteda® (tranexamic acid) 1,300 mg (two 650 mg tablets) three times a day (3,900 mg/day) for a maximum of 5 days during monthly menstruation (to treat cyclic heavy menstrual bleeding)
- Meclofenamate sodium – 100 mg three times a day, for up to six days, starting at the onset of menstrual flow (for the treatment of primary dysmenorrheal and idiopathic heavy menstrual blood loss)

Medical Officer’s Comment:

The most recent approvals for bleeding indications were Mirena (Oct. 2009) and Lysteda (Nov. 2009).

2.3 Availability of Proposed Active Ingredients in the United States

Estradiol valerate is available as an injectable product in the U.S. The indications

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include:

- Treatment of moderate to severe vasomotor symptoms associated with the menopause (10-20 mg every four weeks)
- Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause (10-20 mg every four weeks)
- Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure (10-20 mg every four weeks)
- Treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only) [30 mg or more administered every one or two weeks]

Dienogest represents a new molecular entity for the U.S. market.

2.4 Important Safety Issues with Consideration to Related Drugs

Combination oral contraceptives as a general class have a number of safety issues that have been well recognized since their introduction in the 1960s. The following adverse events represent the major concerns described in contraceptive labeling:

- Vascular events, which may rarely be fatal, including:
 - Deep venous thrombosis, pulmonary embolism, other venous thromboses
 - Myocardial infarction (especially in women >35 years who smoke)
 - Stroke (both ischemic and hemorrhagic types reported)
- Hepatic adenomas, hepatic nodular hyperplasia, cholestasis
- Blood pressure increase
- Gallbladder disease
- Headaches
- Irregular uterine bleeding, amenorrhea, oligomenorrhea
- Nausea
- Breast tenderness
- Mood changes
- Hypertriglyceridemia

2.5 Summary of Presubmission Regulatory Activity Related to Submission

[REDACTED] (b) (4)

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(b) (4)

The INDs pertinent to this application include 64,809 (contraceptive indication)

(b) (4)

IND 64,809

A Pre-IND meeting was held on March 17, 2004. Key clinical DRUP comments from the meeting minutes include the following:

“Because dienogest is a new molecular entity (NME), we will require two adequate and well-controlled studies for efficacy and safety.”

Medical Officer’s Comment:

The Applicant has provided three contraceptive studies for efficacy and safety:

- ***Protocol 306660 (report A35179) – 1,377 subjects in Europe***
- ***Protocol 304742 (report A39818) – 490 subjects in U.S. and Canada***
- ***Protocol 304004 (report A35644) – 399 subjects in Europe***

This reviewer considers the first two studies pivotal for the contraceptive indication. Study 304004 did not specify contraception as a primary endpoint. Both contraception and cycle control were studied in 304004.

“We recommend that at least one of your adequate and well-controlled Phase 3 clinical trials include a substantial number of subjects in North America. An adequate number of subjects from North America (preferably the U.S.) would be the number required to provide efficacy and safety data from approximately 10,000 28-day treatment cycles, with at least 200 women between ages 18-35 completing 13 28-day cycles of treatment.”

Medical Officer’s Comment:

Amendment 1 (dated April 21, 2005) doubled the study population in the U.S./Canadian Study 304742 from 240 subjects to 480 subjects. Although this increase was not anticipated to reach 10,000 cycles (but rather estimated to be 5,500 28-day cycle equivalents) the Division found that number to be acceptable, especially in light of the large number of subjects being studied in Europe, and this was conveyed in a letter to the Sponsor (June 9, 2005).

In Study 304742, 264 subjects (age 18-35) completed 13 full 28-day cycles of study medication. As of Cycle 13, there were 4,386 complete cycles recorded in the study. This increased to 5,974 complete cycles by Cycle 28.

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84 subjects in the U.S. /Canadian bleeding study (Protocol 308960) completed 7 cycles of treatment with EV/DNG, which provided an additional 588 cycles for the North American population.

“We remind you that the primary efficacy analysis acceptable to the Division is an intent-to-treat analysis, using the unadjusted Pearl Index as the primary endpoint based on women 18-35 years of age and the number of pregnancy in cycles during which no back up contraception was used.”

Medical Officer’s Comment:

In addition, DRUP focuses on the contraceptive efficacy manifested in cycles 1-13. Study 306660 and 304742 had treatment durations of 20 and 28 cycles respectively. These added cycles are considered primarily for safety by this reviewer.

IND 64,809 was submitted to the FDA on Nov 17, 2004. The opening study proposed by the Sponsor (Berlex) for this IND was a Phase 1 multiple dose pharmacokinetic study (Protocol 303312) of the proposed to-be marketed product (EV/DNG).

The clinical information on the combination of estradiol valerate and dienogest as a contraceptive came from two large development programs. The development program for menopausal therapy had already produced an approved product (Climodien) in Europe. The development program for an estradiol valerate / dienogest oral contraceptive was very extensive by 2004 because the Sponsor had to make numerous modifications of the contraceptive regimens to provide both ovulation inhibition and bleeding control.

The 4-phasic regimen that Berlex proposed to the FDA in the Nov 17, 2004 submission is the same one that they are proposing for marketing in NDA 22-252 (EV/DNG).

A combination oral contraceptive containing ethinyl estradiol and dienogest (Valette) was approved in Europe in 1995.

No additional clinical or biostatistical comments were sent to the Sponsor after receipt of the Phase 3 contraceptive study protocol (304742) that included sites in the U.S. and Canada.

On December 18, 2007 a Pre-NDA meeting was held with the Sponsor. Discussions centered on a) presentation of safety data from other development programs for estradiol valerate and/or dienogest (different from the product submitted in this application; b) the adequacy of clinical lab safety data; c) labeling instructions for missed pills; and d) specific reporting requests in regard to unintended pregnancies.

2.6 Other Relevant Background Information

All of the relevant background information was conveyed in the preceding sections.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Applicant provided statements in their pivotal contraceptive and DUB clinical trials (study protocols 304742, 306660, 308960 and 308961) that the studies met all local legal and regulatory requirements. Protocols and protocol amendments were reviewed and approved by each of the study site's Independent Ethics Committee (IEC) or Institutional Review Board (IRB). The studies were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization (ICH) guideline E6: Good Clinical Practice (GCP).

The FDA's Department of Scientific Investigations (DSI) at the request of DRUP investigated the following clinical sites (Table 1). These sites were primarily chosen based on the number of subjects and the lack of recent inspections. There was no suspicion in the early data reviews that there were sites suspicious for having data integrity problems.

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Table 1: Division of Scientific Investigations (DSI) Inspections for NDA 22-252

Study	Indication	Site number	Investigator	Action
304742	Contracep	520	Gidday	<u>Voluntary Action Indicated (VAI)</u> Deficiencies noted: <ul style="list-style-type: none"> • Failure to adhere to protocol • Inadequate and inaccurate records • Failure to report drug reactions Recommendation: <ul style="list-style-type: none"> • Although violations noted they are unlikely to impact data integrity. The data generated by this site may be used in support of the respective indication.
306660	Contracep	2325	Sanchez-Borrego	<u>Voluntary Action Indicated (VAI)</u> Deficiencies noted: <ul style="list-style-type: none"> • Failure to adhere to protocol Recommendation: <ul style="list-style-type: none"> • Although violations noted they are unlikely to impact data integrity. The data generated by this site may be used in support of the respective indication.
306660	Contracep	243	Greven	No Action Indicated (NAI)
308960	DUB	123	Raskin	No Action Indicated (NAI)
308961	DUB	104	Hlavackova	No Action Indicated (NAI)
Bayer			Scheeren	<u>Voluntary Action Indicated (VAI)</u> Deficiencies noted: <ul style="list-style-type: none"> • Inadequate monitoring • Failure to maintain adequate written records of drug disposition and used drug Recommendation: <ul style="list-style-type: none"> • The studies appear to have been conducted adequately and the data submitted by the sponsor may be used in support of the respective indication

DUB = dysfunctional uterine bleeding

3.2 Compliance with Good Clinical Practices

The Applicant provided statements in all of their pivotal clinical trials (Study protocols 304742, 306660, 308960 and 308961) that the studies were conducted in accordance with Good Clinical Practice (GCP).

3.3 Financial Disclosures

There were three individuals with financial interest disclosures:

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1) (b) (6) submitted a disclosure of financial interests. She was a clinical investigator in Study (b) (6). She reported significant equity interest in the sponsor of the covered study. The Applicant provided the following information on (b) (6):

(b) (6) was a (b) (6) for Protocol (b) (6) (Report A29849) whose only responsibility was to complete screening mammograms for some of the study subjects at her office location. She did not conduct business from the clinical study site nor did she see all study subjects. Since her involvement in the clinical study was to provide a service to the investigative study site and there was only a possibility that Schering AG stocks were included in the pharmaceutical mutual fund she purchased, no steps to minimize potential bias of the clinical study results were taken nor deemed necessary.”

Medical Officer’s Comment:

(b) (6) site was headed by (b) (6) (principal investigator). This site enrolled (b) (6) subjects. This reviewer does not feel that the study site’s bleeding data would be biased based on her duties (mammograms).

2) (b) (6) submitted a disclosure of financial interests. He was a clinical investigator in Study (b) (6) (contraception). He reported significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study. The Applicant provided the following information on (b) (6)

(b) (6) was a principle investigator for Protocol (b) (6) (Report A39818) and disclosed that he had received payments in excess of \$10,000 for consulting from Bayer. In order to minimize potential bias of the clinical study results by any of his financial disclosures, he was not the sole person responsible for consenting/enrolling subjects and he in addition to a co-investigator were jointly responsible for reporting unanticipated problems. This is in accordance with the Conflict of Interest in Research Disclosure requirement at (b) (6). Additionally, (b) (6) did not personally receive any of the funds from the conduct of this clinical study.”

Medical Officer’s Comment:

(b) (6) site only contributed a small number of subjects (b) (6) of (b) (4) enrolled) to this contraceptive trial and was therefore not chosen as a DSI inspection site.

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3) (b) (6) submitted a disclosure of financial interests. She was a clinical investigator in Study (b) (6) (contraception). She reported significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study. The Applicant provided the following information on (b) (6)

(b) (6) was a principle investigator for Protocol (b) (6) (Report A39818). (b) (6) received honoraria from Bayer Healthcare Pharmaceuticals (formerly Berlex, Inc.) for various speaker engagements (b) (4)

These honoraria covered the period of (b) (4) and totaled \$23,695.47. To minimize potential bias of the clinical study results, none of the monies from the clinical study grants were received personally by (b) (6) .”

Medical Officer's Comment:

(b) (6) **site only contributed a small number of subjects ((b) (6) of (b) (4) enrolled) to this contraceptive trial and was therefore not chosen as a DSI inspection site.**

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Dr. Tarun Mehta reviewed the chemistry aspects for this Application. The recommendation and conclusion on approvability is the following:

“This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. However, labeling issues are still pending and a site recommendation from the Office of Compliance is overall “Withhold” as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until all issues are resolved.”

4.2 Clinical Microbiology

Microbiology was not consulted for this application.

4.3 Preclinical Pharmacology/Toxicology

Dr. Krishan Raheja reviewed the nonclinical pharmacology and toxicology in NDA 22-252 (b) (4). His recommendations include:

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A. Recommendation on approvability: Nonclinical data supports approval of NDA 22-252 for Estradiol valerate/Dienogest.

B. Recommendation for nonclinical studies: No additional nonclinical studies are required

C. Recommendations on labeling: The proposed Prescribing Information is in accordance with the PLR and presented in SPL format and is acceptable.

Medical Officer's Comment:

Since estradiol is approved in many formulations and has decades of clinical experience, the primary focus in Dr. Raheja's review was that of the new molecular entity dienogest. His key findings related to dienogest were the following:

- ***No adverse neurological, cardiovascular, pulmonary, renal or gastrointestinal effects were observed in safety pharmacology studies.***
- ***Dienogest was not mutagenic when tested in Ames assay, chromosomal aberration study using cultured mammalian cells, in the mouse lymphoma test, and in the in vivo mouse micronucleus assay.***
- ***Fertility and early development and embryofetal development studies demonstrated no adverse effects on treated females or the fetuses.***
- ***Carcinogenicity studies conducted in male rats and in male and female mice by oral administration of dienogest for 104 weeks demonstrated findings essentially similar to those with other progestins reviewed and approved previously***

4.4 Clinical Pharmacology

The clinical pharmacology review was performed by Dr. Chongwoo Yu. His conclusions and recommendations are the following:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP/DCP-III) has reviewed NDA 22-252 submitted on July 2, 2009, October 15, 2009, and December 21, 2009. The overall Clinical Pharmacology information submitted to support this NDA is acceptable provided that a satisfactory agreement is reached regarding the labeling language.

Key findings from the biostatistical review of the contraception indication include:

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The absolute BA of DNG is approximately 91%. PK dose linearity of DNG is observed following single dose oral administration of tablets over a dose range of 1-8 mg in Caucasian premenopausal women. The steady-state is reached after 4-5 days of daily dosing.

CYP 3A4 Induction: In Study A24058 investigating the effect of CYP 3A4 inducer rifampicin on EV/DNG PK, co-administration of 600 mg rifampicin daily with 2 mg EV/3 mg DNG tablets resulted in a 52% decrease in the mean C_{max} and an 83% decrease in the AUC(0-24) for DNG. Co-administration of rifampicin resulted in a 25% decrease in C_{max} and a 44% decrease in AUC(0-24) for E2. Dr Yu recommended that in order to ensure contraceptive reliability and sufficient cycle control, EV/DNG should not be co-administered with strong CYP 3A4 inducers such as rifampicin, phenytoin, St. John's Wort, avasimibe, and carbamazepine.

CYP 3A4 Inhibition: In Study A30020 investigating the effect of CYP 3A4 inhibitors on EV/DNG PK, coadministration of 400 mg ketoconazole daily with 2 mg EV/3 mg DNG tablets resulted in a 94% increase in the mean C_{max} and a 186% increase in the AUC(0-24) for DNG. Co-administration of ketoconazole resulted in a 65% increase in C_{max} and a 57% increase in AUC(0-24) for E2. Co-administration of 1500 mg erythromycin daily with EV/DNG tablets resulted in a 33% increase in the mean C_{max} and a 62% increase in the AUC(0-24) for DNG. Co-administration of erythromycin resulted in a 51% increase in C_{max} and a 33% increase in AUC(0- 24) for E2.

No special recommendation concerning food intake is considered to be necessary.

Studies in renal and/or hepatic impaired subjects were not conducted.

4.5 Biostatistics

The biostatistics review for NDA 22-252 was performed by Dr. Xin Fang. His conclusions and recommendations are the following:

- The data support the efficacy of Estradiol Valerate/Dienogest (EV/DNG) in the prevention of pregnancy as demonstrated by the Pearl Index (PI) of < 2.0 in both North American and European studies.

-  (b) (4)

- From a statistical perspective, this application provided adequate data to

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support the efficacy of the EV/DNG (b) (4) as oral contraceptive.

Key findings from the biostatistics review of the contraception indication include:

- Comparison of the European study (Protocol 306660) to the US/Canada study (Protocol 304742) revealed that there were far fewer drop-outs in Europe (21% Europe compared to 51.3% in US/Canada). Loss to follow-up was 1.9% in Europe and 13.0% in US/Canada.

	306660	304742
	EV/DNG & Placebo (N=1391)	EV/DNG & Placebo (N=499)
Discontinuation from study	295 (21.2%)	256 (51.3%)
Lost to follow-up	26 (1.9%)	65 (13.0%)

- There was a greater ethnic mix in the US/Canada study compared to the European.
- The US/Canada study had a greater number of subjects with a history of smoking and regular use of alcohol compared to the subjects in the European study.
- The unadjusted Pearl Index in the European study (Protocol 306660) was 1.04 with an upper bound of the 95% confidence interval equaling 1.98. This determination is for subjects 18-35 years in the first 13 cycles of use, excluding cycles with back-up contraception. Pregnancies within 7 days after the last treatment are also counted as well on treatment.
- The unadjusted Pearl Index in the US/Canada study (Protocol 304742) was 1.69 with an upper bound of the 95% confidence interval equaling 3.94. This determination is for subjects 18-35 years in the first 13 cycles of use, excluding cycles with back-up contraception. Pregnancies within 7 days after the last treatment are also counted as well on treatment.

Key findings from the biostatistical review of the DUB indication include:

- The discontinuation rate and lost to follow-up rate was higher in the US/Canada study (308960) compared to the European/Australia study (308961).

	308960	308961
	EV/DNG & Placebo (N=190)	EV/DNG & Placebo (N=231)
Discontinuation from study	50 (26.3%)	45 (19.5%)
Lost to follow-up	9 (4.7%)	1 (0.4%)

- (b) (4)

4.6 Interdisciplinary Review Team for QT Studies

The Interdisciplinary Review Team's summary for the Applicant's thorough QT (TQT) study is the following:

"No significant QTc prolongation effect of Qlaira® was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between SH T00658M (EV 2mg and DNG 3 mg) and placebo, and between SH T00660 AA (DNG 10mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines."

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Key pivotal and supportive studies are presented in tabular format in this section.

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Table 2: Pivotal Study 306660 (Report A35179) for Contraception

	Study phase	Treatment groups with dosing and duration	Number of subjects who received treatment	Age range in years (mean) <u>Sex</u> Race
	Study design			
	Study duration			
A35179 (306660)	Phase 3	To-be-marketed regimen:	1377	18-50 (30.3)
Apr/2004	Multicenter Open-label Uncontrolled	2 days 3.0 mg EV		
Completed	20 cycles (28 days each)	5 days 2.0 mg EV + 2.0 mg DNG		<u>1377 Females</u>
Germany (27)		17 days 2.0 mg EV + 3.0 mg		1375 Caucasian
Spain (5)		DNG		2 Other
Austria (18)		2 days 1.0 mg EV		
Total (50)		2 days placebo		

EV = estradiol valerate; DNG = dienogest

Source: Section 5.2, Tabular listing of all clinical studies; page 92 of 178

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Table 3: Pivotal Study 304742 (Report A39818) for Contraception

	Study phase	Treatment groups with dosing and duration	Number of subjects who received treatment	Age range in years (mean) <u>Sex</u> Race
A39818 (304742)	Phase 3	To-be-marketed regimen	490	18-35 (24.0)
Mar/2005	Multicenter Open-label Uncontrolled			
Completed				
Canada (9) U.S. (20)	28 cycles (28 days each)			<u>490 Females</u> 371 Caucasian 34 Black 64 Hispanic 16 Asian 5 Other
Total (26)				

EV = estradiol valerate; DNG = dienogest

Source: Section 5.2, Tabular listing of all clinical studies; page 94 of 178

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Table 4: Supportive Study 304004 (Report A35644)

	Study phase Study design Study duration	Treatment group with dosing and duration	Number of subjects who received treatment	Age range in years (mean) <u>Sex</u> Race
A35644 (304004)	Phase 3	<u>EV/DNG</u> To-be-marketed regimen	EV/DNG = 399	18-50 (33.0)
Mar/2005	Multicenter, Double-blind, Double-dummy	<u>EE/LNG</u> <u>Comparator</u>		
Completed	Controlled, active comparator	21 days 0.02 mg EE + 0.10 mg LNG		
Germany (19) Czech Republic (5)	Randomized	7 days placebo		
France (10)	7 cycles (28 days each)			
Total (34)				
			EE/LNG = 399	18-50 (33.4)
			Total = 798	<u>798 Females</u> 796 Caucasian 1 Black 1 Asian

EV = estradiol valerate; DNG = dienogest; EE = ethinyl estradiol; LNG = levonorgestrel
 Source: Section 5.2, Tabular listing of all clinical studies; page 90 of 178

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Table 5: Supportive Phase 2 Study 307300 (Report A25364) for Contraception (Ovulation Inhibition)

Report No. (Protocol No.)	Study phase	Treatment groups with dosing and duration	Number of subjects who received treatment	Age range in years (mean)
Start date	Study design			Sex
Completion status	Study duration			Race
Country (No. of study sites)				
A25364 (307300)	Phase 2 Ovulation inhibition study	<u>EV/DNG</u> To-be-marketed regimen	EV/DNG = 100	18-35 (25.6)
Mar/2003				
Completed	Multicenter, Open-label, Randomized, Comparative study	<u>Reference</u> 2 days 3.0 mg EV		
Germany (1) Netherlands (1)		5 days 2.0 mg EV + 3.0 mg DNG		
Total (2)	3 cycles (28 days each)	17 days 2.0 mg EV + 4.0 mg DNG		
		2 days 1.0 mg EV		
		2 days placebo	Reference = 103	20-35 (26.0)
			Total = 203	<u>203 Females</u> 189 Caucasian 1 Black 4 Asian 9 Other

EV = estradiol valerate; DNG = dienogest

Source: Section 5.2, Tabular listing of all clinical studies; page 81 of 178

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Table 6: Pivotal Study 308960 (Report A29849) for Dysfunctional Uterine Bleeding

Report No. (Protocol No.)	Study phase	Treatment groups with dosing and duration	Number of subjects who received treatment	Age range in years (mean)
Start date	Study design			Sex
Completion status	Study duration			Race
Country (No. of study sites)				
A29849 (308960)	Phase 3	<u>EV/DNG</u> To-be-marketed regimen	EV/DNG = 119	20-53 (36.9)
Dec/2005	Multicenter, Double-blind, Randomized,	<u>Placebo</u>		
Completed	Parallel-group, Placebo- controlled study			
Canada (10) U.S. (37)				
Total (47)	7 cycles (28 days each)			
			Placebo = 66	21-49 (37.0)
			Total = 185	<u>185 Females</u> 117 Caucasian 52 Black 14 Hispanic 3 Asian 4 Other

EV = estradiol valerate; DNG = dienogest

Source: Section 5.2, Tabular listing of all clinical studies; page 97 of 178

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Table 7: Pivotal Study 308961 (Report A42568) for Dysfunctional Uterine Bleeding

	Study phase	Treatment groups with dosing and duration	Number of subjects who received treatment	Age range in years (mean) <u>Sex</u> Race
	Study design			
	Study duration			
A42568 (308961)	Phase 3	<u>EV/DNG</u> To-be-marketed regimen	EV/DNG = 145	18-51(39.4)
Feb/2006	Multicenter, Double-blind, Randomized, Parallel-group, Placebo- controlled study	<u>Placebo</u>		
Completed				
Australia (3) Czech Republic (5) Finland (4) Germany (9) Hungary (3) Netherlands (3) Poland (5) Sweden (4) Ukraine (4) United Kingdom (3)	7 cycles (28 days each)		Placebo = 81	19-54 (38.4)
Total (43)			Total = 226	<u>226 Females</u> 220 Caucasian 1 Black 2 Asian 3 Other

EV = estradiol valerate; DNG = dienogest

Source: Section 5.2, Tabular listing of all clinical studies; page 98 of 178

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Table 8: Supportive Study 301886 (Report A33022) for Effect on Plasma Lipids, Hemostatic Variables and Carbohydrate Metabolism

Report No. (Protocol No.)	Study phase	Treatment groups with dosing and duration	Number of subjects who received treatment	Age range in years (mean)
Start date	Study design			Sex
Completion status	Study duration			Race
Country (No. of study sites)				
A33022 (301886)	Phase 2	<u>EV/DNG</u> To-be-marketed regimen	EV/DNG = 30	19-39 (28.1)
Mar/2005	Multicenter, Double-blind, Randomized, Parallel-group, Placebo- controlled study	<u>EE/LNG</u> <u>Reference</u>		
Completed		6 days 0.03 mg EE + 0.05 mg LNG		
Germany (1)	7 cycles (28 days each)	5 days 0.04 mg EE + 0.075 mg LNG		
		10 days 0.03 mg EE + 0.125 mg LNG	Reference = 28	18-48 (31.1)
		7 days placebo	Total = 58	58 Females 57 Caucasian 1 Asian

EV = estradiol valerate; DNG = dienogest; EE = ethinyl estradiol; LNG = levonorgestrel
 Source: Section 5.2, Tabular listing of all clinical studies; page 82 of 178

Medical Officer's Comment:

The reference product is approved in the U.S. as *Empresse 28* and *Trivora 28*.

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Table 9: Supportive Study 310122 (Report A38220) for Hemostatic Variables

	Study phase	Treatment groups with dosing and duration	Number of subjects who received treatment	Age range in years (mean) <u>Sex</u> Race
A38220 (310122)	Phase 3	<u>EV/DNG</u> To-be-marketed regimen	EV/DNG = 14	20-38 (25.3)
Apr/2006	Crossover, Active treatment-controlled, Randomized, Open-label	<u>EE/LNG</u> <u>reference</u>		
Completed		21 days 0.03 mg EE +0.15 mg LNG		
Netherlands (1)	3 cycles (28 days each)	7 days placebo		
			Reference = 15	18-40 (29.3)
			Total = 299	<u>29 Females</u> 27 Caucasian 1 Asian 1 Other

EV = estradiol valerate; DNG = dienogest; EE = ethinyl estradiol; LNG = levonorgestrel
 Source: Section 5.2, Tabular listing of all clinical studies; page 84 of 178

Table 10: Supportive Safety QT Study 310183 (Report A35653)

	Study phase	Treatment groups with dosing and duration	Number of subjects who received treatment	Age range in years
	Study design			<u>Sex</u>
	Study duration			Race
A35653 (310183)	Phase 1	3.0 mg DNG + 2 mg EV and 10 mg DNG and	53	45-75
Jan/2007	Double-blind, Double-dummy, Placebo-controlled, 4 way cross-over study	Placebo and Moxifloxacin		
Completed				<u>53 Females</u>
Germany (1)				52 Caucasian 1 Black
	4 days each treatment			

EV = estradiol valerate; LNG = levonorgestrel

Source: Section 5.2, Tabular listing of all clinical studies; page 83 of 178

5.2 Review Strategy

Sections 5.3.1 through 5.3.5 contain detailed information about the 2 pivotal contraceptive efficacy and safety studies, 1 supportive comparative study that assessed both contraception and cycle control in addition to safety and the 2 pivotal DUB efficacy and safety studies.

Section 5.3.6 of this section contains summaries of:

- Supportive studies that incorporate the final EV/DNG regimen
- Studies of developmental EV/DNG regimens
- Studies of an estradiol valerate / dienogest tablet used for menopausal therapy
- Studies of ethinyl estradiol / dienogest
- Studies of dienogest alone

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Pivotal Study 306660 (Report A35179) for Contraception

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5.3.1.1 Study Title / Coordinating Investigator / Study Dates

“Multi-center, open, uncontrolled study to investigate the efficacy and safety of a 4-phasic oral contraceptive SH T006581D containing estradiol valerate and dienogest in a 28-day regimen for 20 cycles in 1200 healthy female volunteers”

The coordinating investigator was Dr. Doris Heger-Mahn (Berlin, Germany).

This study ran from Apr 28, 2004 until Jul 27, 2006.

5.3.1.2 Ethics

The Applicant stated that a) this study met all local legal and regulatory requirements, b) this study was conducted in accordance with Good Clinical Practice (GCP), c) this study complied with ethical principles originating in the Declaration of Helsinki and the ICH-GCP guidelines of January 17, 1997, d) the study protocol and amendments were reviewed and approved by each study site's Independent Ethics Committee (IEC) or Institutional Review Board (IRB) before the start of the study or before implementation of the amendment, and e) the study's informed consent form was reviewed and approved by the IECs and IRBs prior to its issue.

5.3.1.3 Study Sites and Investigators

In Study 306660, there were study sites in Germany (27), Austria (18) and Spain (5) that randomized subjects.

Medical Officer's Comment: The study sites and investigators were correlated with the datasets for Study 306660. The only discrepancy found in the datasets was the listing of investigator Wildt with Germany rather than Austria. This discrepancy in the dataset does not impact this clinical review.

5.3.1.4 Study Objectives

The overall objectives of the study were to confirm the safety and efficacy of EV/DNG. The primary efficacy parameters were the number of pregnancies. The secondary efficacy parameters were cycle control and bleeding patterns. The safety parameters were adverse events, compliance, physical exam, gynecologic exam, vital signs, body weight and endometrial biopsy (approximately 250 subjects were planned in the endometrial biopsy subgroup).

5.3.1.5 Study Design

Pivotal Study 306660 was designed as a multicenter, open-label, uncontrolled

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Phase 3 clinical trial. The trial was designed to run for 20 cycles (28 days per cycle). The drugs and drug dosages for each cycle are shown in Table 11:

Table 11: Study 306660 – Dosages for EV/DNG throughout the 28-Day Cycle

Cycle Days	No. of oral intake days	Content
1-2	2	3.0 mg estradiol valerate
3-7	5	2.0 mg estradiol valerate + 2.0 mg dienogest
8-24	17	2.0 mg estradiol valerate + 3.0 mg dienogest
25-26	2	1.0 mg estradiol valerate
27-28	2	placebo

Source: Study Report A35179; page 48 of 3674

The maximum cumulative dose per cycle amounted to 52 mg for EV and 61 mg for DNG.

For both COC switchers and new starters, the first tablet was to be taken on the first day of the withdrawal bleeding, which was counted as day one of the first medication cycle. Thereafter, tablet intake was to follow a predetermined intake plan and was not to be triggered by bleeding events.

The tablets were to be taken in the morning or evening, but the interval between succeeding tablets was to be as close as possible to 24 hours. The protocol for “missed pills” is shown in Table 12.

Table 12: Study 306660 – Protocol for Missed Pills

Days	Content of EV/DNG	Delay of more than 12 hours
1-2	3.0 mg EV	1. Take missed tablet immediately and the following tablet as usual, 2. Use back-up contraception until day 9
3-7	2.0 mg EV + 2.0 mg DNG	1. Take missed tablet immediately and the following tablet as usual, 2. Use back-up contraception for the next 7 days
8-17	2.0 mg EV + 3.0 mg DNG	1. Take missed tablet immediately and the following tablet as usual, 2. Use back-up contraception for the next 7 days
18-24	2.0 mg EV + 3.0 mg DNG	1. Take missed tablet and continue tablet intake as usual (use up the blister in the given sequence) 2. Use back-up contraception until day 9 of the following cycle
25-26	1.0 mg EV	Take missed tablet (no further action)
27-28	Placebo	Take missed tablet (no further action)

Source: Study Report A35179; text table 6, page 48 of 3674

No more than two tablets were to be taken on a given day. In case of vomiting within 4 hours after tablet intake, absorption may not be complete. In such an event, another tablet with the same color was to be taken from the reserve blister. The same procedure applied for diarrhea.

Subjects using short-term antibiotics (and some psychotropic drugs) were to use back-up contraception in addition to the COC until 7 days after discontinuation of the concomitant treatment. Information on back-up contraception had to be recorded on the CRF.

A menstruation-like withdrawal bleed was supposed to occur after day 24 of a treatment cycle. If such bleeding failed to occur, pregnancy was to be ruled out by performing a HCG test immediately before starting the next pill pack.

If a pregnancy occurred in the study, the estimated date of conception was to be determined through (in hierarchal order) - ultrasonography, gynecological examination, last menstrual period / bleeding information provided by the subject, determination of the gestational age at delivery and quantitative HCG determination.

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5.3.1.6 Inclusion Criteria

The following criteria were used to evaluate subjects for inclusion in the study:

1. Signed informed consent
2. Healthy volunteer requesting contraception
3. Age between 18 and 50 years (inclusive), smokers maximum age of 30 at inclusion
4. a. Pap smear taken with non-suspicious result or
b. Non-suspicious Pap smear result within the last six months prior to inclusion in the study and report is available
5. For endometrial biopsy group only: biopsy taken (Visit 1), non-suspicious biopsy result (Visit 2)

Medical Officer's Comment:

The endometrial results were reviewed at Visit 2 and if the biopsy was non-suspicious the subject was allowed to proceed in the study.

5.3.1.7 Exclusion Criteria

The following criteria were used for the exclusion of subjects from the study:

1. Pregnancy, lactation (at least three menstrual cycles have to follow delivery, abortion, or lactation before start of treatment)
2. Substantially overweight (Body Mass Index > 30 kg/m²)

Medical Officer's Comment:

This exclusion of women with BMI >30 kg/m² should be noted in product labeling.

3. Hypersensitivity to any of the study drug ingredients
4. Any disease or condition that can compromise the function of the body systems and could result in altered absorption, excessive accumulation, impaired metabolism, or altered excretion of the study medication
5. Any disease that may worsen under hormonal treatment or might interfere with the conduct of the study or the interpretation of the results (e.g., pemphigoid gestationis or idiopathic icterus during a previous pregnancy; middle-ear

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deafness (otosclerosis); Sydenham chorea, porphyria, disturbances in the bile flow (presence or history of cholestasis, gallstones), systemic lupus erythematosus)

6. Diagnosed or suspected malignant or premalignant disease.

7. Liver diseases: presence or history of severe hepatic diseases including benign or malignant tumors. There should be an interval of at least 3 months between the return of liver function values to normal and start of study medication intake.

8. Vascular diseases: Presence or history of venous thromboembolic diseases (deep vein thrombosis, pulmonary embolism), presence or history of arterial thromboembolic diseases (myocardial infarction, stroke), and any condition which could increase the risk of the above mentioned disorders; e. g., a positive family history (event that occurred in a sibling or a parent at an early age) or a suspected hereditary predisposition.

9. Other diseases: Chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis), hemolytic uremic syndrome, migraine with focal neurologic symptoms (complicated migraine)

10. Undiagnosed vaginal bleeding

11. Uncontrolled thyroid disorders

12. Dyslipoproteinemia

13. Pancreatitis or a history thereof if associated with severe hypertriglyceridemia

14. Uncontrolled arterial hypertension (confirmed systolic blood pressure > 140 mmHg or confirmed diastolic blood pressure > 90 mmHg)

15. Diabetes mellitus with vascular involvement

16. Sickle-cell anemia

17. Current or history of clinically significant depression (depression requiring treatment)

18. Current or history of alcohol or drug abuse (e.g. laxatives)

19. Prohibited concomitant medication: use of additional steroid hormones, anticoagulants (e.g., heparin, coumarin), antiepileptics, (hydantoin derivatives, e.g., phenytoin or carboxamid derivatives; e.g., carbamazepine,

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oxcarbamazepine; other antiepileptics , e.g., Felbamate, Topiramate), hypnotics and sedatives (barbiturate derivatives, e.g., primidone), tuberculostatics (e.g., rifampicin), oral antimycotics (e.g., griseofulvin, ketoconazole, itraconazole, fluconazole), virostatic agents (e.g., ritonavir), products containing St. John's wort, and continuous systemic use of antibiotics

20. Sex hormone therapy / hormonal contraception: I.M. administered within 6 months prior to start of study; implants (still implanted or removed within less than 4 weeks prior to start of study)

21. Other contraceptive methods such as sterilization or intrauterine device (IUD)

22. Intake of an experimental drug within 1 month prior to inclusion in the study

23. Volunteer is a dependent person, e.g., a relative / family member and / or is a member of the investigator's staff

5.3.1.8 Prior and Concomitant Therapy

The medication history of the last month before start of the study was recorded. All concomitant medication used during the whole study was to be recorded in the CRF using the brand name, indication, regimen (total daily dosage) and duration of intake.

5.3.1.9 Study Procedures

The study procedures for pivotal Study 306660 are found in Table 13.

Table 13: Study 306660 – Study Procedures

Visit number Cycle	Treatment								F/u
	V1 S	V2 Ad	V3 3	V4 6	V5 10	V6 13	V7 17	V8 20	V9 >20
Informed consent	X								
Demographic data	X								
Entry criteria	X	X							
Gynecologic, medical, surgical and medication history	X								
Smoking habits, alcohol consumption	X								
Height, Weight, Blood Pressure, Heart Rate	X	X	X	X	X	X	X	X	X
Physical exam	X								X
Gynecologic exam	X			X		X			X
Cervical smear	X	R		X		X			X
Baseline findings	X	X							
Endometrial biopsy (subgroup)	X	R						X	R
Admission to treatment		X							
HCG – urine tests dispensed		X						X	
HCG – urine test results			X		As needed				X
Medication dispensed		X	X	X	X	X	X	X	
Diary cards dispensed		X							
Unused/empty blisters returned			X	X	X	X	X	X	X
Diary cards returned			X	X	X	X	X	X	X
Adverse events/ concomitant medications		X	X	X	X	X	X	X	X
Use of back-up contraception?			X	X	X	X	X	X	X
Discussion of follow up contraception								X	X
End of study evaluation									X
Subjective assessment									X

Abbreviations: V = visit; S = screening; Ad = admission; R = result; F = final examination (days 10-24 after the last tablet intake)

Source: Protocol for Study 306660; page 14 of 117

Medical Officer's Comments:

- **The same procedures listed for visit 9 were employed in the event of premature discontinuation of treatment.**
- **In the endometrial biopsy subgroup, the biopsy was to be taken between days 12-19 of that cycle. If insufficient material was obtained with either biopsy, a repeat biopsy was to be taken within 4 weeks.**

- ***The cervical smear examination could be waived if a result from the last 6 months before Visit 1 was available.***
- ***A non-suspicious cervical smear and normal endometrial biopsy (in the subgroup) were required for admission to the study.***
- ***Height was only measured at Visit 1.***
- ***Urine pregnancy testing was performed before taking the first study drug tablet, which corresponded to the first day of the next menstrual bleed. During the central course of the study, urine pregnancy tests were to be used in the event of absent monthly bleeding. Urine pregnancy testing was performed by all subjects just prior to Visit 9 or during Visit 9 at the study site. However, in Austria, pregnancy tests were performed every cycle.***
- ***In case a subject discontinued study medication due to wish for pregnancy, the time to return to fertility was to be documented for up to one year, if information was available.***
- ***All drop outs were to be observed for three months after study completion to collect data on pregnancies after the end of the study.***

5.3.1.10 Bleeding Record

Bleeding intensity recorded on the diary cards had the following categories:

- None = No vaginal bleeding
- Spotting = Less than associated with normal menstruation relative to the volunteer's experience, with no need for sanitary protection (except for panty liners)
- Light = Less than associated with normal menstruation relative to the volunteer's experience, with need for sanitary protection
- Normal = Like normal menstruation relative to the volunteer's experience
- Heavy = More than normal menstruation relative to the volunteer's experience

Based on the diary cards, the bleeding patterns were to be described using reference periods of 90 days.

A bleeding/spotting episode was defined as the number of days with bleeding/spotting preceded and followed by at least 2 bleeding-free days.

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A spotting-only episode was defined as the number of days with spotting preceded and followed by at least 2 bleeding-free days.

A bleeding-free interval consisted of at least 2 days without bleeding/spotting preceded and followed by at least 1 bleeding/spotting day.

Additionally, regular bleeding and intracyclic bleeding episodes were identified and analyzed. A regular bleeding episode during treatment was defined as the first bleeding episode from Day 25 on. In case a bleeding episode was ongoing on the last day of the EV/DNG administration period and the following day, this episode was regarded as the withdrawal [scheduled] bleeding episode, provided it did not start more than 4 days before EV/DNG withdrawal (i.e., before Day 21). Both the onset and the duration of the episodes were assessed. All other (unexpected) bleeding episodes were considered intracyclic [unscheduled] bleeding. If no bleeding occurred until the next hormonal withdrawal (i.e., Day 25), this was assessed as an absence of regular bleeding in the preceding treatment cycle.

5.3.1.11 Smoking

Women over 30 years who smoke were not to be recruited in this study. Non-smokers, in all age groups, were to be given preference. In case smokers with a maximum age of 30 years at inclusion were recruited, smoking habits were to be entered in the CRF.

5.3.1.12 Primary Efficacy Variables

The primary efficacy variable was the number of observed pregnancies

The investigators were required to submit a complete report for any pregnancy detected during the study (i.e., after the volunteer signed the informed consent form) or which might have been exposed to the treatment (i.e., detected within three months after end of study for volunteers who discontinued the study prematurely).

The investigator was required to document, as far as possible, the calculated time of conception, the diagnostic measures used, and the course of pregnancy, including the pregnancy outcome. All pregnancies occurring in the course of the study were to be followed up by the investigator for the final outcome of both mother and child.

The investigator was also required to ascertain whether the volunteer had taken any other substance or had a concomitant illness which might have affected absorption, or if there were any tablet intake errors, vomiting or diarrhea. The date of conception was to be determined applying the following diagnostic

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measures: Ultrasonography, gynecological examination, last menstrual period and bleeding information from the volunteer, determination of gestational age at delivery, and quantitative HCG determination (pregnancy test). In the case of any inconsistency between the different diagnostic measures, the most accurate one (i.e., higher in hierarchy) was to be used. At each visit, the investigator was required to collect information on back-up contraceptive measures (e.g., condoms) and note them in the CRF.

The Pearl Indices (unadjusted and adjusted) were to be calculated for the group of women aged 18-35 as well as for the women aged 18-50.

Medical Officer's Comment:

The Division traditionally uses the unadjusted Pearl Index for women aged 18-35 in the first 13 cycles. DRUP has recently changed the window for determining "on treatment" pregnancies to any pregnancies that occur within 7 days after the last tablet (active or placebo), and that convention will be followed in this review. However, the Applicant presented data based on a 14 day window, according to the Division's earlier advice.

In addition to the calculation of the Pearl Index, a life table analysis was to be performed for the time to the occurrence of a pregnancy. The cumulative failure rate, i.e., the probability of getting pregnant, was to be calculated using the Kaplan Meier estimator on the basis of pregnancies which are considered as 'during treatment.'

5.3.1.13 Secondary Efficacy Variables

The secondary target variables were bleeding pattern and cycle control parameters.

The bleeding episodes were to be described using the reference period method recommended by the WHO. The length of the reference period is 90 days. The first reference period started on the first day of study medication.

For each woman and for each reference period, the following overall bleeding pattern indices were to be calculated:

- Number of bleeding/spotting days
- Number of spotting only days
- Number (mean length, maximal length, and range of length) of bleeding/spotting episodes
- Number (mean length, maximal length, and range of length) of spotting only episodes

In addition the following cycle control indices were to be computed:

Withdrawal (scheduled) bleeding

- Withdrawal bleeding (yes/no)
- Length of withdrawal bleeding episode
- Maximal intensity of withdrawal bleeding episode
- Onset of withdrawal bleeding episode

Intracyclic (unscheduled) bleeding

- Intracyclic bleeding (yes/no)
- Number and maximal length of intracyclic bleeding episodes
- Number of intracyclic bleeding days
- Maximal intensity of intracyclic bleeding episodes

Women with intracyclic bleeding

- Number of subjects with at least one intracyclic bleeding episode at Cycles 2 to 6, 2 to 13, and 2 to 20

Definitions of Bleeding Patterns

The bleeding intensity codes are the following:

1 = None

2 = Spotting [less than associated with normal menstruation relative to the subject's experience with no need for sanitary protection (except for panty liners)]

3 = Light bleeding (less than associated with normal menstruation relative to the subject's experience with need for sanitary protection)

4 = Normal bleeding (like normal menstruation relative to the subject's experience)

5 = Heavy bleeding (more than normal menstruation relative to the subject's experience)

A bleeding/spotting episode is defined as the days with bleeding/spotting preceded and followed by at least 2 bleed-free days.

A spotting-only episode is defined as the days with spotting preceded and followed by at least 2 bleed-free days.

A bleeding free interval is defined as the days without bleeding/spotting preceded and followed by at least 1 bleeding/spotting day.

5.3.1.14 Statistical Analysis Plan

Full Analysis Set

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The evaluation of the primary efficacy parameter was to be based on the full analysis set (FAS), defined as all volunteers admitted to the treatment phase who took at least one tablet of study medication and for whom at least one observation after admission to treatment was available.

Per Protocol Set

The per protocol set (PPS) was to be defined with respect to the secondary target variables related to bleeding pattern and cycle control. Only the first 7 cycles (which comprise the first two reference periods) were to be used in the definition of the PPS.

The following constituted exclusions from the per protocol set:

- Major violation of entry criteria
- Major non-compliance with study medication intake schedule within the first 7 cycles of treatment (less than 24 tablet intake in any cycle, hormone-free interval longer than 4 days between any two cycles)
- Other major deviation from the protocol within the first 7 cycles of treatment (e.g., missing data for the secondary variable, premature withdrawal)

5.3.1.15 Analysis of Safety

The safety monitoring employed in this protocol included medical history, physical exams, vital sign monitoring, pap smears and adverse event reporting. A subgroup evaluation of endometrial biopsies was also planned in the protocol.

The Applicant listed specific adverse events which would lead to subjects being immediately terminated from the study:

- First signs of arterial or venous blood clot formation (thrombotic or thromboembolic diseases such as deep venous thrombosis, pulmonary embolism, cardiac infarction, stroke), e.g., unusual pain or swelling in the legs, stabbing pain on breathing or cough of unknown origin, pain and a feeling of constriction in the chest
- Before scheduled major operations (6 weeks prior), and/or in case of prolonged immobility (e.g., after accidents)
- Migraine headache occurring for the first time or more frequently with unusual severity
- Sudden sensory disturbances (visual, auditory, etc.)
- Motor disturbances (particularly paralysis)
- Liver inflammation, jaundice, itching over the entire body, disturbances of

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- bile drainage (cholestasis), or clinically significant increase in liver function test values
- Fresh occurrence of epileptic seizures while on the medication
 - Pregnancy
 - Repeated, excessive, persistent intracyclic bleeding
 - Immoderate increase in blood pressure ($\geq 140 / 90$ mm Hg)

5.3.1.16 Protocol Amendments

There were no protocol amendments.

5.3.1.17 Disposition of Subjects

Subject disposition in Study 306660 is presented in Table 14.

Table 14: Study 306660 – Overall Subject Disposition

Disposition / Reason	EV/DNG
Screened	1446 (100%)
Screening failures	55 of 1446 (3.8%)
<ul style="list-style-type: none"> • Withdrawal of consent • Entry criteria not met • Volunteer lost, no further information • Other 	<ul style="list-style-type: none"> • 17 of 55 (30.9%) • 28 of 55 (50.9%) • 3 of 55 (5.5%) • 7 of 55 (12.7%)
Volunteers included in the study	1391 of 1446 (96.2%)
Volunteers who dropped out before start of study medication	14 of 1446 (1.0%)
Volunteers receiving study medication (FAS)	1377
Volunteers receiving study medication age 18-35 years	998 of 1377 (72.5%)
Volunteers discontinuing study medication	295 of 1377 (21.4%)
<ul style="list-style-type: none"> • Withdrawal of consent • Protocol deviation • Adverse event • Death • Lost to follow-up • Pregnancy • Other 	<ul style="list-style-type: none"> • 20 of 1377 (1.5%) • 26 of 1377 (1.9%) • 140 of 1377 (10.2%) • 1 of 1377 (<0.1%) • 26 of 1377 (1.9%) • 11 of 1377 (0.8%) • 71 of 1377 (5.2%)
Unknown when medication stopped	8 of 1377 (0.6%)
<ul style="list-style-type: none"> • Death • Lost to follow-up • Missing • Other 	<ul style="list-style-type: none"> • 1 of 1377 (<0.1%) • 5 of 1377 (0.4%) • 1 of 1377 (<0.1%) • 1 of 1377 (<0.1%)
Volunteers completing study medication	1074 of 1377 (78.0%)
Volunteers in per-protocol set (in first 7 cycles)	1115 of 1377 (80.1%)

EV/DNG = estradiol valerate / dienogest

Source: Study Report A35179 Section 10.1; page 86 of 3674

Medical Officer’s Comment:

The “other” category for subjects discontinuing study medication included those that stopped to get pregnant, moved from the area etc.

In a footnote, the Applicant stated that there were actually 142 subjects (rather than 140) who experienced AEs leading to drug withdrawal. Subjects 4129 and 4164 were recorded as “Protocol deviation” as the main reason for premature study discontinuation.

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- **Subject 4129 (23 year old) had concealed information about alcohol abuse at screening. She was treated with study medication from Aug 20, 2004 through Dec 22, 2004. Liver parenchymal damage and secondary alcohol abuse were detected in Oct 2004. She also had a history of acute psychosis with hospitalization from [REDACTED] (b) (6)**
- **Subject 4165 (45 year old) had a history of Dupuytren’s contraction right hand, breast mastopathy, nervous exhaustion and controlled hypertension. She withdrew due to hypertension, which was in the inclusion limits at study entry, but worsened on treatment.**

5.3.1.18 Protocol Deviations

Protocol deviations in Study 306660 as presented by the Applicant in Study Report A35179 are shown in Table 15.

Table 15: Study 306660 – Protocol Deviations (N = 1377 in FAS)

Type	Assessment	n of PDs	n of volunteers with PDs	% of volunteers with PDs
Any	Major	460	259	18.8
	Minor	1223	646	46.9
Inclusion/exclusion error at entry	Major	16	14	1.0
	Minor	159	146	10.6
Withdrawal criterion present but not withdrawn	Major	4	4	0.3
	Minor	72	59	4.3
Excluded concomitant treatment	Major	2	2	0.1
	Minor	317	222	16.1
Treatment deviation	Major	309	227	16.5
	Minor	314	201	14.6
Time schedule deviation	Major	0	0	0
	Minor	92	87	6.3
Procedure deviation	Major	1	1	< 0.1
	Minor	2	2	0.1
Other	Major	128	44	3.2
	Minor	267	149	10.8

PDs = protocol deviations

Source: Study Report A35179 Section 10.2; page 88 of 3674

Medical Officer’s Comment:

This reviewer analyzed the major deviations in the dataset PD01. The dataset had 463 major deviations overall and 19 major deviations in the inclusion/exclusion errors which differs from results in the preceding

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Applicant's table (460 total and 16 inclusion/exclusion errors).

Major deviations related to inclusion/exclusion errors at study entry included pregnancies, uncontrolled hypertension and medical history findings of an "unhealthy volunteer."

Major deviations related to withdrawal criteria present but not withdrawn included four subjects with medical disorders (celiac disease, ulcerative colitis, liver parenchymal damage and migraine).

Major deviations related to excluded concomitant treatment included some hormonal products. The hormonal products are discussed below. Most of the minor deviations (317) related to excluded concomitant treatment were related to antibiotic and antifungal use.

Major deviations related to treatment deviation included mistakes in pill usage, alterations in cycle length, alterations in length of hormone free interval, and the finding of less than 7 cycles of treatment due to premature withdrawal.

The major deviation related to procedure deviation was a subject with diary information unavailable.

The major deviations classified as "other" included missing or incomplete documentation of bleeding pattern (126 subjects) and 2 subjects with individual cycle diary cards missing.

Of the preceding major deviations, the only ones judged by this reviewer to impact efficacy were those related to excluded concomitant medications. The Applicant reported concomitant use of hormonal products that could impact efficacy. The Applicant was requested to review all cases of excluded concomitant medication that could potentially impact efficacy and provide information as to whether appropriate exclusion of subject cycles was performed in these cases. The Applicant provided information on this request in submission number 11 (dated Dec 18, 2009). Table 16 shows information on subjects who were taking these medications and whose number of evaluable cycles were not adjusted. With over 11,000 cycles in which back-up contraception was not used, the impact of the following subjects is considered negligible by this reviewer.

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Table 16: Subjects Taking Excluded Concomitant Medications Whose Cycles Were Not Adjusted – Study 306660

Subject No.	Medication	Duration of Use (Days)	Notes
4707	Cilest (COC)	12	Occurred in subject cycle 3, no adjustment made
3980	Trigoa (progestin)	4	Occurred in subject cycle 5, no adjustment made
3700	Progestogel (progestin)	15	Overlapped subject cycles 12 to 13, no adjustment made

COC = Combination oral contraceptive

Source = Biometrical report, Attachment 4: OC listings, Submission #11, Dec 18, 2009

5.3.1.19 Demographics

Demographic data for Study 306660 is found in Table 17.

Table 17: Study 306660 – Demographics and Baseline Characteristics

Disposition / Reason	EV/DNG FAS Age 18-35 (n=998)	EV/DNG FAS Age 18-50 (n=1377)
Mean age (years ± SD)	26.2 ± 4.7	30.3 ± 7.9
Ethnic group (%)		
• Caucasian	990 (99.2%)	1366 (99.2%)
• Black	2 (0.2%)	2 (0.1%)
• Hispanic	3 (0.3%)	3 (0.2%)
• Asian	1 (0.1%)	4 (0.3%)
• Other	2 (0.2%)	2 (0.1%)
Smokers	271 (27.2%)	273 (19.8%)
Mean weight (kg ± SD)	63.0 ± 9.2	64.2 ± 9.5
Body mass index (kg/m ² ± SD)	22.4 ± 2.9	22.8 ± 2.9
Mean height (cm ± SD)	167.5 ± 6.1	167.1 ± 6.2

EV/DNG = estradiol valerate / dienogest

Source: Study Report A35179 Text Table 22; page 100 of 3674 and Table 20 page 463 of 3674

The great majority of volunteers, 994 (99.6%) of the subgroup aged 18 to 35-year-old and 1370 (99.5%) of the FAS, were sexually active at study start.

The educational level of the subgroup of the 18 to 35-year-old volunteers consisted of basic mandatory education for 13.7%, of secondary education for 49.8%, and of academic education for 36.5%. The proportions of the different educational levels in the FAS were as follows: basic mandatory education for 14.1%, of secondary education for 53.1%, and of academic education for 32.8%

Medical Officer's Comment:

In pivotal Study 304742 (US/Canada), there was a greater representation of minority racial groups. There is no evidence to suggest that there is a difference in efficacy of combination oral contraceptives based on racial factors.

5.3.1.20 Gynecologic and Obstetric History

Information on the gynecologic and obstetric history for subjects in Study Protocol 306660 is shown in Table 18.

Table 18: Study 306660 – Gynecologic / Obstetric History

	EV/DNG (n=1377)
Mean age at menarche (years ± SD)	13.0 ± 1.3
Nulliparous volunteers – N (%)	835 (60.6%)
History of one birth – N (%)	238 (17.3%)
History of two or more births – N (%)	276 (20%)
Volunteers reporting history of abortion – N (%)	195 (14.2)
History of amenorrhea in the preceding 6 months – N (%)	40 (2.9%)
History of dysmenorrhea in the preceding 6 months – N (%)	195 (14.2%)
History of intracyclic vaginal bleeding in the preceding 6 months – N (%)	89 (6.5%)

EV/DNG = estradiol valerate / dienogest

Source: Study Report A35179 Tables 36-38, pages 505-507 of 3674; Table 40, page 509 of 3674

The record of prior contraceptive use is shown in Table 19.

Table 19: Study 306660 – Contraceptive Methods used by Volunteers Prior to Study Start

Contraceptive Method	EV/DNG (n=1377)
Method	
• None	77 (5.6%)
• Condom	240 (17.4%)
• Oral contraceptive	1006 (73.1%)
• Intrauterine contraceptive device	11 (0.8%)
• Other	43 (3.1%)

EV/DNG = estradiol valerate / dienogest

Note: Other methods included patch, vaginal ring and implant

Source: Study Report A35179; Table 41; page 510 of 3674

5.3.1.21 Smoking

Among the 18- to 35-year-old volunteers, smoking was recorded in 271 (27.2%) of the volunteers in the FAS. There were only 2 smokers of > 30 years of age in the FAS who reported smoking 2 and 9 cigarettes per day, respectively.

5.3.1.22 Treatment Compliance

Subjects were required to record tablet intake on their diary cards. At each visit, completed cards were collected, reviewed and signed by the investigator. Unused study medication and empty blisters were to be returned to the investigator.

Treatment compliance was evaluated using the records of the volunteers in the appropriate diaries. The theoretical maximum was 28 tablets x 20 cycles = 560 tablets defined as a 100% treatment compliance. The mean compliance in the volunteer sample was $86.7 \pm 28.0\%$.

5.3.1.23 Primary Efficacy Results– Pregnancies

There were 13 “during treatment pregnancies (9 of which were in the 18-35 year age range in the first 13 cycles), 5 pre-treatment pregnancies and 12 post-treatment pregnancies. These pregnancies are described in detail in this section.

During Treatment Pregnancies

The “during treatment” pregnancies are shown in Table 20.

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Table 20: Study 306660 – Pregnancies during Study Treatment (Includes Pregnancies with Estimated Date of Conception within 7 Days of End of Treatment)

#	PID (age in yrs)	Treatment start	Treatment end	EDC	Notes
Age 18 to 35 - Within 13 Cycles – EDC while on treatment					
1	3050 (25)	2 Jun 04	28 Mar 05	8 Mar 05 (by TVU)	Pregnancy outcome = normal female at term. Exposure days = 280
2	3406 (29)	16 Jul 04	16 Jan 05	11 Dec 04 (by TVU)	Pregnancy outcome = spontaneous abortion. Exposure days = 149
3	3553 (33)	13 Jul 04	21 Nov 04	15 Oct 04 (by TVU)	Pregnancy outcome = induced abortion. Exposure days = 95
4	3829 (33)	25 Aug 04	8 May 05	17 Apr 05 (by TVU)	Pregnancy outcome = induced abortion. Exposure days = 236
5	4150 (21)	23 Aug 04	25 Nov 04	30 Oct 04 (by TVU)	Pregnancy outcome = normal female at term. Exposure days = 69
6	4505 (29)	4 Nov 04	17 Nov 04	17 Nov 04 (by TVU)	Pregnancy outcome = no information, lost to follow-up. Exposure days = 14
7	3584 (33)	24 Jul 04	18 Mar 05	15-17 Feb 05 (by TVU)	Pregnancy outcome = induced abortion. Exposure days = 207
8	4579 (24)	19 Sep 04	19 May 05	7 Apr 05 (by TVU)	Pregnancy outcome = induced abortion. Exposure days = 201
9	3712 (31)	23 Jul 04	27 Aug 04	4 Aug 04 (by TVU)	Pregnancy outcome = normal male at term. Exposure days = 13
Age > 35 - Within 13 Cycles – EDC while on treatment					
1	4126 (42)	15 May 04	4 Nov 04	7 Oct 04 (by TVU)	Pregnancy outcome = induced abortion. Exposure days = 146
Age 18 to 35 – EDC is past 13 cycles – EDC while on treatment					
1	3399 (26)	26 Jul 04	2 Jan 06	8 Dec 05 (by TVU)	Pregnancy outcome = normal female at term. Exposure days = 501
2	3565 (27)	5 Jul 04	15 Jan 06	31 Dec 05 (by TVU)	Pregnancy outcome = normal female at term. Exposure days = 545
3	4462 (31)	3 Oct 04	2 Jan 06	27 Nov 05 (by TVU)	Pregnancy outcome = normal female at term. Exposure days = 421

PID = patient identification number; TVU = transvaginal ultrasound; EDC = estimated date of conception

Source: Study Report A35179 Section 11.4.6. pages 127-156 of 3674

Medical Officer's Comment:

Of the 13 pregnancies in the preceding table, 1 occurred in a subject > 35 years of age and 3 occurred in subjects subsequent to the first 13 cycles of use. This leaves 9 pregnancies that occurred within the first 13 cycles, during treatment. No pregnancies occurred within 7 days after stopping treatment.

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The Applicant's analysis included subject 3574 as a treatment-related pregnancy because her EDC was 13 days after stopping treatment. However as mentioned earlier, DRUP now uses an inclusion period of 7 days rather than 14 days after last pill taken. The FDA biostatistical analysis of the pregnancy rate calculation based on 9 pregnancies and a post-treatment window of 7 days is presented below.

Protocol =	306660 (Report A35179)
Age group =	18-35
Cycles =	1-13
Exposure time (days) =	323,305
Days with back up contraception =	8,278
Relevant exposure time (days) =	315,027
Total exposure in cycles =	11,576
Cycles with back up contraception =	302
Relevant exposure in cycles =	11,274
Number of pregnancies =	9
Unadjusted Pearl Index =	1.04
Upper limit two sided 95% CI =	1.97

Source: Dr. Xin Fang's (biostatistician) review – Table 3.2.3.1(a+b)

Dr. Xin Fang, the FDA biostatistician calculated the Kaplan Meier life table estimate for Study 306660 (Table 21). This is based on a 7-day post treatment window.

Table 21: Kaplan Meier estimate based on pregnancies that occurred during cycles 1 to 13 including 7 days after treatment in study 306660 – FAS, subjects between 18 to 35 years of age

Relevant exposure time (days)	Probability of no conception	Cumulative failure rate	Lower limit of 95% CI	Upper limit of 95% CI
13	0.9990	0.0010	0.0001	0.0071
14	0.9980	0.0020	0.0005	0.0081
69	0.9969	0.0031	0.0010	0.0095
95	0.9959	0.0041	0.0016	0.0110
149	0.9947	0.0053	0.0022	0.0126
201	0.9936	0.0064	0.0029	0.0142
207	0.9924	0.0076	0.0036	0.0158
208	0.9913	0.0087	0.0044	0.0174
280	0.9901	0.0099	0.0052	0.0190

CI = Confidence interval; FAS = Full analysis set

Source: Dr. Xin Fang's (biostatistician) review – Table 3.2.3.2

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Medical Officer's Comment:

The unadjusted Pearl Index and Kaplan Meier estimate for EV/DNG are well within the range that DRUP finds acceptable for a combination oral contraceptive.

Pregnancies Prior to Study Treatment

The pregnancies identified prior to study treatment in Protocol 306660 are shown in Table 22.

Table 22: Study 306660 – Pregnancies Prior to Study Treatment

PID (age in yrs)	Treatment start	Treatment end	EDC	Notes
3274 (25)	Not started		29 Jun 04 (by TVU)	Pregnancy outcome = normal female at term
3846 (22)	Not started		28 Jul 04 (by LMP)	Pregnancy outcome = normal female at term
3849 (26)	Not started		14 Jul 04 (by TVU)	Pregnancy outcome = spontaneous abortion
4046 (25)	Not started		25 Jul 04 (by LMP)	Pregnancy outcome = induced abortion
4635 (26)	Not started		Mid July 04	Pregnancy outcome = induced abortion

PID = patient identification number; TVU = transvaginal ultrasound; EDC = estimated date of conception

Source: Study Report A35179 Section 11.4.6., pages 127-156 of 3674

The pregnancies conceived more than 7 days after study treatment are listed in Table 23.

Table 23: Study 306660 – Pregnancies Identified > 7 Days After the End of Treatment

PID (age in yrs)	Treatment start	Treatment end	EDC	Days EDC Post Rx	Notes
3001 (31)	26 Jun 04	26 Jun 05	15 Jul 05 (by TVU)	19	Pregnancy outcome = no information, lost to follow-up
3481 (24)	21 Jun 04	27 Mar 05	16 Jun 05	81	Pregnancy outcome = normal female at term
3568 (25)	21 Jul 04	31 Jan 06	8 Mar 06 (by TVU)	36	Pregnancy outcome = missed abortion
3675 (28)	28 Jul 04	26 Jul 05	12 Aug 05 (by TVU)	17	Pregnancy outcome = Male delivered at term with lumbar spina bifida
3928 (39)	11 Aug 04	6 Dec 05	13 Jan 06 (by TVU)	38	Pregnancy outcome = normal male at term
3942 (37)	2 Aug 04	27 Jul 05	13 Aug 05 (by TVU)	17	Pregnancy outcome = normal female at term
4010 (18)	17 Jul 04	31 Dec 04	24 Feb 05 (by TVU)	55	Pregnancy outcome = normal female at term
4084 (27)	29 Jul 04	20 Oct 04	20 Sep 05 (by TVU)	11 months	Pregnancy outcome = normal female at term
4164 (26)	25 May 04	28 Feb 05	24 May 05 (by TVU)	85	Pregnancy outcome = normal male at term
4455 (25)	6 Sep 04	31 Oct 04	17 Dec 04 (by TVU)	47	Pregnancy outcome = normal female at term
4579 (24)	19 Sep 04	19 May 05	2 Aug 05	75	Pregnancy outcome = female at pre-term, induced for IUGR
3574 (19)	10 Jul 04	10 Jun 05	23 Jun 05 (by TVU)	13	Pregnancy outcome = normal female at term

PID = patient identification number; TVU = transvaginal ultrasound; EDC = estimated date of conception

Source: Study Report A35179 Section 11.4.6. pages 127-156 of 3674

5.3.1.24 Secondary Efficacy Results

The data regarding bleeding/spotting days and episodes are summarized in Table 24.

Table 24: Study 306660 – Total Number of Days with Bleeding/Spotting and Number of Bleeding/Spotting Episodes (mean ± SD, [median] - FAS

Reference Period (90 days)	N of subjects	Number of bleeding/spotting days	Number of bleeding/spotting episodes
1	1238	18.2 ± 10.2 [17.0]	4.1 ± 1.5 [4.0]
2	1160	13.6 ± 9.3 [12.0]	3.1 ± 1.5 [3.0]
3	1110	13.1 ± 8.8 [12.0]	3.1 ± 1.4 [3.0]
4	1069	12.5 ± 8.7 [12.0]	2.9 ± 1.4 [3.0]
5	1040	13.9 ± 8.3 [14.0]	3.4 ± 1.5 [4.0]
6	1014	12.1 ± 7.8 [11.0]	2.8 ± 1.4 [3.0]

Source: Study report 35179; Text table 29; page 113 of 3674

Medical Officer’s Comment:

The difference between Period 1 and the remaining periods is attributable to the fact that the pills were started on the first day of menstrual bleeding and so the first 90 day cycle has approximately 4 menstruations compared to 3 in subsequent 90 day cycles.

Table 25 provides data on the number of spotting-only days and episodes.

Table 25: Study 306660 – Total Number of Days with Spotting-only and Number Spotting-only Episodes (Mean ± SD, [Median] -FAS

Reference Period (90 days)	N of subjects	Number of spotting-only days	Number of spotting-only episodes
1	1238	7.0 ± 7.2 [5.0]	1.0 ± 1.2 [1.0]
2	1160	6.0 ± 6.6 [4.0]	0.9 ± 1.2 [0.0]
3	1110	5.9 ± 6.1 [5.0]	0.9 ± 1.1 [0.0]
4	1069	5.8 ± 6.4 [4.0]	0.8 ± 1.1 [0.0]
5	1040	6.1 ± 6.2 [5.0]	0.9 ± 1.3 [0.0]
6	1014	5.6 ± 5.8 [4.0]	0.8 ± 1.2 [0.0]

Source: Study report 35179; Text table 31; page 115 of 3674

Table 26 provides data on the frequency of subjects with withdrawal bleeding and the length of withdrawal bleeding episodes.

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Table 26: Proportion of Subjects with Scheduled Bleeding and Length of Scheduled I Bleeding Episodes (Mean ± SD, [Median]) - FAS

Cycle (28 days)	N (%) of Volunteers	Length in days
1	1000 of 1272 (78.6%)	4.2 ± 2.5 [4.0]
2	1030 of 1263 (81.6%)	4.6 ± 3.8 [4.0]
3	977 of 1238 (78.9%)	4.3 ± 2.3 [4.0]
4	961 of 1198 (80.2%)	4.3 ± 2.4 [4.0]
5	956 of 1180 (81.0%)	4.4 ± 2.5 [4.0]
6	911 of 1162 (78.4%)	4.5 ± 2.6 [4.0]
7	918 of 1133 (81.0%)	4.2 ± 2.4 [4.0]
8	905 of 1123 (80.6%)	4.2 ± 2.4 [4.0]
9	897 of 1114 (80.5%)	4.3 ± 2.3 [4.0]
10	869 of 1103 (78.8%)	4.2 ± 3.0 [4.0]
11	846 of 1072 (78.3%)	4.2 ± 2.5 [4.0]
12	838 of 1072 (78.2%)	4.0 ± 1.9 [4.0]
13	831 of 1060 (78.4%)	4.1 ± 2.0 [4.0]
14	830 of 1044 (79.5%)	4.2 ± 2.1 [4.0]
15	818 of 1040 (78.7%)	4.2 ± 2.0 [4.0]
16	816 of 1035 (78.8%)	4.2 ± 2.1 [4.0]
17	789 of 1028 (76.8%)	4.1 ± 2.1 [4.0]
18	803 of 1017 (79.0%)	4.1 ± 2.3 [4.0]
19	791 of 1013 (78.1%)	4.2 ± 2.6 [4.0]
20	608 of 1007 (60.4%)	2.8 ± 1.8 [2.0]

Source: Study report 35179; Text table 33; page 117 of 3674 and Table 71; pages 1002-08 of 3674

The mean values for onset of scheduled bleeding (after end of exposure to the progestogen compound) were also relatively stable, in the range from 3.5 to 4.4 days after last progestin-containing tablet.

Table 27 provides data on the number of subjects with unscheduled bleeding.

Table 27: Number of Subjects (%) with Unscheduled Bleeding and Mean Number of Unscheduled Bleeding Days- FAS

Cycle (28 days)	N (%) of Volunteers	Days of Unscheduled Bleeding
2	303 of 1263 (24.0%)	1.5 ± 3.7
3	274 of 1238 (22.1%)	1.2 ± 2.9
4	230 of 1198 (19.2%)	1.0 ± 2.8
5	223 of 1180 (18.9%)	1.0 ± 2.7
6	197 of 1162 (17.0%)	0.8 ± 2.4
7	154 of 1133 (13.6%)	0.8 ± 2.6
8	177 of 1123 (15.8%)	0.8 ± 2.3
9	161 of 1114 (14.5%)	0.7 ± 2.4
10	171 of 1103 (15.5%)	0.8 ± 2.5
11	140 of 1080 (13.0%)	0.7 ± 2.4
12	150 of 1072 (14.0%)	0.7 ± 2.4
13	147 of 160 (13.9%)	0.7 ± 2.3
14	127 of 1044 (12.2%)	0.7 ± 2.5
15	115 of 1040 (11.1%)	0.6 ± 2.1
16	129 of 1035 (12.5%)	0.6 ± 2.2
17	116 of 1028 (11.3%)	0.6 ± 2.1
18	104 of 1017 (10.2%)	0.5 ± 2.1
19	143 of 1013 (14.1%)	0.7 ± 2.1
20	140 of 1007 (13.9%)	0.7 ± 2.2

Source: Study report 35179; Text table 36 and 37; page 120 of 3674

Medical Officer's Comment:

This reviewer did not include Cycle 1 information in the previous table because the Applicant coded the menstrual bleeding that started Cycle 1 as unscheduled and thus the numbers were artificially high.

The overall bleeding pattern (total, scheduled, unscheduled) appears acceptable to this reviewer and generally comparable to other approved combination oral contraceptives.

5.3.1.25 Safety – Extent of Exposure

The total extent of exposure to estradiol valerate and dienogest for any subject in Study 306660 is 52 and 61 mg, respectively, per 28 day cycle.

The exposure to EV/DNG in Study 306660 by cycles, partial cycles, days and women-years is the following:

- Number of completed 28 day cycles (23,528)
- Number of partially completed 28 day cycles (430)
- Total days of exposure (669,209)
- Total women-years of exposure (1832.19)

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Source: NDA 22-252; Amendment 17 (3/17/2010)

5.3.1.26 Safety – Event Overview

The safety event overview in regard to number of subjects is shown in Table 28. The total number of adverse events was 2,913.

Table 28: Study 306660 – Overview of the Number (%) of Subjects with Adverse Events (Full Analysis Set)

Subjects	EV/DNG N = 1377 n (%)
With at least 1 AE	917 (66.6%)
With nonfatal SAEs	42 (3.1%)
Who discontinued study drug due to an AE	140 (10.2%)
Who died	2 (0.1%)

EV/DNG = estradiol valerate / dienogest; AE = adverse event; SAE = serious adverse event
Source: Study Report A35179 Text Table 46; page 173 of 3674

Medical Officer's Comment:

As mentioned earlier, the number of subjects who discontinued due to an adverse event should be listed as 142 (10.3%).

5.3.1.27 Safety – Common Adverse Events

The total number of adverse events in Study 306660 was 2,913. A listing of subjects with adverse events occurring in $\geq 2\%$ of the population is shown in Table 29.

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Table 29: Study 306660 – Number (%) of Subjects with Most Common Adverse Events (≥2%) by Preferred Term and Descending Frequency of Occurrence – Full Analysis Set

Adverse Event (PT)	EV/DNG N = 1377 n (%)
Nasopharyngitis	247 (17.9)
Headache / migraine	158 (11.5)
Vulvovaginal infections / candidiasis	139 (10.0)
Cystitis / urinary tract infection	100 (7.3)
Diarrhea	91 (6.6)
Breast pain	66 (4.8)
Vomiting	54 (3.9)
Acne	44 (3.2)
Dysmenorrhea	42 (3.1)
Gastroenteritis	39 (2.8)
Weight increased	37 (2.7)
Sinusitis	36 (2.6)
Tonsillitis	33 (2.4)
Bronchitis	33 (2.4)
Toothache	29 (2.1)
Influenza	27 (2.0)
Metrorrhagia	27 (2.0)

EV/DNG = estradiol valerate / dienogest; PT = preferred term
 Source: Study Report A35179; Table 113; page 1286-1289 of 3674

5.3.1.28 Safety – Nonfatal Serious Adverse Events (SAEs)

Table 30 provides safety data on the nonfatal SAEs in Study 306660.

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Table 30: Study 306660 – Nonfatal Serious Adverse Events

#	PID	Duration of Treatment at SAE onset (days)	SAE(s)	Comment
1	3025	225	Spinal compression fracture	Sledding accident
2	3060	582	Cervical carcinoma-in-situ	
3	3156	228	Myocardial infarction	46 years old, smokes 10-20 cig/day
4	3241	221	Acute sinusitis	
5	3247	362	Presumed ocular histoplasmosis syndrome	
6	3305	330	Pyrexia, bone pain	
7	3309	268	Disc disorder	
8	3309	458	Peritonsillar abscess, dehydration	
9	3313	57	Appendicitis	
10	3406	185	Missed abortion	
11	3476	94	Joint dislocation, muscle atrophy	
12	3564	171	Tonsillitis	
13	3568	559	Missed abortion	
14	3573	259	Appendicitis, uterine infection	
15	3575	270	Basedow's disease	
16	3605	31	Arthralgia	Pre-existing rupture anterior cruciate ligament
17	3617	263	Uterine leiomyoma	Rapid growth and pain
18	3628	515	Appendicitis	
19	3675		Spina bifida (offspring)	Congenital anomaly (EDC approx 17 days after last study drug taken)
20	3698	74	Food poisoning	
21	3747	283	Arthropathy	Cruciate ligament tear
22	3749	511	Inguinal hernia	
23	3772	480	Bacterial meningitis	
24	3786	243	Second degree burn	Scalding
25	3832	276	Varicose vein	29 years old, pre-existing before starting study drug, underwent vein stripping
26	3872	291	Joint dislocation	
27	3888	319	Unilateral deafness	History of otosclerosis in the past
28	3969	280	Cervical dysplasia	
29	4071	292	Diplopia, vertigo	Status post tick bite, evaluated for meningitis
30	4082	89	Focal nodular hyperplasia of liver	
31	4163	96	Tonsillitis	
32	4167	281	Sinusitis	
33	4187	116	Inguinal hernia	
34	4191	214	Drug dependence	Borderline personality disorder
35	4201	452	Breast fibroadenoma	
36	4235	304	Parotitis, lymphadenitis	
37	4299	92	Cystitis, celiac disease	
38	4416	507	Motor vehicle accident	Numerous fractures
39	4420	155	Dermoid cyst, ovary	
40	4562	266	Breast augmentation	
41	4589	164	Breast augmentation	Also liposuction
42	4593	210	Meniscus lesion	
43	4651	90	Optic neuritis	
44	4147		Deep vein thrombosis	One week after finishing treatment

PID = Subject identification number; SAE = serious adverse event
 Source: Study Report A35179; Table 135, pages 2179-2197 of 3674

Medical Officer's Comment:

The total number of subjects with nonfatal SAE(s) is 43. Subject 3309 is listed twice in the preceding table due to separate time points for the SAEs. Subjects 3060 and 4147 were not initially present in the Applicant's list of SAEs but were added later. This reviewer considers the SAEs of myocardial infarction, focal nodular hyperplasia, deep vein thrombosis and growth of uterine leiomyoma to be possibly related to study drug.

5.3.1.29 Safety – Deaths

There were 2 deaths reported in Study 3066660.

Subject 3779 died as a result of a tsunami in Asia on 26 Dec 2004.

Subject 4318 was hospitalized on [REDACTED] (b) (4) for headache and disturbed consciousness. CT and MRI performed on the same day showed subarachnoid and frontal hemorrhage. Angiographically, an aneurysm of the ramus communicans anterior was found, which was operated on by clipping on the day of diagnosis. The aneurysm ruptured at the time of operation. The postoperative period was complicated by respiratory difficulties, brain edema, progressive stroke and finally brainstem herniation and death. No autopsy was performed. The causes of death were, according to the death certificate, subarachnoid and frontal hemorrhage due to aneurysm of ramus communicans anterior.

Medical Officer's Comment:

Neither of these deaths is thought to be related to study drug by this reviewer.

5.3.1.30 Safety – Discontinuations Due to Adverse Events

There were 169 adverse events contributing to discontinuation of study drug in 142 subjects. The number of subjects with discontinuations due to adverse events are shown in Table 31. The most common and most pertinent events are shown.

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Table 31: Study 306660: Proportion of Subjects with the Most Common and Most Pertinent Adverse Events leading to Discontinuation of Study Drug (EV/DNG)

Adverse Event (number of subjects) SOC and PT	N = 1377 No. of subjects (%)
<u>Reproductive system and breast disorders</u>	
Breast discomfort (1), Breast pain (4), Breast tenderness (1)	6 (0.4%)
Menorrhagia (3)	3 (0.2%)
Menstrual disorder (3)	3 (0.2%)
Metrorrhagia (24)	24 (1.7%)
Amenorrhea (2)	2 (0.1%)
<u>Cardiac disorders</u>	
Myocardial infarction (1)	1 (< 0.1%)
<u>Investigations</u>	
Weight increased (12)	12 (0.9%)
<u>Neoplasm (benign, malignant and unspecified)</u>	
Focal nodular hyperplasia (1)	1 (< 0.1%)
<u>Nervous system disorders</u>	
Headache (8), Migraine (4)	12 (0.9%)
<u>Psychiatric disorders</u>	
Depressed mood (3), Depression (7)	10 (0.7%)
Libido decreased (5), Loss of libido (3)	8 (0.6%)
Mood altered (2)	2 (0.1%)
<u>Skin and subcutaneous tissue disorders</u>	
Acne (14)	14 (1.0%)
Alopecia (3)	3 (0.2%)
<u>Vascular disorders</u>	
Hypertension (8)	8 (0.6%)

EV/DNG = estradiol valerate / dienogest; SOC = system organ class; PT = preferred term
 Source: Study Report A35179; Table 120; pages 1503-1516 of 3674

5.3.1.31 Safety – Standard Safety Labs and Cervical Smears.

Hematology, chemistry and urinalysis laboratory studies were not performed in this study. Studies 304004, 308960 and 308961 had standard safety labs performed.

The number of subjects with abnormal cervical smears at the final examination was 16 (1.2%).

Medical Officer's Comment:

Based on text table 54 of the study report, the number of subjects who were listed with either cervical dysplasia or cervical dyskaryosis was 11. This equates to 11 per 1377 subjects in the full analysis set or 0.8%. This percentage of dysplasia is not increased over the 1-2% that is generally seen in this population.

5.3.1.32 Safety – Vital Signs and Weight

Overall, the mean systolic and diastolic blood pressure fluctuated very little during the study course. The shift analysis shows that there were no unfavorable changes (from normal to increased values of > 140 / 90 mmHg for systolic and diastolic blood pressure, respectively) in the values of 1310 volunteers (98.0%). Only minimal fluctuations of heart rate were found in subjects throughout the study visits.

Shift analysis of BMI changes in individual volunteers (using categories of < 20, 20 to < 25, 25 to < 30, and ≥ 30 kg/m²) from Screening to Final examination revealed that in a large proportion of volunteers (78.9%), there were no changes to another category. A change to a higher category was seen in 12.5% of the volunteers while a change to a lower category was seen in 8.6%.

5.3.1.33 Safety – Endometrial Biopsy

Endometrial biopsies were evaluated at LKF (Laboratory for Clinical Research) in Kiel, Germany. Table 32 presents the histologic data from the endometrial biopsies in Study 306660.

Table 32: Study 306660 – Endometrial Biopsy Results

Screening biopsy	n	Final exam biopsy	n
Total number of subjects	283 (100%)	Total number of subjects	219 (100%)
Normal	253	Normal	204
Atrophic	50	Atrophic	54
Inactive	50	Inactive	86
Weakly proliferative	29	Weakly proliferative	18
Active proliferative	15	Active proliferative	3
Disordered proliferative	81	Disordered proliferative	4
Secretory, cyclic type	16	Secretory, cyclic type	14
Secretory, progestational type	6	Secretory, progestational type	23
Menstrual type	1	Menstrual type	1
Not available	1	Not available	1
Not assessable	0	Not assessable	0
Not done	4	Not done	0
Abnormal	2	Abnormal	0
Simple hyperplasia (no atypia)	2	-	-
Not assessable	28	Not assessable	14
Not done	0	Not done	1

Source: Study Report A35179; pages 2307 and 2313 of 3674

Medical Officer's Comment:

The histologic findings are similar to those seen with other combination oral contraceptives. Older pills with stronger progestin doses tend to have

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more progestational secretory stromal changes. There is nothing worrisome in these histological results.

5.3.2 Pivotal Study 304742 (Report A39818) for Contraception

5.3.2.1 Study Title, Coordinating Investigator, Study Dates

“Multi-center, open, uncontrolled study to investigate the efficacy and safety of a 4-phasic oral contraceptive SH T006581D containing estradiol valerate and dienogest in a 28-day regimen for 13 cycles which was extended to a maximum of 28 cycles in healthy female subjects

The coordinating investigator was Steven Drosman, MD (San Diego, California).

This study ran from Mar 2, 2005 until Oct 12, 2007.

5.3.2.2 Ethics

The Applicant stated that a) this study met all local legal and regulatory requirements, b) this study was conducted in accordance with Good Clinical Practice (GCP) as required by 21 CFR Parts 50, 56 and 312, c) this study complied with ethical principles originating in the Declaration of Helsinki and the International Conference on Harmonization guideline E6, d) the study protocol and amendments were reviewed and approved by each study site’s Independent Ethics Committee (IEC) or Institutional Review Board (IRB) before the start of the study or before implementation of the amendment, and e) the study’s informed consent form was reviewed and approved by the IECs and IRBs prior to its issue.

5.3.2.3 Study Sites

In Study 304742 there were study sites in the U.S. (20) and Canada (9) that randomized subjects.

5.3.2.4 Study Objectives

The overall objectives of the study were to confirm the safety and efficacy of EV/DNG. The primary efficacy parameter was the pregnancy rate. The secondary efficacy parameters were cycle control and bleeding patterns. The safety parameters were adverse events, physical exam, gynecologic exam and vital signs.

5.3.2.5 Study Design

The study design is identical to that of Study Protocol 306660 except for the following (Table 33):

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Table 33: Study 306660 vs. 304742 – Comparison of Study Design

Protocol 306660	Protocol 304742
Age between 18 and 50 years (inclusive) 20 cycles of treatment	Age between 18 and 35 years (inclusive) Originally 13 cycles of treatment extended to 28 cycles (for subjects who qualify based on compliance – Amendment #2)
Endometrial biopsy subgroup	No endometrial biopsy subgroup
Urine pregnancy test in the absence of menstrual bleeding.	Urine pregnancy testing twice in the absence of menstrual bleeding

Sources: Respective protocols (306660 and 304742)

Medical Officer’s Comment:

As noted, the Applicant extended the study to 28 cycles for subjects who were willing and who demonstrated compliance. The Applicant’s reasons for the extension are as follows:

“According to Amendment 1 to the protocol, it was estimated to enroll 480 subjects with the aim to have 400 subjects completing the study. For sample size calculation, the cumulative drop-out rate was estimated at 20%. After about 1 year of study conduct, it was assessed that the cumulative drop-out rate was greater than anticipated (approximately 30%). The reasons most often given for drop-out (>10%) were adverse events (AEs) (48.4%), withdrawal of consent (20.0%), and lost to follow-up (13.5%). Additionally, in the original protocol, the use of backup contraception (approximately 20%) was not considered in the sample size calculation. In order to obtain additional experience with the investigational drug in this study population, an extension study has been added.”

The Applicant’s definition of compliance were those subjects who indicated the use of backup contraception due to missed tablet intake during the first 13 cycles of the study in no more than 2 cycles.

The Division has encouraged applicants in the past to focus their contraceptive efficacy analysis in the first 13 cycles of use in the more pregnancy susceptible age range of 18-35. Longer studies tend to show better efficacy because the failures are removed and more compliant/ more successful subjects remain.

This reviewer considers the extension data to mainly provide safety data since the extension population is a select group that is less reflective of “real world” use.

5.3.2.6 Inclusion Criteria

The inclusion criteria are identical to that of Study Protocol 306660 except for the following (Table 34):

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Table 34: Study 306660 vs. 304742 – Comparison of Inclusion Criteria

Protocol 306660	Protocol 304742
Age between 18 and 50 years (inclusive)	Age between 18 and 35 years (inclusive)
For biopsy group only: biopsy taken (visit 1), non-suspicious biopsy result (visit 2)	Note: This protocol did not have an endometrial biopsy subgroup

Sources: Respective protocols (306660 and 304742)

5.3.2.7 Exclusion Criteria

The exclusion criteria are identical to that of Study Protocol 306660 except for the following (Table 35):

Table 35: Study 306660 vs. 304742 – Comparison of Exclusion Criteria

Protocol 306660	Protocol 304742
Any disease or condition that can compromise the function of the body systems and could result in altered absorption, excessive accumulation, impaired metabolism, or altered excretion of the study medication	Any disease or condition that can compromise the function of the body systems and could result in altered absorption, excessive accumulation, impaired metabolism, or altered excretion of the study medication (<u>such as but not limited to duodenal ulcers, gastritis, gastrectomy or gastric resection surgery, or renal compromise</u>)
Any disease that may worsen under hormonal treatment or might interfere with the conduct of the study or the interpretation of the results (e.g. pemphigoid gestationis or idiopathic icterus during a previous pregnancy; middle-ear deafness (otosclerosis); Sydenham chorea, porphyria, disturbances in the bile flow (presence or history of cholestasis, gallstones), systemic lupus erythematoses)	Any disease that may worsen under hormonal treatment or might interfere with the conduct of the study or the interpretation of the results (e.g., pemphigoid gestationis or idiopathic icterus during a previous pregnancy; middle-ear deafness (otosclerosis); Sydenham chorea, porphyria, disturbances in the bile flow (presence or history of cholestasis, gallstones), <u>cholecystitic jaundice or history of jaundice with prior pill use,</u> systemic lupus erythematosus.
Diabetes mellitus with vascular involvement	Diabetes mellitus
Intake of an experimental drug within 1 month prior to inclusion in the study	Intake of an experimental drug within 1 month prior to inclusion in this study <u>or participation in any other clinical trial during the course of this study</u>

Sources: Respective protocols (306660 and 304742)

Medical Officer's Comment:

The differences in study design and entry criteria are not felt by this reviewer to affect the efficacy or safety evaluation of this product.

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5.3.2.8 Prior and Concomitant Therapy

This section is identical to Protocol 306660.

5.3.2.9 Study Procedures

Amendment 2 of the Study Protocol allowed for a study extension based on subject compliance. Table 36 shows the procedures for the study up through 13 cycles of treatment. Table 37 shows the procedures in the extension.

Table 36: Study 304742 – Study Procedures for 13- Cycle Study

Visit number	V1	V2	V3	V4	V5	V6	V7
Cycle	S	BL	3	6	10	13	14
Informed consent	X						
Demographic data	X						
Entry criteria	X	X					
Gynecologic, medical, surgical and medication history	X						
Smoking habits, alcohol consumption	X						
Height, Weight, Blood Pressure, Heart Rate	X	X	X	X	X	X	X
Physical exam	X						X
Gynecologic exam	X			X		X	X
Cervical smear	X	R		X		X	X
Baseline findings	X	X					
Admission to treatment		X					
HCG – urine tests dispensed		X	X	X	X		
HCG – urine test - results			T	T	T	T	X
Medication dispensed		X	X	X	X	X	
Diary cards dispensed		X					
Unused/empty blisters returned			X	X	X	X	X
Diary cards returned			X	X	X	X	X
Adverse events/ concomitant medications		X	X	X	X	X	X
Use of back-up contraception?			X	X	X	X	X
Discussion of follow up contraception							X
End of study evaluation							X
Subjective assessment							X

Abbreviations: V = visit; S = screening; BL = baseline; R = result; F = final examination (days 10-24 after the last tablet intake) T = testing in case of absence of monthly bleeding
 Source: Study Protocol 304742; page 13 of 74

Medical Officer's Comments:

Height was only assessed at visit 1.

The pregnancy test dispensed at Visit 2 was required to be negative to allow subjects to continue in the trial. Pregnancy tests were to be

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performed twice at home by the subject in case of absence of monthly bleeding (represented by T in the table). The pregnancy test at visit 7 was to be performed at the center.

Table 37: Study 304742 – Procedures in Study Extension

Visit number	V6	V8	V9	V10	V11	V12
Cycle	13	16	20	24	28	F/U
Informed consent	X					
Entry criteria	X					
Weight, Blood Pressure, Heart Rate	X	X	X	X	X	X
Physical exam	X					X
Gynecologic exam	X			X		X
Cervical smear	X					X
Admission to treatment	X					
HCG – urine tests dispensed	X	X	X	X		
HCG – urine test - results	T	T	T	T	T	X
Medication dispensed	X	X	X	X		
Diary cards dispensed	X	X	X	X		
Unused/empty blisters returned	X	X	X	X	X	X
Diary cards returned	X	X	X	X	X	X
Adverse events/ concomitant medications	X	X	X	X	X	X
Use of back-up contraception?	X	X	X	X	X	X
Discussion of follow up contraception						X
End of study evaluation						X
Subjective assessment						X

Abbreviations: V = visit; S = screening; R = result; F = final examination (days 10-24 after the last tablet intake) T = testing in case of absence of monthly bleeding
 Source: Study Protocol 304742; Amendment 2; page 59 of 74

Medical Officer's Comment:

Pregnancy tests were to be performed twice at home by the subject in case of absence of monthly bleeding (represented by T in the table). The pregnancy test at Visit 12 was to be performed at the center.

5.3.2.10 Bleeding Record

This section is identical to Protocol 306660.

5.3.2.11 Warnings and Other Notes

This section is identical to Protocol 306660.

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5.3.2.12 Primary Efficacy Variables

This section is identical to Protocol 306660.

5.3.2.13 Secondary Efficacy Variables

This section is identical to Protocol 306660.

5.3.2.14 Statistical Analysis Plan

This section is identical to Protocol 306660.

5.3.2.15 Analysis of Safety

This section is identical to Protocol 306660 except that there is no endometrial biopsy subgroup.

5.3.2.16 Protocol Amendments

Protocol Amendment 1 (Apr 21, 2005):

Key changes consist of the following:

- The number of subjects for this study was increased from 240 to 480
- The Bethesda Classification System was specified for evaluating cervical smears.

Medical Officer's Comment:

The increase in North American participation came after recommendations from the Division of Reproductive and Urologic Products. The cervical cytology performed in Study 306660 utilized a numbered class system.

Protocol Amendment 2 (10 Mar 2006):

Key changes consist of the following:

- Extension of the study for subjects who indicated the use of backup contraception due to missed tablet intake during the first 13 cycles of the study in no more than 2 cycles. The extension was designed to proceed up to a maximum of 28 cycles of exposure.

Medical Officer's Comment:

The primary period that this reviewer will focus on regarding contraceptive efficacy in the North American study (Protocol 304742) is the first 13 cycles.

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5.3.2.17 Disposition of Subjects

Table 38 provides data on the disposition of subjects in Study 304742.

Table 38: Study 304742 – Disposition of Subjects

Disposition / Reason	EV/DNG
Screened	583 (100%)
Screening failures	84 of 583 (14.4%)
<ul style="list-style-type: none"> • Withdrawal of consent • Entry criteria not met • Volunteer lost, no further information • Other 	<ul style="list-style-type: none"> • 9 of 84 (10.7%) • 61 of 84 (72.6%) • 6 of 84 (7.1%) • 8 of 84 (9.5%)
Volunteers enrolled in the study	499 of 583 (96.2%)
Volunteers who dropped out before start of study medication	9 of 499 (1.8%)
Volunteers receiving study medication and had at least 1 post baseline observation (FAS)	490 of 499 (98.2%)
Volunteers not entering the extension phase	343 of 499 (68.7%)
<ul style="list-style-type: none"> Volunteers prematurely discontinuing study medication (prior to extension phase) Completion status unknown (prior to extension phase) Completed study medication (prior to extension phase) 	<ul style="list-style-type: none"> 202 of 499 (40.5%) 11 of 499 (2.2%) 130 of 499 (26.0%)
Volunteers entering extension phase	147 of 499 (29.5%)
<ul style="list-style-type: none"> Volunteers prematurely discontinuing study medication in extension phase Completion status unknown (extension phase) Completed study medication (extension phase) 	<ul style="list-style-type: none"> 33 of 499 (6.6%) 1 of 499 (0.2%) 113 of 499 (22.6%)
Total completers	243 of 499 (48.7%)
Total who prematurely discontinued study medication	235 of 499 (47.1%)
<ul style="list-style-type: none"> • Withdrawal of consent • Protocol deviation • Adverse event • Patient lost, no further information • Pregnancy • Other 	<ul style="list-style-type: none"> • 48 of 499 (9.6%) • 6 of 499 (1.2%) • 73 of 499 (14.6%) • 63 of 499 (12.6%) • 5 of 499 (1.0%) • 40 of 499 (8.0%)

FAS = full analysis set (All subjects admitted to the treatment phase who took at least 1 pill of study medication and from whom at least 1 observation after admission to treatment is available)

EV/DNG = estradiol valerate / dienogest

Source: Study Report 39818 page 50 of 484

5.3.2.18 Protocol Deviations

This reviewer analyzed the major protocol deviations in dataset (DOM.PD) to provide the following information included in Table 39.

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Table 39: Study 304742 - Major Protocol Deviations Identified by Medical Officer in Dataset DOM.PD01

Major Deviation	N (%)
Total	354 (100%)
Inclusion/exclusion error at study entry	4 (1.1%)
Withdrawal criteria present but not withdrawn	0
Excluded concomitant treatment	42 (11.8%)
Treatment deviation	204 (57.6%)
Time schedule deviation	0
Procedure deviation	1 (0.2%)
Other	103 (29.0%)

Source: Dataset DOM.PD for Study 304742

Major deviations related to inclusion/exclusion errors at study entry included pregnancy before start of medication, subject who did not meet age criteria, lack of appropriate number of cycles since subject's last delivery and abnormal pap at screening.

Major deviations related to excluded concomitant treatment mainly appear to be related to antibiotic and antifungal use (In Study 306660, antibiotic and antifungal use were characterized as minor deviations). As in Study 306660, there were also a few cases of hormone use in which cycles were not excluded in Study 304742. These cases are listed in Table 40. Since both of these cases occurred after Cycle 13, the primary efficacy determination is not affected.

Major deviations related to treatment deviation included mistakes in pill usage, the use of less than 24 tablets in any cycle, and alterations in length of hormone-free interval.

The major deviation related to procedure was a subject who started her next pill pack at the wrong time.

The major deviations classified as "other" included missing or incomplete documentation of bleeding pattern, incorrect diary use, missing documentation for the start of a new blister and poor compliance.

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Table 40: Subjects Taking Excluded Hormonal Products Whose Cycles Were Not Adjusted – Study 304742

Subject No.	Medication	Duration of Use (Days)	Notes
510010	Ortho TriCyclen LO	2	This occurred during subject cycle 25. No adjustment was made since this occurred after cycle 13
601011	Levonorgestrel	7	This occurred during subject cycle 18. No adjustment was made since this occurred after cycle 13

COC = Combination oral contraceptive

Source = Biometrical report, Attachment 4-OC listings, Submission #11, Dec 18, 2009

5.3.2.19 Demographics

Table 41 provides demographic data for Study 304742.

Table 41: Study 304742 – Demographic Data - FAS

	EV/DNG (n=490)
Mean age (years ± SD)	25.1 ± 4.4
Ethnic group (%)	
• Caucasian (non-Hispanic)	371 (76.0%)
• Black	34 (7.0%)
• Hispanic	64 (13.0%)
• Asian	16 (3.3%)
• Other	5 (1.0%)
Smoking history (yes)	166 (34.0%)
Current smoker	92 (19.0%)
Mean weight (kg ± SD)	62.5 ± 10.2
Body mass index (kg/m ² ± SD)	23.3 ± 3.3
Mean height (cm ± SD)	163.9 ± 6.9

EV/DNG = estradiol valerate / dienogest

Source: Study Report A39818; Text Table 7; page 55 of 484

5.3.2.20 Gynecologic History

Table 42 presents some of the gynecologic historical data for Study 304742.

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Table 42: Study 304742 – Gynecologic and Contraceptive History – Full Analysis Set

	EV/DNG (n=490)
Mean age at menarche (years ± SD)	12.6 ± 1.54
Subjects with regular cycles – N (%)	474 (97.0%)
History of intercytic bleeding – N (%)	30 (6.0%)
History of dysmenorrhea– N (%)	137 (28.0%)
History of amenorrhea – N (%)	16 (3.0%)
History of OC use – N (%)	287 (59.0%)

EV/DNG = estradiol valerate / dienogest

Source: Study Report A39818 Tables 7-9, pages 216-220 of 484

5.3.2.21 Primary Efficacy Results

During Treatment Pregnancies

Pregnancies during treatment for Study 304742 (includes Pregnancies with EDC within 14 Days of Treatment) are shown in Table 43.

Table 43: Study 304742 – Pregnancies during Study Treatment (Includes Pregnancies with Estimated Date of Conception within 7 Days of End of Treatment)

PID (age in yrs)	Treatment start	Treatment end	EDC	Notes
Age 18 to 35 - Within 13 Cycles – EDC while on treatment				
501028 (26)	21 Jul 05	13 Nov 05	30 Oct 05 (by TVU)	Pregnancy outcome = normal male at term. Exposure days 116
505008 (30)	25 Jul 05	20 May 06	9 Apr 06 (by TVU)	Pregnancy outcome = induced abortion. Exposure days = 300
509008 (29)	23 Apr 05	20 Nov 05	25 Oct 05 (by LMP)	Pregnancy outcome = induced abortion. Exposure days = 212
511005 (19)	31 May 05	25 Aug 05	13 Aug 05 (by TVU)	Pregnancy outcome = normal male at term. Exposure days = 87
602006 (24)	15 Apr 05	8 Jan 06	12 Dec 05 (by TVU)	Pregnancy outcome = normal female at term. Exposure days = 269
Age 18 to 35 – EDC is past 13 cycles – EDC while on treatment				
519007 (28)	12 Apr 05	9 May 07	1-7 May 07 (by TVU)	Pregnancy outcome = induced abortion. Exposure days = 758

PID = patient identification number; TVU = transvaginal ultrasound; EDC = estimated date of conception

Source: Study Report A39818 Section 14.4., pages 187-195 of 484

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Medical Officer's Comment:

Of the 6 pregnancies in the preceding table, 1 occurred in a subject after 13 cycles of use. This leaves 5 pregnancies that occurred in the first 13 cycles during treatment. No pregnancies occurred within 7 days after stopping treatment.

The Applicant's analysis also included subject 604006 as a treatment-related pregnancy because her EDC was 9 days after stopping treatment. However as mentioned earlier DRUP now uses an inclusion period of 7 days rather than 14. The FDA's biostatistics analysis (by Dr. Fang) based on 5 pregnancies and a post-treatment window of 7 days is presented below.

Protocol =	304742 (Report A39818)
Age group =	18-35
Cycles =	1-13
Exposure time (days) =	124,995
Days with back up contraception =	16,797
Relevant exposure time (days) =	108,198
Total Exposure time (cycles) =	4,575
Cycles with back up contraception =	606
Relevant exposure time (days) =	3,969
Number of pregnancies =	5
Unadjusted Pearl Index =	1.64
Upper limit two sided 95% CI =	3.82

Source: Dr. Xin Fang's biostatistical review – Tables 3.2.3.1 (a+b)

Dr. Xin Fang, the FDA biostatistician calculated the Kaplan Meier life table analysis for Study 304742. The results are shown in Table 44.

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Table 44: Kaplan Meier estimate based on pregnancies that occurred during cycles 1 to 13 including 7 days after treatment in study 304742 – FAS, subjects between 18 to 35 years of age

Relevant exposure time (days)	Probability of no conception	Cumulative failure rate	Lower limit of 95% CI	Upper limit of 95% CI
75	0.9973	0.0027	0.0004	0.0187
102	0.9945	0.0055	0.0014	0.0218
186	0.9878	0.0122	0.0046	0.0323
203	0.9843	0.0157	0.0065	0.0375

CI = Confidence interval; FAS = Full analysis set
 Source: Dr. Xin Fang's biostatistical review – Table 3.2.3.2

Medical Officer's Comment:

The unadjusted Pearl Index and Kaplan Meier estimate for EV/DNG in Study 304742 are within an acceptable range for a combination oral contraceptive efficacy analysis. The numbers are higher in the US/Canadian study than in the European study, but that has been typical of contraceptive studies evaluated in DRUP. It has been postulated that the better efficacy results seen in Europe are due to better compliance and lower BMI.

Pregnancies Prior to Study Treatment

Pregnancies conceived before study treatment for Study 304742 are shown in Table 45.

Table 45: Study 304742 – Pregnancies before Study Treatment

PID (age in yrs)	Treatment start	Treatment end	EDC	Notes
512041 (24)	15 Aug 05	19 Sep 05	7 Aug 05 (by TVU)	Pregnancy outcome = not listed. Exposure days = 36
518017 (22)	14 Jun 05	22 Jun 05	1-4 Jun 05 (by abd. sono)	Pregnancy outcome = induced abortion. Exposure days = 9
602016	Not started		14 Jun 05 (by LMP)	Pregnancy outcome = induced abortion

PID = patient identification number; TVU = transvaginal ultrasound; EDC = estimated date of conception

Source: Study Report A39818 Section 14.4, pages 182-186 of 484

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Pregnancies after Study Treatment

Pregnancies after treatment for Study 304742 are shown in Table 46.

Table 46: Study 30472 – Pregnancies after Study Treatment

PID (age in yrs)	Treatment start	Treatment end	EDC	Days EDC is Post Rx	Notes
509027 (19)	6 Sep 05	16 Nov 05	14 Dec 05 (by TVU)	28	Pregnancy outcome = not listed Exposure days = 72
519008 (27)	11 Apr 05	31 Aug 06 (by diary records) 23 Jan 07 (by phone records)	5 Jan 07 (not explained)	Uncertain	LMP = 15 Jan 07 Date of elective abortion 29 Jan 07 However subject did not return to clinic for pregnancy confirmation. Exposure days = The total is uncertain but subject's pregnancy occurred well after 13 cycles.
604023 (28)	13 Jul 05	3 Oct 05	30 Dec 05 (by LMP)	88	Pregnancy outcome = Normal female at term. Exposure days = 81
605004 (19)	24 Apr 05	17 Jul 05	13 Sep 05 (by TVU)	58	Normal delivery. Exposure days = 84
609012 (28)	26 Jul 05	13 Oct 05	15 Nov 05 (by TVU)	33	Pregnancy outcome = Normal male at term. Exposure days = 138
604006 (27)	11 Apr 05	4 Aug 05	13 Aug 05 (by TVU)	9	Pregnancy outcome = normal male at term. Exposure days = 116

PID = patient identification number; TVU = transvaginal ultrasound; EDC = estimated date of
 conception

Source: Study Report A39818 Section 14.4. pages 196-201 of 484

Medical Officer's Comment:

Even if Subject 519008 is considered an on-treatment pregnancy based on one phone record (but no laboratory confirmation,) this pregnancy is past the 13 cycle window used for our primary analysis.

5.3.2.22 Secondary Efficacy Results

The data regarding bleeding/spotting days and episodes are summarized in Table 47.

Table 47: Study 304742 – Number of Days with Bleeding/Spotting and Number of Bleeding/Spotting Episodes (mean ± SD, [median] – Full Analysis Set

Reference Period (90 days)	N of subjects	Number of bleeding/spotting days	Number of bleeding/spotting episodes
1	313	20.4 ± 11.8 [19.0]	4.2 ± 1.7 [4.0]
2	267	14.0 ± 9.2 [12.0]	3.3 ± 1.4 [3.0]
3	239	13.6 ± 9.2 [12.0]	3.0 ± 1.3 [3.0]
4	215	12.2 ± 8.7 [11.0]	2.9 ± 1.5 [3.0]
5	103	13.1 ± 7.8 [13.0]	3.3 ± 1.5 [4.0]
6	100	13.2 ± 8.9 [11.5]	3.0 ± 1.4 [3.0]
7	98	11.5 ± 7.1 [11.0]	2.9 ± 1.6 [3.0]
8	53	10.2 ± 6.3 [11.0]	2.9 ± 1.7 [3.0]
9	6	12.2 ± 6.9 [12.0]	2.8 ± 1.2 [3.0]

Source: Study report 39818; Text table 9; page 60 of 484

Medical Officer’s Comment:

The difference between Period 1 and the remaining periods is attributable to the fact that the pills were started on the first day of menstrual bleeding and the first 90 day cycle has approximately 4 menstruations compared to 3 in subsequent 90 day cycles.

Table 48 provides data on the number of spotting-only days and episodes.

Table 48: Study 304742 - Number of Days with Spotting-only and Number of Spotting-only Episodes (Mean ± SD, [Median] - Full Analysis Set

Reference Period (90 days)	N of subjects	Number of spotting-only days	Number of spotting-only episodes
1	313	9.7 ± 8.0 [7.0]	1.2 ± 1.3 [1.0]
2	267	7.3 ± 5.6 [6.0]	1.1 ± 1.2 [1.0]
3	239	7.4 ± 6.3 [6.0]	1.0 ± 1.2 [1.0]
4	215	6.6 ± 5.4 [5.0]	1.0 ± 1.3 [1.0]
5	103	7.2 ± 5.1 [6.0]	1.2 ± 1.4 [1.0]
6	100	7.7 ± 6.2 [7.0]	1.1 ± 1.3 [1.0]
7	98	6.6 ± 5.4 [6.0]	1.1 ± 1.4 [1.0]
8	53	5.8 ± 4.5 [5.0]	1.2 ± 1.4 [1.0]
9	6	5.5 ± 3.4 [6.0]	1.2 ± 1.6 [0.5]

Source: Study report 39818; Text table 11; page 62 of 484

Table 49 provides data on the frequency of subjects with withdrawal bleeding and the length of withdrawal bleeding episodes.

Table 49: Frequency of Volunteers with Withdrawal Bleeding and Length of Withdrawal Bleeding Episodes (Mean ± SD, [Median]) - Full Analysis Set

Cycle (28 days)	N (%) of Volunteers	Length in days
1	275 of 346 (79.5%)	4.7 ± 4.0 [4.0]
2	259 of 337 (76.9)	4.5 ± 3.2 [4.0]
3	236 of 317 (74.4%)	4.7 ± 3.7 [4.0]
4	223 of 296 (75.3%)	4.2 ± 2.3 [4.0]
5	225 of 280 (80.4%)	4.4 ± 3.0 [4.0]
6	202 of 269 (75.1%)	4.5 ± 2.6 [4.0]
7	207 of 250 (82.8%)	4.4 ± 2.4 [4.0]
8	187 of 243 (77.0%)	4.6 ± 3.1 [4.0]
9	183 of 241 (75.9%)	4.6 ± 2.6 [4.0]
10	160 of 234 (68.4%)	4.4 ± 2.4 [4.0]
11	167 of 224 (74.6%)	4.4 ± 2.4 [4.0]
12	171 of 220 (77.7%)	4.0 ± 2.2 [4.0]
13	137 of 213 (64.3%)	3.6 ± 1.7 [4.0]
15	82 of 104 (78.8%)	4.1 ± 2.1 [4.0]
18	82 of 101 (81.2%)	4.5 ± 2.4 [4.0]
21	78 of 98 (79.6%)	3.8 ± 1.5 [4.0]
24	58 of 88 (65.9%)	3.4 ± 1.6 [3.0]
27	14 of 31 (45.2%)	3.4 ± 1.3 [3.0]

Source: Study report A39818; Table 40 pages 290-293 of 484 and Text Table 13 page 64 of 484

Medical Officer's Comment:

Therefore based on this table the absence of withdrawal bleeding in the first 13 cycles of use varies from 17.2% to 35.7% of subjects.

The mean values for onset of withdrawal bleeding (after end of exposure to the progestogen compound) in the first 12 cycles ranged from 3.8 to 5.4 days.

Table 50 provides data on the number of subjects with intracyclic bleeding.

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Table 50: Number of Subjects (%) with Intracyclic Bleeding and Mean Number of Intracyclic Bleeding Days- Full Analysis Set

Cycle (28 days)	N (%) of Volunteers	Days of Intracyclic Bleeding Mean ± SD
2	97 of 337 (28.8%)	1.7 ± 3.5
3	74 of 317 (23.3%)	1.6 ± 3.7
4	64 of 296 (21.6%)	1.3 ± 3.2
5	60 of 280 (21.4%)	0.9 ± 2.4
6	43 of 269 (16.0%)	0.8 ± 2.6
7	39 of 250 (15.6%)	0.8 ± 2.4
8	36 of 243 (14.8%)	0.9 ± 3.0
9	31 of 241 (12.9%)	0.6 ± 2.2
10	33 of 234 (14.1%)	0.7 ± 2.1
11	25 of 224 (11.2%)	0.5 ± 1.9
12	37 of 220 (16.8%)	0.9 ± 2.6
13	38 of 213 (17.8%)	0.6 ± 1.9
15	14 of 104 (13.5%)	0.6 ± 2.0
18	16 of 101 (15.8%)	0.8 ± 2.2
21	14 of 98 (14.3%)	0.8 ± 3.3
24	10 of 88 (11.4%)	0.4 ± 1.3
27	7 of 31 (22.6%)	1.0 ± 2.3

SD = Standard deviation

Source: Study report A39818; Text table 16 and 19; pages 68 and 71 of 484

Medical Officer's Comment:

This reviewer did not include Cycle 1 information in the previous table because the Applicant coded the menstrual bleeding that started Cycle 1 as unscheduled and thus the numbers were artificially high.

5.3.2.23 Safety – Extent of Exposure

The exposure to EV/DNG in Study 304742 by cycles, partial cycles, days and women-years is the following:

- Number of completed 28 day cycles (6,424)
- Number of partially completed 28 day cycles (294)
- Total days of exposure (183,747)
- Total women-years of exposure (503.07)

Source: NDA 22-252; Amendment 17 (3/17/2010)

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5.3.2.24 Safety - Event Overview

The safety event overview is shown in Table 51.

Table 51: Study 304742 – Overview of the Number (%) of Subjects with Adverse Events (Safety Analysis Set)

Subjects	EV/DNG N = 490 n (%)
With at least 1 AE	379 (77.3%)
With nonfatal SAEs	10 (2.0%)
Who discontinued study drug due to an AE	73 (14.9%)
Who died	0 (0%)

EV/DNG = estradiol valerate / dienogest; AE = adverse event; SAE = serious adverse event
Source: Study Report A39818, Text table 22, page 75 of 484.

5.3.2.25 Safety - Common Adverse Events

Table 52 presents the adverse events occurring in $\geq 2\%$ of subjects

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Table 52: Study 304742 – Number (%) of Subjects (≥2%) with Most Common Adverse Events by Preferred Term and Descending Frequency of Occurrence –Full Analysis Set

Adverse Event (PT)	EV/DNG N = 490 n (%)
Headache	77 (15.7)
Metrorrhagia	64 (13.1)
Nasopharyngitis	51 (10.4)
Amenorrhea	37 (7.6)
Dysmenorrhea	37 (7.6)
Nausea	33 (6.7)
Urinary tract infection	31 (6.3)
Upper respiratory tract infection	30 (6.1)
Abdominal pain	29 (5.9)
Acne	29 (5.9)
Fungal infection	26 (5.3)
Sinusitis	26 (5.3)
Cervical dysplasia	24 (4.9)
Vaginitis bacterial	24 (4.9)
Breast pain	22 (4.5)
Menstruation irregular	21 (4.3)
Vaginal candidiasis	21 (4.3)
Vaginal infection	20 (4.1)
Diarrhea	19 (3.9)
Back pain	18 (3.7)
Vulvovaginal mycotic infection	15 (3.1)
Weight increased	15 (3.1)
Influenza	13 (2.7)
Pelvic pain	13 (2.7)
Vomiting	13 (2.7)
Fatigue	12 (2.4)
Mood swings	12 (2.4)
Abdominal distention	11 (2.2)
Breast tenderness	11 (2.2)
Dizziness	11 (2.2)
Dyspepsia	11 (2.2)
Pharyngolaryngeal pain	11 (2.2)
Seasonal allergy	11 (2.2)
Cough	10 (2.0)
Vulvovaginal pruritus	10 (2.0)

EV/DNG = estradiol valerate / dienogest; PT = preferred term

Source: Study Report A39818; Text Table 23; page 76 of 484 and Table 66; pages 365-366 of 484

5.3.2.26 Safety – Nonfatal Serious Adverse Events

A total of 15 SAEs were reported in 10 subjects. These SAEs are shown in Table 53.

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Table 53: Nonfatal Serious Adverse Events – Study 304742

PID	SAE(s)	Comment
505002	Lower limb fracture (1) Surgery (1)	
511017	Kidney infection (2), kidney stone (1), lymphadenopathy (1)	
511023	Malignant melanoma	
513005	Jaw surgery	
514017	Ovarian cyst rupture	
518001	Perirectal abscess	
601026	Biopsy cervix abnormal (1) Adenocarcinoma-in-situ of the cervix (1)	
606008	Accident	Stab wound with syringe
606015	Appendicitis	
607013	Traumatic pneumothorax	Subsequent to fall on ice

PID = Subject identification number; SAE = Serious adverse event
Source: Study Report A39818; pages 78 of 484

Medical Officer's Comment:

This reviewer considers only the SAE of ovarian cyst rupture to be possibly related to study drug.

5.3.2.27 Safety – Deaths

No deaths were reported in Study 304742

5.3.2.28 Safety – Discontinuations Due to Adverse Events

A total of 73 subjects (14.9%) prematurely discontinued the study medication due to an adverse event. The number of subjects with discontinuations due to adverse events are shown in Table 54. The most common and most pertinent events are shown.

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Table 54: Study 304742: Proportion of Subjects with the Most Common and Most Pertinent Adverse Events leading to Discontinuation of Study Drug (EV/DNG)

Adverse Event (number of subjects) SOC and PT	N = 490 No. of subjects (%)
<u>Reproductive system and breast disorders</u>	
Breast swelling (1), Breast pain (1)	2 (0.4%)
Menorrhagia (4)	4 (0.8%)
Menstrual disorder (2)	2 (0.4%)
Metrorrhagia (9), Menstruation irregular (3)	12 (2.4%)
Dysfunction uterine bleeding (3)	3 (0.6%)
Amenorrhea (1)	1 (0.2%)
<u>Investigations</u>	
Weight increased (2)	2 (0.4%)
<u>Neoplasm (benign, malignant and unspecified)</u>	
Focal nodular hyperplasia (1)	1 (< 0.1%)
<u>Nervous system disorders</u>	
Headache (7)	7 (1.4%)
<u>Psychiatric disorders</u>	
Depressed mood (2)	2 (0.4%)
Libido decreased (1)	1 (0.2%)
Mood altered (2), Mood swings (6)	8 (1.6%)
<u>Skin and subcutaneous tissue disorders</u>	
Acne (9)	9 (1.8%)

EV/DNG = estradiol valerate / dienogest; SOC = system organ class; PT = preferred term
 Source: Study Report A39818; Table 71; pages 406-408 of 484

5.3.2.29 Safety – Laboratory

Hematology, chemistry and urinalysis laboratory studies were not performed in this study. Studies 304004, 308960 and 308961 had standard safety labs performed.

Cervical smears from both subjects who did and did not enter the extension period included 7 low grade smears and 2 high grade smears.

Medical Officer's Comment:

This level of cervical cytology abnormality in over two years of evaluation is not considered to be increased over that observed in the general population.

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5.3.2.30 Safety – Vital Signs and Weight

There were no clinically meaningful mean changes from baseline in systolic blood pressure, diastolic blood pressure or heart rate. After 13 cycles of treatment, mean change in weight was minimal (0.5 kg).

5.3.3 Pivotal Study 304004 (Report A35644) for Contraception (Also Cycle Control)

5.3.3.1 Study Title, Coordinating Investigator and Study Dates

“A multi-center, double-blind, double-dummy, controlled, randomized study to evaluate cycle control and safety of a four-phasic oral contraceptive containing estradiol valerate and dienogest (SH T006581D) in comparison to an oral contraceptive containing ethinyl estradiol and levonorgestrel (SH D 593 B) in healthy female volunteers aged between 18 and 50 years over 7 cycles”

The coordinating investigators for this study were [REDACTED] (b) (6) from Germany and [REDACTED] (b) (6) from France.

This study was conducted from Mar 2, 2005 through Sep 5, 2006.

5.3.3.2 Ethics

The planning and conduct of this study were subject to national law. The study began only when all requirements of the appropriate regulatory authorities had been fulfilled. The study was conducted in accordance with the principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization – Good Clinical Practice (ICH – GCP) Guidelines of 17 Jan 1997.

5.3.3.3 Study Sites

In Study 304004 there were study sites in the Germany (19), France (10) and Czech Republic (5) that randomized subjects.

5.3.3.4 Study Objectives

The aim of the present study was to evaluate bleeding patterns, cycle control, and safety of EV/DNG in comparison to a reference OC (Miranova) containing 0.02 mg EE and 0.1 mg levonorgestrel (LNG) given in a 21/7 day regimen, over 7 cycles.

Contraceptive reliability was documented as number of unintended pregnancies.

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A subjective assessment of treatment was required, as well as characterization of the effects of the investigational product on general well-being and sexual life via appropriate self-administered questionnaires.

Safety (adverse events [AEs], safety laboratory tests, general and gynecological findings) and compliance were also assessed.

5.3.3.5 Study Design

5.3.3.6 Inclusion Criteria

The study was performed as a multi-center, double-blind, double-dummy, controlled, randomized trial in fertile women aged between 18 and 50 years.

- Healthy female volunteers requiring contraception
- Age between 18 and 50 years (inclusive) with smoking habits regulated as follows:
 - a. Between 18 and 30 years of age, daily cigarette consumption not above 10
 - b. Above 30 years of age, no smoking
- Non-suspicious cervical smear taken at Visit 1 or within the last 3 months before Visit 1
- Signed and dated informed consent.

5.3.3.7 Exclusion Criteria

- Pregnancy, lactation
- Occurrence of fewer than three menstrual cycles before Visit 1 following delivery, abortion, or lactation
- Known hypersensitivity to any ingredient of the study drug
- Any known diseases or conditions that compromised the function of the body systems and could result in altered absorption, excessive accumulation, impaired metabolism, or altered excretion of the study medication
- Any known severe systemic disease that possibly interfered with the conduct of the study or the interpretation of the results

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- Known uncontrolled thyroid disorders
- Clinically significant depression (current or in the year before the study)
- Any known abnormal clinically significant findings which, according to the assessment of the investigator, possibly worsened under hormonal treatment
- Laboratory values outside inclusion range at Screening
- Participation in another clinical study or administration of an investigational drug within 1 month (or 6 months in case of long-acting progestins) prior to study entry (Visit 1)
- Operations scheduled in the study period
- Known liver diseases: Previous, acute and chronic progressive liver diseases, e.g., disturbances of bilirubin excretion in the bile (Dubin-Johnson and Rotor syndromes), disturbances of bile secretion, disturbances of bile flow (cholestasis, also a history thereof, idiopathic icterus or pruritus during a former pregnancy or estrogen-progestin treatment). Between the subsiding of a viral hepatitis (normalization of liver parameters) and the beginning of the study there had to be an interval of at least 6 months. Previous or current liver tumors
- Known vascular and metabolic diseases: Existing or previous venous thromboembolic diseases (deep vein thrombosis, pulmonary embolism), existing or previous arterial thromboembolic diseases (myocardial infarction, stroke), as well as any condition increasing the disposition to any of the above, e.g., coagulation disorders with tendency to blood clot formation, hereditary anti-thrombin III deficiency, protein-C and/or protein-S deficiency, any venous thromboembolic event occurred in a sibling or a parent at an early age, valvular heart disease, atrial fibrillation, cardiac dysfunction, strong predisposition to varicose veins, previous phlebitis.
- Known arterial hypertension (systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg).
- Known diabetes mellitus, impaired glucose tolerance.
- Known disturbances of lipid metabolism
- Known sickle-cell anemia

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- Known or suspected malignant or premalignant disease, in particular steroid-hormone dependent malignant or premalignant diseases (e.g., endometrial cancer, breast cancer), also a history thereof
- Other known diseases such as: pemphigoid gestationis during a previous pregnancy, middle-ear deafness (otosclerosis), endometrial hyperplasia, migraine with neurological symptoms (complicated migraine), genital bleeding of unknown origin, manifest kidney disease with impaired renal function, porphyria
- Known alcohol, drug, or medicine abuse (e.g., laxatives)
- Prohibited concomitant medication: Additional sex steroids except for switchers from another OC taken until the end of one blister after randomization (see also Section 9.4.7); anticoagulants (e.g., heparin, coumarin); antiepileptics (hydantoin derivatives [e.g., phenytoin] or carboxamide derivatives [e.g., carbamazepine, oxcarbamazepine], other antiepileptics [e.g., felbamate, topiramate]); hypnotics and sedatives (e.g., barbiturate derivatives, primidone); tuberculostatics (e.g., rifampicin); oral antimycotics (e.g., griseofulvin, ketoconazole, itraconazole, fluconazole); virostatic agents (e.g., ritonavir); products containing St. John's wort; and continuous use of antibiotics for >10 days
- Use of intra-uterine devices (IUD) with or without hormone release, as well as progestin implants within 1 month prior to study entry (Visit 1)
- Use of long-acting progestins within 6 months prior to study entry (Visit 1)
- Considerable overweight (body mass index > 30)
- Requirement of special surveillance due to the following risk factors: Epilepsy, asthma, multiple sclerosis, chorea minor, tetany
- Volunteer was a dependent person, e.g., a relative, family member, or member of the investigator's staff.

5.3.3.8 Prior and Concomitant Therapy

Participation in another clinical study or administration of an investigational drug within 1 month prior to study entry (Visit 1) and during the study was not allowed.

Co-medications possibly jeopardizing the contraceptive efficacy are hydantoins (e.g., phenytoin), barbiturates (e.g., primidone), carbamazepine, rifampicin, griseofulvin, phenylbutazone, and antibiotics. The subjects were to be informed about their potential to reduce the contraceptive efficacy of the study medication.

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Besides the above medications possibly affecting contraceptive efficacy, the use of additional sex steroids was prohibited during the study with the following exception: At the beginning of the study, volunteers switching from another OC were to continue use of the original OC until the end of the current cycle pack after Visit 2 (randomization).

The use of the post-coital pill was not allowed. In case of use of post-coital pill, the volunteer had to discontinue study participation.

Regarding antibiotics, continuous use over a period of > 10 days during the study was not allowed.

The use of progestin implants or IUDs with and without hormone release had to be stopped at least 1 month prior to Visit 1, the use of long-acting progestins at least 6 months prior to Visit 1.

5.3.3.9 Study Procedures

Study 304004 – Study Flow Chart

Assessment Visit Week	Screening 1	Baseline 2 Week -2 to -1	Treatment 3 Week 15-16	End of Study 4 Week 29-30
Informed consent	X			
Entry criteria	X	Update		
Randomization		X		
Medical history	X			
Physical	X			X
Vital signs	X	X	X	X
Gynecologic exam, breast exam, transvaginal ultrasound	X			X
Cervical smear	X	Result		X
Safety labs	X	Result		X
Assessment of treatment				X
PGWBI		X	X	X
MFSQ		X	X	X
Dispense meds		X	X	
Diary card		Dispense	Check / collect	Check / collect
Home pregnancy test		Dispense	Dispense / check	Check
Adverse events			X	X
Concomitant meds		X	X	X

PGWBI = Psychological General Well-Being Index; MFSQ = McCoy Female Sexuality Questionnaire
 Source: Study Protocol 304742; page 41 of 109

Medical Officer's Comment:

Home pregnancy tests were performed for failure of withdrawal bleeding or if the subject had any concerns about forgotten tablets, diarrhea/vomiting or antibiotic treatment. The only required testing was before the first tablet intake.

5.3.3.10 Bleeding Record

Bleeding intensity recorded on the diary cards had the following categories:

- None = No vaginal bleeding
- Spotting = Less than associated with normal menstruation relative to the volunteer's experience, with no need for sanitary protection (except for panty liners)
- Light = Less than associated with normal menstruation relative to the volunteer's experience, with need for sanitary protection
- Normal = Like normal menstruation relative to the volunteer's experience
- Heavy = More than normal menstruation relative to the volunteer's experience

Based on the diary cards, the bleeding patterns were to be described using reference periods of 90 days.

A bleeding/spotting episode was defined as the number of days with bleeding/spotting preceded and followed by at least 2 bleeding-free days.

A spotting-only episode was defined as the number of days with spotting preceded and followed by at least 2 bleeding-free days.

A bleeding-free interval consisted of at least 2 days without bleeding/spotting preceded and followed by at least 1 bleeding/spotting day.

Withdrawal bleeding and intracyclic bleeding episodes were identified and analyzed. A withdrawal bleeding episode during treatment was defined as the first bleeding episode after the last day of EV/DNG or EE/LNG intake. In case a bleeding episode was ongoing on the last day of EV/DNG or EE/LNG intake and on the following day, this episode was regarded as the withdrawal bleeding episode, provided it started not more than 4 days before withdrawal of EV/DNG or EE/LNG.

All other (unexpected) bleeding episodes were considered as intracyclic bleeding. If no bleeding occurred until the next withdrawal of EV/DNG or EE/LNG, this was assessed as absence of withdrawal bleeding in the previous treatment cycle (provided that pregnancy had been excluded).

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5.3.3.11 Unintended Pregnancies

All pregnancies which became known within the framework of this study (i.e., number of unintended pregnancies), including the post-study follow-up (3 months following premature discontinuation, 1 year in volunteers discontinuing the study due to wish of pregnancy), were to be reported in detail on the respective forms until final outcome (mother and child).

The date of conception was to be determined applying the following diagnostic measures:

- Ultrasonography
- Quantitative beta-human chorionic gonadotropin (HCG) determination (blood pregnancy test)
- Gynecological examination
- Record of last withdrawal or menstrual bleeding
- Determination of gestational age at delivery

At each visit, the investigator collected information on back-up contraceptive measures (e.g., condoms, post-coital pill as emergency contraceptive) and noted them in the CRF in relation to the respective cycle. In case of use of post-coital pill, the volunteer had to discontinue study participation.

5.3.3.12 Efficacy Variables

No distinction was made between primary and secondary target variables. The efficacy variables were:

- Bleeding patterns
- Cycle control
- Cycle control for Cycles 2 to 7
- Number of unintended pregnancies
- Subjective assessment of treatment by the volunteer
- Mean change in the Psychological General Well-Being Index (PGWBI) total score and subscale scores from Baseline to Treatment Cycles 4 and 7
- Change in the McCoy Female Sexuality Questionnaire (MFSQ) subscale scores from Baseline to Treatment Cycles 4 and 7.

Medical Officer's Comment:

Cycle control was an overall analysis of withdrawal bleeding and intracyclic bleeding. Cycle control for cycles 2 to 7 evaluated subjects with at least one intracyclic bleeding episode within that time frame. It is not clear why this separate analysis is important.

5.3.3.13 Safety

The safety analysis and monitoring included:

- Monitoring of adverse events
- Safety laboratory testing
- Vital signs
- Entry criteria to rule out pertinent risk factors
- Physical and gynecologic examinations
- Transvaginal ultrasound
- Cervical cytology

5.3.3.14 Statistical Analysis Plan

Pertinent information from the statistical plan include definition of the full analysis set, per-protocol set and the analysis of bleeding patterns and cycle control. The analysis of unintended pregnancies was discussed previously in section 5.3.3.11.

All volunteers admitted to the treatment phase who took at least one tablet of study medication and for whom at least one observation after admission to treatment was available were included in the full analysis set (FAS).

The per-protocol set (PPS) was defined with respect to bleeding patterns and cycle control (Cycles 1 to 7). A volunteer was excluded from the per-protocol analysis if one or more major deviations were present.

Bleeding Patterns

The bleeding patterns were described using the reference period method recommended by the WHO. The length of the reference period was 90 days. The first reference period started on the first day of study medication. For each volunteer and for each reference period, the following bleeding pattern indices were calculated:

- Number of bleeding/spotting days
- Number of spotting-only days
- Number (mean length, maximal length, and range of length) of bleeding/spotting episodes
- Number (mean length, maximal length, and range of length) of spotting-only episodes.

Cycle Control

For each volunteer and for each cycle, the following cycle control indices were calculated:

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Withdrawal bleeding

- Number of volunteers with/without withdrawal bleeding
- Length of withdrawal bleeding episodes
- Maximum intensity of withdrawal bleeding episodes
- Onset of withdrawal bleeding episodes.

Intracyclic bleeding

- Number of volunteers with/without intracyclic bleeding
- Number and maximum length of intracyclic bleeding episodes
- Number of intracyclic bleeding days
- Maximum intensity of intracyclic bleeding episodes.
- Number of volunteers with at least one intracyclic bleeding episode in Cycles 2 to 7

5.3.3.15 Protocol Amendments

Amendment 1 (Jan 6, 2005) applied to the Czech Republic and required that mammography results within one year needed to be non-suspicious for all women ≥ 45 years of age.

5.3.3.16 Disposition of Subjects

Table 55 provides information on subject disposition.

Table 55: Study 304004 – Disposition of Subjects

Disposition / Reason	No. of Subjects
Screened	846 (100%)
Screening failures	42 of 846 (5.0%)
<ul style="list-style-type: none"> • Withdrawal of consent • Entry criteria not met • Volunteer lost, no further information • Other 	<ul style="list-style-type: none"> • 18 • 21 • 1 • 2
Volunteers enrolled in the study	804 of 846 (95.0%)
Treatment	402
Comparator	402
Volunteers who dropped out before start of study medication	6
Treatment	3
Comparator	3
Volunteers receiving study medication (Full analysis set)	798
Treatment	399
Comparator	399
Total who prematurely discontinued study medication	44 of 798 (5.5%)
Treatment	21
Comparator	23
Reasons for premature discontinuation (Treatment)	
<ul style="list-style-type: none"> • Withdrawal of consent • Protocol deviation • Adverse event • Pregnancy • Other 	<ul style="list-style-type: none"> • 6 of 399 (1.5%) • 1 of 399 (0.3%) • 13 of 399 (3.3%) • 0 • 1 of 399 (0.3%)
Reasons for premature discontinuation (Comparator)	
<ul style="list-style-type: none"> • Withdrawal of consent • Protocol deviation • Adverse event • Pregnancy • Other 	<ul style="list-style-type: none"> • 5 of 399 (1.3%) • 1 of 399 (0.3%) • 13 of 399 (3.3%) • 1 of 399 (0.3%) • 3 (0.8%)
Volunteers completing study	754 of 798 (94.5%)
Treatment	378
Comparator	376

EV/DNG = estradiol valerate / dienogest
 Source: Study Report A35644 page 81 of 1799

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5.3.3.17 Protocol Deviations

The proportion of volunteers with major protocol deviations was balanced for Treatment and Comparator (8.5% and 9.3%, respectively).

5.3.3.18 Demographics

The Treatment and Comparator groups were well matched in regard to age and body mass index. Nearly all of the subjects were Caucasian, with the exception of one Black and one Asian. The educational level was relatively well matched between treatment groups and across age strata, with approximately 20% of volunteers with college/university education. The proportion of smokers was relatively well matched between Treatment and Comparator (14.3% and 12.3%, respectively).

5.3.3.19 Gynecologic / Obstetrical / Contraceptive History

The number of nulliparous subjects was slightly higher in the Treatment group (42.1%) than in the Comparator group (38.6%). The two treatment groups were similar in regard to a history of regular menstrual cycles, dysmenorrhea and intracyclic bleeding. The large majority of volunteers reported the use of OC as previous contraceptive method in the last month before the study (91.7% for Treatment and 91.0% for Comparator).

5.3.3.20 Efficacy Results

Unintended Pregnancies

In the course of Study 304004, there were 7 pregnancies; the only two occurring on treatment were in the comparator arm. Pregnancies during treatment (includes pregnancies with EDC within 14 days of treatment) are shown in Table 56.

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Table 56: Pregnancies during Treatment in Study 304004 (and within 14 days of treatment)

PID (age in yrs)	Start of Treatment	End of Treatment	EDC	Notes
1454 (24)	30 Apr 05	27 Sep 05	10 Aug 05 (by TVU)	Treatment = comparator EE+LNG) Pregnancy outcome = normal male at term
0502 (28)	14 Apr 05	9 Jul 05	22 Jul 05	Treatment = comparator EE+LNG) Pregnancy outcome = normal female at term

PID = patient identification number; RN = randomization number; TVU = transvaginal ultrasound; EDC = estimated date of conception; EE = ethinyl estradiol; LNG = levonorgestrel
 Source: Study Report A35644; Section 11.4.6; pages 110- 116 of 1799

Pregnancies conceived before study treatment for 304004 are shown in Table 57.

Table 57: Pregnancies Occurring Before Treatment in Study 304004

PID (age in yrs)	Ts	Te	EDC	Notes
1135 (27)	Not started		31 Jul 05 (by TVU)	Pregnancy outcome = Spontaneous abortion
1465 (30)	Not started		24 Apr 05	Pregnancy outcome = Induced abortion, Trisomy 21

PID = patient identification number; Ts = start of treatment; Te = end of treatment; TVU = transvaginal ultrasound; EDC = estimated date of conception; EE = ethinyl estradiol; LNG = levonorgestrel
 Source: Study Report A35644; Section 11.4.6; pages 110- 116 of 1799

Pregnancies after treatment in Study 304004 are shown in Table 58.

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Table 58: Pregnancies Occurring After Treatment in Study 304004 (past 14 day window)

PID (age in yrs)	Ts	Te	EDC	Notes
0154 (37)	16 Jul 05	4 Nov 05	13 Jan 06	Treatment = EV/DNG Pregnancy outcome = normal male at term
0521 (27)	7 Apr 05	19 Oct 05	3 Feb 06	Treatment = comparator EE + LNG Pregnancy outcome = normal female at term
0523 (28)	7 Apr 05	19 Oct 05	16 Mar 06	Treatment = EV/DNG Pregnancy outcome = normal female at term

PID = patient identification number; Ts = start of treatment; Te = end of treatment; TVU = transvaginal ultrasound; EDC = estimated date of conception; EE = ethinyl estradiol; LNG = levonorgestrel

Source: Study Report A35644; Section 11.4.6; pages 110- 116 of 1799

Medical Officer's Comment:

There were no pregnancies in the EV/DNG treatment group, which equates to a Pearl Index of 0.0.

Bleeding Patterns

Bleeding/spotting days and spotting-only days are shown in Table 59. Reference Period 1 and 2 refer to the first and second 90 day period in the study.

Table 59: Bleeding/Spotting Days and Spotting-only Days in Study 304004

Analysis	Reference Period	Treatment EV/DNG	Comparator EE/LNG
Bleeding/ spotting days (mean ± SD) - FAS	1	17.3 ± 10.4	21.5 ± 8.6
	2	13.4 ± 9.3	15.9 ± 7.1
Spotting-only days (mean ± SD - FAS	1	7.3 ± 7.8	7.3 ± 6.4
	2	6.3 ± 7.1	5.5 ± 5.4

SD = Standard deviation; EV/DNG = Estradiol valerate / Dienogest; EE/LNG = Ethinyl estradiol / Levonorgestrel

Source: Study Report A35644, page 117 of 1799

Cycle Control

Table 60 provides data on:

- The number and percentage of subjects with withdrawal bleeding at different cycles.
- Length of withdrawal bleeding

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- Onset of withdrawal bleeding
- The number and percentage of subjects with intracyclic bleeding at different cycles.

Table 60: Cycle Control in Study 304004

Analysis	Cycle (28 days)	Treatment EV/DNG	Comparator EE/LNG
Frequency of withdrawal bleeding – FAS Number of subjects (%)	1	309 of 392 (78.8%)	351 of 392 (89.5%)
	3	320 of 388 (82.5%)	361 of 385 (93.8%)
	7	298 of 372 (80.1%)	342 of 371 (92.2%)
Length of withdrawal bleeding episode– FAS Days; mean ± SD	1	4.5 ± 3.2	5.0 ± 2.2
	3	4.5 ± 2.9	5.1 ± 1.9
	7	4.1 ± 2.0	5.1 ± 2.1
Onset of withdrawal bleeding episode – FAS Days, mean ± SD	1	3.9 ± 5.4	3.8 ± 5.2
	3	4.2 ± 3.7	3.1 ± 3.7
	7	3.0 ± 4.1	2.9 ± 4.1
Frequency of intracyclic bleeding – FAS Number of subjects (%)	1	36 of 195 (18.5%)	34 of 197 (17.3%)
	3	29 of 192 (15.1%)	29 of 196 (14.8%)
	7	26 of 182 (14.3%)	18 of 187 (9.6%)

SD = Standard deviation; EV/DNG = Estradiol valerate / Dienogest; EE/LNG = Ethinyl estradiol / Levonorgestrel

Onset of withdrawal bleeding was calculated from the end of the exposure to the progestogen component (Day 24)

Source: Study Report A35644; Table 108, page 522 of 1799; Table 113, page 538 of 1799; Text table 33, page 94 of 1799; Text table 35, page 97 of 1799

Medical Officer’s Comment:

In general the cycle control for EV/DNG appeared comparable to the comparator with slight variations of withdrawal bleeding and intracyclic bleeding noted at some cycles. These results are acceptable.

5.3.3.21 Safety – Extent of Exposure

The exposure to EV/DNG in Study 304004 by cycles, partial cycles, days and women-years is the following:

- Number of completed 28 day cycles (2,695)
- Number of partially completed 28 day cycles (27)
- Total days of exposure (76,052)
- Total women-years of exposure (208,22)

Source: NDA 22-252; Amendment 17 (3/17/2010)

5.3.3.22 Safety – Event Overview

In Study 304004, there were a total of 338 adverse events [EV/DNG = 176 (27.1% of FAS); EE/LNG = 162 (25.6% of FAS)]. There were 8 nonfatal serious adverse events (EV/DNG = 5; EE/LNG = 3). There were no deaths. Drug discontinuations for adverse events were similar (3.3% of FAS in both treatment groups).

5.3.3.23 Safety – Common Adverse Events

The most frequent common adverse events are shown in Table 61.

Table 61: Study 304004 – Number (%) of Subjects (>1%) with Most Common Adverse Events by Preferred Term and Descending Frequency of Occurrence –Full Analysis Set

Adverse Event (PT)	EV/DNG N = 399 n (%)	EE/LNG N = 399 N(%)
Breast pain	15 (3.8%)	5 (1.3%)
Headache	10 (2.5%)	13 (3.3%)
Vaginal infection	10 (2.5%)	2 (0.5%)
Cystitis	8 (2.0%)	2 (0.5%)
Vulvovaginal mycotic infection / candidiasis	8 (2.0%)	6 (1.5%)
Nasopharyngitis	6 (1.5%)	7 (1.8%)
Acne	5 (1.3%)	13 (3.3%)
Alopecia	5 (1.3%)	4 (1.0%)
Migraine	4 (1.0%)	6 (1.5%)
Bronchitis	4 (1.0%)	3 (0.8%)
Back pain	3 (0.8%)	4 (1.0%)
Ovarian cyst	3 (0.8%)	4 (1.0%)
Sinusitis	2 (0.5%)	4 (1.0%)
Weight increased	2 (0.5%)	4 (1.0%)
Nausea	1 (0.3%)	4 (1.0%)

EV/DNG = estradiol valerate / dienogest; EE/LNG = estradiol valerate / levonorgestrel;
 PT = preferred term

Source: Study Report A35644; Text Table 51; page 135 of 1799

5.3.3.24 Safety – Nonfatal Serious Adverse Events

The 8 nonfatal SAEs in Study 304004 are shown in Table 62.

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Table 62: Nonfatal Serious Adverse Events – Study 304004

PID	Treatment Group	SAE(s)
1127	EV/DNG	Rupture of ovarian cyst
1127	EV/DNG	Autonomic nervous system imbalance
1360	EV/DNG	Vulvar abscess
119	EV/DNG	Tonsillitis
1630	EV/DNG	Renal colic
1041	EE/LNG	Breast cancer
1113	EE/LNG	Cholelithiasis
1385	EE/LNG	Herniated disc

EV/DNG = estradiol valerate / dienogest; EE/LNG = estradiol valerate / levonorgestrel

PID = Subject identification number; SAE = Serious adverse event

Source: Study Report A35644; pages 1308-9 of 1799

Medical Officer's Comment:

Of the SAEs in the EV/DNG group this reviewer considers the ruptured ovarian cyst possibly related to treatment. Cholelithiasis is possibly related to treatment in the Comparator group.

The subject with breast cancer (#1041) was 30 years of age (BMI = 20kg/m²; non-smoker). She took study medication for approximately 5.5 months (31 Mar 2005 through 12 Oct 2005). She discovered a breast mass on 18 Jan 2006 and a biopsy the following month revealed invasive ductal breast carcinoma.

5.3.3.25 Safety – Deaths

There were no deaths in the study.

5.3.3.26 Safety – Discontinuations Due to Adverse Events

Drug discontinuations due to AEs (AE withdrawals) were limited and balanced (3.3% of FAS in both treatment groups). The most frequent adverse events leading to discontinuation were headache (EVG /DNG = 2; EE/LNG = 4), depression (EVG /DNG = 2) and acne (EE/LNG = 2).

5.3.3.21 Safety – Laboratory

Hematology

The following labs remained normal and stable at the final visit compared to Screening for both treatment groups:

- Erythrocyte count
- Hematocrit
- Hemoglobin

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- Leukocyte count
- Platelets

Chemistry / Carbohydrate Metabolism

The following labs remained normal and stable at the final visit compared to Screening for both treatment groups:

- Sodium
- Potassium
- Creatinine
- Protein
- Albumin
- Alkaline phosphatase
- Cholesterol
- Triglycerides
- Cholinesterase
- Hemoglobin A1C

Minor decreases were noted in HDL and LDL cholesterol in both arms.

Slight increases were noted in gamma glutamyltransferase (GGT) and Alanine aminotransferase (ALT) and are shown in Table 63 and Table 64 respectively.

Table 63: Gamma Glutamyltransferase in Study 304004 – Full Analysis Set

		EV/DNG	EE/LNG
Screening [U/I]		17.4 ± 8.6	18.3 ± 9.1
Final Visit [U/I]		19.3 ± 13.6	21.3 ± 16.0
Relation to normal range (5-39 U/I)	Below	-	-
	Above	13 (3.3%)	14 (3.5%)
	Below	-	-
	Above	20 (5.0%)	23 (5.8%)
Above alert range (>117 U/I) at final visit		1 (0.3%)	3 (0.8%)

EV/DNG = estradiol valerate / dienogest; EE/LNG = estradiol valerate / levonorgestrel
 Source: Study Report A35644, page 161 of 1799

Table 64: Alanine Aminotransferase (ALT) in Study 304004 – Full Analysis Set

		EV/DNG	EE/LNG
Screening [U/I]		15.9 ± 7.0	18.3 ± 9.1
Final Visit [U/I]		17.3 ± 9.9	17.9 ± 10.0
Relation to normal range (5-39 U/I)	Below	-	-
	Above	12 (3.0%)	11 (2.8%)
	Below	-	-
	Above	28 (7.1%)	23 (5.8%)
Above alert range (>93 U/I) at final visit		1 (0.3%)	1 (0.3%)

EV/DNG = estradiol valerate / dienogest; EE/LNG = estradiol valerate / levonorgestrel
 Source: Study Report A35644, pages 161

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Medical Officer's Comment:

None of the "alert" enzyme elevations (either GGT or ALT) was listed as a serious adverse event or qualified for Hy's Law, and the Applicant reported that all resolved. Of the two subjects taking EV/DNG, subject 1514 only had ALT elevation (highest level was 99 U/l – normal to 31 U/l) and subject 1403 only had GGT elevation (highest level was 179 U/l – normal to 39 U/l)

5.3.3.21 Safety – Vital Signs and Weight

The mean levels of systolic blood pressure, diastolic blood pressure and heart rate remained normal and stable throughout all study visits in both treatment groups. The mean body weight and body mass index remained stable in both treatment groups.

5.3.4 Pivotal Study 308960 (Report A29849) for DUB

5.3.4.1 Study Title, Coordinating Investigator and Study Dates

"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."

The global clinical team lead was Matthias Schaefer, MD.

The study ran from Dec 14, 2005 through May 21, 2008.

5.3.4.2 Ethics

The study was conducted in accordance with GCP as required by 21 Code of Federal Regulations (CFR) Parts 50, 56 and 312, and the Applicant's standard operating procedures for clinical investigation and documentation. Compliance with these requirements also constitutes conformity with the ethical principles that have their origin in the Declaration of Helsinki.

Each investigator initiated enrollment only after the protocol and informed consent form was approved by the appropriate IRB and written notification of the approval was received by the sponsor.

5.3.4.3 Study sites

In Study 308960 there were study sites in the U.S. (37) and Canada (10) that randomized subjects.

5.3.4.4 Study Objectives

The primary objective of the study was to determine the efficacy and safety of EV/DNG treatment in patients with DUB, defined as prolonged, frequent, or excessive uterine bleeding, as compared to placebo.

The secondary objectives were:

- To determine the efficacy of EV/DNG in regard to individual DUB symptoms and menstrual bleeding parameters
- To determine the efficacy of EV/DNG in regard to quality of life (QoL) and resource use assessment
- To evaluate the effect of EV/DNG on hemoglobin and serum ferritin concentrations

5.3.4.5 Study Design

This was a multicenter, double-blind, randomized, parallel-group, placebo-controlled study comparing the efficacy of a 4-phasic EV/DNG regimen in patients with DUB. Approximately 180 women, ≥ 18 years age, who had a diagnosis of DUB confirmed to be unrelated to any organic causality were enrolled in this study. The study comprised: screening (up to 28 days), a 90-day run-in phase, 196 days of study drug administration, and a 30-day follow-up.

Qualifying patients were randomized according to a planned 2:1 ratio to receive either active study drug or matching placebo. The first dose was taken on the first day of bleeding following randomization. Each dose consisted of one pill. The dosages were the same as that taken in the contraceptive studies (Table 65):

Table 65: Study 308960 - Cyclic dosages for EV/DNG

Cycle Day	No. of oral intake days	Content
1-2	2	3.0 m estradiol valerate
3-7	5	2.0 mg estradiol valerate + 2.0 mg dienogest
8-24	17	2.0 mg estradiol valerate + 3.0 mg dienogest
25-26	2	1.0 mg estradiol valerate
27-28	2	placebo

Source: Study 308960 – study protocol; page 29 of 96

The duration of study drug administration was 196 days (7 cycles of 28 days each). Using an e-diary, subjects kept a daily record of menstrual bleeding, number of sanitary products used, and study drug intake. Subjects were required to use barrier contraception during the study.

The study drug was to be taken either in the morning or in the evening. For pills taken from day 2 onwards, the interval between 2 doses was to remain as close as possible to 24 hours. In case of a missed pill, the patient was to take the

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missed pill from the previous day as soon as she remembered, at the latest with the next dose. If doses were missed for 2 or more consecutive days, only the pill from the previous day was to be taken, as soon as remembered or with the next dose. No more than 2 pills were to be taken in one day. In case of vomiting or diarrhea within 4 hours of tablet intake, another tablet of the same color was to be taken from the reserve blister card. The reserve blister card was to be used in case study medication is lost.

5.3.4.6 Inclusion Criteria

1. ≥ 18 years of age and be able to read and write. If over 40 years of age, must have FSH < 40 mIU/mL.
2. DUB defined as at least one of the following symptoms within the 90-day run-in phase
 - Prolonged bleeding: 2 or more bleeding episodes, each lasting 8 or more days
 - Frequent bleeding: more 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, as assessed by the alkaline hematin method
3. Willing to use barrier contraception (e.g., condoms) from screening through study completion
4. Willing to use and collect sanitary protection (pads and tampons) provided by the Applicant and compatible with the alkaline hematin test through study completion
5. Normal or clinically insignificant Pap smear results. A report within the last 6 months of visit 1 is acceptable.
6. Endometrial biopsy during the run-in phase OR a valid endometrial biopsy performed within 6 months of visit 1, without evidence of malignancy or atypical hyperplasia, with an available report. Women with simple hyperplasia can be included in the study, but will undergo an endometrial biopsy at the end of treatment.
7. Signed the informed consent form.
8. If ≥ 35 years of age, must have documentation of clinically insignificant mammogram obtained within 6 months

5.3.5.7 Exclusion Criteria

1. Current diagnosis of organic cause for uterine bleeding, such as von Willebrand disease, chronic endometritis, adenomyosis, endometriosis, endometrial polyps, endometrial carcinomas, mixed mullerian mesenchymal tumors, leiomyomas, leiomyosarcomas, or endometrial stromal tumors
2. Signs of hirsutism
3. Atypical endometrial hyperplasia
4. History of endometrial ablation, or dilatation and curettage within 2 months of visit 1
5. Clinically significant abnormal transvaginal ultrasound results
6. Clinically significant abnormal results of breast examination
7. Positive pregnancy test
8. Pregnancy, lactation, or abortion within 3 months of visit 1
9. Not willing to discontinue the use of nonsteroidal anti-inflammatory drugs during menses throughout the study
10. Use of medication intended for treatment of DUB symptoms (e.g., tranexamic acid)
11. Hormonal contraception:
 - oral or intravaginal within 30 days of visit 1
 - IUD still in place within 30 days of visit 1
 - Implants/depots still in place within 30 days of visit 1
 - Intramuscular: visit 1 less than 30 days from the last day of the labeled effective period of use
12. Use of steroidal OC agents during the study
13. Prohibited concomitant medication: Concomitant use of medication inhibiting or inducing cytochrome CYP 3A4 is excluded. In particular is excluded the use of additional steroid hormones, anticoagulants (e.g. heparin, Coumadin), anti-epileptics (hydantoin derivates [e.g., phenytoin] or carboxamide derivates [e.g., carbamazepine, oxcarbamazepine], other anti-epileptics [e.g., Felbamate, Topiramate]), hypnotics and sedatives (barbiturate derivatives [e.g., primidone]), tuberculostatics (e.g., rifampicin), oral antimycotics (e.g., griseofulvin, ketoconazole, itraconazole, fluconazole), virostatic agents (e.g., ritonavir),

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products containing St. John's Wort, and continuous (exceeding 14 days) systemic use of antibiotics

14. Any concomitant or active disease or condition that compromises the absorption, distribution, metabolism, or excretion of the study drug (such as compromised renal function, gastrectomy, pancreatitis, renal insufficiency, hepatic dysfunction, active cholecystitis, and cholestatic jaundice)
15. Known or suspected premalignant or malignant disease including malignant melanoma (excluding other successfully treated skin cancers) or a history of these conditions
16. Abnormal laboratory values that are considered clinically significant at the discretion of the investigator and which give suspicion of a specific organ or system dysfunction
17. History of myocardial infarction or coronary heart disease requiring treatment
18. History of congestive heart failure
19. Uncontrolled hypertension; sitting systolic blood pressure \geq 140 mmHg or diastolic blood pressure \geq 90 mmHg
20. History of stroke or transient ischemic attacks
21. Vascular diseases: Presence or history of venous thromboembolic diseases (deep vein thrombosis, pulmonary embolism), presence or history of arterial thromboembolic diseases (myocardial infarction, stroke), and any condition which could increase the risk to suffer from any of the above mentioned disorders, e.g. a positive family history (event that occurred in a sibling or a parent at an early age) or a hereditary predisposition
22. Uncontrolled thyroid disorders
23. Known sickle cell anemia
24. Known, not adequately controlled diabetes mellitus or with vascular involvement
25. Current or history of migraines with focal neurological symptoms
26. Increased frequency or severity of headaches including migraines during previous estrogen therapy
27. History of drug addiction or alcohol abuse (within the last 2 years)

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- 28. Current or history of clinically significant depression (hospitalization)
- 29. Received an investigational drug or participated in another clinical trial within 1 month prior to study entry at visit 1; prior entry into this study
- 30. Known allergic reactions and/or hypersensitivity to EV, or DNG, or other ingredients of the study drug
- 31. Known allergic reactions and/or hypersensitivity to sanitary protection
- 32. Heavy smoker (more than 10 cigarettes per day) over the age of 35
- 33. BMI > 32, calculated with the following: body weight (kg)/body height (m²)

5.3.4.8 Prior and Concomitant Therapy

All concomitant medication used during the course of the study was to be recorded using the brand name. Details including the dosage, indication, route, and duration of intake (i.e., start and stop dates) were to be recorded. Medication containing acetaminophen (e.g., Tylenol) was allowed during the study.

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5.3.4.9 Study Procedures

Table 66: Study 308960 – Study Procedures Flow Chart

Activities and Assessments Visit	S		Run-In		BL		Treatment				FU	
	1	2	3	4	5	6	7	8	9	10		11
Days			90				196					
Informed consent	X											
Demographics	X											
Physical exam	X				X						X	X
Vital signs, height, weight	X				X	X	X	X	X		X	X
Entry criteria	X	X	X	X	X							
Medical history	X											
Gynecologic exam, breast exam, cervical smear	X											X
Endometrial biopsy				X								X
Transvaginal ultrasound		X										
Mammogram	X											
E-diary training		X										
Instructions regarding sanitary product collection		X										
E-diary review			X	X	X	X	X	X	X		X	X
Chemistry, hematology and urinalysis	X				X			X				X
FSH, prolactin, TSH, LH, SHBG, T, DHEAS	X											X
Serum ferritin					X			X				X
Review of lab results		X					X		V8			
PGWBI, MFSQ, EQ-5D questionnaires					X			X				X
Resource use assessment					X			X				X
Patient's assessment scale								X				X
Investigator's global assessment								X				X
Serum hCG testing	X											
Urine hCG testing (central lab)					X			X				X
Urine hCG testing (home)					X	X		X	X			
Randomization					X							
Study drug dispensed					X							
Pill count for returned study drug						X	X	X	X		X	
Baseline finding assessment	X	X	X	X	X							
AE assessment							X	X	X	X	X	X
Review blood loss volume results			X	X	X	X	X	X	X	X	X	
Concomitant medication		X	X	X	X	X	X	X	X	X	X	X
Contraception methods used by subject		X	X	X	X	X	X	X	X	X	X	
Dispense sanitary protection		X										
Dispense condoms	X											
Patient and investigator opinion concerning treatment received								X			X	

V = visit; S = screening; BL = baseline; FU = follow-up; FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin; LH = luteinizing hormone; T = testosterone; DHEAS = Dehydroepiandrosterone; EQ-5D = EuroQoL 5 Dimensional Questionnaire; MFSQ = McCoy Female Sexuality Questionnaire; PGWBI = Psychological General Well-Being Index; SHBG = sex hormone-binding globulin; TSH =thyroid stimulating hormone
 Source: Study Report A29849; Page 28-29 of 1182

Medical Officer's Comments:

Height was only assessed at visit 1.

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Cervical smear was not required if performed within the preceding 6 months and found to be normal.

Endometrial biopsy was not required if valid endometrial biopsy was performed within the preceding 6 months and found to be free of atypia or malignant changes. Endometrial biopsies at visit 11 were required only for women who enrolled with simple hyperplasia.

Mammograms were only required for subjects ≥ 35 years of age (not required if normal mammogram within the preceding 6 months)

The hematology assessment at visit 1 included von Willebrand factor activity in addition to a standard complete blood count.

The Psychological General Well-Being Index (PGWBI) was developed as an instrument to measure subjective well-being or distress. The PGWBI includes 22 items that, in addition to providing a global overall score, are divided into 6 dimensions: anxiety, depressed mood, positive well-being, self-control, health, and vitality.

The McCoy Female Sexuality Questionnaire (MFSQ) was designed to measure aspects of female sexuality and asks about the subjects' sexual experience during the last 4 weeks. It has been used to study the effect of changes in sex hormone levels (menopause transition) and of birth control pills on women's sexuality.

The EuroQoL 5 Dimensional health questionnaire (EQ-5D) is a multidimensional measure of health-related QoL, capable of being expressed as a single index value within the range of 0 to 100. Assessments can be done by using the Health State Classification or a Visual Analogue Scale ("Thermometer"). The Health State Classification comprises 5 dimensions selected from literature and from existing QoL measures; the dimensions are mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. The "Thermometer," a visual analogue scale, generates a self-rating of current health-related QoL. It has endpoints of 100 (best imaginable health state) at the top, and 0 (worst imaginable health state) at the bottom.

5.3.4.10 Bleeding Assessment

The dysfunctional uterine bleeding symptom assessment (primary endpoint) is based on the symptoms that are recorded in the e-diary.

The following data were captured in the e-diary:


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- Bleeding symptoms
- Number of sanitary protection used
- Results of home pregnancy tests
- Start date of new blister
- Number of tablets taken
- Whether or not all used sanitary protection was collected

Patients were instructed to enter their e-diary data daily and received a reminder via an electronic alarm. However, patients were able to enter data into the e-diary retrospectively up to 72 hours.

Medical Officer's Comment:

The Applicant provided data in the integrated summary of safety that analyzed inter-study and intra-study compliance of electronic alarm diaries compared with written diaries. The compliance results were similar. (b) (4)



The e-diary captured information regarding daily bleeding as none, spotting, light, normal, or heavy. The e-diary also captured information regarding the number and type of sanitary protection used. The e-diary was a Palm Pilot® with proprietary software and programming provided by invivodata, inc. The e-diaries were distributed to all patients at visit 2 and included instructions for use. Patients entered bleeding data and docked the Palm Pilot daily for data transfer. The docking station included a battery charger and a modem for data transfer.

The total menstrual blood loss (secondary endpoint) was determined by the central laboratory using the alkaline hematin method.

The alkaline hematin method measures hemoglobin in a fixed amount of alkaline solution with the use of a spectrophotometer (Hallberg and Nilsson, 1964). The fixed amount of solution is taken from the pool of solution in which all the materials (used sanitary protection) to be tested have been macerated for hemoglobin extraction. The blood loss volume was reported by episode. This test was performed at a central laboratory.

Medical Officer's Comment:

The methodology for the alkaline hematin method and the reference are acceptable. The Division has approved other therapies for bleeding based on this referenced method.

5.3.4.11 Treatment Compliance

In order to monitor compliance, the patients recorded pill intake daily in the e-diary. At each visit, the data in the e-diary was reviewed by study site personnel. Additionally, the patients were to return all used, partly used, or unused blister cards to the investigator. The return was to be documented in the eCRF. The Clinical Research Associate (CRA) was to check all returned blister cards before shipment to the Applicant. A written explanation was to be made for any uneven balance between dispensation, use, and return in the eCRF.

5.3.4.12 Primary Efficacy Variables

The primary efficacy variable was the overall success rate, defined by the number of patients 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 patients having at least one qualifying DUB symptom during the run-in phase.

Absence of DUB symptoms is defined as:

- No bleeding episodes lasting more than 7 days and
- No more than 4 bleeding episodes (in the 90 day assessment period) and
- No bleeding episodes with blood loss volume of 80 mL or more

Medical Officer's Comment:

A bleeding day is a day where sanitary protection is required.

A bleeding-free day is defined as a day with no bleeding or only spotting. No sanitary protection is required (except for panty liners).

A bleeding episode is characterized by the following:

- ***Bleeding for at least 2 days***
- ***Bleeding days can be separated by no more than 1 bleeding-free day***
- ***An episode stops with 2 consecutive bleeding-free days***

In addition absence of DUB symptoms required:

- No more than 1 bleeding episode increase from baseline and
- Total number of bleeding days not to exceed 24 days (in 90 day period)
- No increase from baseline in an individual patient's total number of bleeding days

In addition, for patients enrolled with specific symptoms, the following criteria had to be met:

- If patients enrolled with prolonged bleeding, the decrease between the

- maximum duration during run-in phase and the maximum duration during the efficacy phase should be at least 2 days
- If patients enrolled with excessive bleeding: (1) the blood loss volume associated with each episode should be < 80 mL and (2) the blood loss volume associated with each bleeding episode should represent a decrease of at least 50% from the average of the qualifying bleeding episodes, where the qualifying bleeding episodes are those with a blood loss volume \geq 80 mL (per episode) that occurred during the run-in phase

The definition of overall success requires that

- (1) the proportion of successful responders in the active treatment arm be statistically significantly greater than that in the placebo arm and
- (2) the point estimate for the proportion of successful responders in the active treatment arm EV/DNG be at least 50%.

Medical Officer's Comment:

The Applicant justified this definition of a clinically significant responder rate of 50% with the following statements:

"The primary outcome measure (absence of DUB symptom in a patient presenting with DUB symptoms) has been designed to be immediately relevant to clinical practice. If the study is positive, a physician will know that a patient consulting with one of these symptoms will have at least a 50% chance to be cured from these symptoms.

When compared to other symptomatic treatments, a 50% complete clinical response is clinically relevant. Depending on the field and the nature of the underlying disease, partial responses (e.g., ACR 20 or 70 in rheumatoid arthritis, PASI improvement for psoriasis) or complete responses (e.g., relief of migraine headache) are considered primary outcomes. A complete response is more stringent than a partial response.

Due to the nature of DUB, a disorder without organic cause, and due to the fact that physicians will weigh their treatment decision between a medical treatment or a surgical intervention (e.g., hysterectomy) the selection of a 50% complete response seems relevant to be accepted as a cornerstone of medical practice. The clinical significance of a smaller response in the verum group (e.g., below 40%) will have to be established with the help of secondary outcome of efficacy.

The selection of a 50% threshold is also supported by a review of the DUB and menorrhagia literature, notably when analyzing available individual patient data. The literature suggests that a cyclic treatment incorporating a sufficient duration of a potent progestin could cure the various symptoms of DUB in at least 50% of patients."

The Division accepted the Applicant's proposal. A focus group analysis supporting the 50% responder point estimate as clinically meaningful to women with DUB was not performed.

5.3.4.13 Secondary Efficacy Variables

The secondary efficacy variables include:

- Proportion of patients cured from each individual symptom
- Change in blood loss volume for all patients and for patients with excessive bleeding
- Change in number of bleeding days and bleeding episodes
- Change in number of sanitary protection used
- Proportion of patients with improvement in the investigator's global assessment scale at days 84 and 196
- Proportion of patients with improvement in the patient's overall assessment scale at days 84 and 196
- Change from baseline in QoL scores at days 84 and 196
- Resource use assessment at baseline, days 84 and 196
- Change from baseline in hemoglobin and serum ferritin concentrations at days 84 and 196

5.3.4.14 Statistical Analysis Plan

Any randomized subject, who did not complete at least 90 days of treatment from the beginning or did not have sufficient data to evaluate the absence or presence of DUB symptoms, was considered a treatment failure.

For prematurely discontinued patients, or patients with incomplete data that can not be replaced by applying the rules described below, the efficacy phase was captured by shifting the 90-day treatment period backward to capture days with evaluable data.

Nonconsecutive missing days for bleeding intensity days were replaced using the highest bleeding intensity of the bordering days. For example, if a given 3-day sequence is "normal/missing/spotting," the missing value was replaced by "normal," resulting in a bleeding day. No more than 9 nonconsecutive days per phase were replaced, as long as it did not exceed 10% of actual data available for the respective phase under consideration. Consecutive days with missing bleeding intensity data were not replaced.

For determining patients' eligibility for inclusion in the study during the run-in phase, missing blood loss volume data was replaced by "0" (zero). For the efficacy analysis, an imputation plan (described below) for replacing missing menstrual blood loss volume (MBLV) data was used. Dropout patients were not replaced.

MBLV data for an entire episode is the sum of MBLV data from individual days in the respective episode. Since MBLV data are impacted by the bleeding intensity and by whether or not patients completely collect sanitary protection, missing or incomplete data for single days was imputed as described below.

Table 67: Types of Complete and Partial Missing or Implausible Data

Type	Bleeding intensity on the respective day	Sanitary protection completely collected on the respective day	MBLV data
Type 1	None, spotting, \geq light, or missing	Yes, no or missing	> 0
Type 2	\geq light	Yes, no or missing	Missing / 0
Type 3	None, spotting, missing	Yes, no or missing	Missing

Source: Statistical analysis plan of Study 308960; page 12 of 26.

For type 1, there is no imputation. MBLV for the day was taken as entered.

For type 2, MBLV data was imputed by using the mean MBLV for days of the bleeding episode on which sanitary protection was correctly collected (and MBLV data are available). If no day with correctly collected sanitary protection were available in the episode, missing MBLV data was imputed by using the mean MBLV for days of the preceding bleeding episode in which sanitary protection was correctly collected. For the run-in phase, if there was no preceding bleeding episode, data from the succeeding bleeding episode was taken.

For type 3, where MBLV data is missing and there was no indication of bleeding from the intensity evaluation, the MBLV was considered to be 0 mL.

5.3.4.15 Analysis of Safety

The safety monitoring employed in this protocol included medical history, physical exams, vital sign monitoring, safety labs, pap smears, mammograms, endometrial biopsies and adverse event reporting.

The Applicant listed specific adverse events that would lead to subjects being immediately terminated from the study:

- First signs of venous inflammation or blood clots (thrombosis, embolism), e.g., marked pain or swelling in the legs, stabbing pain on breathing or cough of unknown origin, pain and a feeling of constriction in the chest
- Scheduled major operations (4 weeks prior), and/or in case of prolonged immobility (e.g., after accidents)
- Migraine headache (hemicranial headache with sudden onset, accompanied by dizziness and vomiting), occurring for the first time or more frequently with unusual severity
- Sudden sensory disturbances (visual, auditory, etc.)
- Motor disturbances (particularly paralysis)
- Documented persistent moderate to severe hypertension or unexplained increase in blood pressure
- Jaundice, itching over the entire body, disturbances of bile drainage (cholestasis), or clinically significant increase in liver function test values

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- (3x upper limit of normal)
- Epileptic seizures

5.3.4.16 Protocol Amendments

The original protocol was dated Sept 13, 2005. There was one amendment dated May 5, 2006. This amendment primarily contained changes to the primary efficacy variable regarding DUB symptoms. In addition this amendment also established the 50% responder point estimate. These changes were made based on DRUP recommendations. All of the changes from Amendment 1 are incorporated in section 5.3.3.12 of this review.

5.3.4.17 Disposition of Subjects

Table 68 presents data on the disposition of subjects in Study 308960.

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Table 68: Study 308960 - Disposition of Subjects

Disposition / Reason	EV/DNG
Screened	1077
Screening failures	887
<ul style="list-style-type: none"> • Withdrawal of consent • Entry criteria not met • Volunteer lost, no further information • Other 	<ul style="list-style-type: none"> • 138 • 604 • 88 • 57
Volunteers randomized in the study	190
<ul style="list-style-type: none"> • Randomized to EV/DNG (ITT) • Randomized to Placebo (ITT) 	<ul style="list-style-type: none"> • 120 • 70
Per-Protocol Set ^A	68
<ul style="list-style-type: none"> • EV/DNG • Placebo 	<ul style="list-style-type: none"> • 41 • 27
Safety Analysis Set ^B	185
<ul style="list-style-type: none"> • EV/DNG • Placebo 	<ul style="list-style-type: none"> • 119 • 66
Subjects who completed study	136 of 190 (71.5%)
<ul style="list-style-type: none"> • EV/DNG • Placebo 	<ul style="list-style-type: none"> • 85 • 51
Subjects who prematurely discontinued from study (EV/DNG)	35 of 119 (29.4%)
<ul style="list-style-type: none"> • Adverse event • Other • Subject lost • Pregnancy • Protocol deviation • Withdrawal of consent • Missing 	<ul style="list-style-type: none"> • 12 of 119 (10.1%) • 6 of 119 (5.0%) • 1 of 119 (0.8%) • 0 • 2 of 119 (1.7%) • 11 of 119 (9.2%) • 3 of 119 (2.5%)
Subjects who prematurely discontinued from study (Placebo)	19 of 66 (28.8%)
<ul style="list-style-type: none"> • Adverse event • Other • Subject lost • Pregnancy • Protocol deviation • Withdrawal of consent • Missing 	<ul style="list-style-type: none"> • 3 of 66 (4.5%) • 4 of 66 (6.0%) • 2 of 66 (3.0%) • 1 of 66 (1.5%) • 0 • 4 of 66 (6.0%) • 5 of 66 (7.5%)

A = All randomized subjects who 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

B = All randomized subject who took at least one pill of study medication

EV/DNG = estradiol valerate / dienogest

Source: Study Report A29849; pages 167-168 of 1182

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5.3.4.18 Protocol Deviations

The distribution of protocol deviations are shown in Table 69.

Table 69: Distribution of Protocol Deviations – Study 308960

	EV/DNG (n=119)	Placebo (n=66)
Minor	41 (34.5%)	27 (40.9%)
Major	78 (65.5%)	39 (59.1%)

Source: Study Report A29849; Text table 5, page 57 of 1182

The most frequently reported type of major protocol deviations was time schedule deviations, which consisted of the following:

- Did not complete 7 cycles: treatment phase is less than 174 days or day 174 is a day within a bleeding episode but tablet intake stops before bleeding episode is finished
- Bleeding intensity information missing for 2 or more consecutive days for days 1 to 90 of run-in phase or days 85 to 174 of treatment phase
- Bleeding intensity information missing for more than 10% of days in first 90 days of run-in phase
- Less than 90 diary days reported until first pill intake

Medical Officer's Comment:

The number of protocol deviations is concerning because a lot of the deviations are related to collection of bleeding data. This would lead to increased imputation for missing data.

(b) (4)

5.3.4.19 Demographics

Demographics are presented in Table 70.

Table 70: Study 308960 - Demographic Data - ITT

	EV/DNG (n=120)	Placebo (n=70)
Mean age (years ± SD)	36.9 ± 7.45	37.0 ± 6.67
Ethnic group (%)		
• Caucasian	71 (59.2%)	46 (65.7%)
• Black	38 (31.7%)	14 (20.0%)
• Hispanic	8 (6.7%)	6 (8.6%)
• Asian	1 (0.8%)	2 (2.9%)
• Other	2 (1.7%)	2 (2.9%)
Body mass index (kg/m ² ± SD)	26.3 ± 3.56	25.8 ± 3.61

EV/DNG = estradiol valerate / dienogest

Source: Study Report A29849; pages 177-78 of 1182

Medical Officer's Comment:

The treatment groups appear well matched except for the distribution of Caucasians and Blacks between treatment and placebo. (b) (4)

5.3.4.20 Gynecologic and Obstetric History

The most frequently reported DUB symptom during the 90-day run-in phase in both treatment groups was excessive bleeding (75.8% patients in the EV/DNG group and 85.7% patients in the placebo group), following by prolonged bleeding (21.7% patients in the EV/DNG group and 17.1% patients in the placebo group) as shown in Table 71.

Table 71: Study 308960 – Dysfunctional Uterine Bleeding Symptoms at Baseline - ITT

	EV/DNG n=120 (%)	Placebo n=70 (%)
Prolonged bleeding - yes	26 (21.7)	12 (17.1)
Frequent bleeding - yes	4 (3.3)	2 (2.9)
Excessive bleeding - yes	91 (75.8)	60 (85.7)
Prolonged and frequent bleeding - yes	3 (2.5)	2 (2.9)
Prolonged and excessive bleeding - yes	9 (7.5)	9 (12.9)
Frequent and excessive bleeding - yes	1 (0.8)	0 (0)
All three types - yes	0 (0)	0 (0)

EV/DNG = estradiol valerate / dienogest

Source: Study Report A29849; Text table 8, page 61 of 1182

Medical Officer's Comment:

The n's for prolonged bleeding, frequent bleeding and excessive refers to subjects with and without other symptoms.

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Baseline findings indicated that the treatment and placebo arms had a similar obstetric history in regard to number of pregnancies, the number of births and the mean number of years since the last birth/abortion.

The menstrual cycle history for the subjects is presented in Table 72

Table 72: Study 308960 – Menstrual Cycle History - ITT

	EV/DNG n=120 (%)	Placebo n=70 (%)
Subjects with irregular cycle	29 (24.2%)	10 (14.3%)
Dysmenorrhea	71 (59.2%)	46 (65.7%)
Intracyclic vaginal bleeding	24 (20.0%)	11 (15.7%)
Average intensity of bleeding = heavy	108 (90.0%)	66 (94.3%)

EV/DNG = estradiol valerate / dienogest

Source: Study Report A29849; Text table 9, page 63 of 1182

5.3.4.21 Concomitant Treatments

A total of 84.9% of patients in the EV/DNG group and 84.8% of patients in the placebo group reported concomitant medications. Two patients (both in the EV/DNG group) were noted to have taken progestogens or progestogens and estrogens (fixed combinations) during the study. Patient 208006 took emergency contraception on 03 Aug 2007 (levonorgestrel) one week prior to completing the study (last study drug was 09 Aug 2007). Patient 129010 completed study medication on 25 Apr 2007 and started an OC (ethinyl estradiol with norgestimate) on 06 May 2007.

The use of oral iron bivalent preparations during the study was less frequent in the EV/DNG group (10.1%) than in the placebo group (16.7%).

5.3.4.22 Primary Efficacy Results

The primary efficacy variable was the overall success rate, which was defined by the number of patients 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 with the number of patients having at least one qualifying DUB symptom during the run-in phase.

Absence of DUB symptoms was defined as:

- No bleeding episodes lasting more than 7 days and
- No more than 4 bleeding episodes and
- No bleeding episodes with blood loss volume of 80 mL or more

In addition,

- No more than 1 bleeding episode increase from baseline and

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- Total number of bleeding days not to exceed 24 days
- No increase from baseline in an individual patient's total number of bleeding days

In addition, for patients enrolled with specific symptoms, the following criteria had to be met:

- If patients enrolled with prolonged bleeding, the decrease between the maximum duration during run-in phase and the maximum duration during the efficacy phase should be at least 2 days
- If patients enrolled with excessive bleeding: (1) the blood loss volume associated with each episode be < 80 mL and (2) the blood loss volume associated with each bleeding episode represents a decrease of at least 50% from the average of the qualifying bleeding episodes, where the qualifying bleeding episodes are those with a blood loss volume \geq 80 mL that occurred during the run-in phase

The definition of overall success required that the proportion of successful responders in the active treatment arm EV/DNG

- (1) be statistically significantly greater than that in the placebo arm and
- (2) the point estimate for the proportion of successful responders in the active treatment arm EV/DNG be at least 50%.


Note that for the sake of the primary analysis, any randomized patient who did not complete at least 90 days of treatment from the beginning, or did not have sufficient data to evaluate the absence or presence of DUB symptoms, was considered a treatment failure.

For the ITT population (all randomized subjects), (b) (4)

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Table 73: Study 308960 – Responder Analysis for Overall DUB Symptoms by Treatment (ITT)

	EV/DNG (N = 120)	Placebo (N=70)	
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(b) (4)

EV/DNG = estradiol valerate / dienogest; CI = confidence intervals
Sources: Summary of clinical efficacy, pages 45-47 of 108

Medical Officer's Comment:



(b) (4)

5.3.4.24 Secondary Efficacy Results

5.3.4.24.1 Proportion of Subjects Cured from Each Individual Symptom

The individual symptoms were prolonged bleeding, frequent bleeding and excessive bleeding.

Medical Officer's Comment:



(b) (4)

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(b) (4)

5.3.4.25 Safety – Extent of Exposure

The exposure to EV/DNG in Study 308960 by cycles, partial cycles, days and women-years is the following:

- Number of completed 28 day cycles (673)
- Number of partially completed 28 day cycles (56)
- Total days of exposure (19,155)
- Total women-years of exposure (52.44)

Source: NDA 22-252; Amendment 17 (3/17/2010)

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5.3.4.26 Safety – Event Overview

Study 308960 – Overview of the Number (%) of Subjects with Adverse Events (Safety Analysis Set)

Events	
With at least 1 AE – EV/DNG	80 of 119 (67.2%)
With at least 1 AE – Placebo	36 of 66 (54.5%)
With nonfatal SAEs - EV/DNG	1
With nonfatal SAEs - Placebo	1
Who discontinued study drug due to an AE – EV/DNG	11 of 119 (9.2%)
Who discontinued study drug due to an AE – EV/DNG	46 of 66 (6.1%)
Who died – EV/DNG	0
Who died – Placebo	0

EV/DNG = estradiol valerate / dienogest; AE = adverse event; SAE = serious adverse event
 Source: Study Report A39818, Text table 22, page 75 of 484.

5.3.4.27 Safety – Common Adverse Events

The most frequent common adverse events are shown in Table 77.

Table 77: Study 308960 – Number (%) of Subjects with Most Common Adverse Events (EV/DNG greater than placebo) by Preferred Term –Safety Analysis Set

Adverse Event (PT)	EV/DNG N =119 n (%)	Placebo N = 66 N(%)
Weight increased	7 (5.9%)	0 (0.0%)
Acne	6 (5.0%)	0 (0.0%)
Metrorrhagia	6 (5.0%)	0. (0.0%)
Breast pain	5 (4.2%)	0. (0.0%)
Tension headache	4 (3.4%)	0. (0.0%)
Depression	3 (2.5%)	1 (1.5%)
Dyspepsia	3 (2.5%)	0. (0.0%)
Gastroenteritis	3 (2.5%)	0. (0.0%)
Vaginal infection	3 (2.5%)	0. (0.0%)
Migraine	3 (2.5%)	0. (0.0%)
Anemia	2 (1.7%)	4 (6.1%)

EV/DNG = estradiol valerate / dienogest; PT = preferred term
 Source: Study Report A29849; Table 152; page 433 of 1182

Medical Officer’s Comment: Anemia was also included in this table to show the difference, since it relates to bleeding.

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5.3.4.28 Safety – Nonfatal Serious Adverse Events

In the EV/DNG group, patient No. 131003 (46 years of age) experienced a myocardial infarction. No family history of cardiac diseases was reported prior to study entry. The subject was a non-smoker and had a BMI of 31.4 kg/m². The subject had taken EV/DNG for approximately 6 months prior to the SAE. During hospitalization for myocardial infarction, hospital notes indicate a history of hyperlipidemia and a family history of cardiac diseases, including coronary artery disease and stroke.

In the placebo group, patient No. 208011 (34 years of age) was hospitalized following a suicide attempt. Patient's history shows an attempted suicide in (b) (6)

5.3.4.29 Safety – Deaths

There were no deaths in the study.

5.3.4.30 Safety – Discontinuations Due to Adverse Events

A total of 16 of 185 patients (8.6%) prematurely discontinued the study medication due to an adverse event [12 patients of 119 (10.0%) in the EV/DNG group and 4 patients of 66 (6.1%) in the placebo group].

<u>EV/DNG group</u>	<u>Placebo group</u>
Gastroenteritis (1)	Headache, nausea, vomiting (1)
Acne, Tension headache (1)	Anxiety, hypertension, insomnia, hypoaesthesia (1)
Anemia worsening (1)	Anxiety, depression, insomnia, arthralgia (1)
Myocardial infarction (1)	Headache, hypoaesthesia (1)
Headache, nausea, vomiting (1)	
Menstrual disorder (1)	
Migraine (1)	
Emotional disorder (1)	
Hypertension (1)	
Asthma (1)	
Bacterial vaginitis (1)	
Breast tenderness, libido decreased, metrorrhagia (1)	

5.3.4.31 Safety – Laboratory

Hematology

Hematology testing included erythrocytes, hematocrit, hemoglobin, platelets, leukocytes and Factor VIII (von Willebrand factor). The mean and median values

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were within the normal range for all hematology parameters at all time points and were equivalent between the placebo and EV/DNG treatment groups. Anemia occurred in isolated subjects (5 in the placebo arm and 7 in the EV/DNG arm).

Chemistry

Chemistry testing included:

- Sodium
- Potassium
- Creatinine
- Protein, total
- Albumin
- Alkaline phosphatase
- AST
- ALT
- GGT
- Ferritin

The mean and median values were within the normal range for all serum chemistry parameters at all time points and were equivalent between the placebo and EV/DNG treatment groups.

There were 2 outliers for GGT. Patient No. 109001(EV/DNG) provided the out of range GGT value (128 U/L) at visit 5. No other abnormal serum chemistry test results were noted for this patient and no TEAEs were reported for this subject at or around visit 5.

Patient No. 105002 (EV/DNG) provided the out of range GGT value (265 U/L) at visit 11 and exhibited GGT levels, which increased with time from 61-, 112-, 145-, to 265-U/L from visit 1 to visit 11, respectively. No other abnormal serum chemistry values were noted for this patient and only two events of bacterial vaginitis were listed as adverse events for this subject.

Special Chemistry

Per protocol, special serum chemistry parameters evaluated were follicle stimulating hormone (FSH), prolactin, thyroid stimulating hormone (TSH), luteinizing hormone (LH), SHBG (sex hormone binding-globulin), testosterone, and dehydroepiandrosterone-sulfate (DHEA-S). For all special serum chemistry parameters (hormones), the mean and median values were within the normal range at Screening and were clinically equivalent between the placebo and EV/DNG treatment groups. Mean and median SHBG levels were within the normal range at both time points and were slightly higher for the EV/DNG group compared with the placebo group.

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5.3.4.32 Safety – Vital Signs and Weight

Systolic blood pressure, diastolic blood pressure and heart rate remained normal and stable throughout all study visits in both treatment groups. The mean body weight and body mass index remained stable in both treatment groups.

5.3.5 Pivotal Study 308961 (Report A42568) for DUB

5.3.5.1 Study Title and Coordinating Investigator

“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.”

The global clinical team lead was Susan Zeun, MD.

The study ran from Feb 16, 2006 through May 27, 2008.

5.3.5.2 Ethics

The planning and conduct of this clinical study were subject to national laws. Only when all of the requirements of the appropriate regulatory authority had been fulfilled did the study begin. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the ICH-GCP Guidelines of 17 Jan. 1997.

The study commenced only after the protocol and the ICF had been approved by the appropriate IEC and written notification of the approval had been received by Bayer Schering Pharma AG.

5.3.5.3 Study Sites

In Study 308961 there were study sites in Australia (3), Czech Republic (5), Finland (4), Germany (9), Hungary (3), Netherlands (3), Poland (5), Sweden (4), Ukraine (4) and United Kingdom (3) that randomized subjects.

5.3.5.4 Study Objectives

The study objectives were identical to Study 308960.

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5.3.5.5 Study Design

The study design was identical to Study 308960.

5.3.5.6 Inclusion Criteria

The inclusion criteria were identical to Study 308960 except that:

- a) for Sweden only, all study participants (not just those over 40 years) were required to have an FSH < 40 IU/L
- b) for Germany only - Use of one or more of the following barrier contraception methods was allowed 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

c) for Czech Republic only - For patients ≥ 45 years of age, a non-suspicious mammography was to be obtained within one year before Visit 1. If this was not available, then a non-suspicious mammography was to be obtained prior to randomization.

Medical Officer's Comment:

The changes initiated for individual countries should not impact the primary efficacy endpoint related to dysfunctional uterine bleeding.

5.3.5.7 Exclusion Criteria

The exclusion criteria were identical to Study 308960 except that:

a) for Sweden only, there was an additional listing of erythromycin and grapefruit juice as prohibited concomitant medications.

Medical Officer's Comment:

As a minor point, although grapefruit juice is a CYP inhibitor, it is not considered a medication.

b) for Czech Republic only, "current diagnosis or history of breast cancer"

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Medical Officer's Comment:

***This exclusion was actually covered in the initial exclusion criteria #15
"Known or suspected premalignant or malignant disease"***

c) for Australia and United Kingdom: As opposed to the original exclusion for heavy smoker (>10 cig/d) over age 35, these countries required any smokers over age 35 to be excluded.

d) for United Kingdom only: As opposed to excluding BMI > 32, the UK excluded BMI > 30.

Medical Officer's Comment:

The changes initiated for individual countries in the exclusion are not felt by this reviewer to effect efficacy evaluations for DUB. The differences, however, do impact safety conclusions and labeling.

5.3.5.8 Prior and Concomitant Therapy

The monitoring of prior and concomitant therapy was identical to Study 308960 (as well as allowing acetaminophen use during the study),

5.3.5.9 Study Procedures

The study procedures were identical to Study 308960.

5.3.5.10 Bleeding Assessment

The bleeding assessment was carried out identically to Study 308960.

5.3.5.11 Treatment compliance

Compliance was evaluated identically to Study 308960,

5.3.5.12 – 5.3.5.14 Efficacy Variables, Statistical Analysis Plan

The primary and secondary efficacy variables and statistical analysis plan were identical to Study 308960,

5.3.5.15 Analysis of Safety

The analysis of safety was identical to Study 308960.

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5.3.5.16 Protocol Amendments

The original protocol for Study 308961 was dated October 10, 2005. The amendments include:

Amendment 1 (Dec 20, 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 medication because of the effects on CYP 3A4.

Amendment 2 (Jan 10, 2006) was applicable for UK only and adjusted the exclusion criterion for BMI from >32 to >30 kg/m² and excluded all smokers over the age of 35, not only heavy smokers (more than 10 cigarettes per day).

Amendment 3 (Jan 16, 2006) was applicable for Czech Republic only and excluded explicitly patients with a current diagnosis or history of breast cancer. For patients ≥ 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.

Amendment 4 (Feb 1, 2006) was applicable for 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 5 (Apr 4, 2006) was applicable for Australia only and excluded all smokers over the age of 35, not only heavy smokers (more than 10 cigarettes per day).

Amendment 6 (Jun 13, 2006) had changes to the primary efficacy variable (related to the number of bleeding episodes, total number of bleeding days, and blood loss volume)

In addition, laboratory tests during drug administration that result in clinically significant abnormal values must be documented as AEs and should be repeated until the values return to baseline levels or to normally acceptable levels. Handling of dropouts and missing data was changed in order to follow the FDA's recommendations.

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Amendment 7 (Jun 14, 2006) 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. The introduction of paper diaries at times during technical failure of e-diary brought about another form of source data.

5.3.5.17 Disposition of Subjects

Table 78 presents the data on the subject disposition in Study 308961.

Table 78: Study 308961 - Disposition of Subjects

Disposition / Reason	
Screened	575
Screening failures	344
• Withdrawal of consent	• 50
• Entry criteria not met	• 281
• Volunteer lost, no further information	• 7
• Other	• 6
Subjects randomized in the study	231
• Randomized to EV/DNG (ITT)	• 149
• Randomized to Placebo (ITT)	• 82
Per-Protocol Set ^A	
• EV/DNG	• 55
• Placebo	• 34
Safety Analysis Set ^B	
• EV/DNG	• 145
• Placebo	• 81
Subjects who completed study	
• EV/DNG	• 117
• Placebo	• 65
Subjects who prematurely discontinued from study (EV/DNG)	32 of 145 (22.1%)
• Adverse event	• 12 of 145 (8.3%)
• Other	• 6 of 145 (4.1%)
• Pregnancy	• 0 of 145 (0.0%)
• Protocol deviation	• 3 of 145 (2.1%)
• Withdrawal of consent	• 9 of 145 (6.2%)
Subjects who prematurely discontinued from study (Placebo)	17 of 82 (20.7%)
• Adverse event	• 4 of 82 (4.9%)
• Other	• 6 of 82 (7.3%)
• Pregnancy	• 1 of 82 (1.2%)
• Protocol deviation	• 2 of 82 (2.4%)
• Withdrawal of consent	• 4 of 82 (4.9%)

A = All randomized subjects who 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

B = All randomized subject who took at least one pill of study medication

EV/DNG = estradiol valerate / dienogest

Source: Study Report A42568; pages 228-229 of 1235

5.3.5.18 Protocol Deviations

The distribution of protocol deviations is shown in Table 79.

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Table 79: Distribution of Protocol Deviations – Study 308960

	EV/DNG (n=139)	Placebo (n=76)
Minor	49 (35.3%)	29 (38.2%)
Major	90 (64.7%)	47 (61.8%)

Source: Study Report A42568; Text table 7, page 93 of 1235

The most frequently reported type of major protocol deviations consisted of the following:

- Insufficient treatment length
- Insufficient bleeding intensity information or documentation

Medical Officer’s Comment:

The number of protocol deviations is concerning because a lot of the deviations are related to collection of bleeding data. This would lead to increased imputation for missing data.

(b) (4)

5.3.5.19 Demographics

Demographics are presented in Table 80.

Table 80: Study 308961 - Demographic Data - ITT

	EV/DNG (n=149)	Placebo (n=82)
Mean age (years ± SD)	39.5± 6.57	38.5 ± 7.52
Ethnic group (%)		
• Caucasian	144(96.6%)	80 (97.6%)
• Black	1 (0.7%)	0 (0%)
• Hispanic	0 (0%)	0 (0%)
• Asian	2 (1.3%)	1 (1.2%)
• Other	2 (1.3%)	1 (1.2%)
Body mass index (kg/m ² ± SD)	24.5 ± 3.49	25.6 ± 3.01

EV/DNG = estradiol valerate / dienogest

Source: Study Report A42568; pages 240-1 of 1235

Medical Officer’s Comment:

The treatment groups appear well matched.

5.3.5.20 Gynecologic and Obstetric History

Table 81 shows the DUB symptoms at baseline. The most frequently reported DUB symptom during the 90-day run-in phase in both treatment groups was excessive bleeding.

Table 81: Study 308961 – Dysfunction Uterine Bleeding Symptoms at Baseline - ITT

	EV/DNG n=149 (%)	Placebo n=82 (%)
Prolonged bleeding - yes	20 (13.4)	10 (12.2)
Frequent bleeding - yes	0 (0)	0 (0)
Excessive bleeding - yes	136 (91.3)	76 (92.7)
Prolonged and frequent bleeding - yes	0 (0)	0 (0)
Prolonged and excessive bleeding - yes	15 (10.1)	9 (11.0)
Frequent and excessive bleeding - yes	0 (0)	0 (0)
All three types - yes	0 (0)	0 (0)

EV/DNG = estradiol valerate / dienogest

Source: Integrated summary of efficacy – DUB; page 28-29 of 579

Baseline findings indicated that the treatment and placebo arms had a similar obstetric history in regard to number of pregnancies and the number of births and the mean number of years since the last birth/abortion.

The menstrual cycle history for the subjects is presented in Table 82.

Table 82: Study 308960 – Menstrual Cycle History - ITT

	EV/DNG n=149 (%)	Placebo n=82 (%)
Subjects with irregular cycle	21 (14.1%)	10 (12.2%)
Dysmenorrhea	74 (49.7%)	37 (45.1%)
Intracyclic vaginal bleeding	26 (17.4%)	11 (13.4%)
Average intensity of bleeding = heavy	143 (96.0%)	80 (97.6%)

EV/DNG = estradiol valerate / dienogest

Source: Study Report A42568; Text table 20, page 103 of 1235

5.3.5.21 Concomitant Treatments

Use of oral iron bivalent preparations was similar between the two treatment groups (EV/DNG = 17.2%; Placebo = 17.3%).

[REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

5.3.5.25 Safety – Extent of Exposure

The exposure to EV/DNG in Study 308961 by cycles, partial cycles, days and women-years is the following:

- Number of completed 28 day cycles (859)
- Number of partially completed 28 day cycles (75)
- Total days of exposure (24,538)
- Total women-years of exposure (67.18)

Source: NDA 22-252; Amendment 17 (3/17/2010)

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5.3.5.26 Safety – Event Overview

Table 87 presents an overview of subjects with adverse events in Study 308961.

Table 87: Study 308961- Overview of the Number (%) of Subjects with Adverse Events (Safety Analysis Set)

Events	
With at least 1 AE – EV/DNG	95 of 145 (65.5%)
With at least 1 AE – Placebo	50 of 81 (61.7%)
With nonfatal SAEs - EV/DNG	2
With nonfatal SAEs - Placebo	2
Who discontinued study drug due to an AE – EV/DNG	14 of 145 (9.7%)
Who discontinued study drug due to an AE – EV/DNG	5 of 81 (6.2%)
Who died – EV/DNG	0
Who died – Placebo	0

EV/DNG = estradiol valerate / dienogest; AE = adverse event; SAE = serious adverse event
 Source: Study Report A42568, pages 140 - 150 of 1235.

5.3.5.27 Safety – Common Adverse Events

The most frequent common adverse events are shown in Table 88.

Table 88: Study 308961 – Number (%) of Subjects with Most Common Adverse Events (EV/DNG greater than placebo) by Preferred Term –Safety Analysis Set

Adverse Event (PT)	EV/DNG N =145 n (%)	Placebo N = 81 N(%)
Breast tenderness / Breast pain	14 (9.7%)	3 (3.7%)
Nasopharyngitis / pharyngitis	13 (9.0%)	8 (2.5%)
Metrorrhagia	8 (5.5%)	1 (1.2%)
Nausea	7 (4.8%)	2 (2.5%)
Viral infection	6 (4.1%)	0 (0.0%)
Vulvovaginitis	4 (2.8%)	0 (0.0%)
Vaginal candidiasis	3 (2.1%)	1 (1.2%)
Pneumonia	3 (2.1%)	0 (0.0%)

EV/DNG = estradiol valerate / dienogest; PT = preferred term
 Source: Study Report A42568; Text Table 52; page 142 of 1235

Medical Officer’s Comment:

Pharyngitis, viral infection and pneumonia are not considered by this reviewer to be associated with COCs. The increased numbers compared to placebo are felt to be chance events.

The other common adverse events in the table (breast tenderness, metrorrhagia etc.) are known to occur more frequently in subjects taking COCs

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5.3.5.28 Safety – Nonfatal Serious Adverse Events

There were 4 subjects with nonfatal serious adverse events (Table 89).

Table 89: Nonfatal Serious Adverse Events – Study 308961

PID	Treatment Group	SAE(s)
702019	EV/DNG	Breast cancer in-situ (ductal)
852034	EV/DNG	Cholecystitis
104026	Placebo	Vertigo / Panic attack
201005	Placebo	Spontaneous abortion / Pregnancy complication

EV/DNG = estradiol valerate / dienogest; PID = Subject identification number;

SAE = Serious adverse event

Source: Study Report A42568; page 149 of 1235

Medical Officer's Comment:

The subject with ductal in-situ breast cancer (DCIS) was 44 years of age. She was on study treatment for approximately 5 months when the DCIS was diagnosed. This reviewer does not consider the breast disease related to study treatment.

The subject with cholecystitis was 37 years of age. The subject was hospitalized with acute cholecystitis approximately 3 weeks after the subject had started study treatment. This reviewer considers the SAE possibly related to EV/DNG.

5.3.5.29 Safety – Deaths

There were no deaths in the study.

5.3.5.30 Safety – Discontinuations Due to Adverse Events

Nineteen subjects were withdrawn or withdrew from study medication due to adverse events; 14 subjects (9.7%) from the EV/DNG and 5 subjects (6.2%) from the placebo group. Headache, nausea, altered mood and dysmenorrhea were the most common events in the EV/DNG group (2 each).

5.3.5.31 Safety – Laboratory

Hematology

Hematology testing included erythrocytes, hematocrit, hemoglobin, platelets, leukocytes and Factor VIII (von Willebrand factor) and ferritin.

The mean values of hematocrit, hemoglobin, platelets, erythrocyte count, leukocyte count and Factor VIII (von Willebrand factor) were similar between the

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placebo and EV/DNG treatment groups at all visits evaluated.

Ferritin levels increased in the EV/DNG group more than in the placebo group

- EV/DNG at baseline (13.65) - EV/DNG at end of study (22.40)
- Placebo at baseline (14.01) – Placebo at end of study (15.01)

Chemistry

Chemistry testing included:

- Sodium
- Potassium
- Creatinine
- Protein, total
- Albumin
- Alkaline phosphatase
- AST
- ALT
- GGT

The mean values for all chemistry tests were within the normal range at all time points evaluated and were similar between the placebo and EV/DNG treatment groups.

Special Chemistry

Per protocol, special serum chemistry parameters were follicle stimulating hormone (FSH), prolactin, thyroid stimulating hormone (TSH), luteinizing hormone (LH), SHBG (sex hormone binding-globulin) testosterone, and dehydroepiandrosterone-sulfate (DHEA-S). For all special serum chemistry parameters (hormones), the mean and median values were within the normal range at Screening and were clinically equivalent between the placebo and EV/DNG treatment groups. Mean and median SHBG levels were within the normal range at both time points and were slightly higher for the EV/DNG group compared with the placebo group.

5.3.5.32 Safety – Vital Signs and Weight

Systolic blood pressure, diastolic blood pressure and heart rate remained normal and stable throughout all study visits in both treatment groups. The mean body weight and body mass index remained stable in both treatment groups.

5.3.6 Other Studies

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5.3.6.1 Other Clinical Studies of Combination Products Containing Both Estradiol Valerate and Dienogest

5.3.6.1.1 Additional Completed Studies Utilizing the Final 4-Phasic Regimen

Study report number: A25711

Protocol number: 303312

Study title: An open-label, non-randomized, multiple-dose study to investigate the pharmacokinetics of a 28-day 4-phasic oral contraceptive containing estradiol valerate and dienogest in 18 healthy female subjects

Study drugs:

- Final 4-phasic regimen
Day 1-2 = 3 mg EV
Day 3-7 = 2 mg EV / 2 mg DNG
Day 8-24 = 2 mg EV / 3 mg DNG
Day 25-26 = 1 mg EV
Day 27-28 = placebo

Study period: Jan 2005 – Jun 2005

Study objectives: Multiple-dose pharmacokinetics

Study design: Open, non-randomized, multiple-dose Phase 1 study with duration of 1 cycle of 28 days.

Study enrollment: 18

Study findings:

PK findings

- Both EV and DNG were reported to be well absorbed after oral administration.
- Steady state of DNG was reported to be reached within 2 to 3 days of dosing
- EV was reported to be rapidly converted into E2, which resulted in relatively constant E2 serum levels during the 28-day treatment cycle
- Stable trough concentrations of E2 were reported to be maintained from Day 8 to Day 24.

Safety findings

- There were no deaths or SAEs reported in the study.
- All AEs were of either mild or moderate intensity. The most frequent drug-related AEs were metrorrhagia and headache, reported by 4 (22%) and 3 (17%) subjects, respectively.

Study report number: A25364

Protocol number: 307300

Study title: Multicenter, open-label, randomized, comparative study to evaluate ovulation inhibition with two 4-phasic oral contraceptive regimens containing estradiol valerate and dienogest applied daily for 3 cycles to 200 healthy female volunteers

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Study drugs:

- Final 4-Phasic regimen
Day 1-2 = 3 mg EV
Day 3-7 = 2 mg EV / 2 mg DNG
Day 8-24 = 2 mg EV / 3 mg DNG
Day 25-26 = 1 mg EV
Day 27-28 = placebo
- Reference regimen
Day 1-2 = 3 mg EV
Day 3-7 = 2 mg EV / 3 mg DNG
Day 8-24 = 2 mg EV / 4 mg DNG
Day 25-26 = 1 mg EV
Day 27-28 = placebo

Study period: Mar 2003 – Feb 2004

Study objectives: Compare ovulation inhibition of the two 4-Phasic regimens

Study design: Multicenter, open, randomized, comparative Phase 2 study with duration of 3 cycles of 28 days each

Study enrollment: 203 total (4-Phasic regimen, 100; Reference regimen, 103)

Study findings:

Efficacy findings

- In both cycle 2 and cycle 3 in this ovulation inhibition study, 3 subjects in the PPS had a Hoogland score of 6 (ovulation) – 2 subjects (2.6%) from the 4-Phasic regimen and 1 subject (1.23%) from the reference regimen

Safety findings

- There were no deaths or SAEs reported in the study.
- The most frequently reported AEs in the 4-Phasic regimen were flu syndrome (41.0% of subjects) and headache (35.0% of subjects).
- The most frequently reported AEs in the Reference regimen were flu syndrome (46.6% of subjects) and headache (38.8% of subjects).

Medical Officer's Comment:

The ovulation inhibition is greater than 95% for both regimens in this study.

Study report number: A33022

Protocol number: 301886

Study title: A single-center, open-label, controlled, randomized study to investigate the impact of a sequential oral contraceptive containing estradiol valerate and dienogest as compared to a sequential oral contraceptive containing ethinyl estradiol and levonorgestrel on plasma lipids, hemostatic variables, and carbohydrate metabolism in 60 healthy female volunteers aged 18-50 years over 7 treatment cycles including the pharmacokinetics of E1, E2, and DNG

Study drugs:

- Final 4-Phasic regimen
Day 1-2 = 3 mg EV

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Day 3-7 = 2 mg EV / 2 mg DNG
Day 8-24 = 2 mg EV / 3 mg DNG
Day 25-26 = 1 mg EV
Day 27-28 = placebo

- Reference
Day 1-6 = 0.03 mg EE / 0.05 mg LNG
Day 7-11 = 0.04 mg EE / 0.075 mg LNG
Day 12-21 = 0.03 mg EE / 0.125 mg LNG
Day 22-28 = placebo

Study period: Mar 2005 – Mar 2006

Study objectives: Comparative study to assess effect on plasma lipids, hemostatic variables, carbohydrate metabolism, thyroid parameters, sex hormone binding globulin, cortisol-binding globulin, testosterone (free and total) and dehydroepiandrosterone sulfate. Also the pharmacokinetics of E1, E2, and DNG were evaluated in a subgroup.

Study design: Open-label, active-controlled, 2-arm, randomized, single-center Phase 2 study with duration of 7 cycles of 28 days each

Study enrollment: 58 total (4-phasic regimen = 30; reference regimen = 28)

Study findings:

Laboratory findings

In general, the metabolic investigations showed no clinically relevant differences between the Final 4-Phasic regimen and the Reference drug and no marked changes between baseline and post-treatment levels of numerous metabolic parameters.

In the 4-Phasic regimen lipid analysis there was:

- A slight increase in HDL-cholesterol
- A slight decrease in LDL – cholesterol
- A mild increase in triglycerides but less than comparator

The mean levels of other serum lipids, hemostatic, thyroid, and carbohydrate metabolism parameters remained generally stable and comparable under both study treatments after 7 cycles.

Safety findings

- There were no deaths or SAEs reported in the study.
- Safety profiles of both study treatments were similar.

Study report number: A38220

Protocol number: 310122

Study title: A single-center, open-label, crossover, controlled, randomized study to investigate the impact of a sequential oral contraceptive containing estradiol valerate and dienogest as compared to a monophasic contraceptive containing ethinyl estradiol and levonorgestrel on hemostatic parameters in 30 healthy

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female volunteers aged 18 – 50 years over 3 treatment cycles in each period

Study drugs:

- Final 4-Phasic regimen
Day 1-2 = 3 mg EV
Day 3-7 = 2 mg EV / 2 mg DNG
Day 8-24 = 2 mg EV / 3 mg DNG
Day 25-26 = 1 mg EV
Day 27-28 = placebo
- Reference regimen
Day 1-21 = 0.03 mg EE / 0.15 mg LNG
Day 22-28 = placebo

Study period: Apr 2006 – May 2007

Study objectives: Comparative study on hemostatic parameters

Study design: Crossover, active treatment controlled randomized, open-label, single center Phase 2 study with duration of 3 cycles of 28 days each

Study enrollment: 29 total (4-Phasic regimen = 14; Reference = 15)

Study findings:

Lab findings

- Both the Final 4-Phasic regimen and the reference regimen increased prothrombin and fibrinogen to levels above the reference range.
- While Prothrombin fragment 1+2 levels remained stable (with the final regimen) or slightly increased (with the Reference treatment), D-dimer changes displayed a statistically significant difference ($p=0.0136$) between the 2 study OCs, with a slight increase under the final regimen and a marked rise under the Reference treatment.
- Mean levels of all safety laboratory parameters (hematology, blood chemistry, liver enzymes, carbohydrate metabolism, and serum lipids) assessed in the present study remained well within the reference range and generally stable.

Cycle control findings

- The frequency of volunteers with intracyclic bleeding during the 3 treatment cycles under the final regimen ranged from 8 (29.6%) to 10 (38.5%) volunteers; it was slightly higher as compared to the frequency in the Reference arm, which ranged from 3 (10.7%) to 7 (24.1%) volunteers.

Safety findings

- There were no deaths or SAEs reported in the study.
- The safety profiles were generally comparable between the two study regimens.

Medical Officer's Comment:

Hemostasis studies are often performed in Europe. Prothrombin and fibrinogen changes are commonly seen with COCs. The clinical significance of D-dimer changes differing between the two products is

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unclear. Only extremely large studies could analyze the relationship between a single marker such a D-dimer, a specific COC and a clinical adverse event such as deep vein thrombosis.

5.3.6.1.2 Other Studies Supportive of the Final 4-Phasic Regimen

Study report number: A24058

Protocol number: 308863

Study title: One-arm, open-label, non-randomized study to evaluate the effect of rifampicin 600 mg/ day, given over 5 days p.o., on the steady state pharmacokinetics of SH T00658M (2 mg estradiol valerate and 3 mg dienogest) in healthy postmenopausal volunteers

Study drugs:

- Day 1-17 = 2 mg EV / 3 mg DNG (SH T00658M)
- Day 12-16 = Rifampicin 600 mg

Study period: Mar 2005 – May 2005

Study objectives: CYP interaction study

Study design: Open, non-randomized, multiple-dose Phase 1 study with duration of 17 days

Study enrollment: 16

Study findings:

Efficacy findings

- Co-administration of rifampicin with SH T00658M led to significant **decreases** in steady state concentrations and systemic exposures of dienogest and estradiol, which could potentially affect the contraceptive efficiency of the DNG/E2 combination.

Safety findings

- There were no deaths or serious adverse events in the study.

Medical Officer's Comment:

See the clinical pharmacology review for more specifics. The effect of CYP3A4 inducer rifampicin is included in the proposed labeling from the Applicant.

Study report number: A29143

Protocol number: 304341

Study title: Open-label, single-dose, randomized, two-way crossover study to evaluate the effect of food on the bioavailability of estradiol and dienogest following a single oral administration of SH T00658M (2 mg estradiol valerate and 3 mg dienogest) in healthy postmenopausal women

Study drugs:

- 2 mg EV / 3 mg DNG (2 single administrations)

Study period: Mar 2006 – May 2006

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Study objectives: Evaluation of the food effect on bioavailability of 2 mg EV + 3 mg DNG

Study design: Single center, open, randomized, two-period, two-way crossover Phase 1 study

Study enrollment: 38

Study findings:

Food effect findings

- The current food-effect study in healthy postmenopausal women demonstrated that under fed conditions the C_{max} of DNG was decreased by 28% and the C_{max} of E2 was increased by 23%, while AUC values for both DNG and E2 remained unchanged. The slight changes in C_{max} of DNG and E2 are not considered to be clinically relevant by the Applicant.

Safety findings

- There were no deaths or SAEs reported in the study.

Study report number: A30020

Protocol number: 308862

Study title: Open-label, two-group, one-sequence, one-way crossover study to evaluate the effect of ketoconazole and erythromycin on the steady-state pharmacokinetics of SH T00658M (2 mg estradiol valerate and 3 mg dienogest) in healthy postmenopausal women

Study drugs:

- Group 1 = 2 mg EV / 3 mg DNG and 2 x 200 mg ketoconazole
- Group 2 = 2 mg EV / 3 mg DNG and 3 x 500 mg erythromycin

Study period: Apr 2006 – Jul 2006

Study objectives: Evaluate CYP 3A4 inhibitors on steady state PK

Study design: Open-label, two parallel-groups, one-sequence, one-way crossover Phase 1 study with duration of 14 days

Study enrollment: 24 total (12 in each arm)

Study findings:

PK findings

- This study demonstrated the presence of a significant drug-drug interaction between EV/DNG tablets and CYP3A4 inhibitors, ketoconazole and erythromycin. Co-administration of EV/DNG tablets with ketoconazole and erythromycin resulted in mild to moderate **increases** in systemic exposure for both E2 and DNG.

Safety findings

- There were no deaths or SAEs reported in the study.
- The most frequent adverse events overall in the study were withdrawal bleeding (29.2%) and myalgia (12.5%).

Medical Officer's Comment:

See the clinical pharmacology review for the specifics of this study

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NDA 22-252 (EV/DNG)

Study report number: A29972

Protocol number: 303310

Study title: Open label, randomized, single dose, three way crossover, two parallel group study to evaluate the relative bioavailability of the estradiol valerate and or dienogest tablet formulations contained in SH T00658ID versus suspensions containing the same drugs after oral administration in healthy postmenopausal women

Study drugs:

Group 1

A = 2 mg EV / 2 mg DNG, 1 tablet

B = 2 mg EV / 3 mg DNG, 1 tablet

C = 2 mg EV / 3 mg DNG, suspension

Group 2

D = 3 mg EV, 1 tablet

E = 1 mg EV, 3 tablets

F = 3 mg EV, suspension

Study period: Jun 2006 – Aug 2006

Study objectives: Evaluate relative bioavailability

Study design: Single-center, open-label, randomized, single-dose, three-way crossover Phase 1 study (single administration)

Study enrollment: 36 total (18 in each arm)

Study findings: See the clinical pharmacology review for the specific findings.

Safety findings

- There were no deaths or SAEs reported in the study.

Study report number: A35653

Protocol number: 310183

Study title: Double-blind, double-dummy, placebo-controlled, 4-way cross-over study to investigate QT/QTc prolonging effects in 12-lead ECG after once daily oral dosing over 4 days of drug product SH T 00658M (containing 3 mg dienogest and 2 mg estradiol valerate) and a supra-therapeutic dose of 10 mg dienogest in comparison to placebo and to a single dose of 400 mg moxifloxacin as an open-label positive control in healthy postmenopausal women

Study drugs:

- 2 mg EV / 3 mg DNG
- 10 mg DNG
- Moxifloxacin
- Placebo

Study period: Jan 2007 – Sep 2007

Study objectives: Investigate the potential for DNG at steady state to delay cardiac repolarization in healthy postmenopausal women

Study design: Phase 1 Double-blind, double-dummy, placebo-controlled, 4 way cross-over study with 4 treatments, 4 periods and 4 sequences.

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Study enrollment: 53 subjects

Study findings: See the specific findings in the Interdisciplinary Review Team for QT Studies consultative review.

Safety findings

There were no deaths reported in the study.

There was one SAE – intervertebral disc protrusion.

5.3.6.1.3 Ongoing Studies Utilizing the Final 4-Phasic Regimen

Protocol number: 13108

Study title: A multicenter, randomized, double-blind, active-controlled, parallel group, 2-arm study to show superiority of the oral contraceptive SH T00658ID over Ortho Tri-Cyclen Lo on hormone withdrawal-associated symptoms after 6 cycles of treatment

Study drugs:

- 4-phasic regimen
 - Day 1-2 = 3 mg EV
 - Day 3-7 = 2 mg EV / 2 mg DNG
 - Day 8-24 = 2 mg EV / 3 mg DNG
 - Day 25-26 = 1 mg EV
 - Day 27-28 = placebo
- Ortho Tri-Cyclen Lo
 - Day 1-21 = 0.03 mg EE / 0.15 mg LNG
 - Day 22-28 = placebo

Study period: ongoing

Study objectives: To assess pelvic pain or headache associated with hormone withdrawal

Study design: Multicenter, randomized, double-blind, active control Phase 3 study with duration of 1 year

Study enrollment: To have 616 evaluable subjects

Protocol number: 91548

Study title: Multi-center, double-blind, randomized study to investigate the impact of a sequential oral contraceptive containing estradiol valerate and dienogest, SH T00658ID compared to a monophasic contraceptive containing ethinyl estradiol and levonorgestrel (Microgynon) over 6 treatment cycles on alleviating complaints of reduced libido in women with acquired female sexual dysfunction (FSD) associated with oral contraceptive use

Study drugs:

- 4- Phasic regimen
 - Day 1-2 = 3 mg EV
 - Day 3-7 = 2 mg EV / 2 mg DNG
 - Day 8-24 = 2 mg EV / 3 mg DNG
 - Day 25-26 = 1 mg EV

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- Day 27-28 = placebo
- Microgynon
Day 1-21 = 0.03 mg EE / 0.15 mg LNG
Day 22-28 = placebo

Study period: ongoing

Study objectives: To show non-inferiority of 4-Phasic regimen to Microgynon on libido in women with acquired female sexual dysfunction (FSD) associated with OC-use

Study design: Multicenter, randomized, double-blind, active control Phase 3 study with duration of 6 cycles of 28 days each

Study enrollment: To have 216 evaluable

Protocol number: 91550

Study title: A multicenter, randomized, double-blind, active-controlled, parallel group, 2-arm study to investigate the effect of estradiol valerate/dienogest compared to Microgynon on hormone withdrawal associated symptoms in otherwise healthy women after 6 cycles of treatment

Study drugs:

- 4-phasic regimen
Day 1-2 = 3 mg EV
Day 3-7 = 2 mg EV / 2 mg DNG
Day 8-24 = 2 mg EV / 3 mg DNG
Day 25-26 = 1 mg EV
Day 27-28 = placebo
- Microgynon
Day 1-21 = 0.03 mg EE / 0.15 mg LNG
Day 22-28 = placebo

Study period: ongoing

Study objectives: To show superiority of quadriphasic regimen over Microgynon on hormone withdrawal associated symptoms after 6 cycles of treatment

Study design: Multicenter, randomized, double-blind, active controlled Phase 3 study with duration of 6 cycles of 28 days each.

Study enrollment: To obtain 616 evaluable subjects

Protocol number: 91781

Study title: A multi-center, double-blind, randomized, controlled, parallel-group study to assess efficacy and safety of SH T00658ID compared to Alesse in the treatment of primary dysmenorrhea

Study drugs:

- 4-phasic regimen
Day 1-2 = 3 mg EV
Day 3-7 = 2 mg EV / 2 mg DNG
Day 8-24 = 2 mg EV / 3 mg DNG
Day 25-26 = 1 mg EV

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- Day 27-28 = placebo
- Reference
 - Day 1-21 = 0.02 mg EE / 0.1 mg LNG
 - Day 22-28 = placebo

Study period: ongoing

Study objectives: To show superiority of quadriphasic regimen over reference for dysmenorrhea

Study design: Multicenter, double-blind, double dummy, randomized, controlled Phase 3 with duration of 3 cycles of 28 days each

Study enrollment: Plan for 328 evaluable subjects

5.3.6.1.4 Studies that Analyzed Other Developmental 4-Phasic Regimens

Study report number: A24194

Protocol number: JPH01695

Study title: Randomized study for testing a novel sequential regime with Estradiol in combination with Desogestrel or Dienogest for oral contraception

Study drugs:

- Combination A
 - Day 1-3 = 3 mg EV
 - Day 4-7 = 2 mg EV / 1 mg DNG
 - Day 8-23 = 2 mg EV / 2 mg DNG
 - Day 24-25 = 1 mg EV
 - Day 26-28 = placebo
- Combination B
 - Day 1-3 = 3 mg EV
 - Day 4-7 = 2 mg EV / 0.1 mg DSG
 - Day 8-23 = 2 mg EV / 0.15 mg DSG
 - Day 24-25 = 1 mg EV
 - Day 26-28 = placebo

Study period: 1995 -1996

Study objectives: Cycle control and contraceptive efficacy

Study design: Randomized, open, 2-arm comparative, multicenter Phase 2 study with duration of 6 cycles of 28 days each

Study enrollment: 199 total (Combination A = 100; Combination B = 99)

Study findings:

Contraceptive findings:

There were no pregnancies in the Combination A study arm. There were 2 pregnancies in the Combination B study arm.

Cycle control findings:

Irregular bleeding occurred in 26.2% and 20.7% of the subjects in the Combination A and B study arms respectively.

Safety findings

There were no deaths reported in the study.

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There was 1 SAE in the Combination A arm: Hospitalization for arthropathy
There was 1 SAE in the Combination B arm: Ectopic pregnancy

Study report number: B690

Protocol number: 15672

Study title: Double-blind, randomized dose-finding study for a novel, sequential regimen for oral contraception consisting of estradiol valerate and dienogest

Study drugs:

- Group A
Day 1-3 = 3 mg EV
Day 4-7 = 2 mg EV / 1 mg DNG
Day 8-23 = 2 mg EV / 2 mg DNG
Day 24-25 = 1 mg EV
Day 26-28 = placebo
- Group B
Day 1-3 = 2 mg EV
Day 4-7 = 1 mg EV / 1 mg DNG
Day 8-23 = 1 mg EV / 2 mg DNG
Day 24-25 = 0.5 mg EV
Day 26-28 = placebo

Study period: Apr 1998 – May 1999

Study objectives: Evaluate cycle control and contraceptive efficacy

Study design: Double-blind, randomized, 2-arm Phase 2 study with duration of 6 cycles of 28 days each

Study enrollment: 221 total (Group A = 111; Group B = 110)

Study findings:

Safety findings

- There were no deaths reported in the study.
- All 3 SAEs occurred in Group B: biliary colic (1), cervical dysplasia (1) and cruciate ligament surgery.
- The most frequent AEs in Group A (% of subjects) were headache (36.0%), flu (23.4%) and abdominal pain (13.5%)
- The most frequent AEs in Group B (% of subjects) were headache (33.6%), flu (17.3%) and nausea (10.9%)

Study report number: AZ94

Protocol number: 301740

Study title: Multi-center, open, uncontrolled study to investigate the efficacy and safety of a 4-phasic oral contraceptive SH T 658 I containing estradiol valerate and dienogest over 20 cycles in 1600 healthy female volunteers

- Developmental regimen
Day 1-3 = 3 mg EV
Day 4-7 = 2 mg EV / 1 mg DNG
Day 8-23 = 2 mg EV / 2 mg DNG
Day 24-25 = 1 mg EV

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Day 26-28 = placebo

Study period: Jan 2000 – Sep 2001

Study objectives: Primary was contraceptive efficacy

Study design: Multicenter, open, uncontrolled Phase 3 study with duration of 14 cycles of 28 days each (prematurely discontinued)

Study enrollment: 1779

Study findings:

Efficacy findings

The unadjusted Pearl Index was 5.3.

Safety findings

There was 1 death reported: murder

Pertinent SAEs included: ovarian cyst (2), hypertension (2), suspected biliary stone and pancreatitis (1)

The most frequent AEs (percentage of subjects) were headache (10.1), upper respiratory infection (6.7%) and breast pain (5.7%).

5.3.6.1.5 Studies Related to Climodien (A Combination Product of Estradiol Valerate and Dienogest for Menopausal Symptoms)

Medical Officer's Comment:

In this section only safety findings will be noted since menopausal symptoms are not pertinent to this application.

Study report number: A45526

Protocol number: 306281

Study title: The effect of Climodien on post menopausal symptoms and mood changes

Study drugs:

Climodien = 2 mg EV / 2 mg DNG

Activelle = 1.03 mg estradiol hemihydrate / 1 mg NETA

Study period: May 2003 – Aug 2004

Study objectives: Evaluate post menopausal symptoms and mood changes

Study design: Multicenter, double-blind, randomized Phase 4 study with duration of 6 months

Study enrollment: 139 total (Climodien = 70; Activelle = 69)

Study findings:

Safety findings

There were no deaths reported in this study

There were 3 subjects with SAEs in the Climodien group: urolithiasis (1), breast cancer (1) and uterine cancer (1)

There were 2 subjects with SAEs in the Activelle group: suicide attempt (1) and adenoma of parotid (1)

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Study report number: B464

Study title: Two-arm, double-blind, placebo-controlled, multicenter trial (JPH 04095) of the preparation Climodien (2 mg estradiol valerate 3 mg dienogest) in hormone replacement therapy. A randomized, multicenter, comparative, parallel group, phase 3, double-blind, placebo-controlled trial

Study drugs:

Climodien 2/3 = 2 mg EV / 3 mg DNG

Placebo

Study period: May 1996 – May 1997

Study objectives: Coagulation, lipids and CHO

Study design: Multicenter, double-blind, placebo-controlled, randomized Phase 3 study with duration of 24 weeks

Study enrollment: 83 total (Climodien = 43; placebo = 40)

Study findings:

Safety findings

There were no deaths reported in the study.

There were no SAEs in the Climodien study arm.

Study report number: B578

Protocol number: JPH05295

Study title: Continuous combined estrogen-progestin regimen (Climodien) for the therapy of postmenopausal complaints with particular attention paid to safety, tolerability and efficacy. A multinational, multicenter, open, non-controlled phase 3 study

Study drugs:

Climodien = 2 mg EV / 2 mg DNG

Study period: Sep 1996 – Jun 1998

Study objectives: Assess menopausal symptoms

Study design: Multicenter, open, uncontrolled Phase 3 study with duration up to 18 cycles

Study enrollment: 1501

Study findings:

Safety findings

- There were 2 deaths. One was secondary to gallbladder carcinoma. The other death was secondary to a car accident.
- Pertinent SAEs in this study included: gallbladder conditions (stone, inflammation or surgery = 7), DVT (3), pulmonary embolism (1), vaginal bleeding (14), hypertension, aggravated (4), stroke (2), depression (1), breast cancer (6), endometrial cancer (1)

Medical Officer's Comment:

The number of VTEs and strokes is significantly related to the advanced age of these subjects in addition to hormonal effect. In a postmenopausal osteoporosis study of the selective estrogen receptor modulator (SERM)

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lasofoxifene (0.25 mg), there were 26 VTEs in approximately 2800 postmenopausal women taking the product for 3 years. Therefore 4 VTEs in this Climodien study with an enrollment of 1500 that extends for 18 months is comparable. In the lasofoxifene study, there were 10 VTEs and 35 strokes in a placebo group of approximately 2800 women over 3 years.

Study report number: B481

Protocol number: JPH01093

Study title: Climodien versus Kliogest for the Therapy of Postmenopausal Complaints with Particular Attention Paid to the Endometrial Safety- A Phase III, Double-Blind, Comparator-Controlled Trial

Study drugs:

Group A. Reference = 2 mg estradiol + 1 mg estriol / 1 mg NETA

Group B. Climodien 2/2 = 2 mg EV / 2 mg DNG

Group C. Climodien 2/3 = 2 mg EV / 3 mg DNG

Study period: Nov 1995 – Feb 1998

Study objectives: Assessment of menopausal symptoms by Kupperman Index

Study design: Multicenter, double-blind, randomized 3-arm Phase 3 study with a duration of 12 months

Study enrollment: 581 total (A = 196; B = 199; C = 186)

Study findings:

Efficacy findings

- Both doses of Climodien reduced menopausal symptoms but were not statistically different from the reference product.

Safety findings

- One subject taking the reference product (group A) died in a car accident
- Pertinent SAEs in Group A included: prolonged vaginal bleeding (2) and myocardial infarction (1)
- Pertinent SAEs in Group B included: myocardial infarction (1) and breast cancer (2)
- Pertinent SAEs in Group C included: breast cancer (1) and cholelithiasis

Study report number: A04539

Protocol number: 11641

Study title: Climodien versus Kliogest for the treatment of climacteric complaints with special attention paid to the mammary gland - a double-blind, randomized, prospective, comparator-controlled clinical trial of phase 3.

Study drugs:

- Climodien = 2 mg EV / 2 mg DNG
- Kliogest = 2 mg estradiol / 1 mg NETA

Study period: May 1998 – Oct 1999

Study objectives: Assess proliferation and receptor status of mammary gland

Study design: Single center, double-blind, randomized Phase 3 study with

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duration of 6 cycles of 28 days each
Study enrollment: 50 total (25 in each arm)

Study findings:

Efficacy findings

Both study medications induced increases in the percent of Ki67 positive cells as a marker of cell proliferation.

Safety findings

There were no deaths

There was 1 SAE in the Climodien group: thrombocytopenia

Study report number: A06788

Protocol number: 11481

Study title: Continuous combined estrogen-progestin regimen (Climodien) for the therapy of postmenopausal complaints with particular attention paid to antiandrogenic activity and voice function - a Phase III, double-blind, randomized clinical trial

Study drugs:

- Climodien = 2 mg EV / 2 mg DNG
- Kliogest = 2 mg estradiol / 1 mg NETA

Study period: Mar 1998 – Jul 2000

Study objectives: Assess anti-androgenicity of Climodien via voice function and android fat distribution

Study design: Double-blind, randomized, active controlled Phase 3 study with duration of 12 cycles of 28 days each

Study enrollment: 63 total (Climodien = 31; Kliogest = 32)

Study findings:

Efficacy findings

- No relevant differential effects were noted between the two regimens.

Safety findings

- There were no deaths in the study
- There were 2 SAEs in the Climodien arm: gastrointestinal infection (1) and arterial thrombosis left leg (1)
- There were 2 SAEs in the Kliogest arm: accidental injury (1) and migraine (1)

Study report number: A07979

Protocol number: 306387

Study title: A multicenter, prospective, randomized, double-blind, placebo-controlled, two-arm, Phase IV study over 6 months to investigate the influence of a continuous combined estrogen – progestin regimen containing 2 mg Estradiol valerate and 2 mg Dienogest (Climodien / Lafamme) on the fat distribution in otherwise healthy early postmenopausal women

Study drugs:

- Climodien = 2 mg EV / 2 mg DNG

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- Placebo

Study period: Jul 2002 – Aug 2004

Study objectives: Exploratory study on fat distribution asses by MRI

Study design: Multicenter, randomized, double-blind, placebo-controlled Phase 4 study with duration of 24 weeks

Study enrollment: 67 total (Climodien = 33, placebo = 34)

Study findings:

Efficacy findings

Some reduction in abdominal visceral fat was reported in the Climodien group but a statistically significant difference was not identified

Safety findings

There were no deaths reported in the study.

There were 3 subjects with SAEs in the Climodien arm: pulmonary embolism (1), migraine (1), nephrolithiasis (1).

Study report number: A08611

Protocol number: 12842

Study title: Follow-up of the study 97044: Continuous combined estrogen/progestin regimen (Climodien 1/2 versus Climodien 2/2) for therapy of postmenopausal signs and symptoms with special regard given to efficacy – a multicentric, double-blind, randomized, prospective, verum-controlled Phase III clinical study

Study drugs:

Climodien 2/2 = 2 mg EV / 2 mg DNG

Study period: Apr 1998 – Jan 2002

Study objectives: Allow subjects who completed 6-month main study to continue with Climodien 2 mg EV / 2 mg DNG

Study design: Multicenter, open follow-up Phase 3 study with duration up to 45 cycles of 28 days each

Study enrollment: 215 total

Study findings:

Efficacy findings

- Acceptability and continuing relief from menopausal symptoms were recorded.

Safety findings

- There was one death secondary to pancreatic cancer.
- Pertinent SAEs include: bile duct occlusion (1), breast cancer (3), pulmonary embolism (1), deep vein thrombosis (3), vaginal bleeding (2),

Study report number: A19976

Protocol number: 305222

Study title: Multicenter, controlled, randomized, open clinical study of acceptability and tolerability of a hormone replacement therapy without menses,

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Climodien versus a hormone replacement therapy with menses, Climen, administered to postmenopausal women over twelve 28-day cycles, relaying their previous ongoing sequential hormone replacement therapy

Study drugs:

Climodien = 2 mg EV / 2 mg DNG

Climen = 2 mg EV / 1 mg CPA

Study period: Jan 2002 – Oct 2003

Study objectives: Acceptability as determined by the continuation rate

Study design: Multicenter, controlled, randomized, open Phase 4 study with duration of 12 cycles of 28 days each

Study enrollment: 143 total (Climodien = 75; Climen = 68)

Study findings:

Safety findings

Climodien was associated with more metrorrhagia and breast pain than Climen. One SAE was reported for a subject in the Climen group (wrist fracture).

Study report number: B462

Protocol number: JPH00696

Study title: Effects of estradiol and dienogest on urinary markers of vascular function in postmenopausal women

Study drugs:

Climodien = 2 mg EV / 2 mg DNG

Estradiol valerate 2 mg

Study period: Feb 1997 – Aug 1997

Study objective: Study potential surrogate markers of vascular function

Study design: Open, randomized Phase 2 with duration of 3 months

Study enrollment: 56 total (Climodien = 29; EV = 27)

Study findings:

Efficacy findings

No differences were reported in the surrogate markers between the two treatment groups

Safety findings

There were no deaths.

There was 1 subject with 2 SAEs in the Climodien group; appendicitis and intestinal abscess

Study report number: A02343

Protocol number: 12842

Study title: Continuous combined estrogen/progestin regimen (Climodien 1/2 versus Climodien 2/2) for therapy of postmenopausal signs and symptoms with special regard given to efficacy – a multicentric, double-blind, randomized, prospective, verum-controlled Phase 3 clinical study carried out over 6 months in postmenopausal patients

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Study drugs:

Climodien 1/2 = 1 mg EV / 2 mg DNG

Climodien 2/2 = 2 mg EV / 2 mg DNG

Study period: Nov 1997 – May 1999

Study objectives: Assess menopausal symptoms

Study design: Multicenter, double-blind, randomized Phase 3 study with duration of 6 cycles of 28 days each

Study enrollment: 307 total (Climodien 1 /2 = 147; Climodien 2/2 = 160)

Study findings:

Efficacy findings

The percent of patients with improvement of number and severity of hot flushes was very similar in both treatment groups.

Safety findings

There were no deaths reported in the study.

There were 4 SAEs in the Climodien 1/2 arm: breast biopsy – benign cystic changes (1), depression (1), bladder surgery (1), psoriasis (1)

There were 8 SAEs in the Climodien 2/2 arm: cosmetic surgery (1), appendicitis (1), breast biopsy - fibroadenoma (1), fibroid uterus (1) pulmonary embolism (1), stroke (1), cholelithiasis (1), vaginal bleeding (1)

Study report number: A01625

Protocol number: 301920

Study title: Influence of a combined estrogen-progestin regimen (Climodien) on psychological well-being and quality of life in postmenopausal women. A multicenter, randomized, double-blind, placebo-controlled, two-arm trial over 24 weeks

Study drugs:

Climodien = 2 mg EV / 2 mg DNG

Placebo

Study period: May 2000 – Jan 2002

Study objectives: Assess psychological well being and cognitive function

Study design: Randomized, multicenter, double-blind, placebo-controlled Phase 2 study with duration of 6 cycles of 28 days each

Study enrollment: 129 total (Climodien = 65, Placebo = 64)

Study findings:

Efficacy findings

Improvement of postmenopausal depression was reported.

Safety findings

There were no deaths reported in the study.

There were 4 listed SAEs in the Climodien arm: breast cancer (1), libido decrease (1), thrombosis (2).

The most frequent AEs in the Climodien arm were breast pain / breast engorgement (15.4%) and genital bleeding (4.6%).

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Study report number: A05358

Protocol number: JPH01093

Study title: Climodien for the Therapy of Post-Menopausal Complaints - a Phase 3, Open, Non-Controlled, Follow-Up Trial. Final Report after 36 Months of Follow-up Treatment after the End of the Double-Blind Phase III Trial

Study drugs:

Climodien = 2 mg EV / 2 mg DNG

Study period: Dec 1996 – Mar 2001

Study objectives: Assess endometrial safety of Climodien

Study design: Open, non-controlled Phase 3 study with duration of 36 months

Study enrollment: 318

Study findings:

Safety findings

The incidence of hyperplasia or more severe endometrial outcome was 0.36%.

There were no deaths reported.

Pertinent SAEs in this study include growing leiomyomata of uterus (1), breast cancer (3), vaginal bleeding (1), myocardial infarction (2), endometrial hyperplasia (1), adenocarcinoma of endometrium (1) gallbladder disease (3), thrombosis (1).

Study report number: B596

Protocol number: JPH01595

Study title: Influence of a Combined Estrogen-Progestin Regimen (Climodien) versus Estrogen Alone on Postmenopausal Sleep Disorders A Phase III, Double-blind, Placebo-controlled Clinical Trial

Study drugs:

- Treatment A = 2 mg EV / 3 mg DNG
- Treatment EV = 2 mg EV
- Placebo

Study period: Nov 1995 through Jun 1998

Study objectives: Comparative study of clinically relevant sleep disorders

Study design: Double-blind, placebo-controlled, comparative, randomized, 3-arm Phase 3 study with duration of 2 months

Study enrollment: 55 total (18 each for treatment A & EV, 19 for placebo)

Study findings:

Efficacy findings

- Climodien was reported to significantly ameliorate subjective quality of sleep disorders but only marginally improved objective parameters including the primary variable, nocturnal wakefulness time.

Safety findings

- There were no deaths reported.
- For treatment A, there were 2 SAEs; removal of meniscus (1), removal of metal nail (1).

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- For treatment EV, there was 1 SAE; atrial fibrillation (1).

Study report number: A11355

Protocol number: 305510

Study title: A multicenter, prospective, randomized, double-blind, placebo-controlled study to investigate the efficacy of a continuous combined preparation containing 1 mg Estradiol valerate and 2 mg Dienogest on hot flushes in postmenopausal women

Study drugs:

- Climodien 1/2 = 1 mg EV / 2 mg DNG
- Placebo

Study period: Nov 2001 through Oct 2002

Study objectives: Evaluate for efficacy for hot flushes

Study design: Multicenter, prospective, randomized, double-blind, placebo-controlled Phase 3 study with duration of 3 cycles

Study enrollment: 324 total (162 in each arm)

Study findings:

Efficacy findings

A significant reduction of moderate and severe hot flushes was reported compared to placebo.

Safety findings

- There were no deaths reported in the study.
- There were no SAEs in the Climodien group.
- The most frequent AEs in the Climodien group were breast pain (4.4%), urine abnormal (1.9%) and hypertension (1.9%).

Study report number: A04274

Protocol number: 302320

Study title: A randomized, double-blind, multicenter study to investigate safety and metabolic effects of a continuous-combined estradiol valerate / dienogest preparation (Climodien 1/2) compared to Activelle™ in postmenopausal women over 13 cycles 28 days each

Study drugs:

- Climodien 1/2 = 1 mg EV / 2 mg DNG
- Activelle = 1 mg estradiol / 0.5 mg NETA

Study period: Feb 2000 through Dec 2001

Study objectives: Comparison of therapies in regard to metabolic and hemostatic parameters, bleeding pattern and safety

Study design: Multicenter, multinational, prospective, randomized, double-blind, two-arm comparative study with duration of 13 cycles

Study enrollment: 315 total (Climodien = 159; Activelle = 156)

Study findings:

Efficacy findings

- Both drug regimens reduced HDL cholesterol during treatment but

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- somewhat less with Climodien.
- Other analyses (other lipids, hemostatic parameters, bleeding patterns) were similar between the groups

Safety findings

- There were no deaths reported in the study.
- There were 6 subjects with SAEs in the Climodien group; cerebrovascular ischemia (1), fracture (1), DVT (1), ear canal exostosis (1), cholelithiasis (1) and benign breast neoplasm (1).
- There were 5 subjects with SAEs in the Activellev group; cervical uterine polyp (1), benign breast neoplasm (1), cholecystitis (1), menorrhagia (1), and hypertension / tachycardia (1).
- The most frequent AEs in the Climodien group were hot flushes (10.1%), breast pain (8.8%) and flu-like symptoms (7.5%).

Study report number: A01000

Protocol number: 302321

Study title: A multicenter, prospective, randomized, double-blind, placebo-controlled study to investigate the efficacy of a continuous-combined estradiol valerate/dienogest preparation in postmenopausal women

Study drugs:

- Climodien = 1 mg EV / 2 mg DNG
- Placebo

Study period: Dec 1999 through Oct 2000

Study objectives: Prove efficacy of continuous combined HRT with a lower dose of estradiol valerate

Study design: Multicenter, prospective, randomized, double-blind, placebo-controlled study with duration of 12 weeks

Study enrollment: 140 Total (Climodien 1/2 – 70, Placebo – 70)

Study findings:

Efficacy findings

- There was reduction in hot flushes but also a strong placebo response and thus superiority over placebo could not be shown.

Safety findings

- There were no deaths reported in the study.
- There was one serious adverse event (breast cancer) in the placebo group.
- Vaginal bleeding (18.6%) and headache (4.3) were the most frequent adverse events in the Climodien group.

5.3.6.2 Clinical Studies of a Combination Product Containing Ethinyl Estradiol and Dienogest

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There were no safety concerns identified in the following Phase 1 studies of Valette (0.03 mg EE / 2 mg DNG):

- B712 (JPH03394) = Single administration and repeat dose
- AV41 (98003) = Small comparative carbohydrate metabolism study

Study report number: A42449

Protocol number: 310723

Study title: Monocenter, open-label, randomized study to determine the ovulation inhibitory effect of the combined oral contraceptives SH T04769G (0.015 mg Ethinyl estradiol and 1.5 mg Dienogest in a modified release medicinal product) and SH D00659AF (0.03 mg Ethinyl estradiol and 2.0 mg Dienogest), applied for two treatment cycles to 60 healthy female volunteers

Study drugs:

Test 1 = 0.015 mg EE / 1.5 mg DNG

Test 2 = 0.030 mg EE / 2.0 mg DNG

Study period: Apr 2007- Dec 2007

Study objectives: Ovulatory inhibition study

Study design: Single center, randomized, open, uncontrolled Phase 2 study with duration of 2 cycles of 28 days each

Study enrollment: 60 total (30 in each arm)

Study findings:

Efficacy findings

The test 1 group was reported to have less ovulatory inhibition than test 2.

Safety findings

There were no deaths or SAEs reported.

Study report number: A44564

Protocol number: JPH MM 02

Study title: A prospective, open-label, multicenter, uncontrolled study on the contraceptive efficacy, safety, and cycle stability of Celimona in healthy women in Poland – follow-up

Study drugs:

Celimona (Valette) = 0.03 mg EE / 2 mg DNG

Study period: Oct 1997 – Jul 1999

Study objectives: Contraceptive effectiveness

Study design: Open, uncontrolled Phase 3 study with duration up to 22 cycle of 28 days each

Study enrollment: 266

Study findings:

Efficacy findings

There were no pregnancies reported.

Safety findings

There were no deaths reported in the study.

There was 1 SAE: salpingitis.

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The most frequently reported adverse events were breast tenderness (3.5%), headache (2.2%) and gastric complaints (1.3%).

Study report number: A02256

Protocol number: JPH00693

Study title: MP2000/Micropill (Valette)

Study drugs:

Valette = 0.03 mg EE / 2 mg DNG

Study period: Sep 1993 – Aug 1995

Study objectives: Contraceptive effectiveness

Study design: Open, uncontrolled, multicenter Phase 3 study with duration up to 22 cycles of 28 days each

Study enrollment: 2290

Study findings:

Efficacy findings

The adjusted Pearl Index was 0.21.

Safety findings

There were no deaths reported in the study.

Pertinent SAEs included: ovarian cyst (6), depression (1), gallbladder/ biliary disease (2), cerebrovascular disorder with speech disturbance and numbness of right arm (1) thrombophlebitis, leg (2), pulmonary embolism (1).

Study report number: B854

Protocol number: JPH03294

Study title: The influence of Valette on specific endocrinological and ultrasonographic parameters

Study drugs:

Valette = 0.03 mg EE / 2 mg DNG

AP 2000 = 0.03 mg EE / 2 mg CMA

Study period: Dec 1995 – Jul 1997

Study objectives: Endocrine and sonographic evaluation

Study design: Randomized, double-blind, single center Phase 4 study with duration of 6 cycles of 28 days each

Study enrollment: 57 total (Valette = 28; CMA = 25)

Study findings:

Efficacy findings

- Both combination products were reported to decrease androstenediol and testosterone levels. Both were reported to decrease endometrial thickness and follicle maturation.

Safety findings

- There were no deaths or SAEs.

Study report number: B848

Protocol number: JPH MM 01 CZ

Study title: A prospective, open-label, multicenter, uncontrolled, phase 3 study

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over 12 cycles of the contraceptive efficacy, cycle stability, adverse events and dermatological effects of Celimona in healthy women in the Czech Republic.

Study drugs:

Celimona (Valette) = 0.03 mg EE / 2 mg DNG

Study period: Oct 1996 – May 1998

Study objectives: Contraceptive effectiveness

Study design: Open, multicenter, uncontrolled Phase 3 study with duration of 12 cycles of 28 days each

Study enrollment: 557

Study findings:

Efficacy findings

The Pearl Index was reported as 0.20.

Safety findings

There were no deaths.

There were 5 SAEs; traffic accident (2), bronchitis (1), joint swelling (1), pneumonia (1).

The most frequently reported adverse events were breast tenderness (19%), headache (18%) and gastric complaints (11%).

Study report number: A45697

Protocol number: 302091

Study title: Multicentric study to assess the efficacy, cycle control and tolerability of the association of Dienogest 2 mg plus 30 mcg of ethinyl estradiol as an oral contraceptive.

Study drug:

Valette = 0.03 mg EE / 2 mg DNG

Study period: Oct 1999 – May 2001 (early termination)

Study objectives: Contraceptive efficacy and cycle control

Study design: Multicenter, open Phase 3 study

Study enrollment: 230 (all Hispanic)

Study findings:

Efficacy findings

None reported.

Safety findings

There were no deaths or SAEs reported.

Study report number: A30223

Protocol number: 306903

Study title: Comparative, prospective, multi-center, open, randomized study to investigate bleeding patterns, metabolic effects, contraceptive efficacy, acceptance, and safety of an oral contraceptive containing 0.03 mg ethinyl estradiol and 2 mg dienogest, in two different regimens of intake (four extended cycles of 84 days each versus the conventional regimen of 21 days) in healthy

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volunteers

Study drugs:

Valette = 0.03 mg EE / 2 mg DNG (extended cycle)

Valette = 0.03 mg EE / 2 mg DNG

Study period: Jun 2003 – Feb 2005

Study objectives: Investigate extended use

Study design: Comparative, prospective, multi-center, open, randomized Phase 3 with a duration of 1 year.

Study enrollment: 1315 total (659 extended use; 656 conventional use)

Study findings:

Efficacy findings

Both regimens had similar contraceptive efficacy (PI of 0.489 in conventional regimen and 0.495 in the extended regimen).

Safety findings

- There was one death in a 22 year old taking the extended regimen. The death arose from complications of myocarditis.
- There were 6 subjects with SAEs in the Valette conventional arm; enteritis (1), appendicitis (1), fracture (1), bone disorder post fracture (1), missed abortion (1) and ovarian cyst.
- There were 7 subjects with SAEs in the Valette extended arm; urinary tract obstruction (1), hearing loss (1), autoimmune thyroiditis (1), cholelithiasis (1), appendicitis (2), and dislocated knee (1).
- In the conventional regimen, the most frequent AEs were: nasopharyngitis (5.3%); headache (4.6%) and breast pain (4.1%).
- In the extended regimen, the most frequent AEs were: breast pain (7.6%); nasopharyngitis (3.8%) and vaginal candidiasis (3.8%).

Study report number: A28501

Protocol number: 307760

Study title: Multicenter, double-blind, double-dummy, randomized parallel group study to evaluate the safety and efficacy of 0.030 mg ethinyl estradiol / 2 mg dienogest for 6 treatment cycles in female patients with papulopustular acne in comparison to 0.035 mg ethinyl estradiol / 2 mg cyproterone acetate and placebo

Study drugs:

- Valette = 0.03 mg EE / 2 mg DNG
- Diane = 0.035 EE / 2 mg CPA
- Placebo

Study period: Mar 2004 – May 2005

Study objectives: To show superiority of Valette over placebo in treatment of acne. To show non-inferiority of Valette compared to Diane

Study design: Multicenter, double-blind, double-dummy, randomized parallel group Phase 3 study with duration of 6 cycles of 28 days each

Study enrollment: 1326 total (525 for Valette; 537 for Diana; 264 for Placebo)

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Study findings:

Efficacy findings

- Valette was reported to be non-inferior to Diane 35 and significantly more effective than placebo in the treatment of acne

Safety findings

- There were no deaths reported in the study.
- There were 3 subjects with SAEs in the Valette arm; ischemic stroke (1), cholelithiasis (1) and salpingitis (1).
- There was 1 subjects with an SAE in the Diane arm; cervical dysplasia (1)
- The most frequent adverse events for the Valette group were headache (5.3%) and nausea (4.2%).

Study report number: A07062

Protocol number: 301180

Study title: Multicenter, double-blind, randomized parallel group study on efficacy of 0.03 mg ethinyl estradiol and 2 mg dienogest in comparison to triphasic ethinyl estradiol and norgestimate over six cycles in patients with acne papulopustulosa

Study drugs:

- Valette = 0.03 mg EE / 2 mg DNG
- Pramino = 0.035 EE / triphasic NGM (0.180 mg – 0.215 mg – 0.250 mg)

Study period: Sept 1999 – Nov 2001

Study objectives: Comparative non-inferiority study for therapy of mild to moderate acne

Study design: Multicenter, double-blind, randomized parallel group comparison Phase 3 study with duration of 6 cycles of 28 days each

Study enrollment: 1041 total (527 for Valette; 514 for Pramino)

Study findings:

Efficacy findings

- The non-inferiority of Valette compared to Pramino was reported to be demonstrated for the acne efficacy variables, with a non-inferiority margin of 10%.

Safety findings

- There were no deaths reported in the study.
- There were 4 SAEs in the Valette arm; fibroid degeneration (1), infection (2), pneumonia (1).
- There were 7 SAEs in the Pramino arm; depression (1), gastroenteritis (1), schizophrenic reaction (1), diarrhea (1), Bartholin cyst (1), pyelonephritis (1) surgery - lithotripsy (1).
- The most frequent adverse events for the Valette group were headache (8.2%) and nausea (8.0%).

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Study report number: B846

Protocol number: 97064

Study title: Trial to investigate the antiandrogenic efficacy of Valette in comparison to placebo by evaluation of the number of androgen receptors in the interscapular region of female acne patients before and after treatment

Study drugs:

- Valette = 0.03 mg EE / 2 mg DNG
- Placebo

Study period: Nov 1997 – Jun 1999

Study objectives: Evaluation of the number of androgen receptors

Study design: Monocentric, double-blind, randomized, placebo-controlled, parallel-group Phase 2 study with duration of 3 cycles of 28 days each

Study enrollment: 16 total (8 in each arm)

Study findings:

Efficacy findings

- The number of androgen receptors did not differ after administration of Valette as compared to placebo.

Safety findings

- There were no deaths or SAEs.

Study report number: B605

Protocol number: 300716

Study title: Effects of two oral contraceptives (OC) on potential markers of vascular function in women of reproductive age. Open randomized, parallel-group study

Study drugs:

- Valette = 0.03 mg EE / 2 mg DNG
- Neolest = 0.03 mg EE / 0.06 mg NETA

Study period: Feb 1997 – Jul 1997

Study objectives: Comparative study of effect on endothelial markers of vascular function

Study design: Open-label, randomized, parallel-group Phase 4 study with duration of 10-11 weeks

Study enrollment: 63 total (33 for Valette; 30 for Neorlest)

Study findings:

Lab findings

- The progestins of the 2 contraceptives Valette and Neorlest (DNG and NETA, respectively) do not substantially differ in influencing the urinary levels of endothelial markers of vascular function, if not for a positive effect of Valette on the PGF1 α /DTHxB ratio. Thus, there is a possible slight advantage for DNG according to the Applicant.

Safety findings

- There were no deaths or SAEs.

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Gerald Willett, M.D.
NDA 22-252 (EV/DNG)

Study report number: B503

Protocol number: JPH01293

Study title: Trial to investigate the anti-androgenic effect of MP2000 / micropill (ethinyl estradiol / dienogest combination) versus P21 (ethinyl estradiol / cyproterone acetate combination)

Study drugs:

MP2000 = 0.03 mg EE / 2 mg DNG

P21 = 0.036 mg EE / 2 mg cyproterone acetate

Study period: May 1994 – Jul 1997

Study objectives: Comparative study of anti-androgenic effects

Study design: Randomized, double-blind, multicenter Phase 3 study with duration of 7 cycles of 28 days each

Study enrollment: 40 total (20 in each arm)

Study findings:

Efficacy findings

There was no statistically significant difference between the MP2000 and the P21 groups regarding to the clinical improvement of acne conditions, the hormonal changes and the morphological/histological diminishing of sebaceous gland. Both medications were of equal value in respect to the antiandrogenic potency in female acne patients.

Safety findings

There were no deaths or SAEs reported.

Study report number: B461

Protocol number: JPH02094

Study title: Monocentric Study to examine the influence of MP 2000/micropill (Valette) (ethinyl estradiol/Dienogest combination) on the immune system versus an ethinyl estradiol/Desogestrel combination

Study drugs:

Valette = 0.03 mg EE / 2 mg DNG

Lovelle = 0.02 mg EE / 0.150 mg DSG

Study period: Jun 1994 – Sept 1994

Study objectives: Comparative study on the effect on humoral and cell mediated response

Study design: Open, randomized, two-arm, monocentric Phase 3 study with duration of 1 cycle of 28 days

Study enrollment: 31 total (15 for Valette arm; 16 for Lovelle arm)

Study findings:

Efficacy findings

There was no reported evidence in this study for an immunosuppressive effect of either product.

Safety findings

There were no deaths or serious adverse events reported.

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Gerald Willett, M.D.
NDA 22-252 (EV/DNG)

Study report number: A02262

Protocol number: JPH00392

Study title: Influencing Cycles with Certostat 30 (Valette)

Study drug: Certostat 30 (Valette) = 0.03 mg EE / 2 mg DNG

Study period: Oct 1992 through Oct 1994

Study objectives: Contraceptive efficacy, cycle control and safety

Study design: Multicentric, randomized, open, Phase 3 with 12 treatment cycles

Study enrollment: 97

Study findings:

Efficacy findings

No pregnancies were reported.

No postovulatory increases in progesterone noted in the treatment cycles.

Safety findings

There were no deaths in the study.

There was a single SAE reported (deep vein thrombosis in 5th treatment cycle).

Study report number: A01835

Protocol number: JPH03796/ME97603

Study title: Uncontrolled clinical study to investigate a monophasic oral contraceptive consisting of 17 β -estradiol valerate, ethinyl estradiol, and dienogest (MP10) with regard to ovulation inhibition and residual ovarian activity

Study period: Jan 1998 through Sep 1998

Study objectives: Evaluate ovulation inhibition

Study design: Uncontrolled, 1-arm study

Study enrollment: 22

Study findings:

Efficacy findings

Not reported

Safety findings

- There were no deaths.
- There were two SAEs, bacterial epipharyngitis (1) and pneumonia (1).

Study report number: A01834

Protocol number: JPH05595

Study title: Open phase III study for testing the contraceptive efficacy, cycle control and tolerability of a combination containing dienogest, ethinyl estradiol, and estradiol valerate

Study drug: MP 10 = 0.01 mg EE + 2.0 mg EV / 2 mg DNG

Study period: Oct 1996 through Sept 1999

Study objectives: Contraceptive efficacy

Study design: Uncontrolled, open, multicenter study with duration of 18 treatment cycles

Study enrollment: 1911

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Study findings:

Efficacy findings

- Not reported

Safety findings

- There were no deaths.
- Serious adverse events (considered probably related to study drug by this reviewer) include: deep vein thrombosis (2), retinal vein thrombosis (1), ovarian cyst (4), migraine (1), cholelithiasis (1).

Study report number: A00777

Protocol number: JPH00295

Study title: Randomized study for testing a novel combination of estrogens and dienogest for oral contraception

Study drugs:

Product A = 0.01 EE + 1 mg EV / 2 mg DNG

Product B = 0.01 EE + 2 mg EV / 2 mg DNG

Study period: Jul 1995 through Jul 1996

Study objectives: Primary = cycle control, secondary = contraceptive efficacy and safety

Study design: Randomized, open, two-arm-comparative, multicenter study with duration of 6 treatment cycles

Study enrollment: 115

Study findings:

Efficacy findings

The dosage of EE can be reduced if supplemented by 1 or 2 mg estradiol valerate.

In terms of cycle control, supplementation with 2 mg EV is more suitable than 1 mg EV.

No pregnancies occurred with either regimen.

Safety findings

- There were no deaths reported in the study.
- There were no VTEs reported in the study.
- There were 3 SAEs reported – lymphadenopathy (1), hepatitis (1), and depression (1).

Study report number: A06574

Protocol number: JPH-MM-01 (CZ)

Study title: Follow-up study for prospective, open-label, multicenter, uncontrolled, phase 3 study after 12 cycles of the contraceptive efficacy, cycle stability and adverse events of Celimona in healthy women in the Czech Republic.

Study drug: Celimona = 0.03 mg EE / 2 mg DNG

Study period: Oct 1997 through Aug 1999

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Study objectives: Primary = contraceptive effectiveness, secondary = cycle control and adverse event profile

Study design: Prospective, open-label, multicenter, uncontrolled, phase 3 trial over maximally 23 menstrual cycles.

Study enrollment: 393

Study findings:

Efficacy findings

The adjusted Pearl Index was 0.0.

Safety findings

- There were no deaths reported in the study.
- There were no VTEs reported in the study.
- There were 4 SAEs reported – adnexitis (1), malleolar fracture (1), bronchitis (1) and tonsillitis (1).
- Headache (10.2%) and breast tenderness (6.4%) were the most frequently report common adverse events.

Study report number: A02344

Protocol number: 97087

Study title: Double-blind, controlled, randomized multicenter study to investigate the influence of dienogest-containing oral contraceptives with different estrogen doses on hemostasis and other important metabolic parameters

Study Drugs:

- Valette = 0.03 mg EE / 2 mg DNG
- MP10 = 0.01 EE + 2 mg EV / 2 mg DNG
- MP02 = 0.02 EE / 2 mg DNG
- Leios = 0.02 EE / 0.1 mg LNG

Study period: Mar 1998 through Jun 1999

Study objectives: To investigate the influence of dienogest-containing oral contraceptives on hemostasis, lipids, and other metabolic parameters

Study design: Double-blind, controlled, comparative, randomized, multicenter clinical study

Study enrollment: 99

Study findings:

Lab findings

- All OC formulations induced an enhancement of both the pro-coagulant and fibrinolytics activity.
- In terms of lipid metabolism, DNG-containing OCs appeared to exert a more favorable profile on the lipid pattern.

Safety findings

- There were no deaths reported in the study.
- There were no VTEs reported in the study.
- There was one serious adverse event of appendectomy (Leios group).

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Gerald Willett, M.D.
NDA 22-252 (EV/DNG)

Study report number: A02261

Protocol number: JPH00395

Study title: Uncontrolled Clinical Trial on the Inhibition of Ovulation and the Determination of the Ovarian Residual Activity of the Oral Contraceptive Valette

Study drug:

Study period: Aug 1995 through May 1996

Study objectives: Determination of inhibition of ovulation and modulation of ovarian function by Valette in females with normal ovulatory cycles

Study design: Ovulation inhibition study for 3 cycles

Study enrollment: 20

Study findings:

Efficacy findings

- Valette inhibited ovulation during the 3 treatment cycles studied.

Safety findings

- There were no deaths reported in the study.
- There were no VTEs reported in the study.
- There was one serious adverse event of abdominal pain.

Study report number: A02260

Protocol number: JPH01193

Study title: Monocentric Study to Investigate the Influence of MP2000/Micropill (Ethinyl Estradiol/Dienogest Combination) on the Lipid and Coagulation Status versus an Ethinyl Estradiol/Desogestrel Combination

Study dosages:

MP2000 = 21 tablets of 0.03 mg EE / 2 mg DNG + 7 tablet free days

Lovelle = 21 tablets of 0.02 mg EE / 0.15 mg DSG + 7 tablet free days

Study period: Jun 1994 through Nov 1995

Study objectives: To determine the influence of the dienogest and the desogestrel containing contraceptives on lipids and coagulation parameters

Study design: Controlled, randomized, double-blind, two-arm, monocentric study with a treatment duration of 7 cycles

Study enrollment: 40

Study findings:

Comparative findings

Both products were similar in regard to ovulation inhibition, lipid and coagulation changes.

Safety findings

- There were no deaths reported in the study.
- There were no VTEs reported in the study.
- In the EE/DNG study arm there was one SAE – appendicitis.

Study report number: A01294

Protocol number: 302089

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NDA 22-252 (EV/DNG)

Study title: Multicenter, double-blind, double-dummy, randomized, parallel group study to compare the change in serum endocrine parameters over 6 treatment cycles of oral administration SH D 659 A versus oral administration SH 7.1155 A (Microgynon 30) in contraceptive use in 120 female volunteers.

Study dosages:

- SH D 659 A = 0.03 mg ethinyl estradiol, 2 mg dienogest (DNG) 21 tablets + 7 tablet free days
- SH 7.1155 A (Microgynon 30) = 0.03 mg ethinyl estradiol, 0.15 mg levonorgestrel (LNG) 21 tablets + 7 tablet free days

Study period: Oct 1999 through Jun 2001

Study objectives: To compare the two COCs with respect to their effect on serum endocrine parameters, lipid profile, cycle control, contraceptive reliability and safety parameters

Study design: Multicenter, double-blind, double-dummy, randomized, parallel group study

Study enrollment: 121

Study findings:

Lab findings

- A statistically significant difference was seen between the two treatment groups, with those subjects receiving SH D 659 A showing a greater increase in SHBG compared to SH 7.5511 A.
- SH D 659 A showed a favorable trend overall in increasing HDL and reducing LDL levels.

Safety findings

- There were no deaths reported in the study.
- There were no VTEs reported in the study.
- In the EE/DNG study arm there was one SAE – epigastric pain.

Study report number: A1028

Study title: A prospective, open-label, multicenter, uncontrolled, phase 3 study over 12 cycles of the contraceptive efficacy, cycle stability, adverse events and dermatological effects of Celimona in healthy women in Poland.

Dosage: Celimona = 21 tablets with 0.03 mg EE / 2 mg DNG

Study Period: Nov 1996 through Jul 1998

Study objectives: Primary = contraceptive effectiveness; Secondary = cycle control, adverse event profile, dermatological benefits

Study design: prospective, open-label, multicenter, uncontrolled, phase III study over 12 menstrual cycles.

Study enrollment: 431

Study findings:

Efficacy findings

- The adjusted Pearl Index was 0.0.
- Subjects showed improvement with skin blemishes, hair greasiness and acne.

Safety findings

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- There were no deaths.
- There were no thromboembolic events.
- The serious events included ovarian cyst (2), bronchitis (1) and gastric inflammation (1).

Study report number: A00827

Protocol number: JPH05695

Study title: Placebo controlled double blind phase IV study to investigate the influence of the oral contraceptive Valette on hemostasis

Dosage: Valette = 21 tablets with 0.03 mg EE / 2 mg DNG

Study period: Mar 25, 1996 through Jul 11, 1996

Study objectives: Determination of changes in hemostatic parameters

Study design: Assessment of coagulation and fibrinolysis parameters during pill-free pre-cycle and one treatment cycle.

Study enrollment: 36

Study findings:

Laboratory findings

- Valette was found to have a balanced effect on hemostasis with stimulation of coagulant, anti-coagulant and fibrinolytics activity.

Safety findings

- The most frequently reported adverse events for Valette were breast pain, headache/migraine and acne. The only serious adverse event in the study was a hospitalization for measles (subject taking Valette).

5.3.6.3 Clinical Studies of Dienogest Alone

All studies below are European studies, not being conducted under a FDA IND.

Study report number: A39700

Protocol number: 307059

Study title: A multicenter, open, one-arm study to investigate the safety and efficacy of daily oral administration of 2 mg Dienogest tablets (Visanne1 / SH T00660AA) for the treatment of endometriosis over 52 weeks (European study)

Study drugs:

Visanne = 2 mg DNG

Study period: Jul 2004 – Nov 2007

Study objectives: Safety and efficacy (endometriosis treatment)

Study design: Multicenter, open Phase 3 study with duration of 52 weeks

Study enrollment: 168

Study findings:

Efficacy findings

(b) (4)

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Safety findings

There were no deaths in the study. There were 3 SAEs (cholelithiasis, depression and sinusitis).

Study report number: A32473

Protocol number: 307041

Study title: A multicenter, double-blind, randomized, placebo-controlled, parallel-group study to investigate the efficacy and safety of daily oral administration of 2 mg Dienogest tablets (Visanne1 / SH T00660AA) for the treatment of endometriosis over 12 weeks (European study)

Study drugs:

- Visanne = 2 mg DNG
- Placebo

Study period: Mar 2004 – Sep 2006

Study objectives: To assess superiority of Visanne over placebo for treatment of endometriosis associated pelvic pain (primary variable assessed by visual analog scale and intake of rescue medication)

Study design: Multicenter, double-blind, randomized, placebo-controlled Phase 3 study with duration of 12 weeks

Study enrollment: 198 total (Visanne = 102; Placebo = 96)

Study findings:

Efficacy findings

[REDACTED] (b) (4)

Safety findings

There were no deaths or SAEs reported in the study.

Study report number: A05436

Protocol number: 12302

Study title: Open, randomized Phase II study to compare dienogest with leuprorelin acetate for efficacy as pretreatments in preparation of endometrial ablation (European study)

Study drugs:

- Dienogest 2 mg
- Leuprorelin acetate (LA) 3.75 mg

Study period: Feb 1998 – Apr 1999

Study objectives: To compare the efficacy of DNG with that of LA in preparing the endometrium for ablation.

Study design: Open, randomized, multicenter Phase 2 study with duration of 2 cycles of 28 days each

Study enrollment: 75 total (DNG = 37; LA = 38)

Study findings:

Efficacy findings

- [REDACTED] (b) (4)

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(b) (4)

Safety findings

- There were no deaths or SAEs in the study.

Study report number: AU19

Protocol number: 13861

Study title: A multicenter, open-label, controlled, randomized, parallel-group study to investigate the efficacy and safety of daily oral administration of 2 mg dienogest versus intramuscular administration of 3.75 mg leuporelin acetate every 4 weeks in the treatment of symptomatic endometriosis over 24 weeks (European study)

Study drugs:

Dienogest 2 mg daily

Leuporelin acetate 3.75 mg q 4 week

Study period: Dec 1998 – Apr 2001

Study objectives: To demonstrate non-inferiority of DNG compared to LA in treatment of endometriosis (primary variable = change in pelvic pain as assessed by visual analog scale)

Study design: Multicenter, open-label, controlled, randomized, parallel-group Phase 3 study with duration of 24 weeks

Study enrollment: 248 total (DNG = 120; LA = 128)

Study findings:

Efficacy findings

(b) (4)

Safety findings

- There were no deaths in the study.
- There were 5 SAEs in the dienogest arm; hysterectomy for pain (1), pelvic pain (1), depression (1), abdominal pain (1), kidney calculus (1).
- There was 1 SAE in the LA arm; joint disorder.
- The most frequently observed AEs in the DNG group were headache (20.8% of the women), flu syndrome (10%), abdominal pain (9.2%), weight gain (7.5%), and depression (6.7%).

Study report number: B567

Study title: A multicenter, open, randomized, controlled clinical trial to compare the efficacy of Dienogest (1 mg twice daily) versus Decapeptyl (R) 3.75 (one i.m. injection every 4 weeks) administered for 16 weeks following operative laparoscopy in 2 parallel groups of 52 patients presenting with endometriosis (European study)

Study drugs:

Dienogest 1 mg BID

Decapeptyl 3.75 mg IM injection every 4 weeks

Study period: Jun 1994 – July 1998

Study objectives: Compare the efficacy of the two products for endometriosis

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Study design: Multicenter, open, randomized, parallel-group Phase 3 study with duration of 4 months (laparoscopic assessment)

Study enrollment: Total 142 (74 – DNG; 68 – Decapeptyl)

Study findings:

Efficacy findings

- [REDACTED] (b) (4)

Safety findings

- There were no deaths in the study.
- There was 1 SAE in the dienogest arm; ureteral stenosis.
- There was 1 SAE in the Decapeptyl arm; abdominal pain (hospitalization).
- The most frequently reported adverse events for dienogest users were spotting (61.6%), headache (24.7%) and metrorrhagia (23.3%).

Study report number: A01177

Study title: Treatment of Endometriosis with Dienogest. Clinical Phase 2 Trial (European study)

Study drug: Dienogest 1 mg BID

Study period: 1980 - 1981

Study objectives: Efficacy in treatment of endometriosis

Study design: Laparoscopic-based study design

Study enrollment: 104

Study findings:

Efficacy findings

- [REDACTED] (b) (4)

Safety findings

- There were no reports of deaths or serious adverse events.
- The most frequent side effects for the dienogest treated subjects were loss of libido (21.2%), fatigue (9.6%) and increased appetite (8.7%).

Study report number: A01176

Study title: Treatment of Endometriosis with Dienogest (2 mg) - Phase III Clinical Trial – Open comparison versus Norethisterone Acetate (10 mg) (European study)

Study drugs:

- Dienogest 2 mg
- Norethisterone acetate 10 mg

Study period: 1983 through 1987

Study objectives: Efficacy of treatment of endometriosis

Study design: Controlled, open, multicenter

Study enrollment: 167 total (119 DNG, 48 NETA)

Study findings:

Efficacy findings

- [REDACTED] (b) (4)

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(b) (4)

Safety findings

- There were no reports of deaths or serious adverse events.
- The most frequent side effects for the dienogest treated subjects were increased appetite (37.0%) and loss of libido (33.6%).

Study report number: A02266

Protocol number: JPH03992

Study title: Dienogest for Treatment of Endometriosis Stages I, II and III
(European study)

Study drug: Dienogest 1, 2 or 4 mg per day

Study period: Oct 1993 through Jan 1996

Study objectives: Laparoscopic improvement in endometriosis

Study design: Open, randomized, multicenter comparative study with 24 week duration of treatment (dose finding Phase 2)

Study enrollment: 68

Study findings:

Efficacy findings

-

(b) (4)

Safety findings

- No deaths were reported in the study.
- Two serious adverse events were reported – ovarian cyst (2).
- The most common adverse events were acne (32%), hot flushes (23.5%), abdominal pain (13%) and breast pain (13%).

6 Review of Efficacy

Efficacy Summary

6.1 Contraceptive Indication

6.1.1 Methods

The key sections from NDA 22-252 regarding contraceptive efficacy were found in:

- Clinical Overview
- Summary of Clinical Efficacy - OC
- Integrated Summary of Efficacy - OC
- Report A35179 (Protocol 306660 - Europe)
- Report A39818 (Protocol 304742 – North America)
- Report A35644 (Protocol 304004 - Europe)

6.1.2 Demographics

Table 90 provides pooled demographic data on age and BMI in the pivotal contraceptive trials for EV/DNG.

Table 90: Pooled Analysis Contraceptive Studies (306660, 304742, 304004) – Age and BMI - FAS

	Age Groups	Pooled Data – EV/DNG
Total number of women	18 – 50 years	2266
	18 – 35 years	1687
	36 – 50 years	579
Age (mean years)	18 – 50 years	29.6 ± 8.0 years
	18 – 35 years	25.8 ± 4.6 years
	36 – 50 years	41.0 ± 3.6 years
BMI	18 – 50 years	23.0 ± 3.0 kg/m ²
	18 – 35 years	22.7 ± 3.0 kg/m ²
	36 – 50 years	23.8 ± 2.8 kg/m ²

EV/DNG = estradiol valerate / dienogest

Source: Summary of Clinical Efficacy (OC) Text table 8, page 43 of 132

Table 91 provides pooled ethnicity data from the pivotal contraceptive trials.

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**Table 91: Pooled Analysis Contraceptive Studies (306660, 304742, 304004)
 – Ethnicity - FAS**

	Pooled Data – EV/DNG
Total (Age 18-50 years)	2266
Caucasian	2134
Black	37
Hispanic	67
Asian	21
Other	7
Total (Age 18-35 years)	1687 of 2266 (74.4%)
Caucasian	1559 of 1687 (92.4%)
Black	37 of 1687 (2.2%)
Hispanic	67 of 1687 (4.0%)
Asian	17 of 1687 (1.0%)
Other	7 of 1687 (0.4%)
Total (Age 36-50 years)	579
Caucasian	575
Black	0
Hispanic	0
Asian	4
Other	0

EV/DNG = estradiol valerate / dienogest

Source: Summary of Clinical Efficacy (OC) Text table 9, page 44 of 132

Table 92 provides pooled smoking data from the contraceptive trials.

**Table 92: Pooled Analysis Contraceptive Studies (306660, 304742, 304004)
 – Smoking - FAS**

	Pooled Data – EV/DNG
Total (Age 18-50 years)	2266
Smoking (yes)	422 (18.6%)
Total (Age 18-35 years)	1687
Smoking (yes)	419 (24.8%)
Total (Age 36-50 years)	579
Smoking (yes)	3 (0.5%)

EV/DNG = estradiol valerate / dienogest

Source: Summary of Clinical Efficacy (OC) Text table 12, page 47 of 132

Medical Officer's Comment:

Additionally, the Applicant reported that in the pooled analysis the majority of women reported oral contraceptives as the contraceptive method used before study start (73.2%).

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6.1.3 Subject Disposition

Since the three studies were of different time lengths, refer primarily to the individual studies in Section 5.3 Discussion of Individual Studies/Clinical Trials for disposition information. For the three studies there was a total of 2266 in full analysis set for EV/DNG. Additionally for EV/DNG:

- 1422 women (62.8%) reached cycle 13
- 1397 women (61.7%) reached 1 year
- 1205 women (53.2%) reached cycle 20
- 14 women (0.6%) reached cycle 28

6.1.4 Analysis of Primary Endpoint

6.1.4.1 Primary Endpoint Assessment in the Three Pivotal Studies

Medical Officer's Comment:

Studies 306660 and 304742 specified the number of pregnancies as the primary endpoint. Bleeding patterns and cycle control were considered secondary endpoints.

The Applicant stated that in Study 304004, there was no distinction made between primary and secondary variables.

The PI was the primary criterion to assess the contraceptive reliability of EV/DNG. The unadjusted Pearl Index (PIU) was assessed assuming that all women were at risk of pregnancy in all medication cycles unless backup contraception was documented. Additionally, the adjusted PI (PIA) was calculated taking intake failures into account.

In the contraceptive studies, a negative urine HCG test was a prerequisite for further study participation and medication intake. If, throughout the study, no withdrawal bleeding occurred, a home pregnancy test was also to be performed. If the test proved positive, the medication had to be stopped immediately. The woman was asked to agree to further follow-up examinations. In the case of a (suspected) pregnancy, immediate reporting to the Applicant was required.

6.1.4.2 Primary Endpoint Results in the Individual Studies

Medical Officer's Comment: The pregnancy results will presented for the individual studies according to the pivotal studies 306660 (Europe – Table 93) and 304742 (US/Canada- Table 94). Taken as a whole, these two studies

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provided acceptable contraceptive efficacy results. A pooled analysis will not be presented since separate results will be presented in the clinical section of the label. The results provided will be based on the FDA biostatistical analysis of the data. The Applicant's Pearl Indices were affected by the FDA's use of a post-treatment window of 7 days for conceptions considered to be on-treatment, rather than 14 days as has been done in the past.

Table 93: Study 306660 – Unadjusted Pearl Index Based On Pregnancies That Occurred During Cycles 1 to 13 Including 7 Days After Treatment – FAS (Subjects 18-35 Years of Age)

Women 18-35 years of age	Unadjusted
Total time of exposure (days)	323.305
Backup contraception (days)	8.278
Relevant exposure time (days)	315.027
Total time of exposure (cycles)	11,576
Backup contraception (cycles)	302
Relevant exposure time (cycles)	11,274
Number of pregnancies	9
Pearl Index (unadjusted)	1.04
Upper two-sided 95% CI	1.98

Source: FDA Biostatistical review; Table 3.2.3.1a, page 13 of 25

Table 94: Study 304742 – Unadjusted Pearl Index Based On Pregnancies That Occurred During Cycles 1 to 13 Including 14 Days After Treatment – FAS (Subjects 18-35 Years of Age)

Women 18-35 years of age	Unadjusted
Total time of exposure (days)	124,995
Backup contraception (days)	16,797
Relevant exposure time (days)	108,198
Total time of exposure (cycles)	4,575
Backup contraception (cycles)	606
Relevant exposure time (cycles)	3,969
Number of pregnancies	5
Pearl Index (unadjusted)	1.64
Upper two-sided 95% CI	3.82

Source: FDA Biostatistical review; Table 3.2.3.1a, page 13 of 25

6.1.5 Analysis of Secondary Endpoints

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Medical Officer's Comment:

Studies 306660 and 304742 specified secondary efficacy endpoints of bleeding patterns and cycle control. Study 304004 did not distinguish between primary and secondary variables but did provide data on bleeding patterns and cycle control as compared to an active comparator (EE 20/LNG 100). The reader is referred to the individual studies (Section 5.3 Discussion of Individual Studies/Clinical Trials) for the bleeding pattern and cycle control results.

6.1.6 Other Endpoints

Other endpoints included:

- Subjective assessment of treatment (Studies 306660, 304742, 304004)
- Mean change in PGWBI and change in MFSQ subscale scores (Study 304004)

Medical Officer's Comment:

The reader is referred to the individual studies (Section 5.3 Discussion of Individual Studies/Clinical Trials) for these results.

6.1.7 Subpopulations

Medical Officer's Comment:

The age subpopulation of importance for contraceptive studies (women age 18-35) has already been addressed in regard to efficacy. The Applicant did not enroll subjects with BMI > 30 in Studies 306660, 304742 and 304004. Therefore a subpopulation of obese women has not been studied. This information should be included in the product label.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Medical Officer's Comment:

Although the product regimen varies in dose over a 28-day cycle, the overall regimen is fixed. Clinical information in regard to missing pills will be discussed in the labeling section (9.2 Labeling Recommendations).

6.1.9 Discussion of Persistence of Efficacy

Medical Officer's Comment:

The life table analysis results support persistence of efficacy for subjects who are taking the product.

6.1.10 Additional Efficacy Issues/Analyses

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There are no additional efficacy issues or analyses to discuss in this section.

6.2 Heavy and/or Prolonged Menstrual Bleeding Indication (DUB)

6.2.1 Methods

The key sections from NDA 22-252 regarding DUB efficacy were found in:

- Clinical Overview
- Summary of Clinical Efficacy - DUB
- Integrated Summary of Efficacy - DUB
- Report A29849 (Protocol 308960)
- Report A42568 (Protocol 308961)

The Integrated Summary of Efficacy contained the following appendices:

- 2.1 = Data tables referenced in the Summary of Clinical Efficacy
- 2.2 = Report on alarm function and compliance
- 2.3 = Additional analysis of bleeding intensity and blood loss volume for Study 309860
- 2.4 = Additional analysis of bleeding intensity and blood loss volume for Study 309861
- 2.5 = Statistical Analysis Plan for both pivotal DUB studies

6.2.2 Demographics and Baseline Bleeding Symptoms

Table 95 shows the pooled demographic data for mean age, proportion of ethnic populations and BMI.

Table 95; Pooled Data for Protocols 308960 and 308961 – Demographics - ITT

	EV/DNG (n=269)	Placebo (n=152)
(b) (4)		

EV/DNG = estradiol valerate / dienogest

Source: Integrated Summary of Efficacy – DUB; pages 20-21 of 579

Medical Officer's Comment:

15 pp withheld in full immed. after this page as
(b)(4) CCI/TS.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Components of NDA 22-252 Used to Evaluate Safety

The key sections from NDA 22-252 regarding safety were found in:

- Clinical Overview
- Summary of Clinical Safety
- Integrated Summary of Safety
- 4-month safety update
- Other clinical study reports (which contained safety information for related products containing estradiol valerate and/or dienogest)

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- Reports of postmarketing experience (which contained safety information for related products containing estradiol valerate and/or dienogest)

7.1.2 Categorization of Adverse Events

AEs were monitored throughout the clinical studies, and all reported AEs were included in the safety analyses. For the pivotal studies of the final EV/DNG regimen and the integrated database, AEs were coded using the Medical Dictionary of Regulatory Authorities, MedDRA Version 9.0.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

The Applicant pooled safety data based on indication (i.e., data from Contraception and DUB studies were presented separately). This is acceptable since these populations were somewhat different.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The overall exposure to EV/DNG in the pivotal and other large studies by cycles, partial cycles, days and women-years is shown in Table 104.

Table 104: Overall Exposure to EV/DNG

Study Number	Study type	Number of completed 28 day cycles	Number of partially completed 28 day cycles	Total days of exposure to EV/DNG tablets	Total women-years of exposure to EV/DVNG tablets
304742	PP3, CN	6424	294	183747	503.07
306660	PP3, CN	23528	430	669209	1832.19
304004	P3, CN, CC	2695	27	76052	208.22
301886	P2, L, CHO, HV	181	5	5117	14.01
310122	P2, HV	77	2	2239	6.13
307300	P2, OI	284	5	9591	26.26
308960	PP3, DUB	673	56	19155	52.44
308961	PP3, DUB	859	75	24538	67.18
Total		34721	894	989648	2709.51

EV/DNG = estradiol valerate / dienogest; P2 = Phase 2; P3 = Phase 3; PP3 = pivotal Phase 3; CN = contraception; DUB = dysfunctional uterine bleeding; CC = cycle control; L = lipids; CHO = carbohydrate metabolism, HV = hemostatic variables; OI = ovulation inhibition

Source: NDA 22-252; Amendment 17 (3/17/2010)

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7.2.2 Explorations for Dose Response

The Applicant had extensive clinical studies that explored dose response. These explorations were mainly focused on contraceptive efficacy and cycle control. Different regimens were tested that varied both in the number of days and the dosage. Study 301740, which utilized less dienogest through days 4-23 of the cycle, enrolled 1,779 subjects. This large study identified an unacceptably high Pearl Index and was modified to the final regimen which contained more dienogest. An ovulatory inhibition study (307300) was separately performed to test the final EV/DNG regimen. There was greater than 95% suppression of ovulation identified in this study for the final EV/DNG regimen.

All of the regimens studied had similar safety findings.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable for this submission.

7.2.4 Routine Clinical Testing

For the final EV/DNG regimen, routine clinical lab testing was performed in studies 304004, 308960 and 308961. There were no new or significant findings in the standard safety hematology, chemistry and urine testing performed that differed from changes that are known to occur with combination oral contraceptives.

7.2.5 Metabolic, Clearance, and Interaction Workup

See section 4.4 and the clinical pharmacology review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The most important adverse events when considering the safety of combination oral contraceptives is that of venous and arterial thromboembolic events.

At the request of DRUP, the Applicant provided a detailed analysis of any potential venous and arterial thromboembolic events. Their analysis in this regard identified a case of DVT that was not initially included in Study 306660. The safety results for VTEs and ATEs can be found in Section 7.3.4 of this review.

7.3 Major Safety Results

7.3.1 Deaths

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Table 105 lists deaths reported in clinical studies that assessed final and developmental EV/DNG regimens. None of these 3 deaths are felt to be related to study drug.

Table 105: Deaths in Clinical Studies of the Final and Developmental EV/DNG regimens.

Drug	Study	Age	PID	Cause and other comments
EV/DNG - F	306660	33	3779	Victim of tsunami in Asia
EV/DNG - F	306660	35	4318	Rupture of cerebral aneurysm
EV/DNG - D	301740	30	1357	Murder

Source: Study Reports for protocols 306660 and 301740.

Table 106 lists deaths (where causality cannot be excluded) reported in a summary PSUR provided by the Applicant for COCs containing EE 0.03 mg / DNG 2.0 mg.

Table 106: Spontaneous Reports of Deaths for COCs Containing Ethinyl Estradiol and Dienogest

Drug	Age	Cause and other comments
EE/DNG	16	Pulmonary embolism – factor V Leiden family history
EE/DNG	37	Pulmonary embolism – history of varicosities with sclerosing measures
EE/DNG	33	Pulmonary embolism – BMI = 32.5 kg/m ²
EE/DNG	26	Thrombotic thrombocytopenic purpura
EE/DNG	17	Pulmonary embolism
EE/DNG	37	Pulmonary embolism

Source: Summary PSUR (1995-2007) pages 1-13 of 13.

Medical Officer's Comment:

The 5 deaths (pulmonary embolism) listed in the preceding table for EE 0.03 mg / DNG 2.0 mg were reported in an estimated 8.03 million women-years over a 12 year time period. The incidence is less than 1 per million women-years. Although underreporting would be expected with spontaneous reports, there does not appear to be a signal of increased mortality over other COCs.

The risk of death for users of COCs was estimated by Creinin to be at most, 3 in 1 million. This was based on a case fatality rate of 1% for VTEs. However, in the EURAS study, 3 deaths were felt to be possibly related to COC use (1 VTE and 2 MIs). These 3 occurred during 142,475 women years. Extrapolating from the EURAS data would result in an estimate of about 15-20 deaths per million women-years for COC use.

7.3.2 Nonfatal Serious Adverse Events

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In Table 107 this reviewer has included all of the SAEs felt to be possible related to study drug in the EV/DNG contraceptive clinical studies (both for developmental and final drug regimens).

Table 107: Nonfatal Serious Adverse Events in Final and Developmental EV/DNG Regimens Possibly Related to Study Drug Use (Completed Studies)

Regimen	Indication	Study	PID	SAE		
Final	C	306660	3156	Myocardial infarction		
			3617	Rapid growth of uterine leiomyoma		
			4147	Deep vein thrombosis		
			4082	Focal nodular hyperplasia of liver		
	DUB	304742	514017	304742	Ovarian cyst rupture	
				304004	1127	Ovarian cyst rupture
				308960	131003	Myocardial infarction
				308961	852034	Cholecystitis
Develop	C, CC	15672		Biliary colic		
	C	301740	579	Ovarian cyst		
			929	Ovarian cyst, hypertension		
			790	Biliary stone, pancreatitis		
			1347	Hypertension		

C= contraception; CC = cycle control; DUB = dysfunctional uterine bleeding; PID = patient identification number; SAE = serious adverse event
 Source: Individual studies from NDA 22-252.

As discussed in section 7.3.4, another DVT was identified in an ongoing study utilizing the final EV/DNG regimen (Study 91548)

7.3.3 Discontinuations Due to Adverse Events

Only five subjects in the Phase 1 studies discontinued due to an AE and 12 subjects in the Phase 2 studies discontinued due to an AE.

Of the 2,266 EV/DNG subjects in Phase 3 contraceptive studies, 225 (9.9%) subjects discontinued the study or study medication due to an AE. The most common reasons for discontinuation of EV/DNG tablets in the Phase 3 subjects due to an AE were metrorrhagia in 34 subjects (1.5%), acne in 24 subjects (1.1%), headache/migraine in 20 subjects (0.9%), depression/depressed mood in 14 subjects (0.7%) and weight increase in 13 subjects (0.6%).

Of the 264 EV/DNG subjects in Phase 3 DUB studies, 26 (9.8%) subjects discontinued the study or study medication due to an AE. The most common reasons for discontinuation of EV/DNG tablets were headache/migraine in 4 subjects (1.6%), libido decreased in 2 subjects (0.8%) mood altered in 2 subjects (0.8%), dysmenorrhea in 2 subjects (0.8%), nausea in 2 subjects (0.8%) and anemia in 2 subjects (0.8%).

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7.3.4 Significant Adverse Events

The most important safety issue when considering the safety of combination oral contraceptives is that of venous and arterial thromboembolic events.

In the contraceptive clinical trials (12 studies) of the final regimen (EV/DNG), the Applicant identified one deep vein thrombosis (DVT). Subject 4147 (age 40) in the European contraceptive trial 306660 was diagnosed with a DVT 9 days after end of study drug treatment but before the end of the study. Her limb had been immobilized for about 3 days for a sprained ankle and she had also received a medroxyprogesterone acetate injection at the end of her EV/DNG treatment phase.

In the contraceptive clinical trials of the final regimen (EV/DNG), the Applicant identified one subject who suffered a myocardial infarction. Subject 3156 was 46 years old and a smoker with a history of hypertension. The duration of treatment at the time of the SAE was 228 days.

In the DUB clinical trials (2 studies) of the final regimen (EV/DNG), the Applicant identified one subject with a myocardial infarction. This subject (subject # 131003 in Study 308960) was a 46 year old woman (non-smoker, BMI = 31.4 kg/m²) who had taken study drug for 194 days. The subject had a positive family history for coronary artery disease.

The Applicant reviewed 2,299 women in their developmental regimens and found no VTEs, ATEs, MIs or strokes.

The Applicant also identified one case of DVT in Study 91548, which is an ongoing comparative study of EV/DNG and Microgynon on hormonal withdrawal associated symptoms. This event occurred in a 23 year old woman taking EV/DNG who suffered a knee injury in an auto accident.

Medical Officer's Comment:

In summary, there have been 2 DVTs and 2 myocardial infarctions reported for EV/DNG final regimen studies.

7.3.5 Submission Specific Primary Safety Concerns

The principal safety concern for EV/DNG and other COCs is that of venous and arterial thromboembolic events. These serious adverse events have been described in numerous sections of the NDA application (individual studies, safety summaries and postmarketing reports). In this section the Applicant's plan for incorporating the U.S. population into a large postmarketing surveillance study to further assess thromboembolic events will be discussed.

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International Active Surveillance Study of Women Taking EV/DNG (INAS-EV)

Primary Objective: To assess the risks of short and long-term use of EV/DNG Tablets and of established OCs in a study population that is representative of the actual users of the individual preparations. The main clinical outcomes of interest for the short and long-term follow-up are: DVT, PE, acute myocardial infarction, and cerebrovascular accidents (stroke).

Study Design: This is a prospective, controlled, non-interventional, long-term cohort study that follows a series of cohorts. The cohorts consist of new users (first-ever users or switchers) of two different groups of OCs: EV/DNG and OCs containing other progestogens. There will be active contact with all cohort members at baseline and then every 6 months for up to 60 months. All pertinent adverse events will be verified by blinded independent adjudication.

The 3 to 5 years of follow-up of 50,000 women should result in at least 150,000 documented women-years. The study is powered to exclude a twofold risk of VTE and a threefold risk of ATE

Recruitment: Recruitment of the cohort members will be conducted via a network of approximately 1000 OC prescribing physicians (= study centers) in Europe and approximately 1000 OC prescribing physicians in the United States. The combined cohort will include 50,000 women recruited in the United States and Europe. The study will begin in Europe and will be extended to the United States based on the international registration and launch status of EV/DNG. Recruitment will start approximately 3 months before the launch of EV/DNG to establish the physician network and all necessary study logistics.

Medical Officer's Comment:

This study is similar to postmarketing surveillance studies for the drospirenone containing COCs (Yasmin and Yaz). The study protocol lists a predefined algorithm used to confirm, consider probable or not confirm a VTE case. The Applicant did not provide similar guidance regarding myocardial infarction or stroke.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

A common AE was defined as any AE occurring in $\geq 1\%$ of subjects. In the EV/DNG group, women included in the OC trials most frequently experienced nasopharyngitis (14.5%), headache (11.1%), and diarrhea (5.0%) according to MedDRA preferred terms, while in the EE 20/LNG 100 group acne and headache (both 3.3%), and nasopharyngitis (1.8%) were the most frequently reported AEs.

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In the pooled analysis of the population included in the DUB studies, the most frequently reported AEs in the subjects who received EV/DNG were headache (9.8%), nasopharyngitis (8.0%), breast pain (4.9%), and nausea (4.9%). In the group of subjects who received placebo, the most frequently reported AEs were headache (13.6%), nasopharyngitis (6.8%), back pain (4.8%), and nausea, vomiting, and a decrease in serum ferritin (4.1% each).

7.4.2 Laboratory Findings

There were no standard safety lab evaluations or special evaluations (hemostatic factors, lipids or carbohydrate metabolism) that identified any new safety concerns. Evaluation of cervical cytology did not reveal an increase in abnormalities. An endometrial substudy of Study 306660 did not show any worrisome histologic findings.

7.4.3 Vital Signs / Body Weight

There were no abnormal findings in regard to vital signs (heart rate, blood pressure) or weight changes either in the developmental or final EV/DNG regimen clinical studies. Rare individual subjects were identified with hypertension, which is consistent with a class effect described in labeling for combination oral contraceptives.

7.4.4 Electrocardiograms (ECGs)

See section 4.6 and Interdisciplinary Review Team for QT Studies review.

7.4.5 Special Safety Studies/Clinical Trials

The only special safety studied requested was that of a QT study, which has been previously discussed.

7.4.6 Immunogenicity

Not applicable for this submission.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There were no significant dose dependent safety findings, as evaluated by comparing AE profiles in the developmental EV/DNG regimens compared to the final regimen.

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7.5.2 Time Dependency for Adverse Events

There were no significant time dependent safety findings.

7.5.3 Drug-Demographic Interactions

The drug-demographic interaction of obesity was not studied thoroughly since the key Phase 3 studies of contraception excluded BMI > 30 kg/m² and the key Phase 3 studies of dysfunctional uterine bleeding excluded BMI > 32 kg/m². A comment regarding BMI entry criteria will be incorporated in the label.

7.5.4 Drug-Disease Interactions

In the contraception studies, the subjects were healthy young females. In the DUB studies the subjects were generally healthy except for symptoms related to heavy and/or prolonged bleeding (anemia). No other diseases were specific drug-disease interactions were studied

7.5.5 Drug-Drug Interactions

See section 4.4 and the clinical pharmacology review.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

See section 4.3 and the preclinical review.

7.6.2 Human Reproduction and Pregnancy Data

See section 4.3 and the preclinical review.

7.6.3 Pediatrics and Assessment of Effects on Growth

EV/DNG is not intended for use by premenarchal females. The Pediatric Review Committee (PeRC) agreed to the Applicant's requested partial waiver and extrapolation from adult data to postmenarchal adolescents.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

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The Applicant did not have any reports of deleterious effect from overdose. Symptoms that would probably occur with overdose include nausea and possibly abnormal uterine bleeding. The drug abuse potential for COCs is very low. The primary withdrawal effect is physiologic withdrawal bleeding.

7.7 4-Month Safety Update

The 4-Month Safety Update was submitted Nov 6, 2009 as submission #008. The initial NDA had a 31 Dec 2008 cut-off date for information provided. This 4- Month Safety Update provides information for the period Jan 1, 2009 through Jun 30, 2009.

As of 30 Jun 2009, EV/DNG tablets that are the subject of NDA 22-252 and indicated for the prevention of pregnancy have been approved for marketing in 27 European Union Member Countries (Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Ireland, Iceland, Hungary, Italy, Latvia, Lithuania, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, United Kingdom) and Australia and the Ukraine, with initial approval on 3 Nov 2008. Introduction into the EU market took place in May 2009 under the tradename "Qlaira."

7.7.1 Ongoing Studies

7.7.1.1 Ongoing Studies with final EV/DNG regimen being conducted in part in the US

Protocol 13108

This is a multicenter, randomized, double-blind, active-controlled, parallel group, 2-arm study to investigate the effect of estradiol valerate/dienogest compared to Ortho Tri-Cyclen Lo on hormone withdrawal associated symptoms in otherwise healthy women after 6 cycles of treatment.

As of Jun 30, 2009, there have been 174 subjects randomized. There was one death in a subject during the screening period who had not received medication. The death was found secondary to a congenital Chiari malformation. There were no other SAEs. There have been 3 subjects who discontinued the study due to an adverse event (abdominal cramping in 2 subjects, headaches in 1 subject).

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Protocol 91781

This is a multi-center, double-blind, double-dummy, randomized, controlled, parallel-group study to assess efficacy and safety of EV/DNG compared to Miranova in the treatment of primary dysmenorrhea.

As of Jun 30, 2009 there have been no subjects randomized.

7.7.1.2 Ongoing Studies with final EV/DNG regimen being conducted outside the US

Protocol 91550

This is a multicenter, randomized, double-blind, active-controlled, parallel group, 2-arm study to investigate the effect of estradiol valerate/dienogest compared to Microgynon on hormone withdrawal associated symptoms in otherwise healthy women after 6 cycles of treatment.

As of Jun 30, 2009, there have been 55 subjects randomized. There have been no deaths or SAEs reported. There has been one subject who discontinued due to headache and mood swings.

Protocol 91548

This is a multicenter, randomized, double-blind, active-controlled, parallel group, 2-arm study to investigate the effect of estradiol valerate/dienogest compared to Microgynon on hormone withdrawal associated symptoms in otherwise healthy women after 6 cycles of treatment.

As of Jun 30, 2009, there have been 88 subjects randomized. There have been no deaths. There has been one SAE (appendicitis). There has been 1 subject who discontinued due to bloating and heavy withdrawal bleeds.

7.7.1.3 Ongoing Studies for Products Related to the Final EV/DNG Regimen



(b) (4)

Protocol 13180

This is a double-blind, randomized, dose-controlled study to evaluate pharmacodynamic properties of four oral doses of dienogest (DNG) in 100 healthy young females volunteers over a period of two cycles up to a maximum of 72 days.

As of Jun 30, 2009, there have been 102 subjects randomized with 84 completing treatment. There have been no deaths. There have been 2 SAEs (ingestion of date rape drug, ankle fracture). There have been 4 subjects who discontinued due adverse events (fracture of the left ankle, headache, mood swings, and abdominal pain).

7.7.2 Periodic Safety Reports – Qlaira

The Applicant submitted two periodic safety update reports (PSURs) covering the time from EU approval to September 2009.

PSUR: Qlaira - Estradiol Valerate / Dienogest 4-Phasic COC regimen

Dates: Mar 9, 2009 to Sep 8, 2009

First marketing authorization: Belgium – Nov 3, 2008

Authorization status: Authorized in 30 countries, marketed in 13

Application rejections or withdrawals for safety: None

Safety-related changes to corporate core text: None

PSUR: Qlaira - Estradiol Valerate / Dienogest 4-Phasic COC regimen

Dates: Oct 14, 2008 to Mar 8, 2009

Authorization status: Authorized in 20 countries, marketed in 0

Application rejections or withdrawals for safety: None

Safety-related changes to corporate core text: None

Cumulative exposure post marketing: 29,981 women-years (389,761 cycle packs)

Reports of fatal outcome: None

Reports of thromboembolic events: 23 year old woman with DVT in left calf 11 weeks after initiation of Qlaira while participating in Study 91548 (post car accident and left knee injury)

Reports of stroke: One possible case in 30 year old smoker

8 Postmarket Experience

This section consists of reviewer summaries of the Applicant's submissions to

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Section 5.3.6 of the NDA (Reports of Postmarketing Experience). The summaries focus on the postmarketing surveillance studies and periodic safety reports. Special attention in this section was given to the reports on Climodien (#11A through I) because this combination product contains both estradiol valerate and dienogest.

Medical Officer's Comment:

Note that the PSURs for the final regimen product in Europe (Qlaira) were submitted in the 4-Month Safety Update and are included in the previous section of the review.

1.

Report number: PH-35569

Study dates: Sep 2005 through Jan 2007

Protocol number: 2005/00743 (CZ)

Title: Monitoring of tolerability of Jeanine® in routine gynecology practice. A prospective, non-interventional, non-controlled multi-center observational study.

Study design: This was a prospective, multi-center, non-interventional observational study. The observation period for each subject covered six menstrual cycles. For each participating patient, the physician documented data at an initial visit and one follow-up visit after six cycles of Jeanine treatment.

Study objectives: Evaluation of contraceptive efficacy, cycle stability, course of subjective complaints, and safety of the oral contraceptive (OC) Jeanine in routine gynecological practice

Subjects enrolled: 832 throughout the Czech Republic

Safety summary: There were no deaths. During the study period, there was only one serious adverse event (SAE) reported: A 36 year old women with a genetic thrombophilic mutation (heterozygous for MTHFR 1298) experienced pulmonary embolism after approximately 4 month of exposure to Jeanine (recovered). The incidence rate of AEs was 8.5 %. In total, there were 79 adverse events in 71 patients. The most frequently recorded MedDRA lowest level terms were: mastodynia (16.9%), skin disorder (14.1%) and vaginal spotting (14.1%).

Medical Officer's Comment:

Jeanine is another name for Valette (monophasic COC with 0.03 mg EE / 2.0 mg DNG (1 per day x 21, then 7 placebo). There does not appear to be any new or worsening safety signal for this combination product containing dienogest and ethinyl estradiol.

2.

Report number: A01175

Title: Return of fertility after stopping Valette

Study dates: April 1995 through Jun 1998

Study objectives: Evaluate when women who are stopping Valette to become pregnant have their first stable cycle and when they become pregnant.

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Study design: Post-marketing surveillance study (one year in length)
Study summary: Out of 149 women who reported on the first stable cycle, the first cycle was a stable one in 105 (71%). Within the observation period of one year, 173 of 183 women desiring pregnancy (95%) got pregnant.

Medical Officer's Comment:

Other safety information was not reported for this study. This study reports an acceptable return to fertility for those using Valette.

3.

Report number: A01174

Title: Affects of Valette on skin and hair over 6 cycles of treatment

Study dates: Oct 1995 through May 1997

Study objectives: The primary aim of this post-marketing surveillance study was to examine effects on skin and hair in a large number of women on Valette in the routine practice, irrespective of whether or not there were signs of a hyperandrogenic state (i.e., seborrhea or acne vulgaris) at the start of the study.

Study design: Post-marketing surveillance study (6 cycles). Baseline and post-study report forms were completed regarding skin and hair symptoms.

Subjects evaluated: 10,718 women

Study summary: The study found improvements in women with greasy hair, greasy skin, and acne vulgaris (mild and moderate). Three (3) unintended pregnancies were reported.

Medical Officer's Comment:

This study was conducted by Jenapharm. They stated in the report that it was not the aim of the study to evaluate adverse drug reactions. The data sheet collected at 6 months was focused only on skin and hair changes. Of the spontaneously reported adverse events reported, amenorrhea was at 0.5%, intermenstrual bleeding was at 0.4% and headache/migraine at 0.13%. There were no serious adverse events or deaths listed. For a sample size of 10,000 women, these safety findings are much less frequent than what we would expect to find in a carefully monitored clinical trial. This study does not contribute much from a safety point of view.

4.

Report number: A01173

Title: Efficacy and tolerability of Valette over 6 cycles of treatment

Study dates: Apr 1995 through Apr 1996

Study objectives: It was the primary aim of this postmarketing surveillance study to examine in routine practice contraceptive efficacy, cycle control, tolerability and compliance in a large number of women on Valette.

Study design: Post-marketing non-interventional surveillance study (6 cycles)

Subjects evaluated: 16,267 with 92,146 cycles (7,679 women years)

Study summary: Eleven (11) unintended pregnancies were reported (Pearl

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Index = 0.14). The incidence of breakthrough bleeding and spotting was highest in the first treatment cycle (5.0 % and 3.4 %, respectively) and then rapidly declined to a very low level. The most common side effects were headache/migraine (1.6% of all women), breast tenderness (1.5%) and nausea (0.87%). Of the reported serious events there were two cases of leg thrombosis and one subject with a suspicion for pulmonary embolus.

Medical Officer's Comment:

This study had more focus on safety than the post-marketing study on skin and hair. The percentages listed for common side effects were lower than that typically seen in clinical studies. Narratives were not provided for any of the serious events, including the two cases of thrombosis and the one case suspicious for pulmonary embolism. Assuming the pulmonary embolism case is positive, the finding of 3 VTEs reported for 7,697 woman years is consistent with the European Active Surveillance (EURAS) study findings (reference = Dinger et al, citation found in section 9.1), in which a variety of contraceptives had incidence rates for VTE ranging from 8 to 9.9 per 10,000 women-years.

5.

Title: European Active Surveillance Study of Women Taking HRT (EURAS-HRT)

Study dates: Began Apr 2002 (ongoing)

Study objectives: To compare the drospirenone-containing HRT product Angeliq to other HRT products

Study design: Prospective, comparative cohort study

Medical Officer's Comment:

In the 5th update report, the researchers stated that they anticipate by mid 2010 that there will be 13,000 women-years of exposure to Angeliq and 30,000 women-years exposure to other HRT products, including Climodien. They noted significant recruiting difficulties due to the Women's Health Initiative and Million Women Study. The report did not list any specifics regarding the use or safety findings of Climodien (dienogest/estradiol valerate).

6.

Study Title: Efficacy and tolerability of Lafamme 2 mg / 2 mg, a combined continuous hormone replacement preparation containing 2.0 mg estradiol valerate and 2.0 mg dienogest, over 6 intake cycles of 28 days each (Protocol number Lfa-01-01)

Study dates: Oct 2001 through 2003

Study objectives: Survey usage pattern of Lafamme and collect information on vaginal bleeding, efficacy, safety and acceptance.

Study design: Post-marketing surveillance study

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Study recruitment: 4993 women with postmenopausal symptoms (mean age = 53.8 years)

Study findings: The most frequent adverse events were 1) breast pain / breast tension (3.7%); 2) gynecological bleeding not specified (3.4%); 3) weight gain (1.6%); 4) hot flushes menopausal (0.7%); 5) headache (0.7%); 6) lack of efficacy concerning climacteric complaints (0.6%); 7) spotting (0.5%); and sleep problems (0.5%).

There was one death in a 54 year old woman who took Lafamme for three cycles. She died from complications of a radical hysterectomy for uterine cancer.

Non-fatal serious adverse events included uterine sarcoma with metastases (1), endometrial hyperplasia (1), cerebral insult (1, with no follow up information), VTEs (4), breast cancer (4), angina (1).

Medical Officer's Comment:

Probable age-related higher frequency of VTEs and cancers is noted in this study.

7.

Study Title: Effects of Lafamme® 2 mg/2 mg, a combined hormonal preparation for menopausal complaints containing 2 mg dienogest + 2 mg estradiol valerate, on skin physiology parameters after 12 treatment cycles of 28 days

Study dates: 2001 - 2003

Study objective: To monitor the effects of Lafamme on skin parameters

Study design: Non-interventional post-marketing study

Study enrollment: 12 women

Safety findings: One woman had breast discomfort and discontinued medication.

Medical Officer's Comment:

The report did not provide any information about the skin analysis. There was only one adverse event reported (mastodynia).

8.

Study Title: Efficacy and tolerability of Valette film-coated tablet, a combined oral contraceptive containing 0.030 mg ethinyl estradiol and 2.0 mg dienogest, in extended-cycle use

Study dates: 2001 - 2003

Study objective: To investigate to forms of extended cycle use

Study design: Non-interventional post-marketing study with either extended regimen of 63 active / 7 placebo or 126 active / 7 placebo.

Study enrollment: 992 women

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Safety findings: The most common adverse drug reactions were breast pain/breast tension (1.0%), headache/migraine (0.5%), weight gain (0.3%) and intermenstrual bleeding (0.3%). There were no deaths or serious adverse events reported.

Medical Officer's Comment:
No efficacy results were presented in this report.

9.

Study Title: Tolerability of Valette®, a combined oral contraceptive containing 0.030 mg ethinyl estradiol and 2.0 mg dienogest, using continuous administration regimen over 6 cycles of 28 days

Study dates: Apr 1999 – Dec 2000

Study objective: To investigate extended cycle use

Study design: post-marketing surveillance study

Study enrollment: 178 women

Safety findings: There were no deaths or serious adverse events reported in this study.

Medical Officer's Comment:
No efficacy results were presented in this report.

10.

Study Title: Fertility after discontinuation of Valette® film-coated tablet, a combined oral contraceptive containing 0.030 mg ethinyl estradiol and 2.0 mg dienogest

Study dates: 1995-2004

Study objective: To investigate fertility after discontinuation of Valette due to wish for pregnancy

Study design: post-marketing prospective observational study

Study enrollment: 706 women

Study findings: Within 1 year after discontinuation of Valette, 613 of 706 women (86.8%) included in the full analysis set became pregnant.

11A.

PSUR: Climodien - 2 mg Estradiol Valerate / 2 mg Dienogest

Dates: June 14, 2001 to Dec 13, 2001 (marketing started in Oct 2001)

Marketing at time of this PSUR: Authorized in 16 countries, marketed in 1

Application rejections or withdrawals for safety: None

Safety-related changes to corporate core text: None

Sales volume and patient exposure: (b) (4) = (b) (4) women-years exposure

Spontaneous medically confirmed ADR reports: 8 received, no serious events

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Drug interactions: No reports

Medical Officer's Comment:

The first marketing authorization for Climodien was granted in The Netherlands on Dec 13, 2000. Trade names include Klimodien, Climodien, Convadien and Lafamme.

11B.

PSUR: Climodien - 2 mg Estradiol Valerate / 2 mg Dienogest

Dates: Dec 14, 2001 to Jun 13, 2002

Marketing at time of this PSUR: Authorized in 18 countries, marketed in 10

Application rejections or withdrawals for safety: None

Safety-related changes to corporate core text: None

Sales volume and patient exposure: [REDACTED] (b) (4) = approx [REDACTED] (b) (4)
women-years exposure

Spontaneous medically confirmed Adverse Drug Reaction (ADR) reports (unlisted AEs underlined): 57 received, 10 were serious: depression with psychotic episodes of anxiety and suicidal ideation (1), leg vein thrombosis (3), infarction of left posterior cerebral artery (1), Crohn's disease (1), seizure (1), growth of myomatous uterus (1) gyn bleeding (1), hematometra/salpingitis/hirsutism (1). There were no deaths

Drug interactions: No reports

11C.

PSUR: Climodien - 2 mg Estradiol Valerate / 2 mg Dienogest

Dates: Jun 14, 2002 to Dec 13, 2002

Marketing at time of this PSUR: Authorized in 24 countries, marketed in 15 (additional trade name = Mevaren)

Application rejections or withdrawals for safety: The Swiss authority rejected the application due to safety data regarding endometrium and VTE as well as dose rationale. No withdrawals or suspensions of marketing authorizations due to safety reasons occurred during the reporting period.

Safety-related changes to corporate core text: During the update period, the Corporate Core Text for Climodien was revised according to published results from the HERS I & II as well as the WHI study.

Sales volume and patient exposure: [REDACTED] (b) (4) = approx [REDACTED] (b) (4)
women-years exposure

Spontaneous medically confirmed ADR reports (unlisted underlined): 38 received, 8 were serious: arrhythmia, extrasystoles, retrosternal pain, heart trouble (1), deep leg vein thrombosis (3), pulmonary embolism (1), arterial embolism lower extremity (1), cerebellar infarction (1). There were no deaths.

Drug interactions: No reports

Medical Officer's Comment:

No further information is available regarding the Swiss decision.

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11D.

PSUR: Climodien - 2 mg Estradiol Valerate / 2 mg Dienogest

Dates: Dec 14, 2002 to Dec 13, 2003

Marketing at time of this PSUR: Authorized in 34 countries, marketed in 21

Application rejections or withdrawals for safety: None

Safety-related changes to corporate core text: None

Sales volume and patient exposure: (b) (4) = approx
(b) (4) women-years exposure

Spontaneous medically confirmed ADR reports (unlisted underlined): 47 received, 6 were serious: epileptic seizure (2), pulmonary embolism (2), hypertension (1), insomnia, nervousness, pruritus, paresthesia (1). There were no deaths.

Drug interactions: No reports

11E.

PSUR: Climodien - 2 mg Estradiol Valerate / 2 mg Dienogest

Dates: Dec 14, 2003 to Dec 13, 2004

Marketing at time of this PSUR: Authorized in 35 countries, marketed in 27 (trade name Climodiene added)

Application rejections or withdrawals for safety: None

Safety-related changes to corporate core text: The company decided to harmonize and update the reference safety information for all HRT products on 08 June 2004 following the publication of the results from the Women's Health Initiative (WHI) monotherapy study.

Sales volume and patient exposure: (b) (4) = approx
(b) (4) women-years exposure

Spontaneous medically confirmed ADR reports (unlisted underlined): 27 received, 6 were serious: death, thrombosis (1), cholestatic hepatitis, liver disorder (1), myocardial infarction (1) focal nodular hyperplasia of the liver (1), meningioma (1), cerebral hemorrhage (1)

The death occurred in a 50 year-old who was reported to have suffered chest trauma with secondary vascular injuries. Her Climodien was discontinued. The patient suffered a probable massive pulmonary embolism at home three months after stopping Climodien.

Drug interactions: No reports

11F.

PSUR: Climodien - 2 mg Estradiol Valerate / 2 mg Dienogest

Dates: Dec 14, 2004 to Jun 13, 2005

Marketing at time of this PSUR: Authorized in 35 countries, marketed in 26

Application rejections or withdrawals for safety: None

Safety-related changes to corporate core text: None

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Sales volume and patient exposure: (b) (4) = approx (b) (4)
women-years exposure

Spontaneous medically confirmed ADR reports (unlisted underlined): 8 received, 3 were serious: ovarian neoplasm (1), pulmonary embolism (1), endometrial cancer (1)

Drug interactions: No reports

Medical Officer's Comment:

Climodien 1/2 (1 mg estradiol valerate / 2 mg dienogest) was approved in one country but not yet marketed during the time of this PSUR.

11G.

PSUR: Climodien 2/2 - 2 mg Estradiol Valerate / 2 mg Dienogest and Climodien 1/2 – 1 mg estradiol valerate / 2 mg dienogest

Dates: Jun 14, 2005 to Jun 13, 2007

Marketing at time of this PSUR: Climodien 2/2 is authorized in 29 countries, marketed in 18; Climodien1/2 is authorized in 2 countries and marketed in 1.

Application rejections or withdrawals for safety: None

Safety-related changes to corporate core text: A warning about estrogen-induced exacerbation of hereditary angioedema was added.

Sales volume and patient exposure: (b) (4)
(b) (4) treatment years

Spontaneous medically confirmed ADR reports (unlisted underlined): 42 received, 5 were serious: renal infarct / atrial fibrillation (1), breast cancer (1), intracranial venous sinus thrombosis (1) pulmonary embolism (1), arterial hypertension (1).

Drug interactions: No reports

Medical Officer's Comment:

The decrease in authorization is related to application renewals, not actions related to safety. The PSUR did not specify which dosage strength was related to the adverse event. There were no deaths in the medically confirmed spontaneous reports. The company noted one fatality in a non-medically confirmed consumer report of a 70 year old female with metastatic uterine cancer.

11H.

Addendum report: Climodien 2/2 - 2 mg Estradiol Valerate / 2 mg Dienogest and Climodien 1/2 – 1 mg estradiol valerate / 2 mg dienogest

Dates: Jun 14, 2007 to Dec 31, 2008

Safety-related changes to corporate core text: A warning about estrogen-induced exacerbation of hereditary angioedema was added.

Sales volume and patient exposure: (b) (4)
(b) (4) treatment years

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Spontaneous medically confirmed ADR reports (unlisted underlined): 23 received, 8 were serious: arrhythmia, atrial aneurysm (1), postmenopausal bleeding disorder, endometrial polyp (1), pulmonary embolism, life threatening (1), breast cancer (1) DVT (2) myocardial infarction (1) erythema nodosum, monoclonal gammopathy, esophagitis (1)

Medical Officer's Comment:

It is not clear why postmenopausal bleeding and pulmonary embolism cases were "unlisted." Apparently some minor wording change resulted in that classification.

11I.

Summary PSUR report: Climodien

Evaluation dates: Dec 13, 2000 through Jun 13, 2007

Treatment-years (based on sales data): (b) (4)

Deaths: 2 (pulmonary embolism in 50 year old; metastatic uterine cancer in 70 year old)

VTE reports in PSURs: The reporting frequency ranged from 0.08 to 1.44 per 10,000 treatment years.

12.

Summary PSUR report: Valette – Combination oral contraceptive with 21 active tablets containing 0.03 mg ethinyl estradiol / 2 mg dienogest

Evaluation dates: Mar 15, 1995 through Mar 15, 2007

Authorizations: Valette is currently authorized in 36 countries and marketed in 20 countries.

Trade names: Valette, Jeanine, Celimona, Celimone, Maxim

Treatment-years (based on sales data): (b) (4)

Deaths: There were six deaths reported during this 12 year time period:

- 1) 16 year old female – pulmonary embolism – family history of thrombosis and found to have Factor V Leiden mutation – Valette x 4 months
- 2) 37 year old woman – pulmonary embolism – history of varicosities with 5 sclerosing measures – Valette x 3 months
- 3) 37 year old woman – pulmonary embolism – Jeanine x 4 months
- 4) 33 year old woman – pulmonary embolism – obesity (BMI = 32.5 kg/m²) – Valette x unknown period of time
- 5) 26 year old woman – thrombotic thrombocytopenic purpura
- 6) 17 year old female – pulmonary embolism

VTEs: The reporting frequency for the PSURs varied from 0.038 to 0.2 per 10,000 treatment years.

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13.

Summary PSUR report: Dinagest – 2 mg dienogest

Evaluation dates: Jan 1, 2000 through Dec 31, 2008

Authorizations: Dienogest as sole active ingredient for the treatment of endometriosis is marketed by Mochida Pharmaceutical Co., LTD. since January 2008 in Japan under the trade name Dinagest®. Based on a Pharmacovigilance Agreement, individual adverse events/adverse drug reactions are exchanged between Mochida and Bayer Schering Pharma.

Treatment-years (based on sales data):

Death: There was one death reported by Mochida in a 52 year old woman. The cause of death was not clear from the report, with both cerebral infarction and pulmonary embolism listed. In addition to the dienogest monotherapy, the patient was also taking Triquilar, a combination oral contraceptive with ethinyl estradiol and levonorgestrel.

Serious metrorrhagia (Reported to Bayer by Mochida): As of 31. January 2009, 12 case reports of serious genital bleeding disorders were reported by Mochida to Bayer Schering Pharma in association with Dinagest. Six of the 12 patients were hospitalized due to severe metrorrhagia. In 10 of the 12 cases anemia was reported with hemoglobin values between 4.7 g/dl and 7 g/dl (normal in women: > 12 g/dl). The age of the patients ranged between 33 and 49 years. All women had either adenomyosis uteri (n = 9), uterine leiomyomata (n = 1), or adenomyosis uteri plus uterine leiomyomata (n = 2) as predisposing condition for genital bleeding disorders.

Adverse drug reactions (for Visanne in Bayer's core text): The most frequently reported undesirable effects during treatment that were considered at least possibly related to Visanne were headache (9.0%), breast discomfort (5.4 %), depressed mood (5.1%), and acne (5.1%).

Medical Officer's Comment:

The Bayer name for this product is Visanne. Visanne has not yet been launched by Bayer Schering Pharma. It is difficult to tell in the serious metrorrhagia cases reported from Japan what is related to dienogest. It appears that the drug was being used off-label for adenomyosis and/or leiomyomata. Progestin-only treatment for these disorders historically has not been very effective in preventing blood loss. The adverse effects listed in Bayer's core document for dienogest alone appear consistent with adverse events seen with other progestin-only products. For additional safety information from the clinical trials of Visanne, see section 5.3.6.3.

14.

Study title: Use of Oral Contraceptives Containing Dienogest and Risk of Venous Thromboembolism

Study dates: Jan 2007 through Jan 2008

Study objectives: The primary objective of the study was to clarify whether the use of dienogest/ethinyl estradiol is associated with a higher risk of venous

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thromboembolism than the use of other combined oral low dose contraceptives (i.e., containing 30 mcg or less ethinyl estradiol), particularly oral contraceptives containing levonorgestrel. The secondary objective was to investigate the VTE risk associated with drospirenone/ethinyl estradiol in comparison to low-dose LNG-based COCs.

Study design: Population-based case-control study in Germany

Study enrollment: 680 cases and 2720 controls were included in the primary analysis.

Study findings: Risk estimates for VTE are shown in Table 108.

Table 108: VTE Risk Estimates for DNG/EE

Comparison	Point estimate*	96% Confidence Interval
Current OC use vs. never user	2.36	1.76 – 3.16
DNG/EE vs. other low dose COCs	0.88	0.55 – 1.39
DNG/EE vs. low dose LNG COCs	1.02	0.60 – 1.75

DNG = dienogest; EE = ethinyl estradiol; COC = combination oral contraceptive;
LNG = levonorgestrel; low dose = ≤ 30 micrograms ethinyl estradiol

* Adjusted for 9 covariates: personal history of VTE, family history of VTE, body mass index, duration of COC use, parity, educational level, chronic disease, concomitant medication and smoking

Source: Tables 11 & 12 from DNG Case-control study on VTE risk pages 23-24

Study conclusions: The VTE odds ratios (adjusted and crude) that compared DNG/EE with other COCs (low-dose COCs, low-dose LNG COCs) were close to or lower than unity and do not indicate a higher risk for DNG/EE users.

15.

Summary report: Progynova (estradiol valerate – 1 & 2 mg tablets)

Evaluation dates: Jul 1, 1990 through Jun 30, 2002

Withdrawals or suspension of marketing authorization: None

Estimated treatment years (based on sales data): (b) (4)

Deaths: During this time period two deaths were reported. The causes of death were:

- 1) Pulmonary embolism occurred in 48 year old woman who initially developed deep vein thrombosis following two week hospitalization for herpes encephalitis. The duration of Progynova use was unknown.
- 2) Middle cerebral artery occlusion in 76 year old woman after 3.5 years of Progynova use for osteoporosis.

Spontaneous reports of serious and pertinent ADRs:

- Retinal artery thrombosis – 3
- Upper limb arterial thrombosis – 1
- Middle cerebral artery thrombosis - 1
- Retinal vein thrombosis – 2

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Pulmonary embolus - 1
Deep vein thrombosis – 6
Mesenteric thrombosis – 1
Cerebral ischemia – 1
Cerebral hemorrhage - 1
Cavernous hemangioma, liver - 1
Endometrial hyperplasia – 3
Stevens-Johnson syndrome - 1
Migraine with aphasia and hemianopsia – 1
Non-thrombopenic purpura – 1
Retinal detachment – 1
Breast cancer – 3
Diffuse mucosal and parenchymal hemorrhage – 1
Lupus - 1

16.

Summary report: Progynova (estradiol valerate – 1 & 2 mg tablets)

Evaluation dates: Jul 1, 2002 through Jun 30, 2008

Withdrawals or suspension of marketing authorization: None

Estimated treatment years (based on sales data): (b) (4)

Deaths: None

Spontaneous reports of serious ADRs:

Myocardial infarction - 1
Hearing loss – 1
Deafness from otosclerosis - 1
Pseudotumor cerebri – 2
Stroke – 2
Superior longitudinal sinus phlebitis – 1
Deep vein thrombosis – 2
Portal vein thrombosis – 1
Elevated liver enzymes – 1
Breast cancer – 1
Depression – 1
Soft tissue leg hemorrhage – 1
Subclavian vein thrombosis – 3
Cerebral ischemia – 1
Syncope, blurred vision – 1
Lupus - 1

9 Appendices

9.1 Literature Review/References

Dinger JC, Heinemann LA, Kühl-Habich D. The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance Study on oral contraceptives based on 142,475 women-years of observation. *Contraception*. 2007 May;75(5):344-54.

Creinin MD, Lisman R, Strickler RC. Screening for factor V Leiden mutation before prescribing combination oral contraceptives. *Fertil Steril*. 1999;72:646-651.

9.2 Labeling Recommendations

Labeling negotiations are ongoing. The most significant clinical recommendation for labeling of this product are found in the following sections of the label:

Highlights

The most important recommended clinical changes to the Highlights includes:

- [REDACTED] (b) (4)
- Addition in the indication section that EV/DNG was not studied in women with a body mass index > 30 kg/m²

Section 14 Clinical Studies

The important recommended clinical changes to the clinical studies include:

- Providing the results of the Pearl Index calculation in tabular form for both the US/Canadian study and the European study separately.
- Listing Pearl Index figures based on during treatment pregnancies that extend for 7 days rather than 14 days after last treatment
- [REDACTED] (b) (4)

Patient Labeling

The most important revision in this patient labeling section revolves around establishing the most comprehensible guidance to patients who have missed one or more EV/DNG tablets.

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9.3 Advisory Committee Meeting

Although dienogest represents a new molecular entity in the U.S., there is extensive postmarketing safety experience from Europe over the past 15 years for a combination oral contraceptive containing ethinyl estradiol 0.03 mg / dienogest 2.0 mg. There also exists 9 years of postmarketing experience for a menopausal treatment regimen in Europe that contains estradiol valerate 2 mg / dienogest 2 mg (one of the dosages in the final EV/DNG product proposed in this NDA contains estradiol valerate 2 mg / dienogest 2 mg). Additionally, the same final EV/DNG regimen proposed in NDA 22-252 was approved in Europe in late 2008 and marketing was initiated in 2009. There has been no indication of new or increased safety concerns in the European experiences.

Based on safety data from the clinical studies themselves and the European safety experience, an advisory committee meeting for this product was not deemed necessary.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22252	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	Qlaira

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GERALD D WILLETT
04/30/2010

LISA M SOULE
04/30/2010

I concur with Dr. Willett's recommendations that NDA 22-252 be approved for the primary indication of prevention of pregnancy, and not approved for the secondary indication of treatment of heavy and/or prolonged menstrual bleeding.