CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-252, Original 1

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	May 6, 2010
From	Lisa M. Soule, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	22-252
Applicant	Bayer HealthCare Pharmaceuticals, Inc.
Date of Submission	July 6, 2009
PDUFA Goal Date	May 6, 2010
Proprietary Name / Established (USAN) names	Natazia Estradiol valerate (EV)/Dienogest (DNG) tablets
Dosage forms / Strength	Oral tablets in multiphasic regimen: Days 1-2: 3 mg EV Days 3-7: 2 mg EV/2 mg DNG Days 8-24: 2 mg EV/3 mg DNG Days 25-26: 1 mg EV Days 27-28: placebo
Proposed Indication(s)	**Primary:** Prevention of pregnancy **Secondary:** Treatment of heavy and/or prolonged menstrual bleeding in women without organic pathology who choose to use an oral contraceptive as their method of contraception
Recommended:	***Approval of primary indication,*** (b) (4)

1. Introduction

This NDA seeks marketing approval for a new combination oral contraceptive containing a new molecular entity (NME) progestin, dienogest (DNG) and a prodrug of estradiol, estradiol valerate (EV). EV is currently approved in the US (NDA 09-402, approved in 1954) only in injectable form, for noncontraceptive indications. The product utilizes a novel four-phasic dose regimen, that begins and ends with EV alone, provides EV and DNG on Days 3 -24, and includes two days of placebo over a 28 day cycle.

The Applicant requests marketing approval for two indications: prevention of pregnancy, and treatment of heavy and/or prolonged menstrual bleeding in women without organic pathology who choose to use an oral contraceptive as their method of contraception. (b) (4) This latter indication would be the first such labeled secondary indication for an oral contraceptive, although other hormonal products, such as the Mirena IUD, and several progestin-only

products are approved for similar cyclic bleeding indications. A nonhormonal product that affects the coagulation cascade, Lysteda (tranexamic acid), has also been approved recently for a heavy menstrual bleeding indication. In the past, oral contraceptives had class labeling in the Patient Package Insert that described "non-contraceptive health benefits" – among these was the following paragraph:

Effects on menses:

- *Increased menstrual cycle regularity*
- *Decreased blood loss and decreased incidence of iron deficiency anemia*
- *Decreased incidence of dysmenorrhea*

With the advent of PLR labeling, and increased requirements for evidence supporting statements made in labeling, this class labeling has no longer been included in recently approved OC labels.

The Applicant initially submitted the proprietary name Qlaira, which was not found acceptable by the Division of Medication Errors Prevention and Analysis (DMEPA). The Applicant then submitted the names (b) (4), which was also found unacceptable, and then (b) (4) and Natazia, which were reviewed simultaneously. DMEPA concluded that the name Natazia was acceptable. This review will refer to the product as EV/DNG; however, other reviewers may cite the product as Qlaira or (b) (4)

The Applicant submitted two pivotal open label trials evaluating the contraceptive efficacy of EV/DNG, along with a seven-cycle trial conducted to characterize the bleeding profile of the drug. In addition, the secondary indication was supported by two additional, randomized and placebo-controlled, pivotal trials conducted in women with heavy, prolonged, or frequent bleeding. The data from the contraceptive efficacy trials demonstrated an acceptable Pearl Index whether based on European or North American subjects, and did not signal any unexpected or increased adverse events. Cycle control data from these two trials and from the comparative bleeding profile study showed an acceptable bleeding profile, with no evidence that the multiphasic dosing regimen did improve cycle control over more standard dose regimens.

(b) (4)

The major issues addressed in this review primarily involve acceptability of the proposed secondary indication, and labeling. Areas that required negotiation with the Applicant included:

- (b) (4)
- Acknowledgement that safety and efficacy has not been studied in women with BMI > 32 mg/m^2

- Warning against concomitant use with CYP3A4 inducers due to risk of decreased efficacy
- Provision of clear instructions on what to do in case of missed pills
- Extensive revision of the Clinical Pharmacology section

2. Background

2.1 DESCRIPTION OF PRODUCT

EV/DNG is a combination oral contraceptive (COC) to be taken in a four-phasic regimen over a 28 day cycle for the prevention of pregnancy, as described in the preceding section. The specific dose regimen is:

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

As noted, DNG, a 19-norprogestin, is a new molecular entity in the US. DNG lacks androgenic and antiestrogenic activity and does not bind to sex hormone binding globulin. The EV component would be the first oral formulation of this active moiety approved in the US. EV is currently approved in the US (Delestrogen, NDA 09-402, approved in 1954) only in injectable form for the indications of treatment of vasomotor symptoms, vulvovaginal atrophy, hypogonadal hypoestrogenism (dosed at 10-20 mg every four weeks) and palliation of advanced androgen-dependent prostate cancer (dosed at ≥30 mg every one to two weeks). EV is rapidly hydrolyzed into 17β-estradiol and valeric acid.

An EV 2 mg/DNG 2 mg product (Climodien) has been approved in Europe for menopausal symptom therapy since 2001, and a COC combining 0.03 mg ethinyl estradiol and 2 mg DNG (e.g., Valette) has been approved in Europe since 1995. The currently proposed EV/DNG COC was approved in Europe under a decentralized procedure with review by the Dutch Medicines Evaluation Board in 2008 and has been marketed since 2009.

The Applicant believes that the initial two days of EV will stimulate proliferation of the endometrium and thereby decrease unscheduled (breakthrough) bleeding commonly seen with low estrogen dose OCs. The increasing dose of DNG is intended to provide adequate ovulation inhibition, while the final two days of unopposed EVE are expected to reduce symptoms associated with hormone withdrawal.

2.2 REGULATORY HISTORY

The Applicant has worked on the clinical development program under two INDs: IND 64,809 (contraception) was opened in November 2004 with a pharmacokinetic study, and IND (b) (4) was opened in October 2005 for the bleeding indication. [(b) (4)] General guidance was provided in a March 2005 letter, which granted a waiver for additional chronic toxicity studies of EV or DNG and for carcinogenicity studies of the EV/DNG combination. Segment 1-3 reproduction studies for the EV/DNG combination were also waived provided that these studies had already been conducted with DNG in accord with

GLP regulations. Further, in June 2005, the Division concurred that the Sponsor had provided adequate justification for not conducting studies in renally or hepatically impaired subjects, and that appropriate language would be included in labeling, if the product were approved. The rat and mouse carcinogenicity studies for DNG were reviewed and accepted by the Executive Carcinogenicity Assessment Committee (Exec CAC) in January 2007. The Exec CAC concurred with the Sponsor that there were no drug-related neoplasms in the rat study, and that uterine endometrial stromal polyps in high dose female mice were drug-related.

Contraception Indication

The Applicant initially met with the Division of Reproductive and Urologic Products (DRUP) in March 2004, to discuss the proposed clinical development plan for a contraception indication. The Division agreed that no additional studies were needed to investigate potential drug interaction between DNG and EV, and recommended that the potential effect of CYP3A4 inhibitors and inducers on DNG metabolism be investigated. The Office of Clinical Pharmacology also acknowledged that EV is a prodrug of estradiol that would need no further characterization.

Because DNG is a new molecular entity, the Division requested two adequate and well-controlled studies of safety and efficacy; data from the US would be required (i.e., data on 10,000 28-day treatment cycles with at least 200 women aged 18-35 who completed 13 cycles of treatment) rather than relying entirely on European data.

The Sponsor subsequently requested clarification of the number of North American study subjects required by the Division, and indicated that it planned to enroll 480 subjects in a 13-cycle study in North America. The Division agreed in a June 2005 letter that such a sample size, estimated to provide 5,500 28-day cycles of exposure, would be acceptable for the North American component of the development program. The Division also agreed that the Sponsor had provided adequate justification for not conducting studies in renal or hepatic impairment.

The Sponsor and the Division met again in December 2007, to discuss NDA submission for the contraception indication. The Pharmacology/Toxicology and Clinical Pharmacology reviewers concurred that no additional nonclinical or clinical pharmacology studies appeared necessary. The Clinical reviewer outlined the requested content and organization of safety and efficacy data. The adequacy of the laboratory testing was discussed; the Sponsor did not have 12 month lab data on the 3 mg EV dose, but did have 12 month data on over 1000 subjects from the hormone therapy program, which included EV/DNG doses close to the maximum used in the proposed OC regimen. The Sponsor also proposed modifying missed tablet instructions from those used in the phase 3 programs, such as including instructions for more than one missed pill, which was not discussed in the trials. The Division noted that modification of trial instructions would be a review issue and that the Sponsor should provide justification for any changes. The Division indicated that the Pearl Index and life table pregnancy calculations should be based only on the first 13 cycles of use, including all pregnancies occurring within 14 days after last pill intake.

Bleeding Indication

The Sponsor proposed studying multiphasic EV/DNG for dysfunctional uterine bleeding (DUB), with an initial protocol submitted under IND 64,809. A guidance meeting was held in January 2005 to discuss clinical development for the secondary indication of treatment of DUB in women who also desire contraception. The Division recommended pursuit of a more

focused indication for clinically significant problems related to excessive frequency, duration and/or volume of menstrual bleeding. The Division recommended a 90 day screening period that would include only bleeding episodes, not spotting episodes, in defining the symptoms that constitute the indication. (b) (4) The Division commented on the proposed responder analysis that would evaluate the rates of complete symptom resolution in double-blind, randomized, placebo-controlled trials, and recommended that endpoints be based on a percent or absolute reduction in symptomatology that was clinically meaningful. The primary efficacy outcome variable would need to be compared against placebo, and should use the intent-to-treat (ITT) population. (b) (4) The Division recommended exclusion of women with any history of myocardial infarction, or current use of an IUD, and recommended that women who discontinued oral contraceptives in order to enter the trial should undergo a wash-out period before baseline symptomatology was determined.

A teleconference was held on July 14, 2005, with discussion of the following issues:

- The Division agreed to a seven-cycle study duration for the two pivotal bleeding studies
- (b) (4)
- Changes to the definition of excessive bleeding were recommended
- The Division also recommended several refinements to the criteria for treatment success, including limits on the number of bleeding episodes and total number of bleeding days in the efficacy assessment period
- The Division agreed that a responder analysis would be acceptable, but indicated that in addition to demonstrating a statistically significant difference in the proportion of responders in treatment and placebo arms, the Sponsor should demonstrate that the observed improvement is clinically meaningful, suggesting that the patient-rated overall improvement scale might be used to provide this information
- The Division asked the Sponsor to provide in the protocol a more detailed justification relating to the clinical significance of the assumed treatment responder rate and effect size, and suggested that the Sponsor could propose a minimum performance threshold
- that would denote a clinically relevant treatment response rate
- The Sponsor proposed considering any subject who fails to complete the second 90-day treatment phase a treatment failure; however, the Division preferred using a LOCF approach to maximize the usable data
- The Division recommended allowing for imputation of single non-consecutive days of missing bleeding data, so long as at least 90% of study days have valid data
- The Division agreed with use of the alkaline hematin method to evaluate bleeding volume

- Finally, the Division indicated that health-related quality of life endpoints and secondary endpoints are not typically accepted in support of labeling claims

IND (b) (4) was opened in (b) (4) with a protocol for a North American phase 3 study intended to support a secondary indication for (b) (4) The Applicant proposed conducting a corresponding study in Europe to satisfy the Division's request for two adequate and well-controlled studies. The Division conveyed comments on the following elements of the protocol in a letter dated December 20, 2005:

- Exclusion of subjects on the basis of a suspected genetic thrombophilia or positive family history at under 40 years of age would likely be reflected in labeling if the product were approved
- The proposed use of an alarm to prompt data entry into the electronic diary was discouraged, as this might also serve as a prompt to pill-taking, thus resulting in compliance greater than that achieved in actual clinical use

The Division made no further comments on the proposed definitions of the components of DUB, as provided in the eligibility criteria for the study:

- Prolonged bleeding: ≥ 2 bleeding episodes, each lasting ≥ 8 days, in the 90-day run-in period
- Frequent bleeding: 5 bleeding episodes, with a minimum of 20 bleeding days overall
- Excessive bleeding: ≥ 2 bleeding episodes, each with blood loss volume ≥ 80 ml based on alkaline hematin assessment

The Division agreed in part with the Sponsor's planned criteria for study success, and recommended some additional or modified criteria such that the final determination of efficacy would be based on a primary efficacy endpoint of the proportion of subjects who met all of the following criteria during the 90-day efficacy assessment phase:

- No bleeding episode lasting > 7 days, no increase from baseline in total number of bleeding days and total number of bleeding days ≤ 24 days (in addition, for subjects enrolling with prolonged bleeding, a decrease from baseline of at least 2 days in maximum duration of bleeding)
- No > 4 bleeding episodes and no more than 1 episode increase from baseline frequency
- Blood loss volume per bleeding episode < 80 ml (in addition, for subjects enrolling with heavy bleeding, a decrease of at least 50% from the average of the qualifying bleeding episodes)

The Division noted that the protocol stated that "The primary outcome measure (absence of DUB symptoms in a patient presenting with DUB symptoms) has been designed to be clinically relevant to clinical practice. If the study is clinically 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." The Division also noted that the study was powered based on anticipated response rates of 20% in the placebo arm and 50% in the treatment arm. However, the proposed definition of a successful outcome did not require that the response rate in the active treatment arm be ≥ 50%. Given that the Sponsor was powering the study and determining the clinical meaningfulness of the outcome based on an anticipated response rate of at least 50%, the Division requested that the definition of overall success require that

1) the proportion of successful responders in the treatment arm be statistically significantly greater than that in the placebo arm and
2) the point estimate for the percent of successful responders in the treatment arm be at least 50%

The Division also noted that the cover letter for the protocol stated that "a success rate of less than 50% could still be clinically meaningful," but did not specify as to how a lower treatment effect would be justified as clinically meaningful.

A meeting was held in March 2006 to discuss the protocol comments, the use of the alarm, and possible validation of the health-related quality of life instruments for possible inclusion in labeling. The Division requested a consult from the Study Endpoints and Labeling Division (SEALD), and staff from SEALD attended the teleconference. Discussion included the following points:

- Given the 72-hour window allowed for entry of bleeding data, use of an alarm that only goes off every 72 hours would be acceptable. The Sponsor should also enroll a subset of subjects who do not use an alarm at all, and demonstrate that their compliance with dosing was no better than subjects with an alarm. The Sponsor proposed conducting a small study comparing the effect on compliance of daily vs. every 72 hour alarms, rather than including a subgroup with no alarms in the pivotal trials.
- SEALD recommended that any instrument validation proposed should not wait until phase 3, as it is unlikely that measurement properties of the instrument could be characterized in time to support the interpretation of study results. The Division further noted that any endpoints considered for inclusion in labeling should be agreed to by the Division prior to initiation of phase 3, and that the statistical analysis plan appropriately address such endpoints.
- Imputation of missing data on blood loss volume was discussed and the Sponsor was asked to propose a plan.
- The plan to include secondary efficacy results as supportive (in case the response rate is below 50%) would be a review issue, depending on whether the plan was prespecified in the protocol and the results are both statistically and clinically meaningful.

The protocol for Study 308960, as well as for the identical study 308961, was amended on May 5, 2006 to revise the definition of the primary efficacy variable and to establish the 50% response rate point estimate as an additional criterion for overall study success.

The SAP was submitted in June 2008, and the Division's statistical reviewer indicated that he found the overall plan acceptable. The plan specified that to demonstrate efficacy the success rate in the treatment arm must be statistically significantly greater than that in the placebo arm, and that the point estimate in the treatment arm must be at least 50%. Comments were sent to the Sponsor indicating that handling of missing data would be a review issue.

A pre-NDA meeting was granted for February 2009 to discuss the submission of an NDA including the secondary indication for treatment of heavy and/or prolonged menstrual bleeding in addition to the primary indication for prevention of pregnancy. After receiving DRUP's preliminary responses, the Applicant requested cancellation of the meeting. Important issues addressed in the preliminary comments included:

- The Division's agreement with the proposal to [redacted]" from the secondary indication, [redacted]
- [redacted]

Team Leader Comment

It should be borne in mind that at the time the Division and the Sponsor were discussing the trials to support a DUB indication, COC labeling universally contained the statement about non-contraceptive health benefits that indicated that COCs resulted in decreased menstrual blood loss and more regular menstrual cycles. Given that the Sponsor was trying to single out their product for a more specific claim regarding impact on menstrual bleeding, the Division and the Sponsor agreed to very rigorous endpoints.

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary reviewer, Dr. Gerald Willett, stated in his review, dated April 30, 2010:

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

Dr. Willett noted that the risk/benefit assessment is favorable for the contraception indication, as there is no signal of a new or increased safety concern as compared to other oral contraceptives, and the efficacy data demonstrated an acceptable Pearl Index (1.64 in the US study). [redacted]

Team Leader Comment

I concur with Dr. Willett's recommendations. Unlike Dr. Willett, however, I have potential concerns about safety of EV/DNG in older women, [redacted] This is based both [redacted] and a possible signal of increased cardiovascular and thromboembolic risks in older women who use EV/DNG.

3. CMC/Device

The primary Chemistry reviewer, Tarun Mehta, Ph.D., made the following recommendations in his review dated March 23, 2010:

> *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.*

Relevant Drug Master Files were reviewed and all were found to be adequate. The tablets include five different formulations, and either contain EV alone, EV and DNG, or are inert. EV is noted to be a compendial (USP) drug substance, while DNG is non-compendial as well as an NME. All excipients are compendial (USP/NF). The batches used in clinical trials and stability batches are identical to the proposed commercial product. An expiry period of 48 was granted. Dr. Mehta noted that the Applicant provided sufficient information on raw material controls, manufacturing process and process controls and adequate specifications to assure consistent product quality of the drug substance and drug product. The Applicant also provided sufficient stability information on the drug product to assure strength, purity and quality over the expiration dating period.

Dr. Mehta recommended a categorical exclusion from environmental assessment. An initial recommendation of "withhold" was made on January 4, 2010 by the Office of Compliance. However, after an acceptable reinspection of one site that had previously been found deficient, the Office of Compliance made an overall recommendation of "Acceptable" on April 9, 2010.

CMC labeling revisions were made to the proposed label and to carton/container labeling, and were conveyed to the Applicant, who agreed to incorporate them. Agreement has been reached upon the established name of the product, which reflects the unique multiple combinations of drug substances within one blister card.

Following resolution of the issues outstanding at the time of his original review, Dr. Mehta made the following recommendation in an addendum to his review dated May 6, 2010:

> *Now the Office of Compliance has issued an overall "Acceptable" recommendation…*
>
> *All the labeling issues are satisfactorily resolved, and the revised PI and labels for carton and blister were submitted…*
>
> *Therefore, from a CMC perspective, this NDA is now recommended for approval.*

4. Nonclinical Pharmacology/Toxicology

The Applicant submitted a full nonclinical program for DNG, including pharmacology studies, pharmacokinetic (PK) and toxicokinetic (TK) studies, general toxicology studies, acute, chronic and subchronic toxicology studies, genotoxicity studies, reproductive toxicity studies and carcinogenicity studies. Given that EV is an approved drug in the US, no new toxicology studies of EV were conducted. The primary Toxicology reviewer, Krishan Raheja, D.V.M., Ph.D., concluded that toxicological findings for DNG were similar to those reported for other approved progestins. There were no adverse neurological, cardiovascular, pulmonary, renal or gastrointestinal effects observed in the safety pharmacology program. DNG was negative for mutagenicity and the carcinogenicity studies (presented to and approved by the Executive Carcinogenicity Assessment Committee [CAC]) showed findings similar to those observed with other approved progestins.

Dr. Raheja made the following recommendations in his review dated January 27, 2010:

> ***Recommendations on approvability:*** *Nonclinical data supports approval of NDA 22-252 for Estradiol valerate/Dienogest.*
>
> ***Recommendations for nonclinical studies:*** *No additional nonclinical studies are required.*
>
> ***Recommendations on labeling:*** *The proposed Prescribing Information is in accordance with the PLR and presented in SPL format and is acceptable.*

Dr. Raheja added an addendum to his review on April 7, 2010, that reviewed five additional genotoxicity studies submitted by the Applicant that had not previously been included in his review. He concluded that the studies indicated that dienogest does not induce chromosomal aberrations, does not induce clastogenic activity, did not cause increased unscheduled DNA synthesis *in vitro* or *in vivo*, and did not appear to have initiating activity in the process of carcinogenicity.

5. Clinical Pharmacology/Biopharmaceutics

The Applicant submitted 32 biopharmaceutical and clinical pharmacology studies, of which 22 were relevant to the requested indications. The primary Clinical Pharmacology Reviewer, Chongwoo Yu, Ph.D., did not review those studies pertaining to other indications (e.g., endometriosis) or exploratory studies conducted using different hormone combinations, formulations or dosing regimens.

Dr. Wu stated the following in his review dated April 2, 2010:

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

Dr. Wu entered an addendum to his review on May 6, 2010, which indicated that, after review of the final labeling submitted by the Applicant, there were no outstanding Clinical Pharmacology issues. He concluded:

> *The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds NDA 022252 acceptable from a Clinical Pharmacology perspective.*

No phase 4 commitments were recommended.

The Applicant evaluated a total of five formulations of EV/DNG during clinical development, but the final to-be-marketed formulation was used in all pivotal phase 3 clinical studies and supporting clinical pharmacology studies.

EV is cleaved during absorption by the intestinal mucosa or during first pass through the liver to 17β-estradiol (E2) and valeric acid. Pharmacokinetic (PK) evaluation of EV demonstrated a t_{max} of 6 hours after single dosing (3 hours at steady state), with a $t_{1/2}$ of about 14 hours. Elimination is predominantly through urinary excretion. Absolute bioavailability of metabolically unchanged E2 was 3%; there is about 98% protein binding, to albumin and sex hormone binding globulin (SHBG).

For DNG, PK evaluation demonstrated a t_{max} of 1 hour after single dosing (1.5 hours at steady state), with a $t_{1/2}$ of 11 hours. Elimination is predominantly through urinary excretion. Steady state was reached in 4-5 days with daily dosing. Absolute bioavailability was approximately 91%; there is about 90% protein binding, nonspecifically to albumin. DNG does not bind to SHBG or cortisol binding globulin. PK was linear over a dose range of 1 to 8 mg.

The Applicant submitted studies of EV/DNG and CYP3A4 inducers (rifampicin) and inhibitors (ketoconazole and erythromycin). Dr. Yu is recommending that labeling warn against concomitant use of CYP3A4 inducers and EV/DNG due to possible decreased contraceptive efficacy.

No PK study was conducted in renally or hepatically impaired subjects. Severe liver disease is a contraindication for COCs generally. Product labeling will indicate that these specific populations have not been studied.

A food effect was found for both EV and DNG, such that the 90% confidence interval around C_{max} was not met in the fed state. However, the clinical trials support dosing without regard to food intake, so no specific labeling will be requested.

Results of the thorough QT study are discussed in Section 8.5.1.

6. Clinical Microbiology

A Microbiology consult was not requested for this tablet product.

7. Clinical/Statistical - Efficacy

7.1 OVERVIEW OF CLINICAL PROGRAM

Clinical data submitted in this NDA include two multicenter open-label pivotal phase 3 safety and efficacy trials to support the contraceptive indication (Study 304742 and Study 306660), a seven-cycle study designed to characterize the bleeding profile of EV/DNG (Study 304004), and two multicenter randomized, double-blind, placebo-controlled pivotal phase 3 safety and efficacy studies to support the DUB indication (Study 308960 and Study 308961). All studies included the to-be-marketed formulation of EV/DNG.

Study 304742, conducted in the US and Canada, enrolled 499 women aged 18 – 35 years for up to 28 cycles of 28 days. Study 306660 was conducted in Austria, Germany and Spain, and enrolled 1,391 women aged 18 – 50 years for up to 20 28-day cycles. The total number of 28-day cycles studied for the contraception indication is 29,952 (6,424 cycles in Study 304742 and 23,528 cycles in Study 306660). However, the Division typically evaluates contraceptive efficacy over a 13-cycle period; the two studies provided 16,151 evaluable cycles in the first year of treatment, with an additional 908 cycles in which subjects used back-up contraception at least once.

The additional study, 304004, provided additional data regarding bleeding patterns and cycle control in the contraceptive population, but did not specify contraceptive efficacy as a primary endpoint. This study compared subjects randomized to EV/DNG (N=399) against a European-approved oral contraceptive containing 20 µg ethinyl estradiol (EE) and 100 µg levonorgestrel (LNG) given in a 21/7 day regimen (N=399). A total of 2,695 28-day cycles of exposure were

obtained in this trial. This study will be discussed briefly within the context of the bleeding profile in a contraceptive-aged population, but is not considered a pivotal contraceptive trial.

Study 308960 randomized 190 US and Canadian subjects who had at least one of the three specified DUB symptoms (heavy, prolonged and/or frequent bleeding) to EV/DNG or placebo for two baseline cycles and seven treatment cycles. Study 308961 enrolled 231 subjects meeting the same entry criteria for the same study duration, and recruited subjects from Australia, Czech Republic, Finland, Germany, Hungary, the Netherlands, Poland, Sweden, the UK and Ukraine.

Table 1 displays information about the five major studies supporting this NDA.

Table 1 Summary of Pivotal Studies

Indication	Study	Study Site [1]	Study Design	Number Randomized/ Study Regimens	Duration of Treatment
Prevention of pregnancy, cycle control	**304742**	US: 22 Canada: 9	Multicenter, open-label, uncontrolled one-arm study	**Analyzed**: 490 subjects (Full Analysis Set [FAS]), 305 subjects (Per Protocol Set [PPS]).	Up to 28 cycles of 28 days each.
	306660	Austria: 17 Germany: 28 Spain: 5	Multi-center, open-label, uncontrolled, one-arm study	**Analyzed**: 1377 (including subgroup of 266 for endometrial biopsy)	20 cycles of 28 days each
	304004	Germany: 19 Czech Republic: 5 France: 10	Multi-center, double-blind, double-dummy, active-controlled, randomized study	**Analyzed**: 798 (399 per treatment group; 198 to 201 per age stratum) (FAS)	7 cycles of 28 days each
Heavy menstrual bleeding	**308960**	US: 33 Canada: 9	Multicenter, double-blind, randomized, parallel-group, placebo-controlled study	**Analyzed**: 190 patients (120 EV/DNG and 70 placebo) intent-to-treat (ITT), 185 patients (119 EV/DNG and 66 placebo) safety (SAF), 68 patients (41 EV/DNG and 27 placebo) PPS	196 days (7 cycles of 28 days each)
	308961	Australia: 2 Czech Republic: 2 Finland: 3 Germany: 5 Hungary: 3 Netherlands: 3 Poland: 5 Sweden: 3 UK: 3 Ukraine: 4	Multicenter, double-blind, randomized, parallel-group, placebo-controlled study	**Analyzed**: 231 patients randomized (149 EV/DNG and 82 placebo) ITT, 226 (145 EV/DNG and 81 placebo) SAF, 89 (55 EV/DNG and 34 placebo) PPS	196 days (7 cycles of 28 days)

[1] Includes only those sites having randomized patients

Source: Based on Table 2.1, Statistical review by Xin Fang, Ph.D., dated March 31, 2010

7.2 PRIMARY INDICATION – PREVENTION OF PREGNANCY

7.2.1 DEMOGRAPHICS

Entry criteria for all five studies are detailed in Dr. Willett's review. Briefly, the contraception studies enrolled women aged 18 to 50 (18-35 for Study 304742), with smokers enrolled only if they were 30 years old or younger. Typical exclusions for contraceptive trials were utilized. In addition, women with a body mass index (BMI) > 30 kg/m^2 were excluded. Women with a family history or suspected hereditary predisposition (on the basis of family history) to increased risk of thromboembolism were also excluded.

Team Leader Comments

- **The phase 3 trials met the Division's requirements regarding cycles of exposure and number of women completing 13 cycles of treatment.**
- **The Division has discouraged restricting enrollment in hormonal contraception trials on the basis of weight or BMI. There are both safety and efficacy concerns regarding the use of hormonal contraception by obese women. Obese women may achieve**

lower serum hormone concentrations, which could pose a concern with respect to efficacy. Conversely, obesity is a risk factor for venous thromboembolism (VTE), a major safety issue with hormonal contraceptives. Safety and efficacy data obtained in obese women would be of great interest.

- **It is unclear whether the contraception studies were formally reviewed by the Division, or only discussed in meetings. In any event, it does not appear that the Division ever provided a comment discouraging the Applicant from the BMI exclusion. However, I believe it is important that labeling disclose the fact that safety and efficacy was not studied in heavier women. I recommend the inclusion in appropriate sections of the label of a statement:**

  The safety and efficacy of EV/DNG in women with a body mass index (BMI) of > 30 kg/m^2 has not been evaluated.

Table 2 shows the demographics of the Full Analysis populations in Studies 306660 and 304742. Twenty-five randomized subjects (14 in Study 306660 and 9 in Study 304742) did not start study medication.

Table 2 Studies 306660 and 304742 – Demographics and Baseline Characteristics

Characteristic	Study 306660 N=1,377	Study 304742 N=490
Mean age (years [range])	30.3 [18-50]	25.1 [18-35]
Age group 18-35 years	998 (72.5%)	490 (100%)
Age group > 35 years	379 (27.5%)	0
Ethnic group		
• Caucasian	1366 (99.2%)	371 (76.0%)
• Black	2 (0.1%)	34 (7.0%)
• Hispanic	3 (0.2%)	64 (13.0%)
• Asian	4 (0.3%)	16 (3.3%)
• Other	2 (0.1%)	5 (1.0%)
Smoker	273 (19.8%)	92 (19.0%)
Mean weight (kg) (SD)	64.2 (9.5)	62.5 (10.2)
Mean height (cm) (SD)	167.1 (6.2)	163.9 (6.9)
Body mass index (kg/m^2) (SD)	22.8 (2.9)	23.3 (3.3)
Prior COC use	1006 (73.1)	287 (59.0%)
Naïve COC users	77 (5.6%)	16 (3.3)

Source: Study Report A35179, Text Table 22; p 100 of 3674 and Table 20, p 463 of 3674, and Study Report A39818, Text Table 7; p 55 of 484 and Table 9, p 220 of 484

Team Leader Comments

- **The European trial was the only one to include women over age 35.**
- **Ethnic diversity in the US trial is much more representative of the US population.**
- **Other demographic features such as smoking status, weight and BMI are fairly similar over the two populations.**
- **There were few naïve users in either trial; thus, the study populations predominantly comprised women who had previously tolerated COCs.**

7.2.2 DISPOSITION OF SUBJECTS

A total of 1,446 women were screened for Study 306660, with 1,391 enrolled. Of these, 1,377 women took at least one dose of EV/DNG. For Study 304742, of 583 women screened, 499

enrolled, and 490 took at least one dose. This latter group constituted the safety population and the Full Analysis Set (FAS) population. A total of 295 women from the randomized population in Study 306660 and 235 from Study 304742 discontinued prematurely for the reasons described in Table 3.

Table 3 Studies 306660 and 304742 – Subject Disposition (Full Analysis Population)

Disposition / Reason	Study 306660	Study 304742
Screened	1,446	583
Screening failures	55 (3.8%)	84 (14.4%)
Study medication never administered	14 (1.0%)	9 (1.8%)
Full Analysis Set (a)	**1,377 (100%)**	**490 (100%)**
FAS aged 18-35	998 (72.5%)	490 (100%)
Prematurely discontinued from the study	295 (21.4%)	235 (48.0%)
• Adverse event	142 (10.3%)	73 (14.9%)
• Other*	71 (5.2%)	40 (8.2%)
• Protocol deviation	26 (1.9%)	6 (1.2%)
• Lost to follow-up	26 (1.9%)	63 (12.9%)
• Withdrawn consent	20 (1.5%)	48 (9.8%)
• Pregnancy	11 (0.8%)	5 (1.0%)
• Death	1 (<0.1%)	0
Completed the study medication	1074 (78.0%)	243 (49.6%)
Study medication status unknown	8 (0.6%)	12 (2.4%)

a = Defined as all randomized subjects who took at least one dose of study drug and had at least one post-treatment observation; subsequent percents are based on this denominator
Source: Study Report A35179 Text Figure 2; p 86 of 3674 and Study Report 39818 Text Table 6, p 51 of 484

Team Leader Comments

- **In Study 306660, the 8 women with unknown medication status include 1 who died (Subject #4318), 5 lost to follow-up, 1 missing and 1 other.**
- **In Study 307472, no further information is available on the 12 subjects with unknown medication status.**
- **As is commonly noted in comparing European and US contraceptive studies, the rate of premature discontinuations is considerably higher among US subjects. Among the specific reasons for early discontinuation, US subjects are more likely to withdraw due to adverse events, consent withdrawal, and loss to follow-up.**

7.2.3 EFFICACY FINDINGS

7.2.3.1 Assessment of Efficacy

A Day 1 start was used (i.e., subjects were to begin taking EV/DNG on the first day of withdrawal bleeding) regardless of whether they were switching from another hormonal contraceptive, or beginning for the first time. In subsequent cycles, subjects followed a 28-day schedule, and resumed active pill intake without regard to the occurrence of bleeding. Subjects were instructed to take the pills at intervals as close as possible to 24 hours, and no instructions with regard to timing of food intake were included. Subjects were provided with two reserve pill packs. Women who experienced vomiting or diarrhea within 4 hours of pill-taking were instructed to take an additional pill of the same color from the extra pill pack. Women on antibiotics or certain psychotropic drugs were instructed to use back-up contraception until seven days after discontinuing the concomitant medication. Due to the

multiphasic dose schedule, the missed pill instructions were complex, and are presented in Table 4.

Table 4 Missed Pill Instructions in Contraceptive Trials

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,
8-17	2.0 mg EV + 3.0 mg DNG	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	

Source: Based on Study Report A35179; Text table 6, page 53 of 3674

Subjects did not undergo routine pregnancy testing at study visits, except for just prior to or during the end of treatment visit. At the Austrian study sites in Study 306660, pregnancy testing was conducted during each cycle. In both studies, subjects who missed a period were instructed to take a home pregnancy test, which was provided to them at each study visit (in Study 304742, subjects were instructed to do home testing twice at unspecified intervals in case of a missed period).

Team Leader Comment

The pregnancy testing in these trials was less rigorous than usually employed in contraceptive trials, which typically evaluate for pregnancy three or four times over a 13-cycle study. However, a crude assessment of the impact of testing frequency can be gleaned by evaluating pregnancy data in Study 306660 from those European countries that did or did not utilize pregnancy testing at every cycle. In Austria, the one country that did monthly pregnancy testing, the detected pregnancy rate was 1 in 272 subjects, or 0.3%. In Spain and Germany, which did just baseline and end-of-study testing (in addition to for-cause testing in subjects who missed a period), the detected pregnancy rates were 2 of 54 (3.7%) and 6 of 1,120 (0.5%), respectively. If less frequent testing resulted in under-ascertainment of "chemical pregnancies," it would be expected that Austria would have a higher pregnancy rate. Therefore, there does not appear to be an adverse impact of the pregnancy testing protocol on the detection of pregnancies.

7.2.3.2 Primary Efficacy Analysis

The primary endpoint was the Pearl Index, calculated as

$$\text{Pearl Index} = \frac{100 \times \text{number of pregnancies} \times 13 \text{ cycles/year}}{\text{Number of 28-day cycles of treatment*}}$$

* Only cycles in which no back-up contraceptive methods were used were included.

The analysis population was the Full Analysis Set (FAS) population, defined as all subjects who received at least one dose of study drug, and were evaluated for pregnancy at least once after beginning study drug. This population was further defined as those subjects who were

between the ages of 18-35 years, with exclusion of any cycles in which an alternate method of birth control was used (also known as the pregnancy intent-to-treat [PITT, non-BCM] population). Information on use of back-up contraception was collected by investigators at each study visit and recorded in the CRF; subjects did not record this in the daily diaries.

Team Leader Comment

The PITT, non-BCM population is the appropriate one for evaluation of the primary endpoint (Pearl Index), and cycles in which other contraception (including condoms) was used were appropriately excluded.

Pregnancies conceived on drug or within 7 days after the last pill (whether EV/DNG, or EV only or placebo) were included in calculation of the Pearl Index. The Applicant initially included pregnancies conceived within the first 14 days after the completion of pill-taking; however, the Division analyzed the data to include only those pregnancies conceived within 7 days after the final tablet taken.

Team Leader Comments

- **The Division's recent thinking on the window in which conceptions are counted is that pregnancies conceived within 7 days after the last pill taken (whether active or placebo pill) are to be counted. This allows for inaccuracy in ultrasound dating of pregnancies, but acknowledges that contraceptive protection is not expected to be maintained beyond the "placebo" week in a typical 21/7 regimen. At the time this study was discussed with the Applicant, the Division was recommending a 14-day conception window for calculation of the Pearl Index. For this reason, the Applicant's calculations included all pregnancies conceived in the 14-day window; however, following the Division's subsequent advice, the FDA statistician counted only those pregnancies conceived within the 7-day window.**
- **In addition, the Applicant calculated the Pearl Index on the basis of exposure time in days, while the FDA statistician used exposure time based on 28-day cycles, as is customary. This modification did not change the results of the studies.**

Life table methods are also commonly used to assess contraceptive efficacy; these provide cumulative rates of pregnancy at the end of the study, and at the end of each preceding cycle. Life table methods do not typically exclude individual cycles for a given subject, such as a cycle in which an alternate method of birth control was used, but more commonly censor a subject from the remainder of the trial as soon as she uses back-up contraception. For this reason, life table analyses are often not directly comparable to the Pearl Index based on the PITT, non-BCM population.

The primary efficacy analysis was based on Studies 304742 and 306660. Study 304004 was conducted only for seven cycles, and did not have assessment of contraceptive efficacy as a primary objective.

A total of 16 pregnancies occurred in subjects in Study 304742, with five occurring on-treatment in women <36 years of age. There were no pregnancies conceived within seven days after discontinuing treatment. In Study 306660, a total of 30 pregnancies occurred, with 10 occurring on treatment, and none in the 7 days after last pill intake. An additional three pregnancies occurred, in Cycles 15, 18 and 20, respectively, and were not included in the Year 1 Pearl Index calculation. One other pregnancy occurred in a woman over age 35, which was also not included in the Pearl Index calculation.

Table 5 Timing of Conception

	Study 304742 (US/Canada)		Study 306660 (Europe)	
Timing of conception	**N**	**Comment**	**N**	**Comment**
Total # pregnancies	15		30	
Prior to starting treatment	3		5	
On treatment	**5**		**9**	
≤ 7 days after last E+P pill	**0**		**0**	
Unknown last E+P intake	**0**		**0**	
Other excluded pregnancy	2	1 pregnancy occurred after first 13 cycles of treatment; therefore not counted in Year 1 Pearl Index 1 pregnancy had uncertain date of last pill intake, but pregnancy occurred after first 13 cycles of treatment; therefore not counted in Year 1 Pearl Index	4	3 pregnancies occurred after first 13 cycles of treatment; therefore not counted in Year 1 Pearl Index 1 in woman > 35 years
> 7 to ≤ 14 days after last E+P pill	1	Conceived on Day 9 after last tablet	1	Conceived on Day 13 after last tablet
> 14 days after last E+P pill	4	Occurred 28-88 days after last dose	11	Occurred 17-333 days after last dose

Bold = Pregnancies counted in computing the Pearl Index

Pearl Index

The statistical reviewer, Xin Fang, Ph.D., reviewed the Applicant's data and recalculated the Pearl Index based on pregnancies conceived on treatment or within 7 days after the last pill intake (see Table 6), and using exposure based on 28-day cycles. The "gold standard analysis" relied upon by the Division is the PITT, non-BCM, which gives a Pearl Index of 1.64 (upper bound of the 95% confidence interval [CI] is 3.82) in the North American population.

Table 6 Pearl Index Calculation of Treatment Failure Rates using 7-Day after Last Pill Conception Rule, in the PITT, non-BCM Population

Study	Analysis	Number of 28 day cycles	Cycles with back-up contraception	Number of evaluable cycles	Number of pregnancies	Pearl Index	Upper 95% CI
304742 (US/Canada)	FDA	4,575	606	3,969	5	1.6377	3.8218
306660 (Europe)	FDA	11,576	302	11,274	9	1.0378	1.9700

Source: Table 3.2.3.1b, Statistical review by Xin Fang, Ph.D., dated March 31, 2010

Team Leader Comments

- **As typically seen in data from US and European populations, the Pearl Index in the US population is considerably higher than that in the European subjects. This is likely attributable to both greater weight and BMI in American women, and possibly to improved compliance in Europe.**
- **The Pearl Index based on the US data provides evidence of acceptable contraceptive efficacy.**

Life Table Analysis

The Applicant provided a Year 1 life table estimate of the pregnancy rate for each study, based upon pregnancies that occurred within 14 days after the last pill intake, while the FDA statistician provided life table estimates based on the 5 and 9 pregnancies that occurred within 7 days after the last pill intake (see Table 7). Dr. Fang excluded only those cycles in which back-up contraception was used, rather than censoring a subject as soon as she used back-up contraception.

Table 7 Life Table Estimates of Treatment Failure Rates in the First 13 Cycles – Women 18-35 Years of Age with at Least One Complete Cycle of Treatment (PITT)

Study	Relevant exposure days	Sponsor's analysis[1]		FDA analysis[2]	
		Probability of no conception	Pregnant Rate (95% CI)	Probability of no conception	Pregnant Rate (95% CI)
304742 (US/ Canada)	75	0.9974	0.0026 (0.0004, 0.0186)	0.9973	0.0027 (0.0004, 0.0187)
	88	0.9946	0.0054 (0.0014, 0.0215)	--	--
	102	0.9918	0.0082 (0.0027, 0.0253)	0.9945	0.0055 (0.0014, 0.0218)
	186	0.9851	0.0149 (0.0062, 0.0356)	0.9878	0.0122 (0.0046, 0.0323)
	203	0.9816	0.0184 (0.0083, 0.0406	0.9843	0.0157 (0.0065, 0.0375)
306660 (Europe)	13	0.9990	0.0010 (0.0001, 0.0071)	0.9990	0.0010 (0.0001, 0.0071)
	14	0.9980	0.0020 (0.0005, 0.0081)	0.9980	0.0020 (0.0005, 0.0081)
	69	0.9969	0.0031 (0.0010, 0.0095)	0.9969	0.0031 (0.0010, 0.0095)
	95	0.9959	0.0041 (0.0016, 0.0110)	0.9959	0.0041 (0.0016, 0.0110)
	149	0.9947	0.0053 (0.0022, 0.0126)	0.9947	0.0053 (0.0022, 0.0126)
	201	0.9936	0.0064 (0.0029, 0.0142)	0.9936	0.0064 (0.0029, 0.0142)
	207	0.9924	0.0076 (0.0036, 0.0158)	0.9924	0.0076 (0.0036, 0.0158)
	208	0.9913	0.0087 (0.0044, 0.0174)	0.9913	0.0087 (0.0044, 0.0174)
	280	0.9901	0.0099 (0.0052, 0.0190)	0.9901	0.0099 (0.0052, 0.0190)
	336	0.9887	0.0113 (0.0061, 0.0209)	--	--

[1] Pregnancies are counted based on first 13 cycles and within 14 days after the last treatment.
[2] Pregnancies are counted based on first 13 cycles and within 7 days after the last treatment.
Source: Table 3.2.3.2, Statistical review by Xin Fang, Ph.D., dated March 31, 2010

Team Leader Comment

The life table estimates are similar whether computed based on a 14 or 7 day conception window, indicating few pregnancies occurring after the last pill intake. The life table estimates are also reasonably close to the Pearl Indices, and, like the Pearl Index, provide evidence of acceptable contraceptive efficacy.

Statistician's Conclusion

The statistical reviewer, Xin Fang, Ph.D., confirmed the Applicant's overall primary efficacy findings, although his Pearl Index calculations were actually lower than those provided by the Applicant, due to use of the 7-day conception window and counting only pregnancies occurring in the first 13 cycles of pill use. Dr. Fang noted that the Applicant calculated the Pearl Index based on exposure time in days, whereas the Division bases it on 28-day cycles. He also identified a few subjects the Applicant had included despite additional back-up contraception use, or having vasectomized partners, and ensured that these were not included among the evaluable cycles. However, neither correction made a significant difference in the results. Although the Applicant also provided a Pearl Index based on pooled data from the two studies, Dr. Fang concluded that pooling was inappropriate due to demographic differences in the populations. This is consistent with the Division's usual approach to US and European

studies.

Dr. Fang made the following conclusions and recommendations regarding contraceptive efficacy in his review dated March 31, 2010:

> *The data supported the efficacy of Estradiol Valerate/Dienogest in the prevention of pregnancy as demonstrated by the Pearl Index (PI) of < 2.0 in both the North American and the European studies.*
>
> *From a statistical perspective, this application provided adequate data to support the efficacy of the EV/DNG as oral contraceptive.*

7.2.3.3 Efficacy Analyses in Supportive Studies

Although contraceptive efficacy was not a primary objective in the 7-cycle Study 304004, which was primarily intended to characterize cycle control, it is worth noting that no pregnancies were conceived on-treatment among women randomized to EV/DNG in the trial. In Study 304004, there were 7 pregnancies. Two occurred prior to initiation of treatment, 2 occurred on treatment in the comparator arm, and 3 occurred more than 7 days following the last pill intake (2 in the EV/DNG arm, occurring 2-5 months after end of treatment, and one in the comparator arm, occurring 3.5 months after end of treatment).

7.2.3.4 Secondary Efficacy Analysis

Characterization of the bleeding profile of EV/DNG was the primary objective of Study 304004, and a secondary objective of the pivotal contraceptive studies 304742 and 306660. Subjects completed a daily paper diary that recorded occurrence and intensity of bleeding or spotting. The following bleeding intensity definitions were used:

- None: no vaginal bleeding
- Light: less than the subject's normal menses, but requiring use of sanitary protection
- Normal: like the subject's normal menses
- Heavy: more than the subject's normal menses

Light bleeding that required no use of sanitary protection (aside from panty liners) was classified as spotting.

A bleeding/spotting episode was defined as the number of days of bleeding/spotting that were preceded and followed by at least two bleeding-free days. A bleeding-free interval was defined as at least two days free of bleeding or spotting, and followed by at least one bleeding/spotting day. Bleeding/spotting was characterized as withdrawal (herein referred to as "scheduled") if it started on or after Day 21 of a cycle and before starting the next treatment cycle. All other bleeding/spotting episodes were considered "intracyclic" by the Applicant (herein referred to as "unscheduled"). Amenorrhea was defined as the absence of bleeding from Day 25 of one cycle to Day 25 of the next cycle.

The Applicant initially reported bleeding data using the 90-day reference period recommended by the WHO. However, at the Division's request, the Applicant also provided the following bleeding data based on 28-day cycles, which is consistent with the Division's current thinking on evaluating and reporting cycle control (see Table 8 through Table 11). The Applicant reported that subjects experienced amenorrhea in an average of 16% of cycles. Specific proportions of women experiencing amenorrhea are 14.1 – 18.4% in Study 306660 (first 13

cycles), 14.0 – 28.2% in Study 304742 (first 13 cycles) and 12.3 – 18% in Study 304004 (7 cycles).

Table 8 Studies 306660 & 304742 - Days with Unscheduled Bleeding per 28-Day Cycle (First 13 Cycles)

	Study 30660					Study 304742				
Cycle	N	Mean (SD)	Min	Median	Max	N	Mean (SD)	Min	Median	Max
1	1200	4.4 (2.1)	1	4.0	21	327	4.5 (2.9)	1	4.0	23
2	158	4.5 (3.2)	1	4.0	17	48	4.3 (3.3)	1	3.5	13
3	143	4.0 (2.8)	1	3.0	17	44	4.0 (3.0)	1	3.0	13
4	118	4.1 (2.9)	1	4.0	15	30	5.0 (3.5)	1	4.0	16
5	107	3.7 (2.7)	1	3.0	16	23	3.9 (2.5)	1	3.0	9
6	91	3.7 (2.3)	1	3.0	10	24	5.0 (3.3)	1	4.0	16
7	74	3.7 (3.3)	1	3.0	17	18	3.9 (2.7)	1	3.0	9
8	77	3.8 (2.4)	1	3.0	12	17	4.5 (2.6)	1	4.0	11
9	78	3.9 (2.5)	1	3.0	13	17	3.4 (2.2)	1	3.0	8
10	88	3.9 (2.5)	1	3.0	12	16	4.0 (3.3)	1	4.0	14
11	65	4.6 (3.4)	1	4.0	18	11	4.0 (4.4)	1	1.0	13
12	71	3.7 (2.5)	1	3.0	15	14	4.0 (2.4)	1	3.0	8
13	66	3.6 (2.5)	1	3.0	12	15	2.9 (2.2)	1	2.0	7

Source: Based on Applicant submission dated April 6, 2010

Table 9 Studies 306660 & 304742 - Days with Unscheduled Spotting per 28-Day Cycle (First 13 Cycles)

	Study 30660					Study 304742				
Cycle	N	Mean (SD)	Min	Median	Max	N	Mean (SD)	Min	Median	Max
1	746	3.1 (3.2)	1	2.0	24	272	3.5 (3.6)	1	2.0	24
2	280	4.1 (3.9)	1	3.0	23	94	3.7 (2.8)	1	3.0	14
3	236	3.6 (2.9)	1	3.0	20	71	4.4 (2.6)	1	3.0	16
4	201	3.5 (3.1)	1	2.0	17	63	3.3 (2.3)	1	3.0	10
5	199	3.7 (2.9)	1	3.0	15	59	2.6 (2.1)	1	2.0	11
6	173	3.4 (2.9)	1	2.0	14	38	2.7 (2.7)	1	2.0	17
7	141	4.0 (3.5)	1	3.0	18	38	3.1 (2.7)	1	2.0	12
8	161	3.4 (3.1)	1	2.0	19	35	4.0 (3.0)	1	3.0	12
9	145	3.4 (2.9)	1	3.0	18	26	3.5 (2.8)	1	2.5	11
10	152	3.6 (2.9)	1	3.0	17	31	2.8 (2.1)	1	2.0	9
11	126	3.4 (3.2)	1	2.0	25	23	3.0 (2.3)	1	3.0	8
12	138	3.5 (3.1)	1	2.0	15	36	3.5 (3.0)	1	3.0	12
13	132	3.4 (3.3)	1	2.0	19	36	2.4 (2.2)	1	2.0	13

Source: Based on Applicant submission dated April 6, 2010

Table 10 Studies 306660 & 304742 - Days with Scheduled Bleeding per 28-Day Cycle (First 13 Cycles)

	Study 30660					Study 304742				
Cycle	N	Mean (SD)	Min	Median	Max	N	Mean (SD)	Min	Median	Max
1	761	3.3 (2.0)	1	3.0	31	191	3.2 (1.7)	1	3.0	12
2	822	3.5 (2.1)	1	3.0	18	192	3.4 (2.0)	1	3.0	12
3	776	3.4 (1.8)	1	3.0	12	177	3.1 (2.1)	1	3.0	17
4	771	3.3 (1.7)	1	3.0	17	148	3.1 (1.9)	1	3.0	13
5	756	3.4 (1.8)	1	3.0	14	172	2.9 (1.9)	1	2.0	13
6	729	3.4 (1.7)	1	3.0	12	144	2.8 (1.7)	1	2.5	9
7	725	3.2 (1.7)	1	3.0	11	143	3.0 (1.8)	1	3.0	13
8	701	3.2 (1.8)	1	3.0	16	136	3.0 (1.7)	1	3.0	9
9	693	3.2 (1.7)	1	3.0	17	131	3.2 (2.1)	1	3.0	12
10	667	3.2 (1.7)	1	3.0	12	116	2.9 (1.7)	1	3.0	10
11	645	3.1 (1.6)	1	3.0	17	123	2.9 (2.1)	1	2.0	12
12	642	3.0 (1.5)	1	3.0	12	118	2.8 (1.8)	1	2.0	10
13	628	3.1 (1.6)	1	3.0	18	92	2.5 (1.3)	1	2.0	6

Source: Based on Applicant submission dated April 6, 2010

Table 11 Studies 306660 & 304742 - Days with Scheduled Spotting per 28-Day Cycle (First 13 Cycles)

	Study 30660					Study 304742				
Cycle	N	Mean (SD)	Min	Median	Max	N	Mean (SD)	Min	Median	Max
1	666	2.4 (1.8)	1	2.0	15	247	2.8 (3.5)	1	2.0	49*
2	690	2.6 (3.4)	1	2.0	75*	208	2.5 (2.0)	1	2.0	18
3	677	2.3 (1.7)	1	2.0	14	202	2.7 (2.9)	1	2.0	27
4	664	2.4 (1.9)	1	2.0	17	198	2.3 (1.6)	1	2.0	12
5	660	2.4 (1.9)	1	2.0	18	189	2.6 (2.0)	1	2.0	21
6	622	2.5 (2.1)	1	2.0	27	175	2.8 (2.2)	1	2.0	17
7	647	2.4 (1.8)	1	2.0	22	183	2.6 (1.7)	1	2.0	13
8	643	2.4 (1.7)	1	2.0	17	162	2.7 (2.4)	1	2.0	23
9	648	2.5 (1.9)	1	2.0	18	158	2.6 (1.6)	1	2.0	12
10	620	2.5 (2.9)	1	2.0	63*	142	2.5 (1.6)	1	2.0	10
11	613	2.5 (2.2)	1	2.0	32*	147	2.5 (1.6)	1	2.0	11
12	612	2.3 (1.5)	1	2.0	13	157	2.2 (1.3)	1	2.0	7
13	586	2.4 (1.6)	1	2.0	14	114	2.3 (1.4)	1	2.0	8

* The Applicant has indicated that a very few subjects had bleeding or spotting episodes that continued through more than one cycle; these are indicated as durations > 28 days.
Source: Based on Applicant submission dated April 6, 2010

Team Leader Comments

- **Although Studies 306660 and 304742 collected bleeding data for 20 and 28 cycles, respectively, only the first 13 cycles are reported here. This is the standard cycle control data typically presented for COCs, and there is no reason to change a marked change in bleeding profile after the first year of use.**
- **It is unclear why the number of subject who provided data for scheduled spotting is so much lower than those who provided data for scheduled bleeding.**

- **It should be noted that the Applicant considered the bleeding at the start of Cycle 1 (i.e., the first menses, at which study drug was started) as unscheduled bleeding for that cycle. For this reason, the number of subjects in Cycle 1 who reported unscheduled bleeding/spotting is artifactually high.**
- **The number of scheduled bleeding days decreased slightly over time, and averaged a little over 3 days per cycle, along with about 2.5 days of scheduled spotting per cycle.**
- **For unscheduled bleeding, the duration decreased slightly over time, but averaged about 4 days per cycle. Unscheduled spotting remained relatively stable over time, and averaged about 3.5 days per cycle. However, unscheduled bleeding/spotting figures appear to be reported only for those subjects who experienced any unscheduled bleeding/spotting, and thus would represent over-estimates of the duration in the total population (i.e., women who experienced 0 days of unscheduled bleeding/spotting are not included in the descriptive data).**
- **Unscheduled bleeding/spotting is likely to be more troublesome to women; therefore, a product where unscheduled bleeding/spotting occurs more frequently than scheduled bleeding/spotting may not be well-tolerated.**
- **The profile of both scheduled and unscheduled bleeding/spotting should be described in labeling.**

Table 12 presents cycle control data from Study 304004.

Table 12 Cycle Control in Study 304004 (Full Analysis Set)

	Scheduled Bleeding					Scheduled Spotting				
Cycle	**N**	**Mean (SD)**	**Min**	**Median**	**Max**	**N**	**Mean (SD)**	**Min**	**Median**	**Max**
1	239	3.2 (1.8)	1	3.0	19	228	2.7 (2.8)	1	2.0	26
2	243	3.4 (1.9)	1	3.0	17	235	2.5 (2.3)	1	2.0	23
3	239	3.4 (2.1)	1	3.0	15	229	2.6 (2.3)	1	2.0	21
4	238	3.3 (2.0)	1	3.0	14	231	2.8 (3.1)	1	2.0	41*
5	238	3.1 (1.8)	1	3.0	15	215	2.8 (1.9)	1	2.0	16
6	237	3.4 (1.7)	1	3.0	11	214	2.7 (2.5)	1	2.0	30*
7	238	3.0 (1.6)	1	3.0	10	218	2.3 (1.4)	1	2.0	10
	Unscheduled Bleeding					**Unscheduled Spotting**				
1	23	3.9 (2.9)	1	3.0	13	68	3.6 (2.9)	1	3.0	14
2	31	4.5 (2.8)	1	4.0	10	57	3.8 (2.9)	1	3.0	13
3	22	4.6 (3.7)	1	3.0	12	44	3.6 (3.4)	1	2.0	16
4	29	3.6 (2.1)	1	3.0	8	55	4.4 (3.1)	1	3.0	14
5	20	4.1 (3.2)	1	3.0	12	37	3.1 (3.1)	1	2.0	14
6	18	3.6 (1.8)	1	4.0	8	34	3.6 (2.8)	1	3.0	12
7	30	4.2 (2.8)	1	4.0	10	42	2.9 (2.1)	1	2.0	10

* The Applicant has indicated that a very few subjects had bleeding or spotting episodes that continued through more than one cycle; these are indicated as durations > 28 days.
Source: Based on Applicant submission dated April 30, 2010

Team Leader Comments

- **The bleeding profile in the cycle control study 304004 is comparable to that seen in the two contraception trials.**
- **The withdrawal bleeding/spotting duration is comparable to that seen with COCs containing 20 to 25 µg of EE. In the comparative study 304004, the unscheduled bleeding/spotting profile is similar to that observed with a low dose 21/7 EE/LNG regimen. There is no evidence that the multiphase cycle results in significantly**

improved cycle control. However, I concur with Dr. Willett that the bleeding profile of EV/DNG is acceptable.

7.2.4 Overall Assessment of Efficacy (Contraception)

The two contraceptive efficacy studies conducted by the Applicant provided robust confirmation of the efficacy of EV/DNG in the prevention of pregnancy. While, as frequently observed, the pregnancy rate was greater in US than European subjects, the Pearl Index based on the US study is acceptable. The bleeding profile appears comparable to that observed in women using low dose COCs containing EE and various progestins. There is no evidence that the four-phase dosing regimen results in improved cycle control, as anticipated by the Applicant. However, the bleeding profile for EV/DNG is acceptable.

7.3 SECONDARY INDICATION – TREATMENT OF HEAVY AND/OR PROLONGED MENSTRUAL BLEEDING

Study 308960 was conducted at 47 sites in the US and Canada. Study 308961 was conducted at 43 study sites in 10 European countries. Dr. Willett's review notes that there were frequent protocol deviations in both studies (about 60% of subjects had major deviations in each study), with slightly higher frequency in the EV/DNG arms than the placebo arms. Major deviations included

- Failure to complete 7 cycles – 25-27% of subjects had this deviation
- Bleeding intensity missing for 2 or more consecutive days during run-in or from Day 85 to 174 – 20-35% of subjects had this deviation; more common in Study 308961
- Bleeding intensity data missing for > 10% of days from Day 85 to 174 – 10-17% of subjects had this deviation, more common in Study 308960

Subjects often had more than one protocol deviation.

Team Leader Comment

Although the proportion of major protocol deviations is quite high, it appears that the protocol appropriate addressed the major issues of missing data by considering subjects without sufficient evaluable data as treatment failures (see discussion of missing data in Section 7.3.3.1.

7.3.1 DEMOGRAPHICS

Entry criteria for the two studies were virtually identical and included a diagnosis of DUB unrelated to organic causality. The DUB diagnosis included at least one of the following symptoms during a 90-day run-in period:

- Prolonged bleeding: two or more bleeding episodes, each lasting ≥ 8 days
- Frequent bleeding: more than five bleeding episodes, with a minimum of 20 bleeding days in the 90 day period
- Excessive bleeding: ≥ 2 bleeding episodes, each with blood loss of ≥ 80 ml, assessed by alkaline hematin

Team Leader Comments

- **The entry criteria relating to DUB symptoms are in accord with those agreed-upon by the Division. As requested by the Division, the Applicant limited DUB symptoms addressed to these three aspects of DUB.**
- **Excessive bleeding is described in the proposed indication as "heavy bleeding."**

Additional major entry criteria included age > 18 years (no upper limit, but with FSH < 40 mIU/ml if over age 40). Exclusionary factors were use of hormonal contraception (aside from study drug), concomitant use of medications inhibiting or inducing CYP3A4, and BMI > 32 kg/m2 (> 30 kg/m2 in the three UK sites for Study 308961).

Table 13 shows the demographics of the Intent to Treat (ITT) populations in Studies 308960 and 308961. Five randomized subjects in Study 308960 (one randomized to EV/DNG and four to placebo) did not start study medication. In Study 308961, five randomized subjects (four to EV/DNG and one to placebo) did not start study drug.

Table 13 Studies 308960 and 308961 – Demographics and Baseline Characteristics (ITT Population)

	Study 308960		Study 308961	
Characteristic	**EV/DNG N=120**	**Placebo N = 70**	**EV/DNG N=149**	**Placebo N =82**
Mean age (years (SD) [range])	36.9 (7.5) [20-53]	37.0 (6.7) [21-49]	39.5 (6.6) [18-51]	38.5 (7.5) [19-54]
Ethnic group N (%)				
• **Caucasian**	71 (59.2)	46 (65.7)	144 (96.6)	80 (97.6)
• **Black**	38 (31.7)	14 (20.0)	1 (0.7)	0
• **Hispanic**	8 (6.7)	6 (8.6)	0	0
• **Asian**	1 (0.8)	2 (2.9)	2 (1.3)	1 (1.2)
• **Other**	2 (1.7)	2 (2.9)	2 (1.3)	1 (1.2)
Smoker N (%)	16 (13.3)	10 (4.3)	42 (28.2)	31 (37.8)
Mean weight (kg) (SD)	71.3 (11.1)	69.5 (11.8)	69.8 (11.8)	71.6 (10.2)
Mean height (cm) (SD)	164.6 (6.2)	164.0 (6.9)	168.4 (6.3)	166.8 (6.3)
Body mass index (kg/m^2) (SD)	26.3 (3.6)	25.8 (3.6)	24.5 (3.5)	25.7 (3.0)
Prior COC use N (%) [past 30 days]	0	1 (0.8)	0	0
No contraception [past 30 days]	5 (4.2)	7 (10.0)	30 (20.1)	12 (14.6)

Source: Study Report A29849, Table 8, pp 177-8 of 1182 and Study Report A42568, Table 8, pp 240-1 of 1235

Team Leader Comments

- **The population studied for the DUB indication differed from that in the OC trials, in that the women tended to be considerably older (average age 37-40, as compared to 25-30 for the OC trials) and heavier (average BMI about 25 as compared to 23 for the OC trials). This has been noted in other DUB trials, as women with bleeding concerns tend to be older than the general population that seeks contraception only. As both increasing age and weight are risk factors for VTEs, the risk/benefit profile for the population seeking DUB treatment must be evaluated independently of the risk/benefit profile for the population seeking contraception alone.**

- **Use of hormonal contraception in the 30 days preceding enrollment was an exclusion criterion.**
- **Ethnic diversity is minimal in the European study; the North American study is more representative of the US population of likely users.**

The distribution of DUB symptoms at baseline are shown in Table 14.

Table 14 Studies 308960 and 308961 – DUB Symptoms at Baseline (ITT Population)

	Study 308960		Study 308961	
	EV/DNG N=120 n (%)	Placebo N=70 n (%)	EV/DNG N=149 n (%)	Placebo N=82 n (%)
Prolonged and frequent bleeding	3 (2.5)	2 (2.9)	0	0
Prolonged and excessive bleeding	9 (7.5)	9 (12.9)	15 (10.1)	9 (11.0)
Frequent and excessive bleeding	1 (0.8)	0	0	0
All three types	0	0	0	0
Prolonged bleeding with or without other sx	26 (21.7)	12 (17.1)	20 (13.4)	10 (12.2)
Frequent bleeding with or without other sx	4 (3.3)	2 (2.9)	0	0
Excessive bleeding with or without other sx	91 (75.8)	60 (85.7)	136 (91.3)	76 (92.7)

Source: Study Report A29849; Text table 8, p 61 of 1182 and Study Report A42568, Text table 22, p 105 of 1235

Team Leader Comments

- **The most common complaint in both arms of both studies was excessive bleeding.**
- **No subjects had frequent bleeding in isolation.**

7.3.2 DISPOSITION OF SUBJECTS

A total of 1,077 women were screened for Study 308960, with 190 randomized (120 EV/DNG, 70 placebo). Of these, 119 women in the EV/DNG arm and 66 women in the placebo arm took at least one dose of study drug. For Study 308961, of 575 women screened, 231 were randomized, and 226 took at least one dose. This latter group constituted the safety population and the Full Analysis Set (FAS) population. A total of 54 women from the randomized population in Study 308960 and 49 from Study 308961 discontinued prematurely for the reasons described in Table 15.

Table 15 Studies 308960 and 308961 – Subject Disposition (ITT Population)

Disposition / Reason	Study 308960		Study 308961	
Screened	1,077		575	
Screening failures	887 (82.4%)		344 (59.8%)	
Randomized to:	**EV/DNG**	**placebo**	**EV/DNG**	**placebo**
ITT population	120	70	149	82
Study medication never administered	1	4	4	1
FAS*	**119** (99.2%)	**66** (94.3%)	**145** (97.3%)	**81** (98.8%)
	N (% of FAS)			
Prematurely discontinued from the study	35 (29.4)	19 (28.8)	32 (22.1)	17 (20.7)
• Adverse event	12 (10.1)	3 (4.5)	12 (8.3)	4 (4.9)
• Withdrawn consent	11 (9.2)	4 (6.0)	9 (6.2)	4 (4.9)
• Other	6 (5.0)	4 (6.0)	6 (4.1)	6 (7.3)
• Missing	3 (2.5)	5 (7.5)	--	--
• Protocol deviation	2 (1.7)	0	3 (2.1)	2 (2.4)
• Lost to follow-up	1 (0.8)	2 (3.0)	--	--
• Pregnancy	0	1 (1.5)	0	1 (1.2)
Completed the study medication	85 (71.4)	51 (77.3)	117 (80.7)	65 (80.2)

* Defined as all randomized subjects who took at least one dose of study drug; subsequent percents are based on this denominator

Source: Study Report A29849, pp 167-8 of 1182 and Study Report A42568, pp 228-9 of 1235

Team Leader Comments

- **It is unclear why the rate of screen failures was so much higher in the North American trial.**
- **Rates of premature discontinuations were similar across treatment arms, and tended to be higher in the North American trial. This is commonly seen when comparing US and European trials.**
- **In both studies, withdrawals attributed to AEs and withdrawn consent were more frequent in the EV/DNG group. Other reasons for discontinuation did not differ markedly.**
- **"Missing" and "lost to follow-up" were not included as reasons for premature discontinuation in Study 308961.**
- **In Study 308960, "other" reasons for discontinuation included**
  - **Lack of efficacy (2)**
  - **Patient stopped drug**
  - **Moved out of state**
  - **Withdrawn consent**
  - **Noncompliance**
- **In Study 308961, "other" reasons for discontinuation included**
  - **Patient unsatisfied**
  - **Insufficient effect**
  - **Not all tablets taken by patient (3 subjects)**
  - **Wrong randomization**
  - **Patient occasionally forgot pills while traveling**
  - **Hysterectomy**
  - **Only 171 (vs. 196) pills taken**
  - **Not interested in completing all pills**
  - **Subject moving abroad**
  - **Investigator withdrew subject due to noncompliance**

- **Subjects in Study 308960 whose reason for discontinuation is listed as "missing" include one who was brought in too early for Visit 11 and had not completed Cycle 7, 3 who were lost to follow-up and one with no reason listed.**

7.3.3 EFFICACY FINDINGS

7.3.3.1 Assessment of Efficacy

Dosing was the same as in the contraceptive trials, with intake initiated on the first day of bleeding following randomization. Missed pill instructions were similar to the contraceptive trials, except that in a case of two or more consecutive missed pills, subjects were instructed to take only the one from the previous day before resuming normal intake.

Subjects kept a daily record of bleeding and spotting in an electronic diary, and also recorded number of sanitary products used and medication intake. Subjects also indicated in the diary whether all sanitary products were collected during the relevant cycles. Bleeding was characterized as none, spotting, light, normal or heavy, according to the same definitions used in the contraception trials. Bleeding episodes were defined as at least 2 days of bleeding, separated by no more than one bleeding-free days (themselves defined as days without bleeding or with only spotting). Bleeding days were defined as those on which sanitary protection (beyond panty liners) was required; spotting was defined as requiring no protection, or only panty liners.

The diary was accompanied by an electronic alarm that reminded subjects to enter data daily. Subjects chose either a morning or evening report schedule, each of which had specific time bounds for data entry. If they did not respond within the first few hours of these limits, the alarm beeped hourly until the end of the entry interval to remind subjects to enter data. However, they were afforded a 72 hour retrospective entry window, so subjects who failed to enter data at all for a day were still prompted to enter it retrospectively at the next reporting period. . The Division had raised concerns prior to NDA submission that the alarm might also prompt compliance with pill-taking, resulting in efficacy results better than would be expected in actual use, where women are not reminded to take their pills daily. The Applicant addressed these concerns in the current submission by comparing compliance in the DUB studies (using the alarm) with compliance in the OC studies (paper diary, no alarm), and by evaluating medication compliance in DUB subjects who responded to an alarm. The Applicant reported that compliance in the OC studies was higher than that in the DUB studies (97.1 and 99.6% in the OC studies vs. 95.9 and 94.3% in the DUB studies. For the within-DUB studies evaluation, the Applicant first compared compliance in Study 308961, where 60 subjects used both paper and e-diaries (further discussed below). Compliance was statistically significantly higher (98.9% vs. 97.3%) when subjects used the paper diary with no alarm. Finally, the Applicant evaluated medication compliance within each DUB study by looking at days in which data entry was made spontaneously or in response to the alarm. In Study 308960, the medication compliance rates were 98.6% for days with alarm, and 95.0% for days without alarm, $p < 0.0001$. In Study 308961, the compliance rates were 98.5% with alarm and 96.3% without alarm, $p < 0.0001$.

Team Leader Comments

- **I do not find comparison of compliance in the OC and DUB studies necessarily relevant. Women in the OC trial were relying on their pills for contraception, while women in the DUB studies used nonhormonal contraception. Thus, a major impetus**

to compliance, fear of pregnancy, was not equal in the two programs.

- **I am also not convinced that a comparison of compliance among a small sample of subjects who experienced technical difficulties with use of the electronic diary is pertinent. In fact, the technical difficulties that led to introduction of the paper diary may have adversely affected the alarm function and therefore decreased compliance on the days they used the e-diary.**
- **The most appropriate comparison is that of subjects within each study, based on whether or not their data entry was prompted by an alarm. In both studies, the medication compliance was statistically significantly higher when an alarm prompted the subjects. Although I do not believe the magnitude of the increase in compliance is likely to have a major effect on the treatment response in actual use, I do believe these results indicate that the treatment effects shown in the trials represent a "best case" scenario as compared to what would be expected in actual use.**

Study 308961 experienced technical failures with the e-diary, related to rapid upgrades in technology that were not supported by the e-diary device chosen, and also to lack of technical support in every language needed for use by subjects in the various participating countries. For this reason, a protocol amendment was introduced to allow subjects to enter data in a paper diary if they were unable to use the e-diary. If data were available for a given day in both the e-diary and the paper diary, the e-diary was used as the source. Missing data were imputed according to the rules used for the studies generally only if both paper and e-diary data were unavailable. The Applicant reported that no subjects used a paper diary exclusively; 36% of EV/DNG subjects and 29% of placebo subjects used both paper and e-diaries, but this use of the paper diary impacted only 7% of treatment cycles (i.e., at least one day of data was documented by a paper diary entry). On a per day basis, only 1-2% (placebo and EV/DNG arms, respectively) of daily data was documented by a paper diary entry.

Team Leader Comment

It does not appear that intermittent use of a paper diary had a major impact on data collection in Study 308961. Of greater concern would be that subjects who experienced technical difficulty using the e-diary may have failed to record any data, which could partially account for the fairly high number of protocol violations related to missing data in Study 308961.

Data on menstrual blood loss (MBL) was determined by alkaline hematin analysis of collected sanitary products. The alkaline hematin methodology is well-established, and has been utilized to support the approval of several recent products for heavy menstrual bleeding indications.

The primary endpoint was the overall success rate, defined as the number of subjects with the absence of any DUB symptom, and who met all relevant criteria for success during the 90-day efficacy period. Absence of DUB symptoms was defined as:

- No bleeding episodes lasting > 7 days
- No > 4 bleeding episodes AND
- No bleeding episodes with MBL > 80 ml
- Additionally, the following stipulations also had to be met:
    - No more than 1 bleeding episode increase from baseline
    - Total number of bleeding days ≤ 24

  - No increase from baseline in an individual subject's total number of bleeding days

- Finally, the following two symptom-specific criteria had to be met for subjects in the following diagnostic groups:
  - For subjects enrolling with prolonged bleeding: at least a 2 day decrease in maximum duration of bleeding from run-in to the efficacy period
  - For subjects enrolling with excessive bleeding: the MBL for each bleeding episode should represent at least a 50% decrease from the average of the qualifying bleeding episodes during run-in (where qualifying bleeding episodes are defined as those with MBL > 80 ml)

Overall study success was defined as:

- The proportion of successful responders in the EV/DNG arm is statistically significantly greater than that in the placebo arm AND
- The point estimate for the proportion of successful responders in the EV/DNG arm is ≥ 50%

Team Leader Comments

- **The criteria for treatment success and overall study success were agreed upon between the Applicant and the Division during presubmission guidance meetings.**
- **As noted in Section 2.2, the Division emphasized the need for the demonstration of efficacy to be clinically meaningful as well as statistically significant. This is common advice from DRUP, because even a small, clinically irrelevant change in a continuous variable (such as MBL) can attain statistical significance if the sample size is large enough. In addition, it is important that the efficacy endpoints selected to support an indication represent improvement in aspects of the targeted condition that are important to the affected population.**
- **The Applicant noted in a 2005 communication that it believed that a success rate of less than 50% could still be clinically meaningful, suggesting that this could be supported by other clinically important outcomes. Exploratory interviews suggested that change in sanitary product use was important to women with DUB. The Applicant suggested that, from a physician's perspective, changes in hemoglobin and ferritin would be supportive.**
- **Based on Division's recommendation, the Applicant amended the protocol for Studies 308960 and 308961 (amendments 1 and 6, respectively) to include the additional requirement for definition of overall success of a point estimate of successful responders in the EV/DNG arm of at least 50%.**
- **In the current submission, the Applicant made 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…

  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 Applicant also noted that "the literature suggested that with variable DUB definitions up to 20% of patients on placebo could experience a complete remission of their symptoms." Discussing the features of the study that were expected to have controlled for variability of symptoms, the Applicant concluded that "Hence, the 20% response on placebo hypothesized in this study was a realistic assumption."**

Secondary endpoints included the proportion of subjects cured from each individual DUB symptom, change in MBL for all subjects and for subjects with excessive bleeding, change in number of bleeding days and bleeding episodes, and change from baseline to Day 84 and 196 hemoglobin and serum ferritin concentrations.

Subjects who did not complete the first 90 days of treatment, or who did not have sufficient data to evaluate the presence/absence of DUB symptoms during treatment were considered treatment failures in the responder analysis. For subjects who terminated prematurely after the first 90 days, or who had incomplete data that could not be imputed, the efficacy phase was captured by shifting a 90-day window backward in time to start on the first day of a treatment cycle, in order to capture days with evaluable data. If there was no complete 90-day treatment data with evaluable data, the subject was treated as a treatment failure.

Missing data imputation rules included the following:

- Missing bleeding intensity:
  - Nonconsecutive days replaced using the maximum bleeding intensity of neighboring days. No more than 9 days per 90-day phase were imputed, provided this did not result in imputation of > 10% of the data for that phase.
  - Consecutive missing days were not imputed
- Missing MBL:
  - During run-in, to determine eligibility, missing MBL data was replaced with 0
  - Days with MBL > 1 ml were regarded as bleeding days.
  - If bleeding intensity was missing but MBL was recorded as > 0 but < 1 ml, that day was considered a bleeding-free day.
  - During the efficacy phase, missing or implausible MBL data was imputed based on consideration of available data for bleeding intensity and whether all sanitary products were collected on the respective day. Table 16 presents the algorithm the Applicant used to impute MBL data.

Table 16 Imputation Rules by Type of Missing or Implausible MBL Data

Type	Available data on MBL	Available data on Bleeding intensity on the respective day	Sanitary protection completely collected on the respective day?	MBL data imputed?
Type 1	> 0 ml	None, any level, or missing	Yes, no or missing	No; Recorded as entered
Type 2	Missing / 0 ml	Light, normal or heavy	Yes, no or missing	Yes; using mean MBL for days with correct collection of sanitary products AND available MBL data (in that bleeding episode or preceding episode).
Type 3	Missing	None, spotting, missing	Yes, no or missing	Yes; imputed as 0

Source: Based on statistical analysis plan of Study 308960; p 12 of 26

Team Leader Comments

- **The Statistical Analysis Plan was reviewed by the FDA statistician in the preNDA period, who commented that handling of missing data would be a review issue.**
- **Although the description for handling of Type 3 missing data suggests that there could have been cases where there was imputation of 0 MBL where all data elements are missing, the Applicant has confirmed that this did not occur.**
- **Dr. Fang has indicated that the following numbers of subjects had missing bleeding intensity data for 2 or more consecutive days**
  - **Study 308960: 7 EV/DNG subjects, 4 placebo subjects**
  - **Study 308961: 17 EV/DNG subjects, 16 placebo subjects**
- **The following numbers of subjects had bleeding intensity data missing for >10% of days in an evaluation phase**
  - **Study 308960: 4 EV/DNG subjects, 3 placebo subjects (all during run-in)**
  - **Study 308961: 15 EV/DNG subjects, 14 placebo subjects (all during run-in)**
- **Therefore, it appears that the amount of missing data was similar across treatment arms in both studies, and that the imputation was handled in an appropriate manner. Dr. Fang concurs in this assessment.**

The primary analysis population was the ITT population, defined by the Applicant as all randomized subjects.

7.3.3.2 Primary Efficacy Analysis

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year old subject (#3156) who smoked. She had an MI after almost 8 months on treatment. She was diagnosed on the basis of ECG, echocardiography and lab parameters, and underwent elective angiography two days after the onset of her symptoms, which showed significant stenosis of the right coronary artery. She underwent percutaneous transluminary coronary angioplasty with stent placement, and was discontinued from study drug.

In Study 306660, subject #4147, a 40 year old woman, was diagnosed with a DVT six days after the end of study drug. She had taken EV/DNG for approximately 18 months. She had suffered an ankle sprain after a fall, three days before the DVT was diagnosed, and had received an injection of medroxyprogesterone acetate about one week before. She was a non-smoker, and had previously used Yasmin for three years. This SAE was not included in the Applicant's listings because it occurred following discontinuation of study drug.

Table 22 Studies 306660 & 304742 - SAEs

SAE(s) by System Organ Class	Preferred Term	Study 306660 N=1377 n	Study 304742 N=490 n
Blood & lymphatic	Lymphadenitis[6]	1	
	Lymphadenopathy[11]		1
Cardiac	**Myocardial infarction**	1	
Congenital, familial & genetic	**Dermoid cyst of ovary**	1	
	Spina bifida	1	
Ear & labyrinth	**Deafness unilateral**	1	
	Vertigo[5]	1	
Endocrine	Basedow's disease (hyperthyroidism)	1	
Eye	Diplopia[5]	1	
Gastrointestinal	Celiac disease[7]	1	
	Food poisoning	1	
	Inguinal hernia	2	
General & administration site	Pyrexia[1]	1	
Infections & infestations	Acute sinusitis	1	
	Appendicitis[4]	3	1
	Cellulitis[9]	1	
	Cystitis[7]	1	
	Kidney infection[11]		2
	Meningitis bacterial	1	
	Parotitis[6]	1	
	Perirectal abscess		1
	Peritonsillar abscess[2]	1	
	Presumed ocular histoplasmosis syndrome	1	
	Sinusitis	1	
	Tonsillitis	2	
	Uterine infection[4]	1	
Injury, poisoning & procedural	Accident	1	

complications	Accidental exposure		1
	Brain herniation[8]	1	
	Burns second degree	1	
	Joint dislocation[3]	3	
	Lower limb fracture[10]		1
	Meniscus lesion	1	
	Pneumothorax traumatic		1
	Polytraumatism (car accident)	1	
	Spinal compression fracture	1	
Investigations	**Biopsy cervix abnormal[12]**		1
Metabolism & nutrition	Dehydration[2]	1	
Musculoskeletal & connective tissue	Arthralgia	1	
	Arthropathy	1	
	Bone pain[1]	1	
	Intervertebral disc disorder[2]	1	
	Muscle atrophy	1	
Neoplasms, benign, malignant and unspecified	**Adenocarcinoma of the cervix[12]**		1
	Fibroadenoma of breast	1	
	Focal nodular hyperplasia (liver)	1	
	Malignant melanoma Stage 1		1
	Uterine leiomyoma	1	
Nervous system	Intracranial aneurysm[8]	1	
	Intracranial pressure increased[8]	1	
	Optic neuritis retrobulbar	1	
	Subarachnoid hemorrhage[8]	1	
Pregnancy, puerperium & perinatal conditions	Abortion missed	2	
Psychiatric	**Borderline personality disorder**	1	
	Drug dependence	1	
Renal and urinary	Nephrolithiasis[11]		1
Reproductive system & breast	Breast hypoplasia[9]	2	
	Cervical dysplasia	1	
	Ovarian cyst ruptured		1
Respiratory, thoracic & mediastinal	Pneumonia aspiration[8]	1	
Surgical & medical procedures	Elective surgery		1
	Surgery[10]		1
Vascular	Aneurysm ruptured[8]	1	
	Varicose vein	1	

[1, 2, 3] etc. indicates SAEs that occurred in a single subject
Bold = subject withdrawn due to this SAE
Source: Study Report 35179, Table 112, pp 1273-85 of 3674 and Study Report 39818, Table 69, pp 402-3 of 484

Team Leader Comments

- **Although the DVT occurred after completion of study drug, I would still consider it a treatment-emergent SAE. However, it is not included in the Applicant's tables or**

counts of SAEs.

- **The myocardial infarction, DVT, hepatic focal nodular hyperplasia and fibroid growth are considered likely to be drug-related in Study 306660. In Study 304742, only the ruptured ovarian cyst is likely to be drug-related. [**
- **The myocardial infarction is discussed above. Myocardial infarction is a rare, but labeled, COC-related AE. Women over age 35 who smoke are particularly at risk.**
- **The brain herniation and other superscripted events in that subject are discussed above under the fatality in Subject #4318.**
- **The SAE of spina bifida occurred in a newborn born to a subject who discontinued EV/DNG for an intended pregnancy. Her EDC was 17 days after last tablet intake.**
- **The case of focal nodular hyperplasia occurred in a 22 year old after 3 months on EV/DNG. She was diagnosed on the basis of MRI done after elevated liver enzymes were noted after 2 months on drug. She declined liver biopsy.**
- **The case described as adenocarcinoma of the cervix was characterized as "mild" and treated with cervical conization and endocervical curettage.**
- **The SAE of "accidental exposure" involved a needle stick with a syringe of unknown content.**

Table 23 Serious Adverse Events – Study 304004

Subject ID	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

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

Team Leader Comments

- **The ruptured ovarian cyst in the EV/DNG arm and cholelithiasis in the comparator arm are likely to be drug-related.**
- **The subject in the comparator arm who was diagnosed with breast cancer was a 30 year old woman who took EE/LNG for about six months, and discovered a breast mass three months after discontinuing study drug. A biopsy the following month revealed invasive ductal carcinoma. This is not believed to be drug-related.**

In the DUB trials, there were a total of three SAEs in the EV/DNG arms (1.1%) and three in the placebo arms (2.0%). The subject (# 131003) with an MI was a 46 year old non-smoker with a BMI of 31 kg/m^2 who experienced a myocardial infarction after taking EV/DNG for about six months. She was diagnosed on the basis of EKG and enzyme findings.

Table 24 Serious Adverse Events – Studies 308960 and 308961

Subject ID	Treatment Group	SAE(s)
		Study 308960
131003	**EV/DNG**	Myocardial infarction
208011	Placebo	Suicide attempt
		Study 308961
702019	**EV/DNG**	Ductal breast cancer *in situ*
852034	**EV/DNG**	Cholecystitis
104026	Placebo	Vertigo/panic attack
201005	Placebo	Spontaneous abortion

Source: Based on Study Report A29849, Table 177, pp 932-3 of 1182 and Study Report A42568, Text Table 59, p 149 of 1235

Team Leader Comments

- **I consider the SAE of myocardial infarction likely to be drug-related.**
- **Subject #702019, diagnosed with breast cancer, was a 44 year old woman who took EV/DNG for about 5 months, and was noted to have abnormal results on a routine mammogram. A subsequent biopsy revealed in situ ductal carcinoma, which was treated with mastectomy. This AE is not believed to be drug-related.**
- **Subject #852034 was 37 and was hospitalized with acute cholecystitis about 3 weeks after starting EV/DNG. I consider this likely to be drug-related. She subsequently (later that month) had elevated liver enzymes, and study drug was discontinued for this reason.**

A total of 142 subjects in Study 306660 (10.3%) and 73 subjects in Study 304742 (14.9%) discontinued trial participation prematurely due to adverse events (AEs). See Table 25 for the most common AEs leading to early discontinuation.

Table 25 Studies 306660 & 304742 - Most Common and Most Pertinent AEs leading to Early Discontinuation

Adverse Event (number of subjects) SOC and PT	Study 306660 N = 1377 n (%)	Study 304742 N = 490 n (%)	Total contraception trials N=1,867 n (%)
Reproductive system and breast disorders			
Breast (Breast discomfort, pain, swelling and tenderness)	6 (0.4)	2 (0.4)	8 (0.4)
Menorrhagia	3 (0.2)	4 (0.8)	7 (0.4)
Menstrual disorder	3 (0.2)	2 (0.4)	5 (0.3)
Metrorrhagia, irregular menstruation	24 (1.7)	12 (2.4)	36 (1.9)
Amenorrhea	2 (0.1)	1 (0.2)	3 (0.2)
Dysfunctional uterine bleeding	--	3 (0.6)	3 (0.2)
Psychiatric disorders			
Depressed mood, Depression	10 (0.7)	2 (0.4)	12 (0.6)
Libido decreased, Loss of libido	8 (0.6)	1 (0.2)	9 (0.5)
Mood altered, mood swings	2 (0.1)	8 (1.6)	10 (0.5)
Skin and subcutaneous tissue disorders			
Acne	14 (1.0)	9 (1.8)	23 (1.2)
Alopecia	3 (0.2)	--	3 (0.2)
Nervous system disorders			
Headache, Migraine	12 (0.9)	7 (1.4)	19 (1.0)
Investigations			
Weight increased	12 (0.9)	2 (0.4)	14 (0.7)
Vascular disorders			
Hypertension	8 (0.6)	--	8 (0,4)
Cardiac disorders			
Myocardial infarction	1 (< 0.1)	--	1 (< 0.1)
Neoplasm (benign, malignant and unspecified)			
Focal nodular hyperplasia (hepatic)	1 (< 0.1)	--	1 (< 0.1)

SOC = system organ class; PT = preferred term
Source: Study Report A35179; Table 120; pp 1503-1516 of 3674 and Study Report A39818, Table 71, pp 406-8 of 484

Team Leader Comments

- **Patterns of premature discontinuations were similar in the two trials, with breast, menstrual and psychiatric disorders, along with acne and headaches accounting for the large majority of discontinuations related to AEs. These are all commonly observed AEs in COC users.**
- **I believe that pooled data from the two contraception trials is appropriate to be reported in the Adverse Reactions section of the label.**

In Study 304004, discontinuations due to AEs occurred in 3.3% of each treatment arm, and were generally balanced over treatment groups. AEs that led to discontinuation in more than a single subject included headache (2 EV/DNG, 4 EE/LNG), depression (2 EV/DNG) and acne (2 EE/LNG).

Table 26 lists the AEs leading to discontinuation in the DUB trials. In Study 308960, 12 subjects (10%) in the EV/DNG arm terminated study participation early due to one or more AEs, while 4 placebo subjects (6.1%) did so. The respective rates in Study 308961 were very similar; 14 subjects (9.7%) in the EV/DNG arm and 5 (6.2%) in the placebo arm.

Table 26 Studies 308960 & 308961 - Adverse Events leading to Early Discontinuation

	Study 308960		Study 308961	
Preferred Term	EV/DNG N=119 n	Placebo N=66 n	EV/DNG N=145 n (%)	Placebo N=81 n (%)
Gastroenteritis	1			
Acne, tension headache	1			
Anemia worsening	1			
Myocardial infarction	1			
Menstrual disorder	1			
Migraine	1		2	1
Emotional disorder or Mood Altered	1			
Hypertension	1			
Asthma	1			
Bacterial vaginitis	1			
Breast tenderness, libido decreased, metrorrhagia	1			
Headache, nausea, vomiting	1	1		
Anxiety, hypertension, insomnia, hypoesthesia		1		
Anxiety, depression, insomnia, arthraligia		1		
Headache, hypoesthesia		1		
Mood altered			2	
Headache			1	
Phlebitis, superficial			1	
Dysmenorrhea			2	
Breast pain, nausea			1	
Headache, nausea			1	
Vulvovaginal dryness			1	
Uterine leiomyoma			1	
Libido decreased			1	1
ALT increased 852034			1	
Pregnancy, abortion				1
AST increased				1
Depressed mood				1

Source: Study Report A29849; Table 163; pp 648-50 of 1182 and Study Report A42568, Text Table 60, p 150 of 1235

Team Leader Comments

- **The major reasons for discontinuations due to AEs were headaches, menstrual disorders and psychiatric complaints. Menstrual disorders (including metrorrhagia and dysmenorrhea) were reported only in EV/DNG subjects. Headaches were slightly more frequently the reason for withdrawal in EV/DNG subjects than placebo subjects (2.7% vs. 2.0%), while psychiatric complaints were slightly more frequent among placebo subjects (2.0% vs. 1.1%).**
- **The myocardial infarction in the EV/DNG subject in Study 308960 is discussed in earlier in this section.**
- **The EV/DNG subject with increased ALT was discussed earlier, as she had a preceding SAE of acute cholecystitis.**

- **Little information is provided on the EV/DNG subject who withdrew due to worsening anemia after one month on treatment. She reportedly had a history of anemia dating to 1982. It is not clear whether this was related to menstrual bleeding.**
- **Similarly, there is little information on the subject discontinuing due to abnormal menstruation. This is not characterized further except to note that it resolved on the same day, and was associated with dysmenorrhea.**

8.2 Other Notable Adverse Events

In addition to the DVT and two MIs that occurred in the clinical programs for pregnancy prevention and DUB, the Applicant reported another DVT that occurred in an ongoing trial (Study 91548) comparing EV/DNG and EE/LNG on treatment of reduced libido associated with COC use. The DVT occurred in a 23 year old who had been on EV/DNG for 11 weeks. Two days before the DVT was diagnosed, she suffered a tear to the medial cruciate ligament in the ipsilateral knee. She had also been in a car for five hours the day prior to diagnosis. She did not smoke, had no family history suggestive of thrombophilia and had a BMI of 18.4.

In addition, a 30 year old woman with a history of smoking experienced right-sided facial and arm numbness and 10 seconds of aphasia 17 days after starting EV/DNG. She was hospitalized and diagnosed with a transient ischemic attack (TIA). Cranial magnetic resonance tomography showed no "disturbed diffusion based on post-ischemic lesions" and tranesophageal echocardiography demonstrated a small persistent foramen ovale.

Team Leader Comment

In a relatively large clinical development program, the Applicant has reported two DVTs and two MIs. Postmarketing reports have also documented occurrence of a TIA associated with use of EV/DNG. Three events occurred in women aged over 40. It is expected that the risk of VTEs and ATEs associated with COCs increases with age. However, I believe this is a signal that warrants further exploration before the product is actively marketed to women on the upper end of reproductive capacity.

8.3 Other Adverse Events

The Applicant provided a table of common adverse events, defined as those occurring in at least 1% of the safety population; Table 27 includes only those events that occurred in at least 2% of subjects in Studies 306660 and 304742, and some similar terms have been bundled.

Table 27 Studies 306660 and 304742 - Common Adverse Events (≥ 2% of FAS)

Preferred Term	Study 306660 N=1,377 n (%)	Study 304742 N=490 n (%)	Total contraception trials N=1,867 n (%)
Nasopharyngitis + pharyngitis + sinusitis + upper respiratory infection	296 (21.5)	122 (24.9)	418 (22.4)
Vaginal infection + candidiasis + vaginal candidiasis + fungal infection + genital infection fungal + vulvovaginal mycotic infection + vulvovaginitis	207 (15.0)	84 (17.1)	291 (15.6)
Headache + migraine + tension headache	159 (11.5)	87 (17.8)	246 (13.2)
Metrorrhagia + irregular menstruation	85 (6.2)	64 (13.1)	149 (8.0)
Cystitis + Urinary tract infection	91 (6.6)	34 (6.9)	125 (6.7)
Breast pain + discomfort + tenderness	89 (6.5)	34 (6.9)	123 (6.6)
Vomiting + nausea	75 (5.4)	46 (9.4)	121 (6.5)
Diarrhea	91 (6.6)	19 (3.9)	110 (5.9)
Abdominal pain + upper + lower	53 (3.8)	40 (8.2)	93 (5.0)
Dysmenorrhea	42 (3.1)	37 (7.6)	79 (4.2)
Acne	44 (3.2)	29 (5.9)	73 (3.9)
Tonsillitis + acute tonsillitis + streptococcal tonsillitis	64 (4.6)	9 (1.8)	73 (3.9)
Gastroenteritis + gastrointestinal infection + viral	49 (3.6)	11 (2.2)	60 (3.2)
Weight increased	37 (2.7)	15 (3.1)	52 (2.8)
Bronchitis + acute bronchitis	36 (2.6)	8 (1.6)	44 (2.4)
Back pain	25 (1.8)	18 (3.7)	43 (2.3)
Influenza	27 (2.0)	13 (2.7)	40 (2.1)
Amenorrhea	2 (0.1)	37 (7.6)	39 (2.1)

Source: Based on Study Report A35179, Table 113; pp 1286-9 of 3674 and Study Report A39818, Tables 64, pp 354-64 of 484

Team Leader Comments

- **I believe that pooled data from the two contraception trials is appropriate to be reported in the Adverse Reactions section of the label.**
- **Headaches, menstrual irregularities, breast symptoms, nausea/vomiting, acne, increased weight, and amenorrhea are likely to be drug-related.**

Table 28 Study 304004 - Common Adverse Events (≥ 1% of FAS)

Preferred Term	EV/DNG N=399 n (%)	EE/LNG N=399 n (%)
Vaginal infection + vulvovaginal mycotic infection/candidiasis	**18 (4.5)**	8 (2.0)
Breast pain	**15 (3.8)**	5 (1.3)
Headache + migraine	14 (3.5)	19 (4.8)
Nasopharyngitis + sinusitis	8 (2.0)	11 (2.8)
Cystitis	**8 (2.0)**	2 (0.5)
Acne	5 (1.3)	13 (3.3)
Alopecia	**5 (1.3)**	4 (1.0)
Bronchitis	**4 (1.0)**	3 (0.8)
Back pain	3 (0.8)	4 (1.0)
Ovarian cyst	3 (0.8)	4 (1.0)
Weight increased	2 (1.0)	4 (1.0)
Nausea	1 (0.3)	4 (1.0)

Bold = AE more frequent in EV/DNG arm
Source: Study Report A35644; Text Table 51; p 135 of 1799

Team Leader Comments

- **The table for Study 304004 lists common AEs with a frequency of at least 1%; this lower threshold was chosen due to the shorter duration of this study as compared to the contraception trials and the subsequent decreased frequency of AE reports.**
- **Rates of AEs are general comparable over the two COCs, with EV/DNG associated with slightly higher rates of breast pain and alopecia, which may be hormonally-related.**

Common AEs in the DUB trials are shown in Table 29.

Table 29 Studies 308960 & 308961 - Common Adverse Events (≥ 2% and More Frequent in EV/DNG than Placebo) - Safety Population

	Study 308960		Study 308961		Total DUB Studies	
Preferred Term	**EV/DNG N=119 n (%)**	**Placebo N=66 n (%)**	**EV/DNG N=145 n (%)**	**Placebo N=81 n (%)**	**EV/DNG N=264 n (%)**	**Placebo N=147 n (%)**
Breast pain + discomfort + tenderness	9 (7.6)	1 (1.5)	17 (11.7)	3 (3.7)	26 (9.8)	4 (2.7)
Vulvovaginitis + vaginal candidiasis + candidiasis + vulvovaginal mycotic infection + vaginal infection + fungal infection	9 (7.6)	5 (7.6)	9 (6.2	1 (1.2)	18 (6.8)	6 (4.1)
Metrorrhagia + withdrawal bleeding irregular	6 (5.0)	0	8 (5.5)	1 (1.2)	14 (5.3)	1 (0.7)
Acne	6 (5.0)	0	5 (3.4)	3 (3.7)	11 (4.2)	3 (2.0)
Blood pressure increased + hypertension	3 (2.5)	3 (4.5)	7 (4.8)	2 (2.5)	10 (3.8)	5 (3.4)
Weight increased	7 (5.9)	0	2 (1.4)	1 (1.2)	9 (3.4)	1 (0.7)
Abdominal pain + upper + lower	1 (0.8)	0	7 (4.8)	4 (5.0)	8 (3.0)	4 (2.7)
Fatigue	4 (3.4)	3 (4.5)	4 (2.8)	1 (1.2)	8 (3.0)	4 (2.7)
Viral infection	0	1 (1.5)	6 (4.1)	0	6 (2.3)	1 (0.7)
Influenza	3	0	3 (2.1)	1 (1.2)	6 (2.3)	1 (0.7)
Mood altered + mood swings + affect lability	2 (1.7)	0	4 (2.8)	1 (1.2)	6 (2.3)	1 (0.7)
Bronchitis	3 (2.5)	2 (3.0)	3 (2.1)	0	6 (2.3)	2 (1.4)

Bold = discrepant results over trials
Source: Study Report A29849; Table 152; p 433 of 1182 and Study Report A42568; Table 150; p 474of 1235

Team Leader Comments

- **The AEs that were consistently more common in EV/DNG as compared to placebo subjects in both trials were breast symptoms, vaginal infections, bleeding irregularities (metrorrhagia), increased weight, influenza, and mood symptoms. With the exception of the infectious conditions, these are likely to be drug-related.**
- **Overall, the types of AEs commonly seen in the DUB studies are similar to those observed in the contraception studies. I do not believe that the AE profile needs to be labeled based on the DUB studies.**

8.4 Laboratory and Vital Signs Data

Routine laboratory evaluation was done only in Studies 304004, 308960 and 308961. Complete blood count (CBC) and chemistry parameters were evaluated. In Study 304004, both study arms demonstrated small decreases in HDL and LDL cholesterol. Slight increases from screening to final visit were noted in both arms for gamma glutamyltransferase (GGT) and ALT. For GGT, one EV/DNG subject (0.3%) and three EE/LNG subjects (0.8%) were above the "alert range" at the final study visit. For ALT, one subject in each arm (0.3%) were above the alert range. None of these were reported as SAEs, and all resolved. The elevated values in the EV/DNG arm occurred in two different subjects, and no subject met Hy's Law criteria for hepatotoxicity.

In the DUB studies, laboratory values were generally in the normal range at all time points. Exceptions included two EV/DNG subjects in Study 308960 who showed elevated GGT levels. One (Subject #109001) occurred at Visit 5 and was not associated with any other chemistry abnormalities or AEs. The other (Subject #105002) demonstrated rising GGT levels

from Visits 1 to 11, peaking at 265 U/L (normal range 8-49 U/L). This case also was not associated with any other chemistry abnormalities or pertinent AEs. In Study 308961, subjects in the EV/DNG arm were also noted to have greater increases in ferritin at end of study (8.8 ng/ml) than did placebo subjects (1 ng/ml). There were no chemistry values of concern.

Vital signs data are described in Dr. Willett's review, and did not indicate any signals of concern. In Study 306660 and Study 304742, there were no changes from normal to abnormal for systolic or diastolic blood pressure. The majority of subjects in Study 306660 had no shift in BMI category, while 12.5% shifted into a higher category, and 8.6% shifted into a lower BMI category. In Study 304742, there was little change in weight (0.5 kg increase after 13 cycles). There were no signals of alterations in blood pressure, weight or BMI in Study 304004.

Blood pressure, weight and BMI also remained stable in the two DUB trials.

8.5 Special Safety Studies

8.5.1 Thorough QT Study

The Applicant conducted a thorough QT (TQT) study as requested by the Division, to explore the risk of prolongation of the QT interval by (b) (4) The initial protocol and subsequently the study were reviewed by the Interdisciplinary Review Team for QT Studies (QT-IRT) in the Division of Cardiorenal Products. The primary reviewer, Dr. Joanne Zhang, made the following comments in her review dated March 15, 2010:

> *No significant QTc prolongation effect of Qlaira® was detected in this TQT study. The largest upper bound of the 2-sided 90% CI for the mean differences between SH T00658M and placebo, and between SH T00660 AA and placebo were below 10 ms, the threshold for regulatory concern as described in the ICH4 guidelines.*
>
> **Team Leader Comment**
>
> **SH T00658M contains 2 mg EV/3 mg DNG and SH T00660 AA contains 10 mg DNG (the supratherapeutic dose).**

The results of the TQT are displayed in Table 30.

Table 30 Point Estimates and Confidence Intervals (CIs) for SH T00658M, SH T00660 AA and Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
SH T00658M	3	-0.8	(-3.8, 2.2)
SH T00660 AA	3	-2.8	(-5.8, 0.3)
Moxifloxacin 400 mg*	2	17.8	(15.3*, 20.3)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 14.4 ms.

Source: Table 1, Review of Dr. Joanne Zhang, dated March 15, 2010

Dr. Zhang had the following additional comments in her review:

> *The thorough QT study included only one supratherapeutic dose arm – DNG 10 mg…These concentrations are above those for the predicted worst case scenario (drug*

interaction with ketoconazole) and show that at these concentrations there are no detectable prolongations of the QT-interval…However, exposure data in patients with renal and hepatic impairment is not available.

The supratherapeutic dose of EV has not been tested in the thorough QT study. Administration of ketoconazole resulted in a 1.7-fold increase in C_{max} of E2, a metabolite of the prodrug EV. However, EV has been marketed in various formulations since 1954 and we identified no reports of AEs related to QT prolongation in the literature or post-marketing.

Dr. Zhang recommended labeling language; none was proposed by the Applicant. The Division agrees with Dr. Zhang's recommended language, and it was included in the agreed-upon labeling.

8.5.2 Endometrial Biopsy Substudy

In contraceptive Study 306660, a subgroup of subjects underwent endometrial biopsy at screening and at Visit 8 (Cycle 20). Biopsies were taken between days 12-19 of each cycle. A total of 283 subjects were screened at entry, and 219 of these had biopsies at end-of-study. Ninety-three percent were read as normal, none as abnormal and 6% were not assessable. Dr. Willett reviewed the detailed readings of the biopsies, and concluded that the histologic results are as expected for a combined oral contraceptive, and do not pose any concern.

8.6 Studies of Related Products

Dr. Willett also reviewed a number of additional studies submitted by the Applicant pertaining to combination products containing EV and/or DNG. Four studies were conducted utilizing the final four-phasic regimen; these included PK and ovulation inhibition studies. The studies ranged from 28 days to 7 cycles; no deaths or SAEs were reported in any of them. An additional 5 supportive studies, ranging from single-dose to 14-day administrations (mainly food effect and drug-drug interaction studies), also reported no deaths or relevant SAEs. Three studies evaluating variations of the final dosing regimen, ranging from six to 20 cycles, reported no drug-related deaths or relevant SAEs.

There were 17 studies of Climodien (1 or 2 mg EV/2 or 3 mg DNG), approved in Europe for hormone therapy. These studies focused on postmenopausal women, and ranged from six to 18 cycles. Safety results are displayed in Table 31.

Table 31 Safety Results from Studies of EV/DNG in Postmenopausal Women

Study	Dose (mg EV/DNG)	N	# cycles	Women-years (WY)*	VTE N (rate/10,000 WY)**	MI N (rate/10,000 WY)	Other ATE N (rate/10,000 WY)	Stroke N (rate/10,000 WY)
JPH01695	2/2	70	6	35	0	0	0	0
JPH 04095	2/3	43	6	21.5	0	0	0	0
JPH05295	2/2	1501	18	2251.5	**4**	0	0	**2**
JPH01093	2/2	199	12	199	0	**1**	0	0
	2/3	186	12	186	0	0	0	0
11641	2/2	25	6	12.5	0	0	0	0
11481	2/2	31	12	31	0	0	**1**	0
306387	2/2	33	6	16.5	**1**	0	0	0
12842	2/2	215	Up to 45	430#	**4**	0	0	0
305222	2/2	75	12	75	0	0	0	0
JPH00696	2/2	29	3	7.25	0	0	0	0
A02343	1/2	147	6	73.5	0	0	0	0
	2/2	160	6	80	**1**	0	0	**1**
301920	2/2	65	6	33.5	**2**	0	0	0
A05358	2/2	318	36	954	**1**	**2**	0	0
JPH01595	2/3	18	2	3	0	0	0	0
305510	1/2	162	3	40.5	0	0	0	0
302320	1/2	159	13	159	**1**	0	0	**1**
302321	1/2	70	3	17.5	0	0	0	0
Total	**2/3**	**247**	**2-12**	**210.5**	**0**	**0**	**0**	**0**
Total	**2/2**	**2,721**	**3-45**	**4,125.3**	**13 (31.5)**	**3 (7.3)**	**1 (2.4)**	**3 (7.3)**
Total	**1/2**	**538**	**3-13**	**290.5**	**1 (34.4)**	**0**	**0**	**1 (34.4)**
Total	**All**	**3,506**	**2-45**	**4,626.3**	**14 (30.3)**	**3 (6.5)**	**1 (2.2)**	**4 (8.6)**

*No information is provided about premature discontinuations, so this should be regarded as a maximum estimate of WY of observation.

** Rates computed only for total values

No information provided on mean # cycles duration, so estimated at 24 months.

Team Leader Comments

- **In comparison, rates for estrogen/progestin products (conjugated equine estrogen [CEE]/medroxyprogesterone acetate [MPA]) in the Women's Health Initiative study[1] were 34/10,000 women-years for VTE, 30/10,000 women-years for MI and 29/10,000 women-years for stroke.**
- **In a review of the unapproved selective estrogen receptor modulator (SERM) lasofoxifene that was studied in the postmenopausal population (NDA 22-242), there were a total of 84 VTEs (DVT or PE) in 30,652 women-years in the phase2/3 development program, for a rate of 27.4/10,000 women years[2, 3]. There were 61 MIs, for a rate of 19.9/10,000 women years, and there were 69 strokes/TIAs, for a rate of 22.5/10,000 women years.**
- **In a review of the unapproved SERM tibolone (NDA 21-058), also studied in the postmenopausal population, Dr. van der Vlugt calculated rates of VTE as 15/10,000**

[1] Writing group for the Women's Health Initiative investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. JAMA. 2002; 288 (3): 321-33

[2] Review by Dr. Scott Monroe, NDA 22-242, dated January 16, 2009

[3] Review by Drs. Gerald Willett nad Adrienne Rothstein, NDA 22-242, dated January 15, 2009

women-years, and of MI as 6.1/10,000 women-years[4].

- **Overall, the rate of VTE (~30/10,000 women-years) for EV/DNG appears about equal to that seen with EE/MPA and higher than that seen with other hormonal products (SERMS) used in a postmenopausal population. The rate of MI is equivalent to that seen with tibolone, and lower than that with lasofoxifene or CEE/MPA. The rate of stroke also appears lower than that seen with CEE/MPA or lasofoxifene. However, it must be remembered that the denominator of time at risk for EV/DNG is only an estimate, and is likely over-estimated, which would artificially lower the rates.**
- **It would be expected that the rates of these events would be lower in a younger (premenopausal) population, but it is unknown whether the comparative risk with reference to other hormonal products would be similar in a younger population.**

Finally, there were 24 studies of products containing EE and DNG, with sporadic repots of VTE and stroke. There were eight studies of DNG alone, with no reported deaths, VTEs, MIs or strokes.

8.7 Postmarketing Safety Findings

Dr. Willett has reviewed in detail the postmarketing information provided by the Applicant, which included PSURs for various products containing EV and/or DNG that are approved in other countries. These products include the COCs Jeanine and Valette (both contain EE 30 µg /DNG 2 mg), and the hormone therapy (HT) products Lafamme and Climodien (both contain EV 2 mg/DNG 2 mg) and Climodien 1/2 (EV 1 mg/DNG 2 mg). A PSUR was also provided for a 2 mg DNG-alone product approved in 2008 in Japan for endometriosis. Two PSURs were provided for an EV-alone product (1 and 2 mg) approved for HT. As is common in PSURs for hormonal products, VTEs (both DVTs and pulmonary emboli), arterial thromboembolic events, MIs and strokes were reported. As postmarketing reports do not provide information about the denominator, it is difficult to make any statements about the relative frequency of such events as compared to other hormonal products.

In the PSURs provided by the Applicant, there was information about the European Active Surveillance Study of Women Taking HRT (EURAS-HRT) study, which was initiated to evaluate the safety of a drospirenone-containing postmenopausal hormone therapy product to other hormonal products, including Climodien (EV/DNG). By mid-2010, it is expected that there will be 30,000 women-years of observation on non-drospirenone containing products (including Climodien). Recruiting has been problematic, and no safety results were provided.

The Applicant also provided information on a case-control study of VTE done in Germany, which compared the risk among users of EE/DNG COCs as compared to other COCs. There was no signal of increased risk for EE/DNG, but it is not clear whether the study was powered appropriately. It is also uncertain whether these results are generalizable to EV/DNG.

8.8 Safety Update

The Applicant submitted a safety update on November 6, 2009, which updated the information in the initial submission through June 30, 2009. The submission is thoroughly discussed in Dr. Willett's review. In brief, EV/DNG has been approved for prevention of pregnancy in 27 EU member countries. Four studies of the currently proposed regimen are ongoing (two partially in the US and two outside the US); of 317 subjects randomized, there has been one death that

[4] Review by Dr. Theresa van der Vlugt, NDA 21-058, dated May 31, 2006

occurred during screening and one SAE of appendicitis. An additional SAE of a DVT in an ongoing study has already been discussed in Section 8.2. Two other studies of related products (one of DNG alone and one of EE/DNG and levomefolate) have had no significant safety findings.

In addition, two Periodic Safety Update Reports (PSURs) for the COC approved in the EU have been submitted, covering the time from approval through September 8, 2009. With cumulative exposure of about 30,000 women-years, there has been one reported DVT and one TIA (see Section 8.2).

Team Leader Comment

There do not appear to be any published epidemiologic studies evaluating the safety of DNG with or without EV. At least one non-interventional prospective cohort study (in addition to INAS-EV) may enroll women using EV/DNG. The INAS-OC study intends to enroll 80,000 COC users in the US and Europe, with two to five year follow-up, for a total of 220,000 women-years of observation. Like INAS-EV, the main clinical outcomes of the study include DVT, PE, acute MI and cerebrovascular accidents. The study was initiated with the approval of a 24-day regimen COC containing EE and drospirenone (DRSP), and will include women using EE/DRSP, as well as women using either COCs containing LNG or "all other progestin-containing OCs." In addition, the EURAS-HRT study was started in 2002 to evaluate an EE/DRSP-containing hormone therapy product compared to other oral hormonal therapy products. Although the study was planned to end in 2008, apparently it has encountered difficulty recruiting, and it does not appear to have published any results to date.

8.9 Overall Assessment of Safety Findings

Contraception indication

In the contraceptive trials, the extent of exposure was beyond that requested by the Division, with 29,952 28-day cycles completed over the two studies. Study 304004 contributed an additional 2,695 cycles of exposure to the safety database. There were two deaths in this development program, but I do not believe either can be attributed to EV/DNG. The rate of SAEs was about 2-3% in the contraception/cycle control trials, and very few events are likely to be drug-related. Notable exceptions to this include an MI and a DVT, which both occurred in women ≥ 40 years old. Discontinuations due to AEs occurred in 10-15% of subjects in the contraception trials, and were generally attributable to breast symptoms, menstrual disorders, psychiatric complaints, acne and headaches. This is a common profile for a COC. In the cycle control study, which had an EE/LNG comparator, the rate of withdrawals due to AEs was similar in each treatment arm. The common AEs (>2%) likely to be drug-related in the contraception studies included headaches, menstrual disorders, breast symptoms, nausea/vomiting, acne and weight gain. In the comparator-controlled cycle control study, breast symptoms were three times more frequent in the EV/DNG arm than the EE/LNG arm, but occurred in <5% of subjects.

There were no signals of concern regarding laboratory values or vital signs. Special safety studies of QT prolongation and endometrial safety also do not suggest reason for concern. Overall, the safety profile of EV/DNG for use in the prevention of pregnancy is acceptable.

DUB indication

In the DUB studies, a total of 1,532 28-day cycles of exposure were contributed by the two studies (673 in Study 308960 and 859 in Study 308961). No deaths occurred in these trials;

however, another MI occurred in this clinical program, in a 46 year old nonsmoker. About 1% of participants on EV/DNG experienced an SAE, with the MI and a case of cholecystitis likely to be drug-related. Discontinuations due to AEs occurred in about 10% of EV/DNG subjects, as compared to 6% of placebo subjects, and were most likely to involve headaches, menstrual disorders, and psychiatric complaints, with the first two more common among EV/DNG subjects. The pattern is similar to that seen in the contraception trials. Common AEs (>2% of subjects) that occurred more frequently in EV/DNG subjects than placebo subjects and that are likely to be drug-related include breast symptoms, menstrual disorders, acne, weight increase and psychiatric complaints.

The population studied for the DUB indication differed from that in the OC trials in that the women tended to be considerably older (average age 37-40, as compared to 25-30 for the OC trials) and heavier (average BMI about 25 as compared to 23 for the OC trials). This has been noted in other DUB trials, as women with bleeding concerns tend to be older than the general population seeking contraception only. As both increasing age and weight are risk factors for cardiovascular and thromboembolic events, the risk/benefit profile for the population seeking DUB treatment must be evaluated independently from the risk/benefit profile for the population seeking contraception only.

The risks of venous and arterial thromboembolic events may be heightened in such a population, and some evidence of this is provided by the observation of two MIs in subjects over the age of 40 in this clinical development plan. It is rare that MIs are observed in COC clinical trials, although they are a known and labeled risk of COC use. If the risk of MI is evaluated according to the underlying population studied, the contraception studies, which provided a total of 2,304 women-years of observation in a population with an average age of about 25-30, have a rate of 4.3 MIs per 10,000 women-years. In the DUB studies, which had a total of 118 women-years of observation in a population with an average age of about 37-40, the rate of MI is 84.9 per 10,000 women-years. Clearly these point estimates would have very wide confidence intervals, but this serves to illustrate the increased risk expected when EV/DNG is used by an older population. It is true that this increased risk in older premenopausal women may occur with other COC products as well, but, if approved, EV/DNG would be the only COC with an indication for DUB, which would position it as the treatment of choice for women with bleeding problems, and shift the marketing and uptake of the product to an older segment of the reproductive-aged population.

As noted above, there does not appear to be any signal of concern for QT prolongation with EV/DNG. While exposure data on women with renal and hepatic impairment is not available, general language about use in situations of impaired renal or hepatic function is in the label. An endometrial safety substudy also did not indicate any signal of concern for this novel dosing regimen.

Overall, I conclude that the safety profile for EV/DNG, when used by the population seeking contraception, appears similar to that of other approved COCs. I am concerned about potential increased risk when used by older premenopausal women (i.e., those women likely to seek this product to treat bleeding problems). The occurrence of two MIs is unusual in trials enrolling reproductive aged women, and I attribute this in part to the inclusion of older women than usually studied in COC trials. Comparison of the rates of MIs in the trial populations according to average age of enrolled subjects provides support for the concern that the safety

profile will be different, and less acceptable, if EV/DNG is used by older premenopausal women.

9. Advisory Committee Meeting

The Division determined that an Advisory Committee was not needed to review this application because this drug is not the first in its class, the clinical study design for the contraception indication was acceptable, the application did not raise significant safety or efficacy issues, the application did not raise significant public health questions and outside expertise was not necessary. The prevention of pregnancy indication was supported by standard contraceptive studies, and the data supported acceptable safety and efficacy for this indication. Although DNG is a NME, there is a large body of experience with EV and DNG in the European market.

10. Pediatrics

The Applicant requested a waiver of pediatric studies. The Pediatric Review Committee (PeRC) granted a partial waiver for ages 0 to 11 years (i.e., premenarcheal patients), because the risk of pregnancy does not exist in this population. The remainder of the PREA requirement has been fulfilled by extrapolation from studies on adult women. DRUP's long experience with a variety of hormonal contraceptives has supported the expectation that efficacy and safety results in postmenarchal adolescents do not differ from those in adult women. The Applicant intends to conduct a large, noninterventional postmarketing study in Europe and the US (see Section 13.3), which has no planned age criteria. The Division has informed the Applicant that it will require this planned study as a postmarketing requirement upon approval of the contraception indication, and that it will be particularly interested in safety data on women under the age of 18, because there were not studied in the preapproval trials.

11. Other Relevant Regulatory Issues

The Applicant indicated that the majority of investigators had no financial interests to disclose, and submitted financial disclosure information for three investigators, (b) (6) (b) (6) sole trial responsibility was to complete screening mammograms at one clinical site in Study (b) (6); her financial interest was ownership of a pharmaceutical mutual fund that may have included Schering AG stocks. (b) (6) received payments over $10,000 for consultation from Bayer; in order to minimize any bias, he and another co-investigator were jointly responsible with for consenting and enrolling subjects and for reporting unanticipated problems. His site enrolled only (b) (6) of (b) (6) subjects in Study (b) (6) (b) (6) was paid over $23,000 for speaking engagements for the (b) (6) products and participation in regional sales meetings. She enrolled only (b) (6) of (b) (6) subjects in Study (b) (6)

Site inspections by the Division of Scientific Investigation (DSI) were requested for three sites in the contraceptive trials (one from Study 304742 and two from Study 306660), and for one site in each of the DUB trials. Sites were selected for inspection on the basis of high enrollment; there were no issues of concern noted that warranted inspection. In addition, inspection of the Applicant's clinical study activities was conducted in accordance with the

Sponsor/Monitor/CRO compliance program, as is customary in the case of NME products. Results are described in Table 32. Three inspections found no regulatory violations (no action indicated or NAI) and concluded that

> *The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective application.*

For the remaining three sites, some regulatory violations were noted, but in all cases, the DSI conclusion was that

> *The study(ies) appears to have been conducted adequately, and the data generated by this site (submitted by the sponsor) may be used in support of the respective application.*

Table 32 Inspection Findings for Pivotal Trials

Study/Site	Investigator /Country	Indication	# Subjects Enrolled	Findings	Comments
304742/520	Lisa Gidday US	Contraception	24	Voluntary Action Indicated (VAI)	Failure to adhere to protocol, inadequate and inaccurate records, failure to report adverse drug reactions
306660/20	Klus Greven Germany	Contraception	120	No Action Indicated (NAI)	
306660/82	Sanchez Borrego Spain	Contraception	33	VAI	Failure to adhere to protocol
308960/123	Damon Raskin US	Bleeding	13	NAI	
308961/103 & 104	Olga Hlavackova Czech Rep.	Bleeding	16	NAI	
Bayer Healthcare Pharmaceuticals	N/A US	N/A	N/A	VAI	Inadequate monitoring of studies; failure to maintain adequate records of drug disposition

Team Leader Comments

- **The violations noted for Drs. Gidday and Borrego appeared to be of potential concern. Dr. Gidday was noted to have reported AEs late or not at all for 15 subjects, including reports of intracyclic bleeding, prolonged bleeding and irregular cycles. Dr. Gidday noted that the AEs were minor and expected, relating to the start of contraceptives. Given the overall acceptable bleeding profile for EV/DNG, I do not believe that inclusion of several additional AEs related to bleeding would significantly impact the approvability of the contraceptive indication.**
- **Dr. Borrego failed to send pregnancy letters to 13 subjects who discontinued prematurely from the trial, and failed to follow up a pregnancy that occurred within three months after study discontinuation. Given the overall acceptable contraceptive efficacy data, I do not believe that the addition of a few additional pregnancies from any of the discontinued subjects who were not appropriately**

followed would significantly impact the approvability of the contraceptive indication.

- **Therefore, I concur with DSI that the data from all inspected sites are adequate to support the NDA.**

12. Labeling

After review of a number of proposed names, including Qlaira and (b) (4) that were determined to be unacceptable, DMEPA has accepted the name Natazia.

The label was submitted in the format prescribed by the Physician Labeling Rule (PLR), and was modeled after the first PLR label approved for an OC. DRUP's review of this label was also informed by the internal updated draft Guidance for oral contraceptive (OC) labeling, as well as the first approved OC label in PLR format. Consultative reviews were provided by the Division of Drug Marketing, Advertising and Communication (DDMAC) and the Division of Risk Management (DRISK), and their comments were incorporated into the label as appropriate.

The major issues addressed in labeling negotiations with the Applicant included:

- Removal of language (b) (4)
- Acknowledgement that safety and efficacy has not been studied in women with BMI > 32 mg/m^2
- Revision of the Clinical Pharmacology section use
- Discussion of risk of decreased efficacy if used concomitantly with strong CYP3A4 inducers
- Extensive revision of the instructions for missed pills

Agreement with the Applicant on labeling was reached on May 6, 2010. Final carton and container labeling was submitted and found to be acceptable on May 6, 2010.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend that EV/DNG be approved for the indication of prevention of pregnancy, based on acceptable evidence of efficacy and a favorable risk/benefit profile. (b) (4)

13.2 Risk Benefit Assessment

EV/DNG demonstrates an acceptable risk/benefit profile for the contraceptive indication, with a Pearl Index indicating efficacy comparable to other approved oral contraceptives, and no signal of unexpected or higher frequency adverse events in the population of women who enrolled in the contraceptive trials. The bleeding profile is acceptable, although not markedly

different from monophasic low dose COC products. As noted in Section 8.9, I believe that use of EV/DNG in the reproductive-aged population likely to seek contraception is not likely to result in disproportionate risks as compared to other COCs used by reproductive-aged women for contraception.

In the contraception safety database, there is no signal that EV/DNG has a different risk profile than other COCs. However, we have little data on older women in other COC trials, because few have studied significant numbers of women over 35. For this reason, it is difficult to put into perspective the safety findings relating to older women in the trials. It is possible that any COC, if studied in an older premenopausal population, would show similar cardiovascular and VTE risks. It may also be that EV/DNG is particularly problematic in such a population.

(b) (4) Nonetheless, the 7 women who received no treatment benefit would still be exposed to the known cardiovascular and VTE risks of a COC.

(b) (4)

(b) (4)

I believe that the INAS-EV postmarketing study may provide data on women at the upper end of the reproductive age spectrum that may be helpful in further characterizing the risk in older women who use EV/DNG. (b) (4)

13.3 Recommendation for Postmarketing Risk Evaluation and Management Strategies

No postmarketing risk management activities beyond labeling are recommended.

13.4 Recommendation for Other Postmarketing Requirements and Commitments

I recommend that the postmarketing study proposed by the Applicant be specified as a postmarketing requirement. The Applicant has initiated in Europe a postmarketing observational study to assess the short-term and long-term risks of EV/DNG use as compared to the risks associated with other hormonal contraceptives, in particular venous and arterial thromboembolic events. The study will be extended to the US, and plans to enroll a total of 50,000 women, to be followed for a minimum of three years. The study represents an "actual use" noninterventional design, where women are recruited after they have selected the particular COC they feel is right for them. There are no age or other restrictions in the study. The postmarketing requirement will stipulate that the Division is particular interested in an analysis of safety data in women under age 18, because they have not been studied in the clinical trials supporting this product. The Applicant was informed of the postmarketing requirement and agreed to the following timetable in submissions dated April 21 and May 10, 2010:

Protocol Submission:	September 1, 2010
Study/Clinical Completion:	September 1, 2015
Final Study Report Submission:	September 1, 2016

13.5 Recommended Comments to Applicant

(b) (4)

In addition, the occurrence of two MIs and a DVT in women over age 40 in the current submission has raised concerns about the safety profile of EV/DNG if used by women in the older range of the reproductive-aged population. Data from INAS-EV and other

epidemiologic studies that include EV/DNG should be submitted to better characterize the risk of cardiovascular and VTE events in this population.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22252	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	Natazia

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/s/

LISA M SOULE
05/06/2010

SCOTT E MONROE
05/06/2010

I concur with the recommendation of Dr. Soule that (estradiol valerate and estradiol valerate/dienogest) tablets be approved for the indication of "use by women for prevention of pregnancy.