CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 24, 2010
From	Lisa M. Soule, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	22-532
Applicant	Bayer HealthCare Pharmaceuticals, Inc.
Date of Submission	August 24, 2009
PDUFA Goal Date	September 24, 2010 (extended)
Proprietary Name / Established (USAN) names	Beyaz Drospirenone (DRSP)/ethinyl estradiol (EE)/levomefolate calcium tablets and levomefolate calcium tablets
Dosage forms / Strength	Tablets; 3 mg DRSP/20 µg EE/451 µg levomefolate calcium for 24 days, followed by 451 µg levomefolate calcium for 4 days
Proposed Indication(s)	**Primary:** Prevention of pregnancy **Secondary:** 1. treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive for contraception 2. treatment of moderate acne vulgaris in women at least 14 years of age only if the patient desires an oral contraceptive for birth control 3. in women who choose to use an oral contraceptive as their method of contraception, to raise folate levels for the purpose of potentially reducing the risk of a neural tube defect in a pregnancy conceived while taking the product or soon after discontinuing the product.
Recommended:	***Approval***

1. Introduction

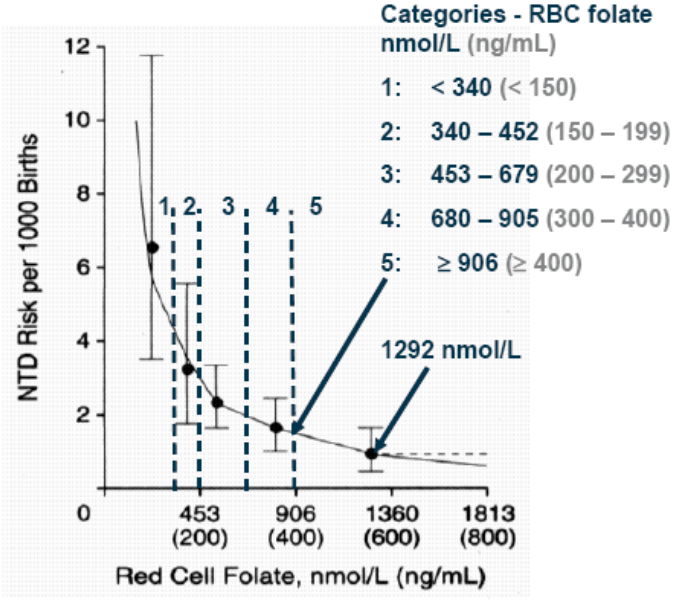
This NDA seeks marketing approval for a new product containing 3 mg drospirenone (DRSP), 20 µg ethinyl estradiol (EE), and 451 µg levomefolate calcium. Levomefolate calcium is a new chemical entity (NCE) that has not previously been approved in a prescription product.

The product is administered in a regimen of 24 days of the active combined tablets, followed by 4 days of tablets containing only the levomefolate component. The dose and dose regiment of the DRSP and EE component is identical to that in the approved combined oral contraceptive (COC) YAZ. The levomefolate component is included to provide daily folate

supplementation in women of childbearing potential. The indications sought include the three approved indications for YAZ (contraception, treatment of PMDD and treatment of acne) and a new secondary indication of (b) (4) Improvement in folate status prior to pregnancy is highly desirable due to the association of neural tube defects (NTDs), which include spina bifida and anencephaly, with low periconceptional folate levels.

NTDs are the second most common group of serious congenital anomalies and are largely preventable. It is estimated that the rate of NTDs may be reduced by as much as 50-70% (to about 6 NTDs per 10,000 pregnancies) with adequate consumption of folic acid. While folic acid has been shown to reduce the incidence of NTDs, no studies of levomefolate and NTD risk have been conducted. However, a case-control study by Daly et al1 evaluated the incidence of NTDs according to levels of RBC folate. Blood obtained at the first prenatal visit from over 56,000 Irish women was available. From this population, 84 women who had a fetus/child with an NTD and 266 controls were selected, and their pre-diagnosis samples were analyzed using the same microbiological assay used in the clinical studies in this NDA. Subjects were stratified by RBC folate level, and an inverse exposure-response relationship was demonstrated, as shown in **Figure 1.**

Figure 1 Relationship of RBC Folate Level to NTD Risk (Daly et al. 1995)



Note: The solid line refers to a **continuous risk reduction** beyond the RBC folate level of 1292 nmol/L. The dotted line refers to a constant risk reduction beyond the RBC folate level of 1292 nmol/L and was termed **conservative approach**.

Source: Summary of Clinical Efficacy, Figure 3-5, p 66

[1] Daly LE et al. Folate levels and neural tube defects: Implications for Prevention. JAMA 1995; 274 (2): 1698-702

The US Public Health Service and the Institute of Medicine[2] recommend that all women of reproductive age consume 400 µg of folic acid daily in addition to a diet rich in natural folates, regardless of whether they are practicing contraception. Since 1998, FDA has required the fortification of enriched cereal grain products with 140 µg of folic acid per 100 g of cereal grain. Since federally mandated fortification of cereals began, daily folic acid intake has increased by approximately 200 µg/day and the incidence of neural tube defects has declined by an estimated 30%. There has been ongoing discussion in the literature as to whether additional decreases in NTD rates, either nationally or in specific subpopulations, are possible through provision of additional folic acid to reproductive-age women.

Folic acid is available in a number of prenatal vitamins, both OTC and prescription products. L-methylfolate (Metafolin) is contained in at least one prescription prenatal vitamin (Prenate Essential); however, it appears that this is an "unapproved" product. While obstetricians typically prescribe folate-containing prenatal vitamins at the first pregnancy visit, often this visit does not occur until after the first four weeks of pregnancy, the critical period in which the neural tube closes.

The Applicant submitted two bioequivalence (BE) studies to evaluate the potential for drug-drug interactions between the contraceptive steroid hormones and levomefolate. The efficacy data comes from two pharmacodynamic (PD) studies. One compared the impact on plasma and RBC folate levels of YAZ + levomefolate to YAZ alone; the other compared the effect on plasma and RBC folate levels of Yasmin + levomefolate compared to Yasmin + folic acid. In this latter study, the persistence of benefit was also evaluated in a 20 week period during which folate treatment was discontinued.

(b) (4)

the accepted name is Beyaz. I will refer to the product in this review as Beyaz; however, other reviewers' may refer to it as YAZ Plus, YAZ + Metafolin or YAZ + folate. The folate component, levomefolate calcium, may also be referred to as Metafolin, L-5-MTHF, or levometafolate.

Labeling not only involved addition of a new indication, but also represented development of a label in the Physician Labeling Rule (PLR) format where the precedent product (YAZ) is not yet in PLR format. Areas that required negotiation with the Applicant included:

- Specification of the folate supplementation indication
- Description of Adverse Drug Reactions in PLR format
- Revision of the Clinical Pharmacology section

2. Background

2.1 DESCRIPTION OF PRODUCT

EE and DRSP have been used in COCs since 2001. They are found in two approved COC products, Yasmin, which contains 3 mg of DRSP and 30 µg of EE administered in a 21/7 regimen, and YAZ, which contains 3 mg of DRSP and 20 µg of EE administered in a 24/4

[2] Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes: Thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin and choline. National Academy Press. Washington, DC, 1998

regimen. Levomefolate was approved as a food additive under DSHEA in 2001 and is designated a GRAS (generally regarded as safe) compound. It is a NME insofar as it is considered an active pharmaceutical ingredient in this product. It is the calcium salt of L-5-methyltetrahydrofolate, the predominant folate found in foods. While natural food folates are unstable, folic acid and levomefolate are stable. Both natural folates and synthetic folic acid are converted into L-5-methyltetrahydrofolate in the intestine following ingestion.

Both Yasmin and YAZ have acceptable Pearl Indices for the prevention of pregnancy (0.4 in the two pivotal safety and efficacy trials for Yasmin and 1.4 for YAZ). As for other COCs, the risk of arterial thrombotic (ATEs) and venous thromboembolic events (VTEs) are among the most significant safety concerns. However, as pregnancy itself is associated with even higher rates of VTEs, the risk-benefit profile of COCs for prevention of pregnancy is considered favorable. A safety issue unique to DRSP-containing COCs is that of hyperkalemia. DRSP has antimineralocorticoid activity, and has the potential to increase serum potassium levels, particularly in women with impaired renal function and women on other medications that may increase serum potassium. However, in postmarketing surveillance, this has not been demonstrated to be a notable safety concern. Yasmin and YAZ are contraindicated in women with renal impairment, and there are labeled warnings about the potential for hyperkalemia.

Levomefolate calcium is the calcium salt of L-5-methyl-tetrahydrofolate (L-5-methyl-THF), which is the predominant form of folate found naturally in foods. While natural food folates are unstable, folic acid and levomefolate are stable. Both natural folates and synthetic folic acid are converted into L-5-methyl-THF in the intestine following ingestion. Levomefolate calcium was determined to be generally regarded (GRAS) as safe by an FDA-appointed expert panel in 1999. L-5-methyl-THF (synthesized by Merck as Metafolin) was approved for use as a dietary ingredient under the Dietary Supplement Health and Education Act (DSHEA) in 2001.

2.2 REGULATORY HISTORY

Discussion within FDA of an oral contraceptive/folate combination began in 2002; a Center Director briefing regarding the possible inclusion of folic acid in a COC was held in 2003. In December 2003, the Advisory Committee for Reproductive Health Drugs met to discuss the concept, and was strongly supportive (see Section 9).

In September 2005, Bayer met with the Division to discuss development of an oral contraceptive with 451 µg levomefolate (Metafolin), equimolar to 400 mcg of folic acid. The Applicant noted that the short-term bioavailability of levomefolate is at least as high as that of folic acid, and that equimolar doses are equally effective at increasing plasma and red blood cell folate levels. At this preIND meeting, the Division acknowledged the benefit of folate supplementation in reducing NTD risk, but did not concur that the proposed COC/levomefolate product would be exempt from combination drug regulations. The Division regarded levomefolate in such a product as an active pharmaceutical ingredient, not a food supplement. No additional nonclinical studies were recommended. The Division did not agree that sufficient data existed that levomefolate is the principal active form of folic acid, or that the selected dose of levomefolate was the appropriate dose to reduce the risk of an NTD. The Applicant was asked to document that plasma and RBC folate levels could be used to

estimate the risk of NTDs when supplementation is done with levomefolate, rather than folic acid.

A guidance meeting was held in March 2006, and included experts from CFSAN and the National Institute of Child Health and Human Development. The discussion centered on the Applicant's attempt to support that levomefolate, rather than folic acid, would have a high probability of reducing the likelihood of NTD. Discussion questions included whether plasma and RBC folate levels were appropriate markers for NTD risk reduction, and whether demonstration of equivalence of levomefolate and folic acid as measured by plasma and RBC folate and patterns of circulating folate metabolites would provide adequate evidence of the comparability of levomefolate and folic acid. The Division was also concerned about the possibility of safety issues unique to levomefolate. The Division agreed that folate status could be characterized by measurement of plasma and RBC folate. The Division stated that

> *If for both 400 μg folic acid and a to-be-determined dose of L-5-MTHF a comparable pharmacodynamic effect on [folate]$_{RBC}$ and [folate]$_{plasma}$ and a similar pattern of circulating folate metabolites could be demonstrated, this would be supportive of linking L-5-MTHF to the dose of folic acid that has been determined by the USPHS as appropriate for use by women of reproductive potential to lower the risk of NTDs.*

The Division recommended that the Applicant conduct

- A BE study of the COC with and without levomefolate
- An "equivalence" study of the PD effects of levomefolate as compared to folic acid
- A comparative trial showing superiority of a COC + levomefolate to a COC alone in terms of a clinically relevant change in folate status

The Division provided comments on Study A43598 in August 2007, and recommended that plasma folate be added as a co-primary endpoint.

A preNDA meeting was requested, but was cancelled by the Applicant after receiving preliminary responses to its questions in April 2009. The Division recommended submission of a new NDA, rather than an efficacy supplement to the YAZ NDA.

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary reviewer, Dr. Dan Davis, stated in his review, dated September 24, 2010:

> *I recommend approval of Beyaz for the following indications:*
>
> *A secondary indication not found in labeling for YAZ: "Beyaz is indicated in women who choose to use an oral contraceptive as their method of contraception, to raise folate levels for the purpose of reducing the risk of a neural tube defect in a pregnancy conceived while taking the product or shortly after discontinuing the product."*
>
> *Three indications are already approved for YAZ and I recommend that they also be approved for Beyaz on the basis of demonstrated bioequivalence of pharmacokinetic parameters for the estrogen and progestin in both Beyaz and YAZ:*
>
> - *Prevention of pregnancy*
> - *Treatment of symptoms of premenstrual dysphoric disorder (PMDD)*
> - *Treatment of moderate acne for women of at least 14 years old*

Team Leader Comment
I concur with Dr. Davis' recommendation.

3. CMC/Device

The primary Chemistry reviewer, Hitesh Shroff, Ph.D., made the following recommendations in his review dated June 2, 2010:

> *This NDA has provided sufficient/adequate information to assure identity, strength, purity, and quality of the drug products. An "Acceptable" site recommendation from the Office of Compliance has been made. However, labeling issues are still pending as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until the labeling issues are resolved.*

No postmarketing commitments or risk management steps were recommended.

Dr. Shroff entered an addendum dated September 23, 2010 when labeling was finalized, stating:

> *Now the labels have adequate information as required. Therefore, from the CMC perspective, this NDA is recommended for approval.*

3.1 General product quality considerations

The drug substance levomefolate is a new chemical entity. It is manufactured by Merck AG; the most recent CMC review of the drug master file (DMF) was in 2009 and found adequate. The DMFs for DRSP and for EE-beta-cyclodextrin clathrate were reviewed in 2010 and 2009, respectively, and were found adequate.

The release specifications for the drug product were acceptable to address identification and assay of each active ingredient, degradation products, dissolution, content uniformity and microbial purity.

The Applicant provided long-term stability data up to 12 months, and accelerated stability data up to six months for the drug substance. Stability data permitted granting a 24 month expiry for the drug product, with a notice not to store above 25° C. The Applicant's proposal to continue ongoing stability studies up to 24 months was acceptable.

3.2 Facilities review/inspection

Eight facilities involved in manufacture, testing, packaging and release of the drug product were evaluated by the Office of Compliance, which issued an overall satisfactory facilities recommendation on May 20, 2010. Three sites were found acceptable by District recommendation and five by profile.

3.3 Other notable issues (resolved or outstanding)

A biopharmaceutics review addressed the dissolution method development and specification. The reviewer, Sandra Suarez Sharp, Ph.D., concluded in her review dated July 28, 2010 that the NDA was acceptable from the biopharmaceutics perspective. However, she requested the Applicant to change the dissolution specification to NLT (not less than) (b) (4) in 15 minutes for both EE/DRSP/levomefolate tablets and levomefolate tablets. The Applicant had proposed the same limit in 30 minutes.

This recommendation was conveyed to the Applicant, and the Applicant agreed to the proposed criterion for the levomefolate tablets. The Applicant requested maintaining the 30 minute criterion for the combination tablets, stating that a "15 minute draw time is overdiscriminatory" and that they might "unnecessarily risk batch failures even though there is no impact on the *in-vivo* performance of the product." Dr. Suarez concurred, and concluded in her memo dated August 13, 2010

> *Given that YAZ and YAZ + Metafolin were found bioequivalent and YAZ showed a slower dissolution profile with a mean value of* (b) (4) *dissolved in 30 min., this reviewer agrees with the sponsor's original proposal for the dissolution specification of drospirenone+ethinylestradiol+levomefolate calcium tablets.*

4. Nonclinical Pharmacology/Toxicology

The primary Toxicology Reviewer, Leslie McKinney, Ph.D., made the following recommendations in her review dated April 5, 2010

> ***Approvability:*** *NDA 22-532* (b) (4) *(* (b) (4) *), drospirenone 3 mg, ethinyl estradiol 0.02 mg, and levometafolate 0.451 mg has been submitted by Bayer Healthcare Pharmaceuticals, inc. for improvement in folate status in women using oral contraceptives. YAZ® (drospirenone 3 mg, ethinyl estradiol 0.02 mg) is an FDA approved contraceptive, and levometafolate is both a naturally occurring human metabolite and an FDA approved food additive. There were no new non-clinical safety concerns for the addition of levometafolate to YAZ® at the proposed dose. Based on previous approval for drospirenone and ethinyl estradiol as YAZ®, as well as previous designation of levometafolate as a GRAS compound and FDA approval of levometafolate as a food additive, Pharm/Tox recommends approval of* (b) (4) *.*
>
> ***Additional Non Clinical Recommendations*****:** *There are no nonclinical recommendations.*

4.1 Summary of Nonclinical Findings

The proposed dose of levomefolate is below that considered to be the acceptable level in foods of 1 mg/day. The pharmacology/toxicology data has been reviewed previously by the Center for Food Safety and Nutrition (CFSAN) and there were no new nonclinical findings in this NDA submission.

(b) (4)

Levomefolate undergoes a natural process of oxidation, so a number of breakdown products are formed, including other folates, occur, none of which are of toxicological concern. Two impurities. (b) (4) were tested for acute oral toxicity and genotoxicity. Oral toxicity was not reported for a dose of 2,000 mg/kg in the rat, and no genotoxicity was noted in an Ames test at 5,000 µg/plate. No carcinogenicity studies have been conducted for levomefolate.

Dr. McKinney's safety evaluation stated:

> *The human metabolite L-methylfolate has no known toxicities when administered exogenously in synthetic form. As a food additive, and now as a pharmaceutical additive, it can serve to maintain plasma levels of folate. From a PharmTox perspective, there are*

no safety concerns related to addition of L-methylfolate (0.451 mg) to the formulation of Yaz®.

5. Clinical Pharmacology/Biopharmaceutics

The NDA included a pharmacokinetic (PK) study (A28575) intended to show that the PK parameters for EE and DRSP in Beyaz are bioequivalent (BE) to those in YAZ. An additional BE study (A27410) was conducted to demonstrate the BE of PK parameters for levomefolate in Yasmin + levomefolate and in levomefolate-only tablets. The BE studies were reviewed by the primary Clinical Pharmacology Reviewer, Doanh Tran, Ph.D.

Dr. Tran stated the following in his review dated July 29, 2010:

The Division of Clinical Pharmacology 3/Office of Clinical Pharmacology finds NDA 022532 Acceptable from a Clinical Pharmacology perspective, pending agreement on labeling changes.

No phase 4 commitments were recommended.

Dr. Tran provided an addendum dated September 24, 2010 following submission of final labeling by the Applicant. He concluded that:

The Division of Clinical Pharmacology 3/Office of Clinical Pharmacology finds NDA 022532 Acceptable from a Clinical Pharmacology perspective.

5.1 Pharmacokinetics

The PK of EE and DRSP have been characterized previously. The Applicant did not conduct any studies to characterize absorption, distribution, metabolism or excretion of Beyaz, but provided the following information from published literature. There is extensive first pass hepatic metabolism following absorption of oral folate. Following hepatic uptake, some folate is excreted into bile, where it undergoes enterohepatic recirculation and can be reabsorbed. Folate kinetics is biphasic, with a fast-turnover pool half-life of 10-32 hours, and a slow-turnover pool half-life of 10 to over 100 days. Elimination is mainly by urinary and fecal excretion.

Little information was provided on effects of intrinsic factors; there are limited published data that suggest that renal impairment may increase exposure of levomefolate. Several drugs, including methotrexate, cholestyramine and certain antiepileptics can reduce folate concentrations. Folates may also alter the PK or PD of certain antifolate drugs.

The BE of DRSP and EE in YAZ and Beyaz was evaluated in Study A28575. Concentrations of EE, DRSP and levomefolate were assayed using validated LC/MS/MS methods. The DSI inspection of the analytic site revealed issues regarding the robustness of the lower limit of quantitation (LLOQ) for EE and DRSP, as well as additional issues pertaining to the DRSP analyses, which are further discussed in Dr. Tran's review. The Applicant was asked to raise the LLOQ for EE and DRSP assays, and to exclude samples not meeting acceptance criteria. The Applicant did so, and Dr. Tran considered the revised dataset acceptable. Results for both hormones were within the 80-125% BE limits for C_{max} and AUC_{tlast}, indicating that they are bioequivalent.

5.2 Pharmacodynamics

The pharmacodynamic (PD) characteristics of Beyaz for the indication of folate supplementation were demonstrated in two clinical studies, A43598 and A39814, which are discussed in Section 7.

6. Clinical Microbiology

As the product is an oral tablet, no clinical microbiology review was warranted.

7. Clinical/Statistical - Efficacy

7.1 OVERVIEW OF CLINICAL PROGRAM

The Applicant submitted four studies, including two safety and efficacy (PD) studies to support the indication of improvement in folate status, and two PK (BE) studies to demonstrate the lack of significant drug-drug interaction between the contraceptive hormones and levomefolate, and to provide support for extending the three YAZ indications to Beyaz (see Table 1). Throughout this review, studies are referred to by their study report number (beginning with A); although the Applicant and other reviewers may sometimes refer to them by the Study number (six-digit number).

Study A43598 was a multicenter 24-week, randomized, double-blind, comparator-controlled trial that compared the plasma and RBC folate levels in 385 healthy women following treatment with Beyaz or with YAZ alone. Women at eight US study sites were randomized in a 3:1 ratio (291 Beyaz, 94 YAZ).

Study A39814 was a single center randomized, double-blind, double-dummy, parallel group, phase 1 trial to evaluate plasma and RBC folate, compare the profile of circulating metabolites of folate, and to evaluate the maintenance of increased folate levels following discontinuation of Beyaz. One hundred seventy two subjects at a single German site were randomized to Yasmin + levomefolate or to Yasmin + folic acid (FA) for 24 weeks of treatment (Period 1), and then followed for 20 weeks of open label treatment with Yasmin alone in a folate elimination phase (Period 2).

Baseline plasma and RBC folate levels were based on the median of three pre-treatment samples. Blood samples were then collected every two (Study A39814) to four weeks (Study A43598) on treatment; they were to be prepared at the study site and analyzed at a central laboratory.

Entry criteria are detailed in Dr. Davis' review and were similar for both clinical studies, including healthy women aged 18-40 who sought contraception. In Study 39814, baseline RBC folate levels had to be between 318-905 nmol/L and women with B12 deficiency (plasma B12 < 110 pmol/L were excluded. In addition, regular intake of vitamins or medications containing or interacting with folate within four months before entry was exclusionary. There were no such restrictions in Study 43598. Study 43598 had a body mass index (BMI) restriction of ≤ 30 kg/m^2, while the restriction was ≤ 30 kg/m^2 in Study 39814.

Table 1 Studies Supporting Four Proposed Beyaz Indications

Study Protocol # (No. of Sites / Country)	Subject Population	Treatment	Number Randomized (ITT*)	Design**
309662 **A27410** 1/Germany	Healthy young women	Yasmin + Metafolin vs. Yasmin-alone Yasmin + Metafolin vs. Metafolin-alone	45	OL, R, 3-way cross-over BE study
309664 **A28575** 1/The Netherlands		Beyaz (YAZ + Metafolin) vs. Beyaz-alone Beyaz (YAZ + Metafolin) vs. Metafolin-alone	44	OL, R, 3-way cross-over BE study
310662 **A43598** (8 / United States)	Healthy female subjects of reproductive age, 18 to 40 years old	Beyaz (YAZ + Metafolin) YAZ **Total**	291 94 **385**	DB, R, PG, AC, MC, 24 week PD study
309763 **A39814** (1 / Germany)		Yasmin/Metafolin + Placebo Folate (Period 1) followed by Yasmin (Period 2) Yasmin + Folate (Period 1) followed by Yasmin (Period 2) **Total**	86 86 **172**	OL, SC, PG, 44 week PD study

* ITT = Intent to Treat
** DB = Double-blind, OL = Open-label, R = Randomized, AC = Active Control, PG = Parallel Group, MC = Multicenter, SC = Single Center, BE = Bioequivalence, PD = Pharmacodynamic

The PK studies that demonstrated absence of any drug-drug interaction between levomefolate and the contraceptive hormones, and that provided support for extending the YAZ indications to Beyaz, are discussed in Section 5.1.

7.2 DEMOGRAPHICS

Demographic characteristics of the two arms in Study A43598 and in Study A39814 were similar, and are presented in detail in Dr. Davis' review. In Study A43598, the mean age in each treatment group was 25 years, the mean BMI was 24, and the populations were largely (64%) Caucasian, followed by black, Hispanic, Asian and other. In Study A39814, the mean age in the Yasmin + levomefolate treatment group was 28 years vs. 27 in the Yasmin + FA, the mean BMI was 23 and 22, respectively, and the populations were 100% Caucasian.

Team Leader Comment

The demographic characteristics in Study A43598 are generally representative of the US population, particularly in terms of ethnicity. BMI in both studies is well below the average US BMI, but this is a common flaw in clinical trials.

7.3 DISPOSITION OF SUBJECTS

Subject disposition in each study is described in Table 2 and Table 3. Study completion was relatively high, particularly in German Study A39814, and was similar across treatment arms.

Table 2 Study A43598 – Subject Disposition (Randomized Population)

Disposition / Reason	Beyaz	YAZ
Randomized	291	94
Study medication never administered	6 of 291	0
Study medication status unknown (included in FAS)	11 of 291	0
Full Analysis Set (FAS)*	285 (100%)	94 (100%)
Per Protocol Set (PPS)**	196 (68.8%)	66 (70.2%)
Completed study medication	203 (71.2%)	70 (74.5%)
Prematurely discontinued from the study	82 (28.8%)	24 (25.5%)
• Lost to follow-up	26 (9.1%)	8 (8.5%)
• Protocol deviation	17 (6.0%)	8 (8.5%)
• Withdrawal of consent	13 (4.6%)	3 (3.2%)
• Adverse event	12 (4.2%)	3 (3.2%)
• Other	11 (3.9%)	2 (2.1%)
• Unknown	3 (1.1%)	0

* Defined as all randomized subjects who took at least one dose of study medication
** Defined as all FAS subjects who met all the inclusion/exclusion criteria, did not take any medications influencing folate status, had at least 75% study drug compliance per cycle, had no major protocol violations, completed 24 weeks of treatment, and had valid baseline and week 24 plasma and RBC folate values
Source: Summary of Clinical Efficacy, Table 3-1, p 23 and Table 3-22, p 43

Table 3 Study A39814 – Subject Disposition (Randomized Population)

Disposition / Reason	Yasmin + Levomefolate	Yasmin + Folic Acid
Randomized	86	86
Study medication never administered	0	0
Study medication status unknown (included in FAS)	0	0
Full Analysis Set (FAS)*	86 (100%)	86 (100%)
Per Protocol Set (PPS)**	75 (87.2%)	75 (87.2%)
Completed study medication	81 (94.2%)	83 (96.5%)
Prematurely discontinued from the study	5 (5.8%)	3 (3.5%)
• Withdrawal of consent	2 (2.3%)	0
• Other	2 (2.3%)	0
• Adverse event	1 (1.2%)	3 (3.5%)

* Defined as all randomized subjects who took at least one dose of study medication and had at least one post-treatment clinical observation
** Defined as all treated subjects who had no major protocol violations
Source: Summary of Clinical Efficacy, Table 3-1, p 23 and Table 3-23, p 44

Team Leader Comments

- **The "other" reasons for discontinuation in Study 43598 included subject relocation and noncompliance.**
- **The rate of adverse events leading to study discontinuation was relative low in both studies.**

7.4 EFFICACY FINDINGS

7.4.1 Assessment of Efficacy

7.4.1.1 Study A43598

The co-primary efficacy endpoints in Study A43598 were plasma and RBC folate levels at Week 24 of treatment. The protocol defined two analysis populations – the Full Analysis Set (FAS), which included all randomized subjects who took at least one dose of study drug, and

the Per Protocol Set (PPS), defined as FAS subjects who did not violate entry criteria that might impact the primary endpoints, did not use medications that would affect folate status, had at least 75% medication compliance, had no other major protocol violations, completed 24 weeks of treatment and had valid Baseline and Week 24 data for plasma folate or for RBC folate. The PPS was identified as the primary efficacy analysis population in Amendment 4 for reasons related to exclusion of data from sites with sample handling problems (see below). Analyses were also conducted for the FAS with and without last observation carried forward (LOCF); LOCF was used where subjects discontinued prematurely or had missing folate data at Week 24. The analysis used ANCOVA with treatment as a factor and baseline folate level as a covariate. Only women with both baseline and Week 24 folate levels were included in the analysis.

The Applicant originally powered the study based on an expected change from baseline in mean RBC folate of 100 ng/ml in the Beyaz group. Plasma folate was added as a co-primary endpoint after the start of the study, based on the Division's recommendation.

Plasma and RBC folate was measured at three pre-treatment visits, and baseline values were based on the mean and standard deviation of the median value of these measurements. In both studies, folate levels in plasma and whole blood were analyzed using a validated microbiological assay that measures all active forms of folate. The Daly paper discussed in Section 1 also used this assay in correlating NTD risk with RBC folate level. RBC folate was calculated by the equation:

> RBC folate = [(whole blood folate * 100) – (plasma folate *(100 – hematocrit))]/hematocrit (%)

Whole blood folate levels required dilution by a factor of 0.1, and sample handling was evaluated by analyzing hemoglobin concentration from these samples and comparing that to the same subject's hemoglobin concentration from safety labs. The Applicant discovered that two of the eight study sites (which together enrolled 133 subjects) had improperly diluted samples, resulting in invalid values for whole blood folate. As whole blood folate is necessary for the calculation of RBC folate levels, the Applicant conducted the pre-planned analysis and two sensitivity analyses of RBC folate:

- the protocol-specified analysis (**Scenario A**), which included all valid RBC values from all sites
- **Scenario B**, which excluded all data from the two sites
- **Scenario C**, which evaluated all RBC folate data after normalizing the whole blood folate value to account for errors in dilution

For plasma folate, which was not affected by the sample handling problems, the Applicant conducted Scenario A and B, but not C, analyses.

After recognizing these issues, the Applicant modified the intended primary analysis population from the FAS, using LOCF, to the PPS. This was done because it was recognized that the number of valid RBC folate samples was lower than intended due to exclusion of invalid samples. As RBC folate reaches steady state only towards the end of the study, use of LOCF imputation would not accurately reflect the values expected later in treatment.

7.4.1.2 Study A39814

The efficacy endpoints differed a bit in Study A39814, as the absolute value and change from baseline for plasma and RBC folate during Period 1 and Period 2 (elimination phase) were considered secondary endpoints. However, the assay used for folate analyses was the same, and the PPS was also the primary efficacy analysis population. There were no sample handling issues on the order of that experienced in Study A43598, so only straightforward FAS and PPS analyses were conducted.

Team Leader Comment

This study did not use the product for which marketing authorization is requested in this NDA (Beyaz), but rather a related COC that contains a higher dose of estrogen (Yasmin). However, the BE studies discussed in Section 5.1 demonstrate the absence of a drug-drug interaction between levomefolate and the contraceptive hormones DRSP and EE. Therefore, the combination of levomefolate with a higher dose of EE should have no effect on the impact of levomefolate on folate levels.

7.4.2 Primary Efficacy Analysis

7.4.2.1 Study A43598

Although the Applicant conducted numerous sensitivity analyses (for plasma folate – Scenarios A and B for each of PPS, FAS with LOCF and FAS without LOCF populations; for RBC folate – Scenarios A, B and C for each of PPS, FAS with LOCF and FAS without LOCF populations), only results for FAS without LOCF, Scenario A and the two PPS analyses for Scenarios A and B are discussed here, as these are considered the most important of the analyses. The protocol-specified primary analysis is the PPS, Scenario A. Results for plasma folate are shown in Table 4, and results for RBC folate are shown in Table 5.

Table 4 Study A43598 – Baseline and Post-treatment Plasma Folate Levels (nmol/L)

Analysis Population	Treatment Group	N at Baseline	Median Baseline Plasma Folate Mean (SD)	N at Week 24	Week 24 Plasma Folate Mean (SD)	Change from Baseline (Least Squares Mean)	P-value for difference between treatment arms
FAS without LOCF – Scenario A	YAZ + LMF	285	44.4 (18.9)	201	61.1 (19.8)	16.0 (20.4)	P<0.001
	YAZ	94	41.6 (16.9)	66	41.0 (17.6)	-2.2 (14.6)	
PPS – Scenario A	YAZ + LMF	196	45.0 (17.6)	196	60.8 (19.9)	15.8 (20.4)	P<0.001
	YAZ	66	43.1 (16.2)	66	41.0 (17.6)	-2.2 (14.6)	
PPS – Scenario B	YAZ + LMF	129	42.0 (17.7)	129	58.0 (20.7)	16.1 (20.4)	P<0.001
	YAZ	47	41.2 (16.6)	47	40.3 (18.3)	-1.0 (14.7)	

LMF = levomefolate; SD = standard deviation
Source: Based on Study Report for A43598, Table 142, p 598; Table 143, p 600; Table 146, p 603; Table 147, p 605; Table 153, p 613 and Table 155, p 616

Team Leader Comment

There is minimal difference in sample size, or in results, between the FAS and the PPS – Scenario A population analyses. The exclusion of two study sites that improperly

handled samples, and which enrolled a total of 133 (12 at 104, 121 @ 108) subjects, accounts for the loss of 67 subjects from the Beyaz arm and 19 subjects from the YAZ arm under Scenario B. As Scenario A was restricted to subjects with valid data, a number of the subjects from the two sites had already been omitted from Scenario A. The actual folate levels remain quite consistent under either scenario, and the treatment effect is statistically significant under all three analyses (and under those analyses not shown here).

Table 5 Study A43598 – Baseline and Post-treatment RBC Folate Levels (nmol/L)

Analysis Population	Treatment Group	N at Baseline	Median Baseline RBC Folate Mean (SD)	N at Week 24	Week 24 RBC Folate Mean (SD)	Change from Baseline (Least Squares Mean)	P-value for difference between treatment arms
FAS without LOCF – Scenario A	YAZ + LMF	200	976 (385)	142	1,404 (433)	416 (343)	P<0.001
	YAZ	71	1,017 (359)	47	1,027 (292)	34 (171)	
PPS – Scenario A	YAZ + LMF	144	990 (390)	124	1,406 (440)	420 (347)	P<0.001
	YAZ	52	1,014 (308)	45	1,024 (293)	34 (171)	
PPS – Scenario B	YAZ + LMF	129	957 (314)	122	1,398 (438)	436 (289)	P<0.001
	YAZ	47	1,016 (314)	44	1,021 (295)	33 (173)	

LMF = levomefolate; SD = standard deviation
Source: Based on Study Report for A43598, Table 106, p 550; Table 107, p 552; Table 110, p 555; Table 111, p 557; Table 118, p 566 and Table 119, p 568

Team Leader Comments

- **The effect of excluding all invalid samples in the PPS is shown by the marked reduction in sample size between the FAS and the PPS – Scenario A. The exclusion of two study sites that improperly handled samples resulted in minimal additional loss of subjects because Scenario A was restricted to subjects with valid data, so the majority of the subjects from the two sites had already been omitted from Scenario A. The actual RBC folate levels remain quite consistent under either scenario, and the treatment effect is statistically significant under all three analyses (and under those analyses not shown here).**
- **FDA statistician, Dr. Castillo, has recommended reporting confidence intervals around the treatment differences, rather than p-values, due to the large percent of data that had to be discarded due to improper sample handling. This is most applicable to the RBC folate data. I concur that labeling should not describe p-values or statistical significance.**
- **However, despite loss of a considerable amount of data due to sample handling errors, the analyses of both plasma and RBC folate is extremely robust. It is clear that folate supplementation with Beyaz results in a marked increase in both plasma and RBC folate that is statistically significantly greater than that seen in subjects taking YAZ alone.**
- **Plasma folate actually decreased over the 24 week study period in YAZ subjects, while it increased by about 35% in Beyaz subjects.**
- **RBC folate increased by about 3% over the course of the study in subjects using YAZ, while Beyaz subjects experienced about a 45% increase in RBC folate.**

- **Although the mean baseline RBC folate value in these US subjects already exceeded the 906 nmol/L described in the Daly paper as resulting in the greatest reduction in NTD risk among the five strata of RBC folate levels examined, it is unknown whether there is a ceiling effect for RBC folate level. At lower levels, there appears to be a continuous inverse relationship between RBC folate level and NTD risk (i.e., the greater the rise in RBC folate, the greater the decrease in NTD risk).**

7.4.2.2 Study A39814

This study protocol identified the primary endpoints as pharmacodynamic, not efficacy, variables. The primary pharmacodynamic endpoint was equivalency of $AUC_{0\text{-}24\ weeks}$ for plasma and RBC folate. Secondary endpoints were absolute value and change from baseline for plasma and RBC folate during Period 1 (treatment) and Period 2 (elimination phase). The PPS was the primary analysis set. There was no significant sample handling problem in this study, so no alternative analysis scenarios were used.

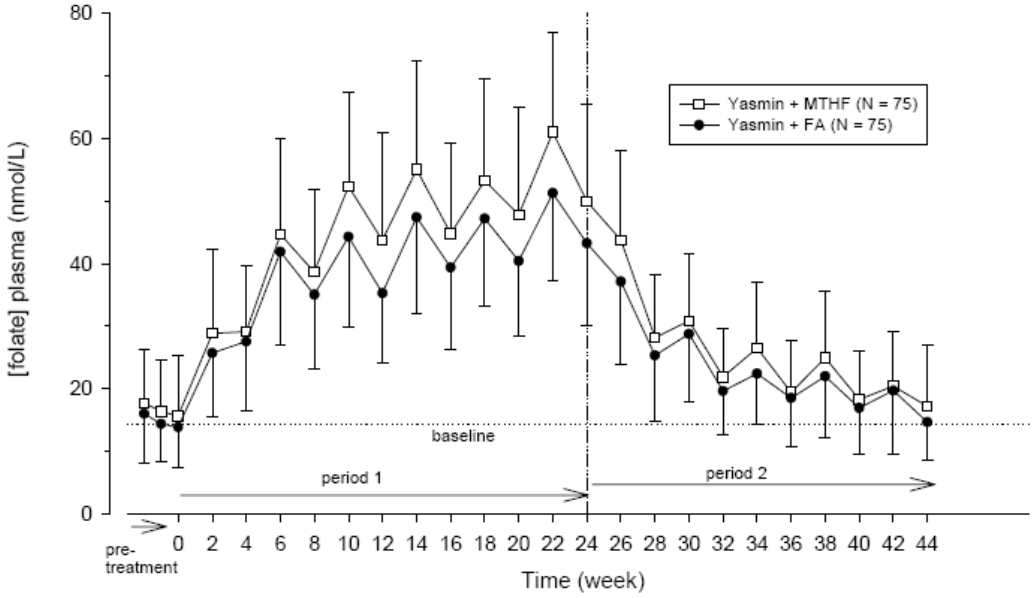
The decrease in RBC folate to below 906 nmol/L in the elimination phase was calculated only for those subjects who entered Period 2. Data for plasma and RBC folate are shown in Table 6 and Table 7, respectively, and in Figure 2 and Figure 3, respectively.

Table 6 Study A39814 – Baseline and Post-treatment Plasma Folate Levels (nmol/L)

Analysis Population	Treatment Group	N at Baseline	Median Baseline Plasma Folate Mean (SD)	N at Week 24	Week 24 Plasma Folate Mean (SD)	Change from Baseline (Least Squares Mean)	N at Week 44	Week 44 Plasma Folate Mean (SD)	Change from Baseline (Least Squares Mean)
FAS without LOCF	Yasmin + LMF	86	15.5 (9.3)	81	49.2 (15.4)	33.1 (14.4)	79	17.0 (9.6)	0.7 (9.8)
	Yasmin + FA	86	14.0 (6.5)	82	44.0 (13.5)	29.4 (12.5)	81	14.7 (6.0)	0.3 (6.4)
PPS	Yasmin + LMF	75	15.6 (9.7)	75	49.9 (15.5)	33.5 (14.5)	75	17.2 (9.8)	0.8 (10.0)
	Yasmin + FA	75	13.8 (6.4)	75	43.3 (13.3)	29.1 (12.6)	75	14.7 (6.2)	0.5 (6.5)

LMF = levomefolate; FA = Folic acid; SD = Standard deviation
Source: Based Study Report for A43598, Table 110, pp 750-1, Table 111, pp 752-3, Table 112, pp 754-5 and Table 113, pp 756-7

Figure 2 Study A39814 – Mean Concentration-Time Curves for Plasma Folate



Source: Study Report for A39814, Text Figure 3, p 103

Team Leader Comments

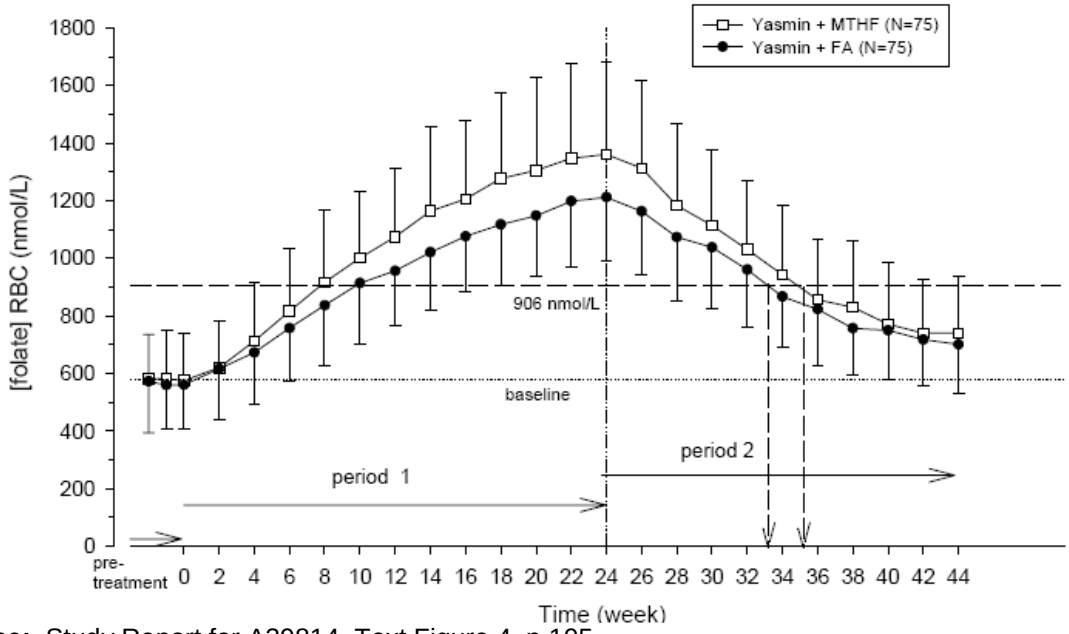
- **The increase in plasma folate from baseline to Week 24 was similar in both arms; although slightly greater in the levomefolate arm than the folic acid arm. In both arms, the plasma folate levels decreased similarly in the elimination phase.**
- **Plasma folate increased from baseline by 200-300% in Yasmin + levomefolate subjects.**
- **The Applicant could not explain the biweekly variation in plasma folate levels that resulted in the observed sawtooth pattern, but speculated that it might represent loss of folate in menstrual blood.**
- **Overall, it is apparent that the effect of levomefolate on plasma folate levels is virtually identical to that of an equimolar amount of folic acid.**
- **Despite fairly rapid fall-off in levels once folate supplementation was discontinued, the mean levels in both arms remained slightly above baseline at 20 weeks post-discontinuation. Data based on 95% confidence intervals (email submission by Applicant dated September 20, 2010; not shown) suggests that plasma folate remains above baseline in 97.5% of women on Yasmin + levomefolate for 14 weeks after discontinuation.**

Table 7 Study A39814 – Baseline and Post-treatment RBC Folate Levels (nmol/L)

Analysis Population	Treatment Group	N at Baseline	Median Baseline RBC Folate Mean (SD)	N at Week 24	Week 24 RBC Folate Mean (SD)	Change from Baseline (Least Squares Mean)	N at Week 44	Week 44 RBC Folate Mean (SD)	Change from Baseline (Least Squares Mean)
FAS without LOCF	Yasmin + LMF	84	585 (156)	81	1,373 (335)	796 (278)	79	733 (198)	159 (159)
	Yasmin + FA	85	559 (146)	82	1,202 (222)	649 (173)	79	698 (175)	145 (141)
PPS	Yasmin + LMF	75	576 (161)	75	1,361 (322)	782 (260)	75	740 (198)	162 (162)
	Yasmin + FA	75	555 (145)	75	1,207 (217)	657 (175)	74	701 (171)	149 (139)

LMF = levomefolate; FA = Folic acid; SD = standard deviation
Source: Based on Study Report for A39814, Table 102, pp 736-7; Table 103, pp 738-9; Table 105, pp 742-3 and Table 106, p 744-5

Figure 3 Study A39814 – Mean Concentration-Time Curves for RBC Folate



Source: Study Report for A39814, Text Figure 4, p 105

Team Leader Comments

- **The much higher baseline values for plasma and RBC folate in the US study (A43598) as compared to the German study (A39814) likely reflects the impact of food fortification with folic acid, which is not done in Germany.**
- **In this study, the change from baseline was evaluated biweekly, so the pattern of change over time could be assessed. Plasma folate increased maximally by about 22 weeks of treatment, while RBC folate values increased continually throughout the full 24 weeks of treatment.**

- **The increase in RBC folate from baseline to Week 24 was similar in both arms; although slightly greater in the levomefolate arm than the folic acid arm. In both arms, the plasma folate levels decreased similarly in the elimination phase.**
- **Overall, it is apparent that the effect of levomefolate on RBC folate levels is virtually identical to that of an equimolar amount of folic acid.**
- **RBC folate increased by about 130% over the course of the study in subjects using Yasmin + levomefolate.**

The Applicant provided a Kaplan Meier analysis to describe the proportion of Yasmin + levomefolate subjects who maintained RBC folate levels above the Daly criterion once folate supplementation had been discontinued (see Table 8). More than 50% remained above this level eight weeks after levomefolate was stopped.

Table 8 Study A39814 – Kaplan Meier Estimate of Proportion of Yasmin + Levomefolate Subjects Maintaining a RBC Folate Level of ≥ 906 nmol/L in the Elimination Phase

Week	No. of volunteers with RBC folate ≥ 906 nmol/L	KM estimate (Proportion of volunteers with RBC folate ≥ 906 nmol/L)
24	71	0.9467
26	70	0.9333
28	64	0.8533
30	59	0.7867
32	45	0.6000
34	35	0.4667
36	22	0.2933
38	18	0.2400
40	13	0.1733
42	10	0.1333
44	7	0.0933

Source: Study Report for A39814, Text Table 19, p 102

Team Leader Comment

In these unsupplemented German subjects, the mean baseline RBC folate value was well below the 906 nmol/L described in the Daly paper. It appears that any magnitude of increase from a level below this will result in reduction in NTD risk. The mean level for Yasmin + levomefolate subjects exceeded the 906 nmol/L criterion by about eight weeks of treatment and was maintained for eight weeks following discontinuation in more than 50% of subjects.

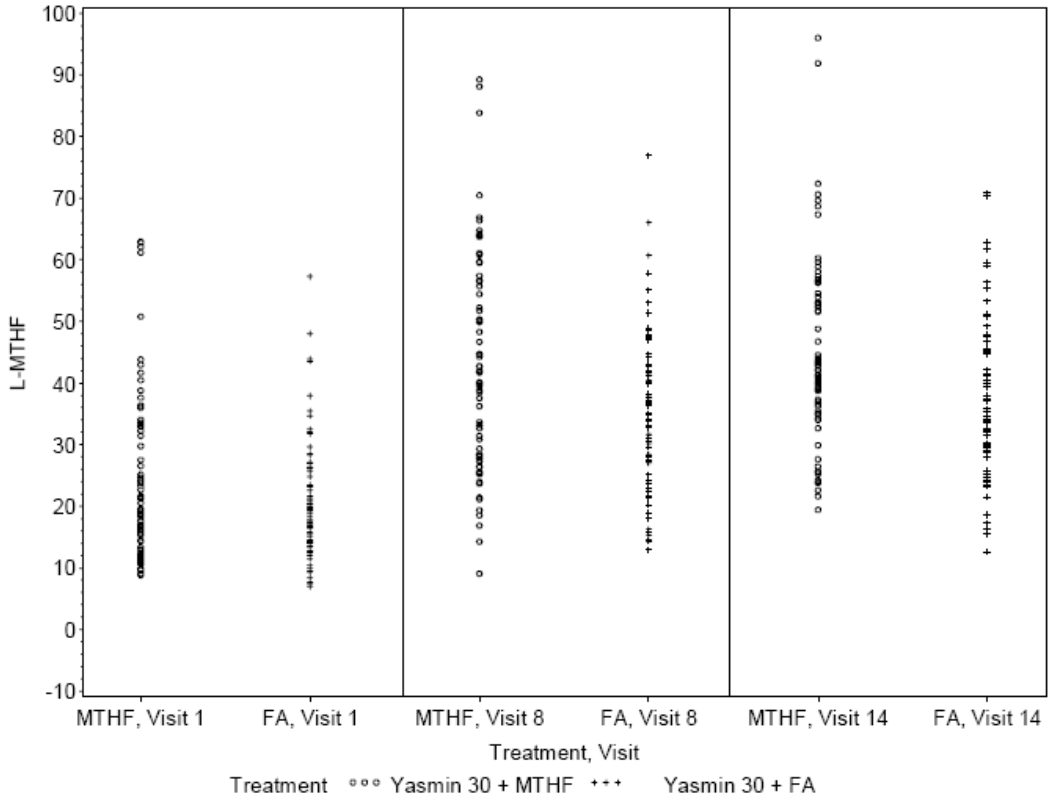
An additional endpoint of importance was comparison of the relative proportions of circulating folate metabolites following treatment with levomefolate as compared to folic acid. The Division has requested this analysis due to uncertainty about which specific metabolite(s) of folic acid might actually be responsible for the reduced NTD risk.

The Applicant analyzed the following metabolites in plasma:

- Folic acid
- L-5-methyl-THF
- THF
- 5-formyl-THF/10-formyl-THF
- 5,10-methenyl-THF

Plasma L-5-methyl-THF concentrations were measureable in almost all samples, but the concentrations of the other four metabolites were below the lower limit of quantitation (LLOQ) in the majority of samples. Albeit based on very few quantifiable samples, there did not appear to be a difference in plasma concentrations between Yasmin + levomefolate and Yasmin + folic acid for any of these metabolites. The pattern of plasma L-5-methyl-THF is shown in Figure 4.

Figure 4 Study 39814 – Dot Plot of Plasma L-5-methyl-THF



Source: Study Report for A39814, Text Figure 8, p 110

Team Leader Comment

The data regarding folate metabolites is extremely limited. However, the microbiological assay used to assess folate levels in both PD studies, as well as in the Daly study, measures all biologically active folate forms. Evaluation of the circulating pattern of folate metabolites had been requested to provide a "bridge" between epidemiologic data based on folic acid supplementation and the PD data in this application based on levomefolate. Understanding now that both the epidemiologic data and the PD data

evaluated the same "biologically active folate forms," I believe this provides sufficient bridging to conclude that increased folate levels that result from levomefolate supplementation is likely to have the same impact on the risk of NTDs as do the increased folate levels that result from supplementation with folic acid.

Statistician's Conclusion

The statistical reviewer, Sonia Castillo, Ph.D., conducted analyses of the data that differed slightly from the Applicant's. She excluded additional samples (beyond those excluded by the Applicant in Scenario B) that were recommended to be omitted by DSI (see Section 11). She reached the following conclusions in her review dated September 2, 2010:

A large amount of data submitted in support of this application was invalid due to poor blood sample preparation and was discarded from the efficacy evaluation. Blood sample preparation problems were discovered at two of the eight study sites during an interim analysis of blinded baseline plasma and red blood cell (RBC) folate data for all pre-treatment samples for all 385 randomized subjects in Study A43598. One of the sites was the largest study site that enrolled 31.2% of all subjects (120 of 385) and the other site enrolled 3.4% of all subjects (13 of 385).

Samples from both sites were not processed correctly due to incorrect dilution during sample preparation and/or a failure to protect blood samples from excessive light exposure. This resulted in higher than expected levels of folate which were invalid and/or biologically implausible. Valid plasma folate, whole blood folate, and hematocrit values are needed to calculate RBC folate. Both the clinical reviewer and the Division of Scientific Investigations report recommended that these RBC folate samples be removed from the RBC folate primary efficacy analysis. There were no sample preparation issues with plasma folate levels.

Due to these blood sample preparation errors, the analysis for RBC folate dropped 41% of the Beyaz data and 34% of the comparator data. So instead of declaring statistical significance, a descriptive presentation using the 95% confidence interval for the treatment difference is used.

Despite dropping this substantial amount of data, the two submitted studies provide supportive evidence demonstrating the efficacy of the oral contraceptive Beyaz (0.020 mg ethinyl estradiol + 3.0 mg drospirenone + 0.451 mg levomefolate calcium) to improve the folate status in women who elect to use an oral contraceptive. There was an increase in RBC folate and plasma folate levels with Beyaz use.

Dr. Castillo entered an addendum to her review on September 22, 2010 that corrected a typographical error in her Table A.4.

7.4.3 Secondary Efficacy Analysis

The precedent COC product, YAZ, has secondary indications for treatment of PMDD and of moderate acne, as well as a primary indication for prevention of pregnant. The Applicant did not conduct any efficacy studies with Beyaz to support extending these indications to Beyaz. Rather, the Applicant states that demonstration of bioequivalence of the PK parameters for EE and DRSP between Beyaz and YAZ justify inclusion of these same indications in the Beyaz label. The Division concurred with this rationale regarding the pregnancy prevention

indication. The Division of Dermatologic and Dental Products (DDDP) was asked to consider the acne indication. DRUP and DDDP asked the Applicant to review the scientific literature in order to demonstrate that there is no known adverse impact of levomefolate on either PMDD or acne.

The Applicant submitted a literature review on July 15, 2010, in which they summarized 11 articles relating to acne and folate, and one article relating to PMDD and folate. The single article purportedly about PMDD reported higher homocysteine levels during various phases of the menstrual cycle in depressed women as compared to nondepressed controls.

Team Leader Comment

The article provided is not really relevant to the question at hand. A search through PubMed did not reveal any additional articles pertaining to PMDD and folate. Thus, there appears to be no evidence of an adverse impact of folate on PMDD. If homocysteine were causally related to depression, the reduction of homocysteine levels seen with folate supplementation could conceivably be beneficial.

Snezana Trajkovic, MD, of DDDP reviewed the acne articles, and concluded in her memorandum dated August 31, 2010 that

> *This sponsor submitted literature, and this reviewer's independent literature search, did not result in any relevant studies that evaluated the safety and efficacy of levomefolate calcium in treatment of acne vulgaris, or any impact of levomefolate calcium on the treatment of acne vulgaris in combination with hormonal oral contraceptives.*
>
> *Due to lack of any submitted scientific evidence, no meaningful conclusions can be drawn about the impact of levomefolate calcium on the safety and efficacy of Beyaz for the treatment of acne vulgaris.*

Team Leader Comment

In the absence of any data indicating that levomefolate has an adverse impact on the symptoms of PMDD or acne, and recognizing that the steroid hormones responsible for the treatment benefit for both indications are bioequivalent in Beyaz to those used in the approved drug YAZ, I agree that Beyaz may be labeled as indicated for prevention of pregnancy (primary) and for the secondary indications of PMDD and moderate acne. The same labeling pertaining to these indications should be used for Beyaz as is provided in YAZ.

7.4.4 Overall Assessment of Efficacy

The two PD studies conducted by the Applicant provided robust confirmation of the efficacy of levomefolate when combined with an EE/DRSP COC to increase both plasma and RBC folate levels. Despite numerous methodological issues in Study 43598, various sensitivity analyses all demonstrated a marked increase in folate following treatment with levomefolate. Data from Study 39814 following folate levels after discontinuation of levomefolate (or folic acid) showed that the increases attributable to folate supplementation begin decreasing upon discontinuation, but that folate levels remain above baseline levels for a number of weeks after treatment is stopped. This would provide an important advantage for a pregnancy conceived on treatment or shortly after discontinuation of treatment, as it would provide higher folate levels in early pregnancy than would otherwise be the case. Given that pregnant women often do not obtain obstetric care or begin prenatal vitamins with folate supplements in the first

weeks of a pregnancy, entering pregnancy with an increased folate level should provide some protection against NTD at the period at which the neural tube is closing.

While the Applicant did not (and indeed, could not have) conduct a randomized trial designed to demonstrate a reduction in NTD incidence with levomefolate treatment, I believe that the following indication is warranted, despite the fact that randomized clinical trials that have demonstrated an association of folate supplementation with NTD incidence have all used folic acid and not levomefolate:

> *Beyaz is indicated in women who choose to use an oral contraceptive as their method of contraception, to raise folate levels for the purpose of reducing the risk of a neural tube defect in a pregnancy conceived while taking the product or shortly after discontinuing the product.*

The Daly study that showed that RBC folate level is strongly inversely related to NTD risk used the same microbiological assay that the two PD studies in this NDA used. Thus, Daly's data shows that the downstream metabolites of both folic acid and levomefolate are associated with NTD incidence.

The Applicant relies on the demonstration of bioequivalence of the steroid hormones in YAZ and Beyaz to support extension of the three indications for YAZ to Beyaz. I concur that this is a reasonable basis on which to approve the indications of contraception, PMDD and acne, and that there is no indication in the literature that folate would be expected to adversely impact the treatment benefit of EE/DRSP on acne or PMDD.

8. Safety

This review of the safety of Beyaz is primarily based on data from Studies A43598 and A39814, supplemented by the limited safety data from the two BE studies. The safety evaluation is also informed by years of postmarketing experience with the EE/DRSP products Yasmin and YAZ.

The safety population in Study A43598 included 285 women who took at least one dose of Beyaz, and that in Study A39814 included 86 women who took at least one dose of Yasmin + levomefolate. The two BE studies included a total of 86 women who took Beyaz, Yasmin + levomefolate and/or levomefolate alone.

Safety evaluations included vital signs and laboratory monitoring, pregnancy testing and adverse event reporting.

8.1 Deaths and Serious Adverse Events

There were no deaths in any of the clinical trials. There were two serious adverse event (SAE) in Study A43598, a cervical carcinoma in situ (CIS) and pneumonia, both in women treated with Beyaz. Only the cervical CIS was considered possibly drug-related, and the subject with cervical CIS was discontinued prematurely due to this AE.

In Study A39814, there were a total of 16 SAEs occurring in nine women. The only two occurring (in a single subject) during treatment with Yasmin + levomefolate were an acoustic neuroma, and impaired healing (following surgical treatment of the neuroma). In the Yasmin + folic acid group, pyelonephritis and ulcerative colitis occurred during Period 1 in one subject each. In Period 2 (treatment with Yasmin alone), a total six subjects experienced 12 SAEs (see Table 9). None of these were considered drug-related. There were no SAEs in the BE studies.

Table 9 SAEs in Study A39814

Study arm/phase	Subject No.	SAE(s) Preferred Term
Yasmin + levomefolate; Period 1	32	Acoustic neuroma
		Impaired healing
Yasmin + FA; Period 1	53	Pyelonephritis
Yasmin + FA; Period 1	68	Ulcerative colitis
Yasmin alone; Period 2 (formerly Yasmin + levomefolate)	54	Arthralgia
Yasmin alone; Period 2 (formerly Yasmin + levomefolate)	110	Esophageal food impaction
Yasmin alone; Period 2 (formerly Yasmin + levomefolate)	173	Appendicitis
Yasmin alone; Period 2 (formerly Yasmin + levomefolate)	150	Abdominal pain lower
		Hemorrhagic ovarian cyst
(Yasmin alone; Period 2 (formerly Yasmin + levomefolate)	151	Abdominal pain
		Nausea
		Diarrhea
		Cholelithiasis
Yasmin alone; Period 2 (formerly Yasmin + FA)	109	Loss of consciousness
		Hyperventilation
		Alcohol poisoning

There were no SAEs in the two bioequivalence studies.

Team Leader Comment

The ovarian cyst may be drug-related, but the association is likely with the contraceptive hormones, rather than with levomefolate, as it occurred during the Yasmin-alone phase.

Eleven Beyaz subjects (3.9%) and three YAZ subjects (3.2%) discontinued the trial due to adverse events (AEs) in Study A43598, as did three Yasmin + levomefolate subjects (3.5%) and four Yasmin + FA subjects (4.7%) in Study A39814 (see Table 10). A single subject in BE Study A27410 discontinued due to vasovagal syncope during treatment with Yasmin + levomefolate.

Table 10 Adverse Events Leading to Discontinuation in the PD Studies

Subject Number	Treatment Group	Reason for Discontinuation MedDRA preferred term (AE text)
	Study A43598	
101030	YAZ + levomefolate	Nausea Dizziness
101053	YAZ + levomefolate	Menstrual disorder (abnormal bleeding)
103003	YAZ + levomefolate	Cervical CIS*
103097	YAZ + levomefolate	Affect lability
104002	YAZ + levomefolate	Libido decreased Dysmenorrhea Menorrhagia
104006	YAZ + levomefolate	Hypothyroidism
106003	YAZ + levomefolate	Genital hemorrhage (vaginal spotting)
106026	YAZ + levomefolate	Libido decreased
106044	YAZ + levomefolate	Libido decreased
108101	YAZ + levomefolate	Depressed mood
108139	YAZ + levomefolate	Weight increased
104004	YAZ	Migraine (increased)
108030	YAZ	Systemic lupus erythematosus
108063	YAZ	Abdominal pain Cholelithiasis
	Study A39814	
32	Yasmin + levomefolate	Acoustic neuroma
54	Yasmin alone (Period 2; previously Yasmin + levomefolate)	Arthralgia (pain in R knee, requiring surgery)
151	Yasmin alone (Period 2; previously Yasmin + levomefolate)	Cholelithiasis
25	Yasmin + FA	Hyperthyroidism
53	Yasmin alone (Period 2; previously Yasmin + FA)	Pyelonephritis
68	Yasmin + FA	Ulcerative colitis
152	Yasmin + FA	Basedow's disease**

*SAE
** Graves' disease
Source: Based on Tables 11 and 12, primary medical review by Dr. Davis, dated September 24, 2010

8.2 Other Notable Adverse Events

There was one pregnancy in Study A43598 that was conceived during the treatment phase in a woman randomized to Beyaz, in addition to two conceived prior to treatment. However, it was determined that the woman had never taken any study medication. She experienced a spontaneous abortion. Two pregnancies were noted in Study A39814, one occurred prior to treatment, and the other was conceived during Period 2 treatment with Yasmin alone. The latter pregnancy was medically terminated. There were two pregnancies in the BE studies. One occurred during Beyaz treatment in Study A28575, and one occurred in Study A27410 on Yasmin-only treatment. Both were attributed to "insufficient use of non-hormonal methods of contraception" and both pregnancies were electively terminated.

Team Leader Comment

A total of four on-treatment pregnancies occurred during use of Beyaz, Yasmin + levomefolate or Yasmin alone. With approximately 4,000 28-day cycles of treatment, this would represent a Pearl Index of 1.3, very comparable to the labeled Pearl Index for YAZ. Thus, there is no indication that addition of levomefolate adversely affects the contraceptive efficacy of YAZ.

8.3 Other Adverse Events

Table 11 includes only adverse reactions (ARs - i.e., AEs likely to be drug-related) that occurred in ≥ 1% of subjects in either arm; some similar terms have been bundled. In Study A43598, the only ARs that occurred more frequently in the Beyaz vs. YAZ arm were headache and decreased libido. However, when migraine was bundled with headache, there was no excess in the Beyaz arm. In Study A39814, only nausea was more common in Beyaz subjects.

Table 11 Common Adverse Reactions (≥ 1% of Safety Population)

Preferred Term	COC + Levomefolate Arm n (%)	COC – No Levomefolate Arm n (%)
Study A43598		
	Beyaz N =285	**YAZ N=94**
Headache + migraine	7 (2.5)	3 (3.2)
Libido decreased	4 (1.4)	0
LDL increased	3 (1.1)	3 (3.2)
GGT increased	2 (0.7)	1 (1.1)
Vaginal hemorrhage + menorrhagia	3 (1.1)	1 (1.1)
Study A39814		
	Yasmin + Levomefolate N=86	**Yasmin + FA N=86**
Nausea	5 (5.8)	0
Dysmenorrhea	2 (2.3)	3 (3.5)
Headache	2 (2.3)	3 (3.5)
Breast discomfort	2 (2.3)	2 (2.3)
Vaginal hemorrhage + menorrhagia	2 (2.3)	7 (8.1)

Source: Based on Integrated Summary of Safety, pp 17-22

In the PK studies, common ARs were metrorrhagia, abdominal discomfort, headache, nausea, vomiting and dizziness. With the exception of headache, these rarely occurred on levomefolate alone, and were similarly prevalent in the COC + levomefolate or the COC-alone arm.

Team Leader Comment

The labeling should include pooled AEs for YAZ and Beyaz, as the safety profile appears to be largely driven by the contraceptive steroids. Labeling should not include data from Study A34918, as this used a higher-estrogen COC product.

Laboratory and vital signs data are discussed in Dr. Davis's review, and did not provide any signal of concern. Due to the possibility of DRSP resulting in elevated potassium, this was specifically evaluated, and no cases of potassium levels above 5.5 nmol/L were observed.

8.4 Postmarketing Safety Findings

Beyaz has not been marketed anywhere in the world, so there are no postmarketing data. There are substantial postmarketing data on YAZ, which will be included in the Adverse Reactions – Postmarketing section of labeling. Levomefolate appears to be marketed in the US only in an unapproved prescription prenatal vitamin, so safety reports are not available.

8.5 Safety Update

The Applicant submitted a safety update on December 16, 2009, which included a literature review through June 2009. A Periodic Safety Update Report for YAZ was submitted on November 5, 2009. Neither submission suggested any new safety concerns. The label for YAZ was revised on April 7, 2010, to report on two epidemiologic studies relating to VTE risk over various COCs. FDA did not consider that the safety profile for YAZ or Yasmin was altered based on the findings of these studies. The VTE labeling for Beyaz will be consistent with that for YAZ.

8.6 Overall Assessment of Safety Findings

Addition of levomefolate to the approved COC YAZ for the purpose of folate supplementation does not appear to present an unusual or concerning safety profile. The adverse event profile is similar to that observed for COCs generally.

Issues that are specific to the folate component of Beyaz include the possible masking of B12 deficiency by folate supplementation, and a potential adverse impact on the efficacy of antifolate medications. These will be addressed in labeling. The Applicant will monitor postmarketing safety reports for terms that might indicate symptoms of undiagnosed B12 deficiency.

Dr. Davis' review also notes several recent publications that report an increased risk of childhood asthma in children exposed to high folate levels, particularly during late pregnancy. I concur with Dr. Davis' conclusion that this concern is not relevant to use of Beyaz in a COC. The dose is lower than that routinely given to pregnant women in prenatal vitamins and the levomefolate will be discontinued as soon as a woman realizes she is pregnant.

9. Advisory Committee Meeting

The Advisory Committee on Reproductive Health Drugs (ACRHD) met in December, 2003 to discuss the safety and potential benefit of adding folic acid to an OC. Questions posed to the Committee and the votes are listed below.

1. **Are further increases in folic acid intake, beyond what is available in fortified cereals, likely to result in public health advances in preventing further neural tube defects?**

   Yes - 18 No - 0 Abstain – 0

2. **Is it necessary to define a subpopulation among women of reproductive age that needs additional folic acid?**

   Yes - 4 No - 14 Abstain – 0

3. **Are there any safety issues associated with folic acid supplementation targeted at reproductive-age women?**

   Yes - 7 N -11 Abstain – 0

   Safety issues discussed included the potential for folic acid supplementation to mask symptoms of vitamin B12 anemia (pernicious anemia), and to adversely affect the activity of antifolate drugs such as valproic acid and methotrexate.

4. **Would the benefit of prior folic acid use persist if conception occurs after discontinuation of folic acid?**

   Yes - 12 N - 2 Abstain – 1

   Members noted that red blood cell folate increases would be maintained for up to 90 days following discontinuation of supplementation.

5. **Is an oral contraceptive pill a reasonable delivery vehicle if additional folic acid supplementation is likely to provide public health advances in preventing further neural tube defects? If so, would 400 micrograms (mcg) be a reasonable dose?**

   Yes - 18 N - 0 Abstain – 0 [both questions]

   While all felt this was a reasonable dose, some members recommended that additional studies be conducted to further define the optimal dose.

10. Pediatrics

(b) (4) The Pediatric Review Committee (PeRC) considered this application on April 14, 2010, and 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 and with YAZ specifically has supported the expectation that efficacy and safety results in postmenarchal adolescents do not differ from those in adult women. There is not expected to be any difference in the impact of folate supplementation in adolescent users.

11. Other Relevant Regulatory Issues

The Applicant submitted financial disclosure information for investigators in the PD studies, none of whom reported disclosable information. The Applicant also reported that no investigators were debarred from the practice of medicine during the course of the study.

The Applicant reported in the original submission that Sites 104 and 108 in Study A43598 had improperly handled samples such that dilutional errors invalidated whole blood folate levels needed for the calculation of RBC folate levels. The Applicant conducted a sensitivity analysis omitting data from these two sites (see Section 7.4.2.1).

Site inspections by the Division of Scientific Investigation (DSI) were requested for various clinical and analytic sites associated with the two PK and two PD studies. Because the endpoints in all studies were based on laboratory analyses, the inspections were requested to be performed by the GLP branch of DSI. There were numerous findings of concern that resulted in Voluntary Action Indicated (VAI) classifications at all inspected sites, and also necessitated elimination of a number of samples, reanalyses of several of the studies, and revision of study reports. Findings at the various sites are summarized in Table 12.

Table 12 Inspection Findings for Pivotal Trials

Study (Report #) Description	Site	Result	Findings	Actions Taken/ Recommendations
A28575 309664 BE study with YAZ	Dinox BV, The Netherlands (Clinical site)	VAI	1. Sample processing records do not document appropriate timing of centrifugation of samples. 2. Incomplete or illegible records 3. Revised Informed Consent not resubmitted to IRB 4. Errors in drug accountability records	1. N/A – samples stable for up to 2 hours 2. N/A – internal review documented correct information 3. N/A – revisions were minor **4. Firm needs to verify dispensing by seeing if EE, DRSP and Metafolin levels consistent with scheduled study treatment**
	(b) (4) (Analytic site)	VAI	1. Failure to evaluate stability of 5MTHF in blood over 30" clotting period 2. Failed to document freeze/thaw and long-term frozen stability of 5MTHF	1. N/A – (b) (4) showed no 5MTHF stability problem if sera obtained within 30" of sampling 2. N/A – (b) (4) showed 5MTHF is stable after 4 freeze/thaw cycles; new long-term stability data to be submitted, but DSI does not believe it should delay approval.

Study (Report #) Description	Site	Result	Findings	Actions Taken/ Recommendations
			3. Quantitation method (integration parameters) modified without appropriate justification 4. Failure to report all pre-study validation experiments 5. Criteria for re-assaying certain samples not specified by Applicant	3. N/A – (b) (4) reintegrated all runs and differences between original and re-integrated data very small 4. N/A – unlikely to affect study outcomes re 5MTHF 5. N/A – Applicant's rationale for selection of samples found to be adequate **Overall, 5MTHF data can be accepted**
A43598 310662 PD study with YAZ	Coastal Carolina Research Center, NC Lori Lyles (Clinical site)	VAI	Concomitant medications violated study exclusions or prohibitions	**DSI recommended exclusion of subjects' data; clinical reviewers determined concomitant medications unlike to affect study results**
	Medical Center for Clinical Research, CA Wm. Koltun (Clinical site)	VAI*	1. Timing guidelines for specimen processing not met. 2. Source worksheets do not agree with sample processing forms inadequate.	**1. Samples exposed to light > 5" should be removed from analysis.** 2. N/A – staff re-educated **This site was excluded in Scenario B analyses**
A39814 309763 PD study with Yasmin **A43598** 310662 PD study with YAZ	(b) (4) (Analytic site)	VAI	**Re: Microbiological folate assay:** 1. Long-term stability of folate assay only completed for 10 months, while samples analyzed at up to 19 (A39814) and 22 months (A43598); freeze/thaw stability only done with previously frozen RBC and plasma 2. Validation of QCs done only at a single concentration	1. Stability demonstrated to 35 months for plasma assays. Stability testing failed to meet 15% criteria for whole blood assays; however, **clinical and clin pharm reviewers concluded data acceptable despite being outside 15% acceptance criterion.** Freeze/thaw stability using never-frozen samples was satisfactory. 2. Validation at three concentrations acceptable, except accuracy of the 3 ng/ml folate spike in plasma cannot be assured; **DSI recommends omitting**

Study (Report #) Description	Site	Result	Findings	Actions Taken/ Recommendations
				plasma folate results < 3 ng/ml
			3. Failure to demonstrate sufficient dilution linearity	3. Validation only confirmed the 5x dilutions as accurate; **DSI recommends to omit 6 8x diluted samples from analysis**
			4. Runs accepted despite lack of high-concentration quality controls (QCs)	**4. Assay results from cited runs should be excluded from analysis**
			5. Failed to document procedure used to generate calibration curves	5. N/A – (b) (4) used procedure consistently, SOP updated **Overall, clinical and clin pharm reviewers found QCs outside the 15% acceptance criteria to be acceptable.**
			Re: Mass Spec (MS) folate assay: 6. Audit trail for MS folate assay software not available; inspection cannot reconstruct modified chromatograms	6. N/A – Data usable for semi-quantitative purposes of this assay
			7. Peak baselines manually adjusted w/o adequate justification	**7. Response does not correct objection**
			8. Assays repeated at Applicant request without predefined criteria	**8. DSI recommends using original data, rather than re-assays**
			9. Preparation of QCs and calibrators not adequately documented	**9.** N/A – available records indicate preparation done according to documented procedure **Overall, this assay was used for circulating folate metabolites; only qualitative results, rather than precise quantitative levels were needed.**
			Re: both microbiological and MS folate assays: 10. Storage freezer thermometers not calibrated	10. N/A – does not affect study data integrity

*This classification was downgraded from OAI as Applicant adequately addressed concerns
Source: DSI reviews dated May 24, 2010 and June 30, 2010

12. Labeling

The proprietary name Beyaz was found acceptable by DMEPA.

The Beyaz label was submitted in the format prescribed by the Physician Labeling Rule (PLR). DRUP's review of this label was informed by the internal updated draft Guidance for oral contraceptive (OC) labeling, as well as by several other approved OC labels in PLR format. Consultative reviews were provided by the Division of Drug Marketing, Advertising and Communication (DDMAC), and the Study Endpoints and Label Development (SEALD) group, and their comments were incorporated into the label as appropriate.

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

- Clarification of the specifics of the folate supplementation indication
- Addition of detailed information on bleeding irregularities, (b) (4)
- Description of Adverse Drug Reactions in PLR format, with reporting separately for the contraception/acne/folate supplementation trials (pooled) and the PMDD clinical trials. The current, non-PLR, YAZ label is primarily class labeling, with minimal detailed information about ARs seen in the clinical trials and postmarketing reports for YAZ.
- Revision of the Clinical Pharmacology section

Agreement with the Applicant on labeling was reached on September 23, 2010.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend that Beyaz be approved for the secondary indication "*Beyaz is indicated in women who choose to use an oral contraceptive as their method of contraception, to raise folate levels for the purpose of reducing the risk of a neural tube defect in a pregnancy conceived while taking the product or shortly after discontinuing the product*" as well as for the indications approved for YAZ of prevention of pregnancy (primary) and treatment of PMDD and acne (both secondary indications).

13.2 Risk Benefit Assessment

Beyaz demonstrated a consistent increase in plasma and RBC folate in two studies in heterogeneous populations (a US population, where folate-fortified food is widely available and a German population without food fortification, where baseline folate levels were considerably lower. While folate levels decline once levomefolate is discontinued, mean levels remain above the baseline levels for several months after discontinuation. As shown by Daly et al, there appears to be a continuous inverse relationship between RBC folate levels and risk of NTD. Therefore, it is expected that the higher levels of RBC folate attributable to use of Beyaz will translate into a lower risk of NTDs in pregnancies that are conceived by women during use of Beyaz (contraceptive failures) or by women who discontinue contraception for

the purpose of getting pregnant and conceive shortly after discontinuing Beyaz. As it is actually the plasma folate to which a fetus is exposed, it is likely that higher plasma folate levels should also be protective; however, the epidemiologic data are mainly based on RBC folate levels because this is a better marker for long-term folate status.

The safety profile of Beyaz does not vary from that observed for the COC YAZ. As the folate supplementation indication is only a secondary indication, the product should only be used by women who choose to use an oral contraceptive for contraception. The risk/benefit profile of YAZ has been determined to be favorable in this population, and there is not signal that levomefolate will alter this unfavorably. Theoretical safety concerns relevant to levomefolate will be appropriately addressed by the Applicant in labeling and through pharmacovigilance and a postmarketing observational study.

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

No postmarketing studies are recommended. (b) (4)

While such postmarketing data is always useful to further characterize a drug's safety profile when a large and heterogeneous population is exposed, I do not consider that such a study is mandatory for this product.

13.5 Recommended Comments to Applicant

None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LISA M SOULE
09/24/2010

SCOTT E MONROE
09/24/2010
I concur with the recommendation of Dr. Soule that Beyaz be approved.