CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022532Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-532
Priority or Standard	Standard
Submit Date(s)	21 August 2009
Received Date(s)	24 August 2009
PDUFA Goal Date	24 June 2010, extended to 9-24-10
Division / Office	DRUP/ODE III
Reviewer Name(s)	Daniel Davis, MD, MPH
Review Completion Date	September 24, 2010
Established Name	Drospirenone (DRSP)/ethinyl estradiol (EE)/levomefolate calcium tablets and levomefolate calcium tablets
(Proposed) Trade Name	Beyaz
Therapeutic Class	Hormonal contraception
Applicant	Bayer Schering Pharma AG
Formulation(s)	Oral tablet
Dosing Regimen	One tablet daily; DRSP/EE/levomefolate tablets for 24 days; levomefolate-only tablets for 4 days
Indications	-Prevention of pregnancy -To raise folate levels -Treatment of symptoms of PMDD -Treatment of moderate acne for women at least 14 years old
Intended Population(s)	Women of reproductive age

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

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

1.2 Risk Benefit Assessment

The risk-benefit assessment for Beyaz [YAZ + Metafolin] is acceptable. The risks associated with all combination hormonal contraception are well-established and the overall risk-benefit assessment is favorable in general for healthy women choosing to use such products. The benefit of adding Metafolin is that it supplements (increases) the folate levels in both plasma and red blood cells in women taking Beyaz. There is evidence from the medical literature that increased folate levels decrease the risk of a neural tube defect in the fetus. Thus, the increased folate levels obtained by use of Beyaz should provide a benefit to a woman in whom a pregnancy occurs while taking Beyaz or within the first couple of months of stopping Beyaz. There does not appear to be any increase in the risks associated with YAZ for up to 24 weeks of exposure when 0.451 mg levomefolate calcium (Metafolin) is added.

Reviewer Comment:
Throughout this review the term metafolin is used; metafolin is the same as levomefolate calcium, the crystalline form of the calcium salt of L-5-methyltetrahydrofolate (L-5-methyl-THF).

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

I do not recommend a postmarketing risk evaluation and mitigation strategies (REMS) for this product. YAZ and an earlier drospirenone-containing oral contraceptive, Yasmin, which contains a higher dose of ethinyl estradiol (0.03 mg instead of 0.02 mg) have been marketed for many years. Yasmin was approved in 2001 and YAZ in 2006; both have had extensive sales in the US and Europe. The addition of metafolin does not warrant any postmarketing REMS.

1.4 Recommendations for Postmarket Requirements and Commitments

In a meta-analysis based on 20 studies, Fernandez et al. (British J Cancer, 2001) obtained a relative risk for colorectal cancer of 0.82 (95% CI: 0.74-0.92) among ever users of combination

oral contraceptives (COCs), suggesting a moderately protective effect of COCs against colorectal cancer. A prospective cohort study published by Lin et al. (Am J Epidemiology, 2007) also demonstrated an inverse association between colorectal cancer and duration of OC use. This agrees with the results of the Nurses Health Study (Martinez et al. Cancer Epidemiology, 1997).

Current data demonstrate that poor folate status is associated with an increased risk for colorectal cancer (CRC). The evidence that high folate intake increases growth of pre-existing tumors is less convincing (see Section 7.6.1). Thus the effect of folates on CRC risk remains undetermined and will depend on the relative size of the two potential effects, and of the timing and level of folate intake. In conclusion, the overall effect of YAZ + Metafolin on CRC risk is currently unknown.

(b) (4)

Reviewer's comment:

(b) (4)

2 Introduction and Regulatory Background

2.1 Product Information

YAZ + Metafolin provides a folate-fortified oral contraceptive (OC) regimen. There is a need for strategies that ensure that women of reproductive age consume sufficient amounts of folate in order to reduce the risk of a neural tube defect (NTD) in the newborn. One such strategy is to supplement OCs with metafolin, the crystalline form of the calcium salt of L-5-methyltetrahydrofolate (L-5-methyl-THF), the predominant form of dietary folate. YAZ + Metafolin consists of 24 pink, film-coated tablets each containing 3 mg of drospirenone (DRSP), 0.02 mg of ethinyl estradiol (EE) stabilized by betadex as a clathrate (molecular inclusion complex) and 0.451 mg of Metafolin, and 4 light-orange, film-coated tablets containing 0.451 mg of Metafolin only. The dosage of YAZ + Metafolin is one pink hormone-containing tablet daily for 24 consecutive days followed by one light-orange tablet daily for 4 days per treatment cycle.

In the current clinical program, Metafolin has been added to the approved OC YAZ to provide women, who are using this product for oral contraception, with the added benefit of daily supplementation with folate. The potential, but not proven, benefit of this supplementation is to reduce the incidence of neural tube defects (NTDs) in the offspring of these women should a pregnancy occur either while taking the product or shortly after stopping the product. It is postulated that even with a folate-fortified American diet, ingestion of YAZ + Metafolin will

result in a further improvement in folate status among reproductive-age females, and that any individual elevation in folate status is considered to be clinically relevant. This is because an increase in folate level has been shown in several studies to result in a decrease in NTD risk (Daly LE et al. *JAMA*- 1995;274:1698-1702 and Berry RJ et al. *NEJM* 1999;341:1485-90). The relationship does appear to be linear, but an upper threshold value for folate levels (plasma and RBC) and reduction in NTD risk has not been established.

For YAZ fortified with Metafolin, 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" is proposed in addition to the already approved three indications for YAZ (without Metafolin).

2.2 Tables of Currently Available Treatments for Proposed Indications

YAZ is readily available by prescription along with many other brand name and generic hormonal contraceptive choices. There are currently no FDA-approved products that contain a combination oral hormonal contraceptive (COC) with either folic acid or metafolin. Women on COCs, however, may take a folic acid supplement as desired.

2.3 Availability of Proposed Active Ingredients in the United States

Both EE and DRSP are available in the approved OC products Yasmin, YAZ, and generic versions of both, and in Angeliq, approved for the treatment of menopausal symptoms. EE in combination with various progestins is the estrogen in almost all COCs. Levomefolate is approved as a food additive and is designated a GRAS (generally regarded as safe) compound. Levomefolate 600 mcg is also found in a prescription prenatal vitamin (Prenate Essential), although the product is not FDA-approved. Folic acid is readily available in certain prescription multivitamins and over-the-counter multivitamins at pharmacies and health food stores.

2.4 Important Safety Issues with Consideration to Related Drugs

All combination hormonal contraceptives carry some risk, especially an increased risk of venous thromboembolic events, but the overall risk in healthy women is lower than that of a pregnancy. YAZ has the same class labeling contraindications as other COCs. YAZ has two additional contraindications, namely renal and adrenal insufficiency, and it should not used in women with conditions that predispose to hyperkalemia. In addition, there are many benefits of hormonal contraception and YAZ is approved for pregnancy prevention, symptoms of premenstrual dysphoric disorder (PMDD), and moderate acne in women who are at least 14 years old. YAZ and metafolin in the dose proposed by the Applicant are considered to be safe. Folic acid supplementation in many food items has been in effect in the U.S. since January 1, 1998. Excessive folic acid has been associated with masking pernicious anemia (a rare condition) and could impact the activity of antifolate drugs such as antiepileptics (valproic acid) and methotrexate. This is unlikely, however, with the proposed product because it is taken as a once daily tablet and contains approximately 400 mcg of the active metabolite of folic acid (L-5-methyl THF).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A pre-IND meeting was held with the Applicant on 9-08-05. The following clinical and pharmacology items were discussed:

- The Division agreed that based on the existing bioequivalence data on ethinyl estradiol and ethinyl estradiol beta-cyclodextrin clathrate (in YAZ), in addition to the proposed bioequivalence study, the betacyclodextrin formulation in Yaz can be used without further bioequivalence testing.
- The Division does not concur that sufficient data exists demonstrating that L-mefolinate (metafolin) is the principal active form of folic acid
- The proposed clinical efficacy study might be sufficient to demonstrate clinical evidence of adequate folate supplementation but would not be sufficient to support approval of your proposed combination drug product. The critical question is not "adequate folate supplementation" but rather the likelihood that the risk of an infant having a NTD will be reduced in women using the proposed combination drug product. The Division is not aware of any clinical data that have shown that increasing the daily intake of L-mefolinate, per se, will reduce the risk of developing a NTD. If the Sponsor can provide adequate evidence that plasma and RBC folate concentrations can be used to estimate the risk of developing a NTD when the intake of L-mefolinate, instead of folic acid, is increased, the approach that you have proposed, with significant modification, would appear to be acceptable.
- Since this unresolved question is critical to the Division's agreeing to the proposed clinical development program, only general comments will be provided at this time. These comments are relevant only if the concerns expressed above regarding the substitution of L-mefolinate for folic acid are resolved.
    - The Division cannot concur with the choice of dose for L-mefolinate at this time since it is not known what dose would be optimal for reducing the incidence of NTDs.
    - The Division recommends that the clinical trial include 3 treatment arms: (1) Yasmin alone, (2) the proposed combination drug product containing Yasmin and L-mefolinate, and (3) Yasmin and 0.4 mg of folic acid.
    - The study should be randomized and blinded and of sufficient size to demonstrate equivalence of plasma and RBC folate concentrations in the treatment arms containing the combination drug product (Yasmin plus L-mefolinate) and Yasmin plus 0.4 mg of folic acid.
    - The Division concurs with your plan to assess folate concentrations both during and following the period of treatment with L-mefolinate.
- The Division concurs that changes in plasma homocysteine levels are influenced by folate activity, but the Division does not consider this a valid surrogate endpoint for the reduction of NTDs.

A type C Guidance meeting was held with the Applicant on 3-10-06 and the following items were discussed:

- The Division concurs with measurement of folate RBC concentration and folate plasma concentration for the determination of folate status. Plasma homocysteine levels would

not be an appropriate surrogate endpoint (marker of folate status) for the reduction of NTDs.

2.6 Other Relevant Background Information

In December 2003, an FDA Advisory Committee (AC) meeting was held to discuss the safety and potential clinical benefit associated with combining folic acid and an OC into a single combination product. The Committee voted the following on several key questions:

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?
   The vote: Yes- 18, No- 0.
2. Is it necessary to define a subpopulation among women of reproductive age that needs additional folic acid?
   The vote: Yes- 4, No- 14.
3. Are there any safety issues associated with folic acid supplementation targeted at reproductive-age women?
   The vote: Yes- 7, No- 11.

   Some committee members raised the concern that too much folic acid has been associated with masking pernicious anemia (a rare condition) and could also impact the activity of antifolate drugs such as antiepileptics (valproic acid) and methotrexate.
4. Would the benefit of prior folic acid use persist if conception occurs after discontinuation of folic acid?
   The vote: Yes- 12, No- 2, Abstain- 1.

   The members agreed that increased red cell folate levels (following folic acid supplementation) would be maintained for up to 90 days following discontinuation.
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?
   The vote for both questions: Yes- 18, No- 0.

   Many members stated that this dose was reasonable, but might not be ideal and that additional studies should be conducted to further define an ideal dose. The members did not provide a recommendation for alternative dosing.

Reviewer's comment:

In essence, the AC members agreed that the concept of combining an OC with 400 mcg of folic acid was reasonable. It would provide a public health advance in lowering the risk of neural tube defects in those women who conceive while on the OC or within 90 days following discontinuation of the OC. Based on the results of this AC meeting, Bayer Schering pursued a development plan for both their already approved Yasmin and YAZ oral contraceptive products.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

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, which 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. This 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 as the samples did not need to be diluted.

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 rather than declaring statistical significance, a descriptive presentation using the 95% confidence interval for the treatment difference is used by the Division statistician. Despite dropping this substantial amount of data, the two submitted studies provide evidence demonstrating the efficacy of Beyaz to improve the folate status in women who elect to use an oral contraceptive. There was a definite increase in RBC folate and plasma folate levels with Beyaz use.

Reviewer Comment:
In my opinion, the overall quality and integrity of the NDA submission is still acceptable. Findings and recommendations by the Agency's Division of Scientific Investigations (DSI) were acknowledged by the Applicant, and appropriate actions taken during the course of the approval process. Data that should not be included in the various final analyses were excluded. Furthermore, the Applicant analyzed the RBC folate data from the US study using three different scenarios which are discussed later in this review.

3.2 Compliance with Good Clinical Practices

All clinical studies performed in the framework of this submission were conducted in accordance with Good Clinical Practice, the principles of the Declaration of Helsinki, and all applicable national regulations valid at the time the studies were performed. The protocols and protocol amendments were reviewed and approved by independent Ethics Committees or Institutional Review Boards.

Reviewer's comment:

Two clinical sites (both in the US) in Study A43598 were inspected by the Agency's DSI and were found to have minor protocol violations (Mt. Pleasant, SC site) and some inaccurate case report

forms and major blood sample processing errors (San Diego, CA site). Further discussion of the analytical sites and FDA inspections of those sites is found in Sections 6.1.1 and 6.1.10 of this review.

3.3 Financial Disclosures

The Form FDA 3454 and Financial Certification/Disclosure Tables for the two clinical pharmacodynamic studies are included with this submission and none of the investigators had financial disclosures. Financial Certification was not provided in the NDA Financial Certification Disclosure Module for the two bioequivalence studies A28575 and A27410.

Reviewer's comment:

This is acceptable as the Division does not usually ask for financial disclosure from non-clinical sites.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

Levomefolate calcium (L-5-MTHF-Ca, also referred to as L-methylfolate, calcium L-mefolinate, and L 5 methyl-tetrahydrofolic acid) is a readily dissociable calcium salt of L-5-methyltetra-hydrofolate (L-5-MTHF), the predominant natural form of folate in many foods and in the human body. Levomefolate calcium is a synthetic alternative for folic acid, an essential B vitamin that is crucial for 1-carbon transfer reactions. Note: L-methylfolate is not a reference listed drug, but is a GRAS compound approved by CFSAN as a food additive. The daily dose of levomefolate calcium to be administered with the YAZ® + levomefolate calcium drug product for oral contraception is 451 mcg, which is equivalent to 400 mcg folic acid.

On 6-02-10, Hitesh Shroff, PhD, from the Office of New Drug Quality Assessment (ONDQA) concluded in his Chemistry review:

> *This NDA has provided sufficient 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.*

Reviewer's comment:

From the Chemistry reviewer, the CMC is acceptable and the site inspection by the Office of Compliance is acceptable. All chemistry labeling issues were resolved, so the NDA submission is satisfactory from the CMC perspective.

4.2 Clinical Microbiology

No clinical microbiology review was required for this NDA submission.

4.3 Preclinical Pharmacology/Toxicology

It was the intention of Bayer Schering to cross-reference the previously submitted nonclinical information for drospirenone, ethinyl estradiol, and β-cyclodextrin in this submission, and to include a literature-based summary of the pharmacology and toxicology of levomefolate calcium. In 1999, an independent expert panel appointed by the FDA reviewed the literature for levomefolate calcium and recommended that levomefolate calcium, when meeting appropriate food grade specifications in accordance with good manufacturing practices, is generally recognized as safe (GRAS) based upon scientific procedures for use as a source of folate in conventional foods and dietary supplements.

The results of four reproductive toxicology studies of drospirenone in combination ethinyl estradiol (100/1 ratio) that were not described in the initial IND, were described in the 2008 Annual Report (Serial No. 0007).

In summary, the results of the nonclinical toxicology and ADME/pharmacokinetics studies support the preclinical safety of drospirenone, in combination with ethinyl estradiol, for use as an oral contraceptive when supplemented with levomefolate calcium. As is the case with all products containing estrogen, the use of this product by pregnant women, or women who suspect that they may be pregnant, is contraindicated.

The FDA preclinical toxicology reviewer, Leslie McKinney, PhD, concluded in the Executive Summary of her 4-05-10 review:

> *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, PharmTox recommends approval of* (b) (4).

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

L-5-methyl-THF (Metafolin is the calcium salt form) offers an alternative to folic acid for the improvement of folate status. The Division requested supportive evidence that L-5-methyl-THF is as effective as folic acid in improving folate status and therefore in potentially reducing the risk of NTD in a pregnancy. L-5-methyl-THF is the predominant form of folate found naturally in food and the principal form of folate normally found in the blood circulation. It is the folate that is normally transported from the plasma into peripheral tissues and used for cellular folate metabolism. Folic acid is a very stable synthetic form of the folate found in fortified foods, supplements and pharmaceuticals. It is incapable of being used for cellular folate metabolism, unless it is first reduced to active folate forms. Metafolin, the calcium salt of L-5-methyl-THF, used here for fortification of YAZ, is similarly as stable as folic acid.

4.4.2 Pharmacodynamics

Human pharmacodynamics of L-5-methyl-THF (Metafolin) was characterized with regard to its effect on plasma folate, RBC folate and homocysteine based on two long-term studies A43598 (24 weeks) and A39814 (44 weeks) and supported by relevant literature. The change from baseline folate values over 24 weeks and the persistence of such changes for 20 weeks after drug discontinuation were studied in the two controlled trials.

4.4.3 Pharmacokinetics

No modifications were made to the formulations during the development of YAZ + Metafolin tablets; the final formulations or an almost identical formulation with a higher EE content (Yasmin + Metafolin) were used in the four key studies submitted with the NDA application. The biopharmaceutical properties of the tablets were studied *in vivo* in the 2 bioequivalence studies and *in vitro* in the dissolution tests.

Data to characterize the clinical pharmacology of L-5-methyl-THF were obtained from the four above-mentioned studies and from the relevant scientific literature on L-5-methyl-THF and other folates. Human pharmacokinetics of L-5-methyl-THF were assessed based on relevant literature and were supported by the two bioequivalence studies.

Reviewer's comments:

For a detailed discussion of the biopharmaceutical properties (pharmacodynamics [PD] and pharmacokinetics [PK]) of YAZ + metafolin, see the review by the clinical pharmacology reviewer Doanh Tran, Ph.D. In the single-dose bioequivalence study with YAZ + Metafolin (Study A28575), it was shown that concomitant administration of Metafolin does not affect the bioavailability of DRSP and EE and, that the concomitant administration of DRSP and EE does not affect the bioavailability of L-5-methyl-THF administered as Metafolin. These findings were also confirmed in a three-arm bioequivalence study (Study A27410) with Yasmin + Metafolin versus unfortified Yasmin and Metafolin-only tablets.

The clinical pharmacology team reviewed the following data:

- **YAZ bioequivalence study**
- **Summary of ADME properties for folate**
- **Method validation reports and Division of Scientific Investigation (DSI) reports relating to the assays for total folate values and the bioequivalence studies**
- **Effect of polymorphism of the 5, 10-methylenetetrahydrofolate reductase (MTHFR) gene**

5 Sources of Clinical Data

Bayer's development program was undertaken to provide data confirming that fortification of an OC with Metafolin, the calcium salt of L-methyl-THF, is clinically beneficial, and to provide evidence confirming that Metafolin has effects similar or equivalent to folic acid. Four clinical studies were conducted. These studies were discussed with the Division at meetings held on September 8, 2005 and March 10, 2006. The IND was submitted on March 01, 2007 and a pre-meeting package was submitted for the pre-NDA meeting scheduled for April 6, 2009. The meeting was subsequently cancelled upon receipt of preliminary responses from the Division.

5.1 Tables of Studies/Clinical Trials

There were two pivotal efficacy pharmacodynamic studies and one bioequivalence clinical pharmacology studies that were essential in the review of this NDA. They are listed in Table 1.

Table 1: Pivotal Clinical Studies

Study # and location	Design	# Women by treatment group	Main Objectives
A43598 United States	MC, DB, randomized, controlled; 24 weeks	YAZ+Metafolin: 285 YAZ alone: 94	Measure Δ in RBC and plasma folate levels over time
A39814 Germany	One site, DB, double-dummy, pharmaco-dynamic 24-wk trial; then 20-wk open-label Yasmin only for folate elimination phase	Yasmin+Metafolin: 86 Yasmin+folic acid: 86	Compare two arms for RBC and plasma folate levels; determine time for RBC folate to decline below 906 nmol/L in the 20-wk elimination phase
A28575 Netherlands	One site, open-label, single dose, crossover, randomized, three treatments, three periods, 6 treatment sequences	YAZ+Metafolin: 41 YAZ: 43 Metafolin: 43	**Bioequivalence** of DRSP and EE in YAZ and YAZ + Metafolin (Study A28575) **Bioequivalence** of Meta-folin in 2 different formulations containing Metafolin without and with EE/DRSP

MC- multicenter; DB= double blind; RBC= red blood cell; DRSP= drospirenone; EE= ethinyl estradiol.
Source: Condensed from Applicant Table 1-1 on page 13 of their Clinical Overview.

Reviewer's comment:

These three studies were discussed and agreed to by the Division. The Division wanted to be assured that the addition of Metafolin to Yaz did the following:

- **significantly increase the plasma and RBC levels of folate from the baseline levels**
- **produce folate results similar to adding 400 mcg of folic acid**
- **did not significantly alter the levels of drospirenone and ethinyl estradiol in YAZ**

The second part of Study A39814 evaluated how long it takes for the improved RBC folate level to drop below the desired (believed to be therapeutic) level of 906 nmol/L. Plasma levels of homocysteine (A43598 and A39814) and circulating folate metabolites (A39814) were also studied, but were defined as secondary endpoints.

5.2 Review Strategy

The two efficacy (PD) studies were reviewed by the medical officer and the two bioequivalence studies by the clinical pharmacology reviewer, Doanh Tran, Ph.D. The statistician, Sonia

Castillo, Ph.D., reviewed the statistical findings in the two efficacy studies. The label was reviewed by all the disciplines, including chemistry, pharmacology/toxicology, DDMAC, SEALD and DMEPA.

5.3 Discussion of Individual Studies/Clinical Trials

As the YAZ component of the new Metafolin-fortified tablet is an approved and well-characterized product, the clinical development program focused exclusively on the Metafolin component. No new studies regarding clinical pharmacology, efficacy or safety of the hormonal components ethinyl estradiol (EE) and drospirenone (DRSP) were conducted for this program, except for the bioequivalence studies evaluating pharmacokinetic interactions between Metafolin and the hormonal components.

Two bioequivalence studies (A28575: YAZ + Metafolin and A27410: Yasmin + Metafolin) were performed in order to demonstrate that the addition of Metafolin has no influence on the rate and extent of absorption of both the estrogen and progestin, and that the presence of estrogen and progestin has no influence on the rate and extent of absorption of Metafolin. Study A28575 was conducted with YAZ + Metafolin, containing 0.02 mg EE, 3 mg DRSP and 0.451 mg Metafolin, the formulation relevant for this NDA; the other Study A27410 was conducted with Yasmin + Metafolin, containing 0.03 mg EE, 3 mg DRSP and 0.451 mg Metafolin, an almost identical formulation except for a higher EE content. Both studies were performed at single clinical sites in Europe. In summary, bioequivalence was demonstrated between YAZ + Metafolin / Yasmin + Metafolin and the marketed YAZ / Yasmin tablet formulations with regard to the active ingredients EE and DRSP. In addition, pharmacokinetics of L-5-methyl-THF, administered as Metafolin, were not influenced by the concomitant administration of 3 mg DRSP and 0.02 mg EE (YAZ), or 3 mg DRSP and 0.03 mg EE (Yasmin). Bioequivalence for PK parameters of L-5-methyl-THF was also demonstrated between the YAZ + Metafolin or Yasmin + Metafolin tablet formulations and the Metafolin alone tablets.

The third study (A39814), conducted in Germany, was performed to investigate the long-term use of folate. This study was conducted to investigate plasma and RBC folate as well as homocysteine levels during 24 weeks of administration of a folate-fortified OC (Yasmin), and to demonstrate that 0.4 mg folic acid and the equimolar dose of 0.451 mg Metafolin result in very similar levels of plasma and RBC folate, as well as a similar pattern of folate metabolites in plasma. Furthermore, after cessation of folate supplementation, the depot effect during a 20-week elimination phase was investigated. For this reason, the time period after cessation of folate supplementation for which RBC folate remains above 906 nmol/L was chosen as a primary variable of this study. The study was intended to demonstrate that Metafolin is as effective as folic acid in improving folate status, and that folate supplementation via an OC produces a measurable increase in plasma and RBC folate that persists after the treatment is stopped.

Reviewer's Comment:

The 906 nmol/L RBC folate level is based on the 1995 paper by LE Daly et al, which examined plasma and RBC folate level from over 55,000 pregnancies in Ireland between March 1986 and March 1990. The risk of NTD per 1000 births was 6.6 for women with a RBC folate ≤ 339 nmol/L

and dropped in a continuous dose-response fashion to 0.8 for women with a RBC folate ≥ 906. Although the logistic model used by the authors suggests that risk would continue to decrease as RBC folate levels increase to higher than 1,292 nmol/L (the mean level of all controls in the > 906 nmol/L grouping), there were too few cases for a stratified analysis to confirm this. Thus, the authors were unable to definitively determine an optimal level of RBC folate for NTD prevention.

The fourth study (A43598) was conducted in the US and investigated plasma folate, RBC folate and homocysteine levels during 24 weeks of oral administration of an OC with or without Metafolin. The OC used in this study was YAZ. It was postulated that even in the US, where women have a folate-fortified diet, the intake of YAZ + Metafolin would result in a clear improvement in folate status among reproductive-age females, and thereby provides a potential clinical benefit of improved folate status, which might lead to a reduced NTD risk. The latter 2 studies are considered pivotal with regard to the efficacy assessment of the investigational product to improve the folate status in women who elect to use an OC.

6 Review of Efficacy

6.1 Indication

YAZ + Metafolin is indicated for the new 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."

YAZ is already approved for contraception, as well as for the treatment of symptoms of premenstrual dysphoric disorder (PMDD) and the treatment of moderate acne for women of at least 14 years old. The Applicant seeks the three YAZ indications as well as the folate supplementation indication for Beyaz.

6.1.1 Methods

Inclusion and exclusion criteria were mostly identical in studies A43598 and A39814. Healthy women of reproductive age (18 to 40 years of age inclusive) who were seeking contraception and for whom OC use was not contraindicated were included. Because the folate elimination aspect of the A39814 study in Germany was very important, key restrictions for only this study included the following:

- At baseline the women had to have RBC folate levels between 318 nmol/L and 905 nmol/L, whereas no limitation with regard to baseline folate levels was set for the US Study A43598
- Women with vitamin B12 deficiency (plasma B12 < 110 pmol/L) were excluded;
- Regular intake of vitamin supplements or medication containing folate or interacting with folate during the 4 months prior to enrollment was not allowed, in contrast to Study A43598
- Body mass index (BMI) of 18.5-30.0 kg/m^2, in contrast to ≤ 35.0 for Study A43598

Reviewer's comment:

The above inclusion and exclusion criteria are acceptable given the primary objectives of the two pharmacodynamic studies. The women were basically healthy and needed certain RBC folate and plasma B12 parameters in the German pharmacodynamic study so the results would be

interpretable and meaningful. Testing was done to rule out pregnancy prior to and throughout the studies.

Analysis Sets: there were two analysis sets for the studies. The full analysis set (FAS) includes all randomized women who took at least one dose of study medication. The primary analysis set is the per protocol set (PPS), which includes all treated women who did not present any major protocol deviation.

6.1.1.1 Folate levels in plasma and RBC:

The technical pathway for measuring folate levels involved the following: venous blood samples were drawn at each sampling time (once every 4 weeks in study A43598, and once every 2 weeks in study A39814) during the study period for evaluation of plasma folate, RBC folate, and plasma homocysteine. All blood samples were drawn by direct venipuncture applied to a forearm vein. The exact date and time (24-hour clock) of each blood sample obtained were recorded on the appropriate case report form page.

For the determination of hematocrit and folate in whole blood and plasma, 4.5 mL blood was collected in plasma tubes coated with lithium-heparin. Parallel to the determination of the hematocrit, 3 whole blood samples were prepared as follows: in a 1.8 mL NUNC tube, 0.1 mL of the whole blood sample were diluted with 0.9 mL of freshly prepared 1% ascorbic acid solution, vortexed and incubated for 30 minutes in the dark before storage at approximately -80°C. The remaining sample was centrifuged for 10 min at 3000 rpm at 4°C. For the determination of folate in plasma, 3 x 0.3 mL of supernatant were transferred into NUNC tubes and stored at approximately -80°C. Any remaining plasma from the supernatant was stored in additional NUNC tubes for potential reanalysis.

Assays of folate concentration: Folate concentrations in plasma and whole blood were determined by a validated microbiological assay. Analyses were performed by the Contract Research Organization (b) (4) and supervised by the Pharmacokinetics function at Bayer Schering Pharma AG. In short, samples were thawed, hemolyzed and whole blood as well as plasma samples were diluted to an appropriate concentration with buffer containing ascorbate. Samples were incubated with folate-deficient growth medium in 96 wells plates and inoculated, with defined amounts of folate-dependent, chloramphenicol-resistant Lactobacillus casei. After approximately 40 hours of growth, the turbidity was determined spectrophotometrically. The folate concentration was calculated using an appropriate calibration curve. The performance of the analytical methods was monitored by the analyses of calibration standards and quality control samples. The calibration curve using folic acid as a reference ranged for whole blood samples from 25 to 500 ng/mL folate, for plasma samples from 1 to 20 ng/mL folate. A World Health Organization (WHO) folate standard control was included on each plate. The analyses were conducted in compliance with the Organization for Economic Cooperation and Development (OECD) principles of Good Laboratory Practice.

Reviewer's comment:

There were three major review issues concerning the total folate assay:

- **Accuracy and precision of the LLOQ (lower limits of quantification)**
- **Quality control preparation methods**

- **Long term stability of the samples**

The Division of Scientific Investigations inspected the analytical portion of the German Study A39814 (Yasmin + metafolin) and the analytical and clinical portions of US Study A43598. Sean Kassim, Hyojong Kwon, and Martin Yau submitted a 95-page review (dated May 24, 2010) with recommendations for the three folate assay validation issues. Several information requests were sent to the Applicant and responses received back by the Division. Agreement was reached between the Applicant and both the DRUP clinical and clinical pharmacology teams concerning valid data for plasma and RBC folate samples. As a result, some samples were excluded as not valid, but the overall results were not significantly impacted by the three validation issues. For greater details, see the Clinical Pharmacology review by Doanh Tran, the DSI reports, and comments in Section 6.1.10, Additional Efficacy Issues/Analyses.

In the US pharmacodynamic trial (Study A43598), there were two sites with major procedural errors for the determination of RBC folate values. The Applicant detected this at the time of an interim analysis and addressed the issue in the original NDA submission with three different analyses of the data for RBC folate values. DSI confirmed the problem and agreement was reached on which samples were valid from the US Study A43598. This is discussed further in Section 6.1.4.

6.1.2 Demographics

In **US Study A43598**, the demographic characteristics were comparable between the YAZ + Metafolin and the YAZ groups (see Table 2). The mean age of the women was 24.8 years (range 18 to 40 years) in the YAZ + Metafolin group, and 24.6 years (range 18 to 39 years) in the YAZ group. The mean values for height and body weight were very similar for the two groups. The BMI was approximately 24 kg/m^2 for both groups. One woman in the YAZ group had a BMI higher than 35 kg/m^2. Approximately two thirds of the women in either group were Caucasian and one third were either Black, Hispanic, Asian or 'Other'.

The two treatment groups were homogeneous and the women in each group were comparable for smoking behavior and alcohol use. Overall, the majority (more than 70% in both groups) of women had no smoking history. Approximately 10% of the women in each group were still smoking at study entry. The largest proportion of women (>40% in either group) stated that they occasionally drink alcohol (i.e. an average of 3 drinks per week).

Table 2: Demographic Parameters- FAS (US Study A43598)

	YAZ + Metafolin N = 285 (100.0%)		YAZ N = 94 (100.0%)	
Age, height, body weight, BMI (mean ± SD, range)				
Age (years)	24.8 ± 5.2	(18–40)	24.6 ± 4.9	(18–39)
Height (cm)	163.9 ± 6.6	(147.0–184.4)	164.9 ± 6.4	(149.9–180.3)
Body weight (kg)	64.7 ± 11.0	(44.3–95.7)	65.3 ± 10.8	(42.2–100.0)
BMI (kg/m^2)	24.1 ± 3.9	(17.0–34.9)	24.0 ± 3.6	(16.5–35.4)
Ethnic groups (number of women, %)				
Caucasian	181	(63.5%)	60	(63.8%)
Black	35	(12.3%)	10	(10.6%)
Hispanic	34	(11.9%)	13	(13.8%)
Asian	24	(8.4%)	6	(6.4%)
Other	11	(3.9%)	5	(5.3%)
Smoking habits (number of women, %)				
Smoking history				
No	204	(71.6%)	69	(73.4%)
Yes	81	(28.4%)	25	(26.6%)
Still smoking	27	(9.6%)	9	(9.6%)
Alcohol consumption (number of women, %)				
Never	66	(23.2%)	25	(26.6%)
Seldom	46	(16.1%)	10	(10.6%)
Occasionally	137	(48.1%)	42	(44.7%)
Regularly	36	(12.6%)	17	(18.1%)

FAS= full analysis set.
Source: Applicant Table 3-8, page 31 of the Summary of Clinical Efficacy.

In European **Study A39814**, the Yasmin + Metafolin and Yasmin + FA treatment groups were comparable with respect to demographics (see Table 3). The mean age of the women was 28.4 years in the Yasmin + Metafolin group and 27.0 years in the Yasmin + FA group (range 18 to 40 years in both groups). The mean values for height were similar for both groups, but body weight and body mass index (BMI) were slightly higher in the Yasmin + Metafolin group (64.1 kg and 23.2 kg/m^2, respectively) compared to Yasmin + FA (62.5 kg and 22.4 kg/m^2), but these differences are not considered to be of any clinical relevance. All women included were Caucasian.

Approximately half of the women in both groups reported to have smoked in the past, and a similar number of women in each group were still smoking at the time of the screening examination. In the Yasmin + Metafolin group, approximately one third (each) of the women reported to have never, seldom, or occasionally drunk alcohol. In the Yasmin + FA group, slightly more than half of the women reported to have seldom drunk alcohol, and around 20% never did and 20% occasionally consumed alcohol. There were no relevant differences between the full and per protocol sets for any of these demographic parameters.

Table 3: Demographic Parameters- FAS (European Study A39814)

	Yasmin + Metafolin N = 86 (100.0%)		Yasmin + FA N = 86 (100.0%)	
Age, height, body weight, BMI (mean ± SD, range)				
Age (years)	28.4 ± 5.8	(18–40)	27.0 ± 5.0	(18–40)
Height (cm)	166.2 ± 6.4	(152.0–185.0)	166.9 ± 5.4	(157.0–186.0)
Body weight (kg)	64.1 ± 8.6	(47.0–87.7)	62.5 ± 8.7	(48.2–92.1)
BMI (kg/m^2)	23.2 ± 2.7	(18.5–30.0)	22.4 ± 2.6	(18.5–29.9)
Ethnic groups (number of women, %)				
Caucasian	86	(100.0%)	86	(100.0%)
Smoking habits (number of women, %)				
Smoking history				
No	36	(41.9%)	45	(52.3%)
Yes	50	(58.1%)	41	(47.7%)
Still smoking	25	(29.1%)	22	(25.6%)
Alcohol consumption (number of women, %)				
Never	29	(33.7%)	18	(20.9%)
Seldom	33	(38.4%)	48	(55.8%)
Occasionally	22	(25.6%)	20	(23.3%)
Regularly	2	(2.3%)	0	(0.0%)

FAS= full analysis set.
Source: Applicant Table 3-9, page 32 of the Summary of Clinical Efficacy.

The Applicant also reported on several other parameters for the two groups enrolled in the two clinical efficacy trials. There were no major differences between the groups. The parameters included the following:

- Previous diseases or surgeries
- Gynecological and menstrual history
- Prior and concomitant medications

6.1.3 Subject Disposition

The majority of women in **Study A43598** completed the study medication: 203 of 285 women (71.2%) in the YAZ + Metafolin group and 70 of 94 women (74.5%) in the YAZ group (see Table 4). In the YAZ + Metafolin group, 82 women (28.8%) prematurely discontinued the study medication, and the most frequently reported reasons were loss to follow-up, protocol deviation, withdrawal of consent, and adverse events (AEs). A 3:1 randomization was used for the study; in the much smaller YAZ alone group, 24 women (25.5%) prematurely discontinued the study medication, and the most frequently reported reasons were loss to follow-up and protocol deviation.

Table 4: Subjects Disposition- FAS (US Study A43598)

	YAZ + Metafolin		YAZ	
Total	285	(100.0%)	94	(100.0%)
Completed study medication	203	(71.2%)	70	(74.5%)
Prematurely discontinued study medication	82	(28.8%)	24	(25.5%)
Reason for discontinuation of study medication [a]				
Lost to follow-up	26	(9.1%)	8	(8.5%)
Adverse event	12	(4.2%)	3	(3.2%)
Withdrawal of consent	13	(4.6%)	3	(3.2%)
Protocol deviation	17	(6.0%)	8	(8.5%)
Other reason [b]	11	(3.9%)	2	(2.1%)
Reason unknown	3	(1.1%)	0	(0.0%)

[a] Due to the different assignment of women with "unknown" study medication status and women who never took any study medication in the individual study report as compared to the integrated data base, slight but clinically irrelevant differences in the reasons for discontinuation of study medication are possible.

[b] Note: the majority of women in this category were withdrawn because of relocation or noncompliance (see module 5.3.5.3 Integrated Efficacy Analysis, Table 46)

FAS= full analysis set.
Source: Applicant Table 3-22, page 43 of the Summary of Clinical Efficacy.

In **Study A39814**, 164 women completed the study medication in period 1 (i.e., through week 24, see Table 5): 81 of 86 women (94.2%) in the Yasmin + Metafolin group and 83 of 86 women (96.5%) in the Yasmin + FA group. In all, 8 women discontinued their participation in period 1 of the study. The premature discontinuations were due to AEs, withdrawal of consent, and other reasons. Notably, two women who completed period 1 never took any study medication in period 2. As a result, 80 women from the previous Yasmin + Metafolin group and 82 women from the previous Yasmin + FA group entered period 2 (folate elimination phase with the administration of Yasmin alone for 20 weeks). Over 92% (150/162) of the women who started the elimination phase of this study were in the PPS at the end of period 2.

Table 5: Subjects Disposition- FAS (German Study A39814)

	Yasmin + Metafolin		Yasmin + FA	
Total	86	(100.0%)	86	(100.0%)
Completed study medication [a]	81	(94.2%)	83	(96.5%)
Prematurely discontinued study medication	5	(5.8%)	3	(3.5%)
Reason for discontinuation of study medication				
Adverse event	1	(1.2%)	3	(3.5%)
Withdrawal of consent	2	(2.3%)	0	(0.0%)
Other reason	2	(2.3%)	0	(0.0%)

[a] The assignment of women to this group (completed study medication) was based on the entry in the case report form

FAS= full analysis set.
Source: Applicant Table 3-23, page 44 of the Summary of Clinical Efficacy.

Reviewer's comment:

The completion rates in these two studies are acceptable and the reasons for premature discontinuation are expected. Both studies were 24 weeks in active treatment duration, with the German study continuing with Period 2 for the 20-week assessment of folate elimination. Although the German study had about half (45%) as many women as the US study, the combined completion rate of 95% at Week 24 is impressive. The overall 2.3% discontinuation rate due to adverse events is discussed in the safety section of this review.

6.1.4 Analysis of Primary Endpoint(s)

In Studies A43598 and A39814, plasma folate and RBC folate were determined at 3 visits before the treatment was started. The baseline plasma folate and RBC folate values are based on the median value of the measurements taken at these visits. In order to obtain stable baseline values, the 3 measurements were taken at least one week apart. A woman had to have at least 1 valid value over the 3 pre-treatment visits to have a valid baseline value. For all analyses using folate baseline values, the median of the valid pre-treatment levels was taken.

In US Study A43598, plasma folate and RBC folate levels were determined every 4 weeks during the treatment phase and at the final examination (week 26 to 27 or in the event of premature discontinuation). In the German Study A39814, these levels were recorded every 2 weeks during the 24-week treatment phase with Yasmin + Metafolin or Yasmin + FA and during the 20-week treatment with Yasmin only (folate elimination phase).

The RBC folate determination is calculated by an equation that depends upon an accurate value for hematocrit, whole blood folate, and plasma folate. The whole blood folate measurement was dependent on a 1:9 dilution of whole blood with a 1% ascorbic acid solution, whereas plasma folate is directly measured from plasma without any dilution. Samples for whole blood and plasma folate levels are stored at -80°C and later thawed, hemolyzed and processed by the (b) (4) The analyses were conducted in compliance with the Organization for Economic Cooperation and Development principles of Good Laboratory Practice. Due to dilution errors at two (San Diego, CA and Tacoma, WA) of the eight US study sites, there were a large number of invalid whole blood samples. This meant that the determination of RBC folate for these subjects was invalid and the results were not included in the endpoint analysis.

Whole blood samples were accepted as valid if the actual dilution factor was in the range of 0.08-0.12 (0.10 was the intended factor). Hematocrit values were accepted as valid if the hematocrit value was either in the range of 0.8 to 1.2 times the mean individual hematocrit value, or not evaluated as an outlier for the individual subject. Outliers and invalid samples for whole blood or hematocrit were not included in any efficacy evaluation. If plasma folate concentrations were >120% above the upper limit of the calibration curve, these values were flagged by the bioanalytical lab and were excluded from the analysis.

Reviewer's comments:

The validation criteria are reasonable given the intra-individual and bioanalytical variability for the three key measurements (hematocrit, whole blood folate and plasma folate). All folate levels in plasma and whole blood were analyzed using the same microbiological assay, which measures all

active folate forms. This same assay has been used in several previous epidemiological and interventional studies concerning folate levels and the risk of NTDs, including the Daly study previously discussed. As noted, results from US sites 104 (Tacoma, WA) and 108 (San Diego, CA) had a large number of invalid samples for determining the RBC folate values and a few invalid samples for plasma folate values. The Applicant did sensitivity analyses using three different scenarios with and without data from the two sites; all three analyses showed significantly increased folate levels as compared to baseline values. See additional discussion that follows in this Section under the heading Study A43598 Primary Efficacy Results.

Median baseline plasma folate values:

In the FAS of the US Study A43598, mean ± SD for median baseline plasma folate values were 44.4 ± 18.9 nmol/L for the YAZ + Metafolin group, and 41.6 ± 16.9 nmol/L for the YAZ group. In the PPS, mean ± SD for median baseline plasma folate values were 45.0 ± 17.6 nmol/L for the YAZ + Metafolin group, and 43.1 ± 16.2 nmol/L for the YAZ group. Thus, both treatment groups and analysis sets are considered comparable with regard to their baseline plasma folate values.

In the FAS of the German Study A39814, mean ± SD for median baseline plasma folate values were 15.5 ± 9.3 nmol/L for the Yasmin + Metafolin group, and 14.0 ± 6.5 nmol/L for the Yasmin + FA group. In the PPS, mean ± SD for median baseline plasma folate values were 15.6 ± 9.7 nmol/L for the Yasmin + Metafolin group, and 13.8 ± 6.4 nmol/L for the Yasmin + FA. Both treatment groups and analysis sets are considered comparable with regard to their baseline plasma folate values.

Reviewer's comments:

The PPS values are the ones that I believe should be used in the analysis for the primary endpoint, and this was the Applicant's specified primary analysis population. The PPS does not use any LOCF data. See Figures 1 and 3 for the PPS baseline values. I have primarily used the values determined by the FDA statistician Sonia Castillo, PhD.

Notably, the study populations of studies A43598 and A39814 differed considerably with regard to their baseline plasma folate levels. The baseline plasma folate levels were higher (~43-45 nmol/L) in the US population (Study A43598) as compared to the 14-16 nmol/L range in the German study (A39814). This finding is related to the fact that in the US, the FDA required the addition of folic acid to all enriched breads, cereals, flours, corn meal, pasta products, rice, and other cereal grain products beginning in 1998. In contrast, food fortification with folic acid is not mandatory in Germany, where study A39814 was performed.

Median baseline RBC folate values:

In the FAS of the US Study A43598, mean ± SD for median baseline RBC folate values were 976 ± 385 nmol/L for the YAZ + Metafolin group, and 1,017 ± 359 nmol/L for the YAZ alone group. In the PPS, the mean baseline values were 990 for YAZ + Metafolin and 1,104 for YAZ alone. Both treatment groups and analysis sets are considered comparable by the Applicant with regard to their baseline RBC folate values.

In the German Study A39814, per protocol inclusion criteria, the baseline RBC folate had to be > 317 nmol/L and < 906 nmol/L for all women. For this inclusion criterion, a non-validated

screening RBC method was used by the local laboratory. Using the validated RBC folate method for pharmacodynamic assessment, the individual values ranged from 257 to 979 nmol/L. In the FAS, median baseline RBC folate values (mean ± SD) were 585 ± 156 nmol/L for the Yasmin + Metafolin group, and 559 ± 146 nmol/L for the Yasmin + FA group. In the PPS, mean baseline RBC folate values were virtually the same.

Reviewer's comment:

See Figures 2 and 4 for baseline RBC folate values in the PPS analysis population. As was observed for baseline plasma folate levels, the study populations of Studies A43598 and A39814 differed considerably with regard to their baseline RBC folate levels. The median baseline folate levels were ~990 nmol/L in the US Study A43598 as compared to ~570 nmol/L in the German Study A39814. As described above, this finding is considered to be related to the fact that in the US, the FDA required the addition of folic acid to several food products beginning in 1998; the effect of food fortification is clearly seen in the baseline results from the two studies. Furthermore, this baseline mean value in the US population is already above the 906 nmol/L level that is desirable for NTD risk reduction based on the previously noted Daly data from 1995. However, it is clear from the standard deviations that a sizeable proportion of the US population fell below this level.

Plasma and RBC folate levels during treatment (Weeks 2-24):

The evaluation of plasma and RBC folate levels during treatment with YAZ + Metafolin and Yasmin + Metafolin is based on the data from the two clinical efficacy studies.

In US Study A43598, the primary efficacy variables were the plasma folate and RBC folate levels at week 24 (cycle 6). The mean changes from baseline to weeks 4, 8, 12, 16, and 20 in plasma folate and RBC folate levels (cycles 1 through 5) were secondary efficacy variables. In this study women received YAZ + Metafolin or YAZ alone for 24 weeks.

In the German Study A39814, equivalency of AUC $_{(0\text{-}24\ \text{weeks})}$ for plasma and RBC folate between Yasmin + Metafolin and Yasmin + FA was evaluated as the primary pharmacodynamic variable. Absolute levels and change from baseline for plasma folate and RBC folate levels were evaluated as secondary pharmacodynamic variables during the blinded treatment phase (i.e., 24-week treatment with Yasmin + Metafolin or Yasmin + FA in period 1 of the study) and during the open-label folate elimination phase (i.e., 20-week treatment with Yasmin alone in period 2 of the study). The primary pharmacodynamic study objective during period 2 was to determine the duration of time following the blinded 24-week period 1 during which the RBC folate concentration of ≥ 906 nmol/L was maintained in the Yasmin + Metafolin group. Plasma folate and RBC folate levels for the PPS during the elimination phase (period 2) are presented in Figure 3 and Figure 4 of this review.

Reviewer's comment:

The medical literature for the reduction in NTD risk is based primarily on RBC folate levels. Therefore, it is my opinion that the change from baseline RBC folate values is most relevant clinically since the mean baseline RBC folate values were greater than 906 nmol/L. The absolute value at Week 24 is also important. Regardless of whether plasma folate and RBC folate levels were investigated as primary (i.e., at Week 24) or secondary variables (at the other four-week intervals) in the efficacy or pharmacodynamic analyses, plasma folate and RBC folate levels are presented in Figures 1-4 as the relevant surrogate endpoints to support the proposed indication.

A RBC folate level above 906 nmol/L is the value associated with a marked reduction of fetal NTD risk as described by Daly et al. Furthermore, as discussed earlier, Daly et al suggest that the NTD

risk would continue to decrease as RBC folate levels increase to higher than 1,292 nmol/L (the mean level of all controls in the > 906 nmol/L grouping of their large study), but there were too few cases for a stratified analysis to statistically confirm this hypothesis. The folate results are presented by individual study. The pooling of plasma folate and RBC folate values from studies A43598 and A39814 is not appropriate based on the different baseline folate levels of the German and US populations (due to the food fortification program in the US).

Study A43598 Primary Efficacy Results:

Only subjects with both baseline and week 24 folate levels were included in the primary analysis based on the agreed-to statistical analysis plan (ANCOVA, which used treatment as factor and baseline as covariate). As valid baseline or week 24 folate levels were not available for some women, the number of women included in individual analyses could vary.

Because of sample handling problems with regard to whole blood folate at 2 out of 8 study sites (see above: validation process for whole blood folate), it was decided to analyze RBC folate levels in two additional ways as well as the preplanned analysis. Therefore, there are three analysis Scenarios for the per protocol set (PPS):

- Scenario A is the preplanned analysis and included all valid RBC values from all sites.
- Scenario B analyzed all data as described in Scenario A, but excluded all data from the two noted US sites 104 and 108.
- Scenario C was an evaluation of all RBC folate data after normalization of the whole blood folate value to a dilution factor of 0.1, based on the individual hemoglobin concentrations that should be accurate for all subjects at the eight US sites.

The comparative results for mean change from baseline for RBC folate for the three scenarios using the three different data sets are shown in Table 6.

Table 6: Mean Change from Baseline at Week 24 for RBC Folate (Study A43598)

YAZ Plus Group						
Analyses	**PPS**		**FAS**		**FAS (LOCF)**	
	N	**RBC Folate levels**	**N**	**RBC Folate levels**	**N**	**RBC Folate levels**
Scenario A	124	419.9 ± 347	128	415.5 ± 343	170	390.8 ± 350
Scenario B	122	436.0 ± 289	126	431.0 ± 287	167	403.1 ± 312
Scenario C	194	452.9 ± 308	199	451.5 ± 306	264	422.8 ± 321
YAZ Group						
Analyses	**PPS**		**FAS**		**FAS (LOCF)**	
	N	**RBC Folate levels**	**N**	**RBC Folate levels**	**N**	**RBC Folate levels**
Scenario A	45	34.3 ± 171	45	34.3 ± 171	65	37.1 ± 184
Scenario B	44	32.8 ± 173	44	32.8 ± 173	62	31.4 ± 187
Scenario C	66	49.9 ± 215	66	49.9 ± 215	89	36.9 ± 235

Source: Applicant Table 16, page 93 0f 870 in A43598 Study Report.

Although plasma folate is not affected per se by the above-described sample-handling problems of whole blood, evaluation of plasma folate levels according to Scenario B (excluding all data from sites 104 and 108) was also performed. Thus for plasma folate, Scenarios A and B are presented, whereas Scenario C was only relevant to data for RBC folate levels.

Reviewer's comment:

Plasma folate levels are expected to reach steady state within a month or two, whereas RBC folate is expected to reach steady state at the end of 24-weeks treatment or later. There is a known time lag for folate levels to increase in RBCs after folate is present in the plasma. This is because the plasma folate needs to be incorporated into newly formed RBCs which have a lifespan of ~100-120 days. The primary analysis set for efficacy was changed from the FAS, using the LOCF approach, to the PPS with the Applicant's Amendment 4 (November 6, 2008). This change is acceptable and preferable from the clinical point of view, as it is the most accurate set of data to analyze. Because all three scenarios provided consistent results as shown in Table 6 **above, I believe that the original preplanned analysis (Scenario A) is best and I have primarily used the values determined by the FDA statistician, Sonia Castillo, PhD.**

Scenario C, however, is reasonable, as the individual hemoglobin levels should be accurate and extrapolation of the RBC folate data would be relatively accurate, although not as accurate as Scenario B. Fortunately there were 385 women in the US trial at baseline, so even when excluding all women from the San Diego and Tacoma sites, this leaves 251 women in the Scenario B analysis set at baseline. In the PPS at Week 24, there were 176 women in the Scenario B analysis with valid plasma folate values.

Plasma and RBC folate levels at Week 24:
See Figures 1 and 2, and Table 7 and Table 8: the levels for YAZ + Metafolin intake were statistically significantly higher than with YAZ alone. For the PPS in Scenario A (all valid samples), plasma folate levels increased after 24 weeks of treatment in the YAZ + Metafolin group to 60.8 ± 19.9 nmol/L (mean difference between week 24 and baseline of 15.8 ± 20.4 nmol/L), but remained constant over time in the YAZ group (43.1 ± 16.2 nmol/L at baseline and 41.0 ± 17.6 nmol/L at week 24).

Table 7: Plasma Folate Levels (nmol/L) - Treatment Difference for Change from Baseline at Week 24 (Per Protocol Population, Scenarios A and B)

	N at Week 24	Baseline value	Week 24 value	LS Mean Change from Baseline[1]	LS Mean Difference (YAZ + Metafolin vs. YAZ)[1] (95% C.I.)	p-value
Using All Sites (Scenario A)						
YAZ + Metafolin	196	45.0	60.8	16.0	18.9 (14.0, 23.7)	< 0.0001
YAZ	66	43.1	41.0	-2.9		
Excluding Sites 104 and 108 (Scenario B)						
YAZ + Metafolin	129	41.9	58.0	16.2	17.4 (11.5, 23.3)	< 0.0001
YAZ	47	41.2	40.3	-1.2		

Source: Statistical Reviewer's Table A.4 and Table 140, page 766 of 870, and Table 152, page 782 of 870 of Study A43598 report.
[1] Least Squares mean estimates, confidence intervals, and p-values based on an ANCOVA model with treatment as factor and baseline value as covariate.

Similarly, RBC folate levels increased after 24 weeks of treatment in the YAZ + Metafolin group to 1406 ± 440 nmol/L (mean difference of 420 ± 347 nmol/L between week 24 and baseline), but remained stable over time in the YAZ group (990 ± 308 nmol/L at baseline and 1024 ± 293 nmol/L at week 24). Only small differences were found between the PPS and FAS (with or without the LOCF approach). The increase in both plasma and RBC folate levels during YAZ + Metafolin treatment is considered by the Applicant to be clinically relevant.

Table 8: Study A43598: Red Blood Cell Folate Levels (nmol/L) - Treatment Difference for Change from Baseline at Week 24 (Per Protocol Population, Scenario A))

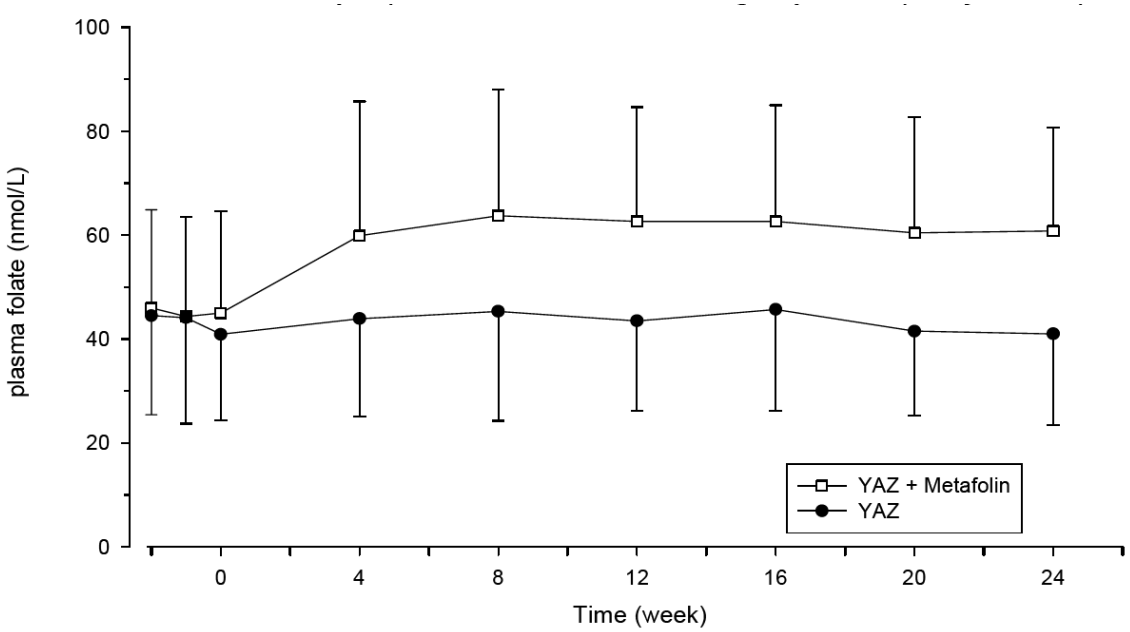
	N at Week 24	Baseline value	Week 24 value	LS Mean Change from Baseline [1]	LS Mean Difference (YAZ + Metafolin vs. YAZ)[1] (95% C.I.)	p-value*
Using All Sites (Scenario A)						
YAZ + Metafolin	124	986.2	1406	419.7	384.7 (282.4, 487.0)	< 0.0001
YAZ	45	990.0	1024	35.0		
Excluding Sites 104 and 108 (Scenario B)						
YAZ + Metafolin	122	961.4	1,398	436.1	403.4 (311.4, 495.4)	< 0.0001
YAZ	44	987.6	1,021	32.7		

Source: Statistical Reviewer's Table A.1 and Table 104, page 718 of 870, and Table 116, page 734 of 870 of Study A43598 report.
[1] Least Squares mean estimates, confidence intervals, and p-values based on an ANCOVA model with treatment as factor and baseline value as covariate.
*** p-value should be used with caution since more than 56% (161/285) of the YAZ + Metafolin folate data and more than 52% (49/94) of the YAZ RBC folate data were dropped from the analysis.**

Statistically significant differences for plasma and RBC folate between the YAZ + Metafolin compared to the YAZ group at week 24 were consistently demonstrated for all preplanned analysis sets (PPS, FAS with and without LOCF for Scenario A). Accounting for the sample-handling errors, the results for the additional analyses (Scenario B for plasma folate; Scenarios B and C for RBC folate) support those of the preplanned analysis (Scenario A using the PPS).

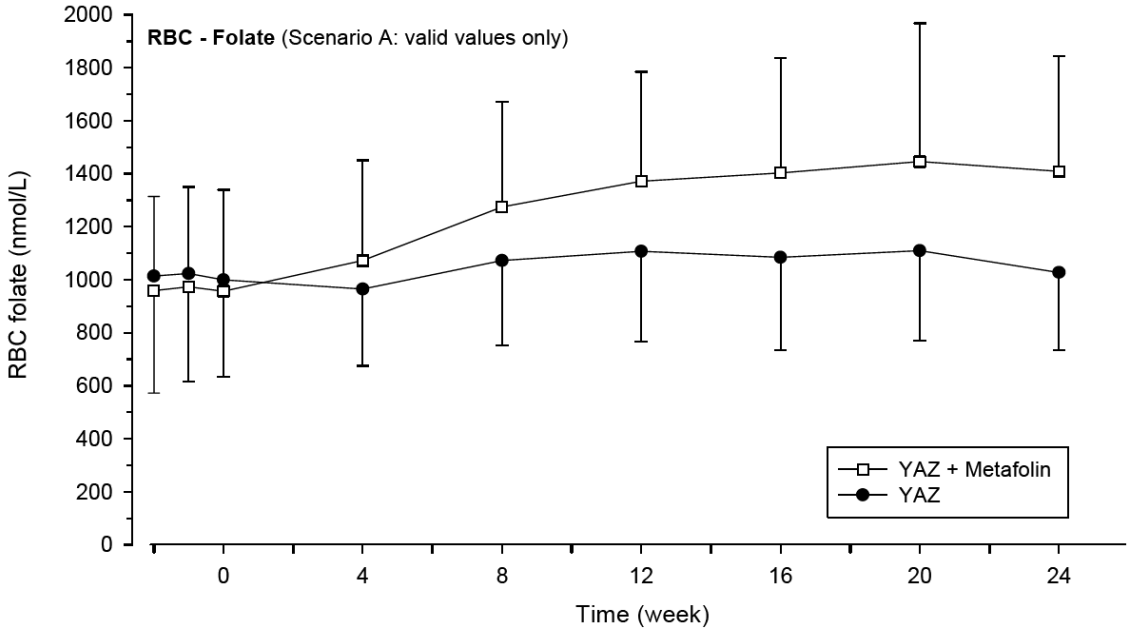
The concentration-time curves depicting mean plasma folate after treatment with YAZ + Metafolin showed an increase during the first 4 to 8 weeks after start of treatment; for the remainder of the study, there was a mean steady state concentration of approximately 60 nmol/L (see Figure 1). In the YAZ-only group, very minor fluctuations of the mean plasma folate levels were observed from baseline values through the treatment phase. Mean RBC folate levels during YAZ + Metafolin treatment increased throughout the first 16 weeks of treatment, and reached a mean steady state concentration of about 1400 nmol/L for the remainder of the study (see Figure 2). At week 20, mean RBC folate was at a maximum (1446 ± 523 nmol/L). As would be expected, in the YAZ-alone group, only minor fluctuations of the mean RBC folate levels were observed from baseline through the treatment phase.

Figure 1: Plasma Folate Concentration-Time Curve- Study A43598 (Scenario A- PPS)



Note: Arithmetic mean values are displayed with standard deviations in only one direction to improve readability. N= 196 for YAZ + Metafolin and 66 for YAZ alone.
Source: Applicant Figure 4-1, page 37 of Clinical Overview.

Figure 2: RBC Folate Concentration-Time Curve- Study A43598 (PPS)



Note: Arithmetic mean values are displayed with standard deviations in only one direction to improve readability. N= 124 for YAZ + Metafolin and 45 for YAZ alone.
Source: Applicant Figure 4-2, page 37 of Clinical Overview.

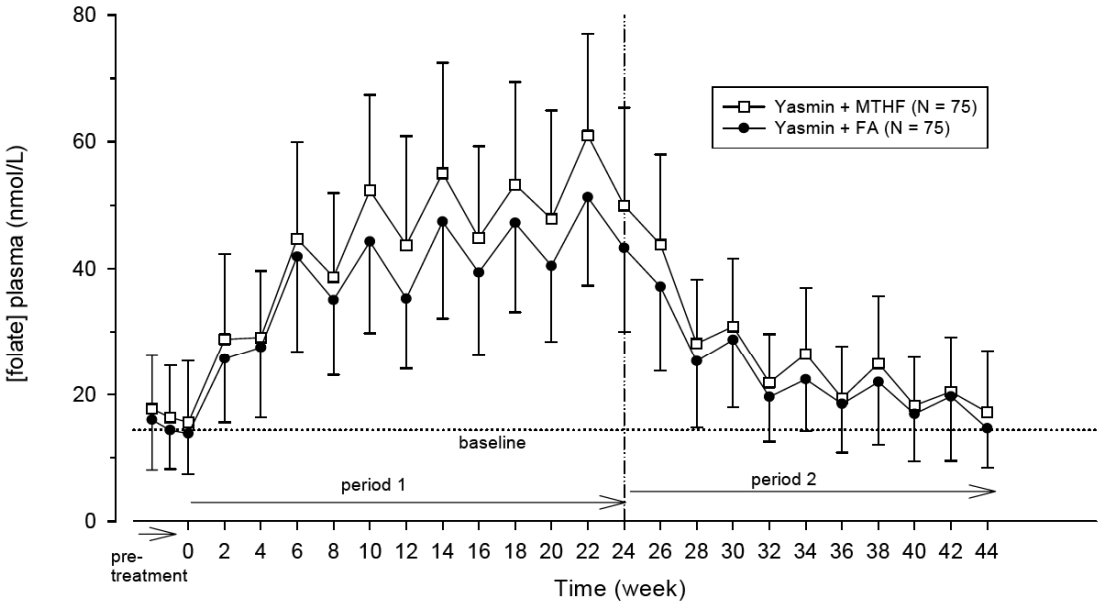
European Study A39814:
Plasma and RBC folate levels at week 24 were analyzed as part of the evaluation of concentrations over time, in contrast to Study A43598, for which the analysis of this time point was the primary efficacy variable. The results were similar between the FAS and PPS; the Applicant's findings are summarized below for the PPS.

Plasma and RBC folate levels at week 24 of Yasmin + Metafolin and Yasmin + FA intake increased to a similar extent in both treatment groups. After 24 weeks of treatment with Yasmin + Metafolin, plasma folate levels increased to 49.9 ± 15.5 nmol/L, corresponding to a mean increase between week 24 and baseline of 33.5 ± 14.5 nmol/L. In the Yasmin + FA group, plasma folate levels increased to 43.3 ± 13.3 nmol/L at week 24 corresponding to a similar mean difference of 29.1 ± 12.6 nmol/L. RBC folate levels increased to 1361 ± 322 nmol/L at week 24 in the Yasmin + Metafolin group, and 1207 ± 217 nmol/L in the Yasmin + FA group, corresponding to mean differences between week 24 and baseline of 782 ± 260 nmol/L and 657 ± 175 nmol/L, respectively. No relevant differences were found between the PPS and FAS. The increase in plasma and RBC folate levels is considered to be clinically relevant for both treatment groups.

With regard to concentration-time curves, mean plasma folate levels increased during the 24-week treatment period as compared to baseline, reaching maximum values and maximum changes at week 22 in both treatment groups (see Figure 3). Mean RBC folate levels increased continuously during the 24-week treatment period with Yasmin + Metafolin and Yasmin + FA, reaching maximum values and maximum changes at week 24 (see Figure 4).

Mean plasma folate levels were generally higher during treatment with Yasmin + Metafolin as compared to Yasmin + FA despite very similar baseline values. For both Yasmin + Metafolin and Yasmin + FA, the mean concentration-time curves of plasma folate had a sawtooth pattern independent of folate supplementation; i.e., values at mid cycle (weeks 2, 6, 10 etc.) were higher than values at the end of the cycle (weeks 4, 8, 12 etc.) in both periods (period 1 and elimination phase period 2). The Applicant does not have an explanation for this observation. It may be caused by physiological changes that occur during the menstrual cycle, e.g. loss of folate due to menstrual bleeding at the end of each cycle. This pattern of a biweekly fluctuation has not been observed in studies in which 4-weekly sampling intervals were used.

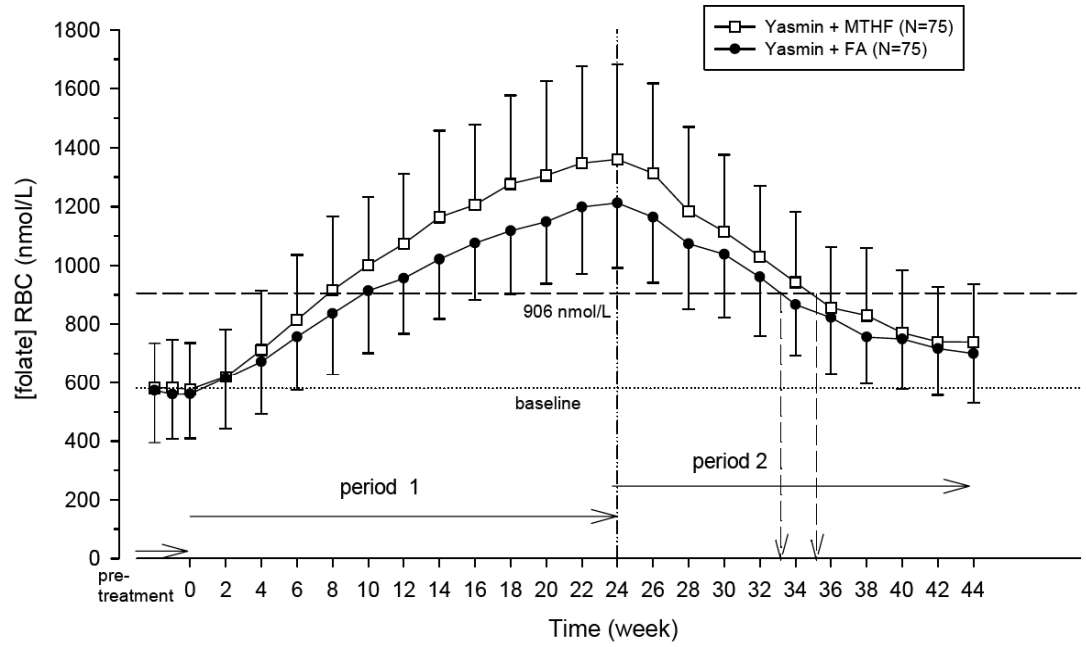
Figure 3: Plasma Folate Concentration-Time Curve- Study A39814 (PPS)



Note: arithmetic mean values based on biweekly measurements are displayed with arithmetic standard deviations which are shown in only one direction to improve readability. In period 1, women were treated with Yasmin + Metafolin (MTHF), or Yasmin + FA; in period 2, all women received Yasmin only.

Source: Applicant Figure 4-3, page 39 of Clinical Overview. Based on PPS.

Figure 4: RBC Folate Concentration-Time Curve- Study A39814 (PPS)



Note: arithmetic mean values based on biweekly measurements are displayed with arithmetic standard deviations which are shown in only one direction to improve readability. In period 1, women were treated with Yasmin + Metafolin (MTHF) or Yasmin + FA; in period 2, all women received Yasmin only.

Source: Applicant Figure 4-4, page 39 of Clinical Overview. Based on PPS.

Study A39814 Folate Elimination Phase:

In Study A39814, the 24-week treatment period with Yasmin + Metafolin or Yasmin + FA (period 1) was followed by a 20-week open-label folate elimination phase with all the subjects taking Yasmin only (period 2). During the folate elimination phase, plasma folate and RBC folate were measured every 2 weeks. A total of 162 women (80 from the Yasmin + Metafolin group and 82 from the Yasmin + FA group) entered the folate elimination phase taking only Yasmin. The concentration-time curves of plasma and RBC folate during the folate elimination phase are graphically shown in Figure 3 and Figure 4. Starting by week 26 (two weeks after cessation of active treatment), mean plasma folate and RBC folate levels decreased for the next 18 weeks, through the end of period 2 for both treatment groups. The proportion of women with folate levels above the median baseline value was evaluated. In the Yasmin + Metafolin group, at 12 weeks after stopping folate intake, 69% of women had plasma folate levels above baseline and 97% had RBC folate levels above baseline. , In the Yasmin + FA group, 41% had plasma folate levels above baseline and 89% had RBC folate levels above baseline 20 weeks after stopping intake of folate.

Sonia Castillo, PhD, the Division statistician confirmed the Applicant's Kaplan-Meier estimates for the proportion of subjects with RBC folate values falling below 906 nmol/L using the PPS population. The results are shown in Table 9.

Table 9: Study A39814- Estimates for the Time for RBC Folate Falling Below 906 nmol/L for Yasmin + Metfolin Treatment Group

Week	Number of subjects with RBC folate ≥ 906 nmol/L	KM estimate (Proportion of subjects with RBC folate ≥ 906 nmol/L)
24	71	0.947
26	70	0.933
28	64	0.853
30	59	0.787
32	45	0.600
34	35	0.467
36	22	0.293
38	18	0.240
40	13	0.173
42	10	0.133
44	7	0.093

Source: FDA Statistician Table 3.4 derived from Applicant Table 117, page 762 of 942, Study A39814 report.

Reviewer's comments:

The following patterns are clearly demonstrated from the data in the two clinical efficacy trials:

- **In the US population in Study A43598, the mean baseline plasma and RBC folate levels were higher than in the German population in Study A39814. This difference is most probably due to the mandatory folate food fortification program in the US.**
- **In the YAZ + Metafolin and Yasmin + Metafolin treatment groups in both studies, an increase in plasma and RBC folate was seen at all time points during the 24-week treatment period compared to baseline.**

Plasma folate levels at the end of the 24-week treatment period were increased on average by ~61 ± 20 nmol/L in the US study and by ~50 ± 16 nmol/L in the German study. RBC folate levels at the end of the treatment period were ~1406 ± 440 nmol/L in the US study and ~1360 ± 320 nmol/L in the German study. In the US study, the plasma and RBC folate levels after 24 weeks were statistically significantly higher in women who took YAZ + Metafolin compared to those who took YAZ alone. This increase was consistent across all analysis sets (PPS and FAS with and without LOCF). The results were also significant for RBC folate when using the three sensitivity analyses (Scenarios A, B, and C) designed to correct for the sample handling (dilution) problems which occurred at two of the US sites.

In the German Study A39814, mean plasma and RBC folate levels were generally numerically higher during treatment with Yasmin + Metafolin as compared to Yasmin + FA despite very similar baseline values. This findings, however, is probably not clinically significant. At 20 weeks after either metafolin or folic acid was stopped in the study, the mean values for plasma and RBC folate were above the mean baseline values. During the elimination phase, the proportion of women with RBC folate levels ≥ 906 nmol/L decreased over time: 85% of the women had RBC folate levels ≥ 906 nmol/L after stopping folate intake for 4 weeks, 60% after stopping for 8 weeks, 29% after

stopping for 12 weeks, and 9% at the last sampling point (20 weeks after stopping) in the Yasmin + Metafolin treatment group. These proportions in a German population are reassuring as the baseline RBC folate values are considerably lower than found in the US population due to the lack of folate fortification in the German food supply. It would be anticipated that the proportions of women in the US population maintaining RBC folate values above the 906 nmol/L level would be greater than seen in the German study, because the starting levels would, on average, be higher as demonstrated in US Study A43598. This pattern of a gradual decrease in RBC folate level with no additional folate supplementation is directly due to the average 100-120 day lifespan of all RBCs. As RBCs turn over, the cellular population is increasingly made up of RBCs that have not been exposed to folate supplementation. The plasma folate drop-off is more rapid, but the data for reduction in the risk of NTDs is based primarily on RBC folate values.

6.1.5 Analysis of Secondary Endpoints(s)

The calculation of the NTD risk in Study A43598, based on the equation developed by Daly et al. (*JAMA*, 12/6/95, pp 1698-1702) was a secondary study objective. In Study A39814, the calculation of NTD risk was a post-hoc analysis, rather than planned according to protocol. The calculations were performed using both the continuous risk reduction (assumes the NTD risk continues to decrease as RBC folate levels increase above 1292 nmol/L) and the conservative approach (assumes a constant risk above an RBC folate level of 1292).

The NTD risk, described as the estimated number of NTD cases per 1000 births, is presented as the mean ± SD. In US Study A43598 (PPS), the NTD risk at baseline, assuming continuous risk reduction, was similar in both treatment groups (1.35 ± 0.55 per 1000 births for YAZ + Metafolin; 1.26 ± 0.46 per 1000 births for YAZ). The decrease from baseline in NTD risk was minus 0.51 in the YAZ + Metafolin compared to the YAZ group, where a minus 0.02 change was detected. The mean relative risk reduction at week 24 compared to baseline was also larger in the YAZ + Metafolin group (33%) than in the YAZ group (1%). The differences between the treatment groups were smaller when the conservative approach was used. According to the conservative approach, a decrease from baseline in NTD risk was observed in the YAZ + Metafolin group (-0.42 ± 0.43 per 1000 births) compared to almost no change in the YAZ group (-0.02 ± 0.26 per 1000 births). The estimated mean relative risk reduction at week 24 compared to baseline was also greater in the YAZ + Metafolin group (25%) than in the YAZ group (1%) when the conservative approach was used.

In Study A39814 (PPS), the NTD risk at baseline, assuming continuous risk reduction, was similar in both treatment groups (2.46 ± 0.88 per 1000 births for Yasmin + Metafolin; 2.55 ± 0.78 per 1000 births for Yasmin + FA). This was a greater risk reduction than in the US study, likely because the baseline RBC folate levels were lower. The decrease from baseline in NTD risk was also similar in both groups (approximately -1.61 ± 0.69 per 1000 births for both groups). When compared to baseline, the mean relative risk reduction estimated at week 24 was 64% in the Yasmin + Metafolin group, and 61% in the Yasmin + FA group. Using the conservative approach, the decrease from baseline in NTD risk in the Yasmin + Metafolin group was similar to that for the Yasmin + FA group. The estimated mean relative risk reduction at week 24 compared to baseline was 59% in both treatment groups.

The Applicant concludes that despite the lower mean NTD risk at baseline in the US population because women consume a folate-fortified American diet, as compared to the European

population of Study A39814, a potential reduction in NTD risk based on Daly's model after 24 weeks of treatment with YAZ + Metafolin or Yasmin + Metafolin was demonstrated in both studies based on the increased levels of plasma and RBC folate.

Reviewer's comment:

I agree with the Applicant's general conclusions. Because this was a secondary endpoint, however, no claim can be made in the label for a proven reduction in the risk of NTDs should the woman become pregnant while taking the YAZ + Metafolin product. The claim will be that the new product increases the folate level in women who use the product for the purpose of reducing the risk of NTDs in pregnancies conceived while taking the product or shortly after discontinuing the product.

Because YAZ + Metafolin is highly effective for the prevention of pregnancy and the incidence of NTDs is very low in the first place (~1.3 per 1,000 births), it would take an extremely large study to unequivocally demonstrate that there is a statistically significant reduction in the risk of NTDs in women who become pregnant while taking, or within 2-3 months of stopping, the YAZ +Metafolin product compared to women not taking the product.

6.1.6 Other Endpoints

See the discussion with the header titled Study A39814 Folate Elimination Phase at the end of Section 6.1.4. At 20 weeks after either metafolin or folic acid was stopped in the German Study, the mean values for plasma and RBC folate were above the mean baseline values. During the 20-week elimination phase, the proportion of women with RBC folate levels ≥ 906 nmol/L decreased over time: 85% of the women had RBC folate levels ≥ 906 nmol/L after stopping folate intake for 4 weeks, 60% after stopping for 8 weeks, 29% after stopping for 12 weeks, and 9% at the last sampling point (20 weeks after stopping) in the Yasmin + Metafolin treatment group. These values demonstrate that the increased folate effect on RBCs did persist after the YAZ + Metafolin was discontinued.

6.1.7 Subpopulations

Subgroup analyses of the above efficacy variables (plasma folate and RBC folate, NTD risk reduction according to Daly et al.) were performed using the PPS and FAS, in order to assess whether the claimed treatment effect was observed consistently throughout the overall study population. The efficacy analysis was performed for the following subgroups in Study A43598:

- Age: 18-19, 20-35, ≥ 36
  - A trend towards lower plasma and RBC folate levels at baseline and higher mean changes from baseline after 24 weeks of treatment for women 18 to 19 years, or women 20 to 35 years of age, as compared to women older than 35 years of age was noted.
  - The mean relative NTD risk reduction for the PPS was 44% and 32% in the 18-19 and 20-35 year old groups, respectively. There were too few women above age 35 to make an assessment.
- Ethnic group:
  - A trend towards higher baseline plasma and RBC folate levels was seen for Caucasian and Asian women compared to Black and Hispanic women.

  - The mean change from baseline after 24 weeks was highest in the Caucasian group (445 ± 392 nmol/L) compared to the other groups (Black: 393 ± 251 nmol/L, Hispanic: 394 ± 308 nmol/L, Asian: 362 ± 247 nmol/L).
  - A mean relative NTD risk reduction which was lowest in Asian women (21%), compared to Caucasian (24%), and Hispanic (25%) and Black women (32%).
- Additional supplement use of folic acid: there was no restriction on additional folate supplementation throughout the duration of the US trial.
  - At the end of the treatment period, RBC folate levels of 1500 ± 526 nmol/L were observed for the YAZ + Metafolin group with additional folate intake (N= 51) compared to 1355 ± 365 nmol/L for the YAZ + Metafolin group without additional folate supplementation (N= 87).
  - In women without prior additional supplementation, there was a more pronounced increase from baseline values in plasma and RBC folate levels during YAZ + Metafolin treatment.
- Genotypes of the MTHFR 677 C>T polymorphism were studied in both trials. One of the key intrinsic factors linked to increased risk of NTDs are polymorphisms in several enzymes involved in folate metabolism. The most established genetic risk factor for NTDs is the single nucleotide polymorphism (SNP) 677 C>T in the MTHFR gene.
  - Mutant (TT) genotypes of the MTHFR polymorphism 677 C>T showed lower RBC and plasma folate values at baseline in both studies. A benefit from folate intake similar to that for the wild type (CC) genotypes was demonstrated for the mutant (TT) genotypes. A parallel increase of plasma and RBC folate between all genotypes was shown.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Based on the chemistry and medical literature, the Applicant determined that 0.400 mg folic acid and the equimolar dose of 0.451 mg Metafolin result in near equivalent levels of plasma and RBC folate as well as a similar pattern of folate metabolites in plasma. The results of the clinical trials in this NDA support the choice of 0.451 mg metafolin to be used in combination with the already approved YAZ product. As shown in the German study, metafolin has a slightly greater effect on mean folate levels compared to folic acid.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

See the discussion with the header titled Study A39814 Folate Elimination Phase at the end of Section 6.1.4. At 20 weeks after either metafolin or folic acid was stopped in the German Study, the mean values for plasma and RBC folate remained above the mean baseline values.

The dose of metafolin was constant during the 24 weeks of treatment. There was no evidence for tolerance effects: the plasma folate level reached a steady state at ~8 weeks of treatment with YAZ + Metafolin, and the RBC folate level reached steady state ~20-24 weeks. As soon as the metafolin was stopped, both the plasma and RBC folate levels began to decrease.

6.1.10 Additional Efficacy Issues/Analyses

All primary efficacy endpoints for the four trials centered on blood and serum levels of DRSP, EE, metafolin, folic acid, hemoglobin and hematocrit values, plasma folate, and whole blood folate (from which RBC folate is calculated). Several analytical sites were used for the analysis of the primary endpoints and routine laboratory tests:

- The DNA extraction laboratory was (b) (4)
- Analyses of all pharmacogenetic data were performed by (b) (4)
- All routine laboratory tests for the US study were performed by (b) (4)
- Central sample repository and homocysteine analyses were performed by (b) (4)
- Analyses of plasma and whole blood folate were performed by (b) (4)
- (b) (4) for routine laboratory tests for the bioequivalence study.
- (b) (4) was an analytical site for the YAZ bioequivalence Study A27410.

Reviewer's comment:

Some of the sites above were inspected by a team from the Agency's DSI. The Applicant responded to several information requests (IRs) from the Division and submitted the requested data. The Applicant agreed to follow the recommendations of the detailed DSI reports. As noted earlier, several samples from the studies were considered non-valid and were not included in the final determinations for the bioequivalence and two pharmacodynamic studies.

For the two pharmacodynamic studies, analytical and clinical site inspections by DSI noted the following issues and subsequent resolutions:

- **Long-term frozen stability evaluations for whole blood at the (b) (4) were not adequate for the period of study sample storage. Stability data was requested by the Division and was determined to be acceptable by the Bioequivalence DSI team (6-30-10 review).**
- **(b) (4) needs to evaluate the recovery of folate in plasma and whole blood at three concentrations to ensure the accuracy of study sample determinations. DSI concluded that the accuracy of the 3 ng/ml folate spike in plasma cannot be assured and results below 3 ng/ml should be omitted from analysis.**
- **In the absence of demonstration of dilution linearity for 8-fold diluted samples, the validation by DSI has only confirmed 5-fold dilutions as accurate; the six samples requiring 8-fold dilution should be omitted from analysis. This was done by Sonia Castillo, the Division statistician.**
- **The subject samples accepted with only 4 QCs (two concentrations each in duplicate) should be omitted from analysis. This was done.**
- **In the German study, the lack of audit trail during manual chromatogram reintegrations prevents assurance of the data. DSI determined that for semi-quantitative purposes of this assay, the data could be used.**

- **The original folate metabolite values from the German study should be used for pharmacokinetic assessments. The clinical pharmacology review used the original values for the Metafolin metabolites.**

The above items were resolved to the satisfaction of the DSI, clinical pharmacology, clinical, and biometric (statistical) teams. Samples that were determined to be non-valid were not included in the data analysis by the Division statistician and clinical pharmacologist.

7 Review of Safety

Safety Summary

The data from the four clinical studies show a favorable safety profile for YAZ and Yasmin fortified with Metafolin, and there are no new safety issues in comparison to YAZ and Yasmin only. The adverse event profile compares with those for other COCs. Based on the two long-term studies, AEs which occurred in at least 3% of the study population were nausea, breast pain, dysmenorrhea, headache, metrorrhagia, and increased low density lipoprotein values, all of which are well-established side effects of COCs. There were no safety-relevant effects observed with regard to laboratory variables, vital signs, and the other measured safety parameters. The limited new safety data show no signal of an increased risk of venous thromboembolism, other cardiovascular events, or events of cancer, compared to other marketed COCs.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Four clinical studies (phases 1 and 3) were included in the Integrated Summary of Safety (ISS) to demonstrate the safety of both YAZ and Yasmin fortified with Metafolin. Two of these studies (A43598 and A39814) are the long-term studies discussed in Section 6 of this review. In addition, the safety data from the two European bioequivalence studies (A28575 and A27410) are also included.

The assessment of safety includes all women who took study medication at least once and for whom at least one post-baseline observation was available. The safety data set corresponds to the FAS. The safety data of Study A39814 were assessed for each treatment period (phase 1 was the 24-week treatment with Yasmin + Metafolin; phase 2 was the 20-week treatment with Yasmin only, i.e., the folate 'elimination phase'), as well as for the data pooled across both periods. The safety data of the single-dose, cross-over bioequivalence studies A28575 and A27410 were evaluated by treatment group, and a treatment period was considered as starting from the day of study medication intake, until the day before the next dose of medication was taken.

7.1.2 Categorization of Adverse Events

Standard methods were used: all adverse events, most common events by MedDRA primary system organ class (SOC) and preferred terms, and treatment emergent adverse events were analyzed.

7.1.3 Pooling of Data across Studies/Clinical Trials to Compare Incidence

The safety data are presented by individual study because it was considered by the Applicant inappropriate to pool safety information from the different treatment groups of the 2 long-term studies (e.g., YAZ + Metafolin, Yasmin + Metafolin), or to pool long-term safety data with single-dose safety data obtained from the 2 bioequivalence studies.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics

Table 10 presents the enrollment figures for the two larger clinical trials.

Table 10: Enrollment in Study A4359 and A39814

Analysis Set	Study A43598 (US)		Study A39814 (EURO)	
	YAZ + metafolin	YAZ	Yasmin + metafolin	Yasmin
FAS, Safety	285	94	86	86
PPS	196	66	75	75

Source: Adapted from Applicant Table 4-3, pg 32 of Clinical Overview.
FAS = all randomized women who took as least one dose of study medication
PPS = all treated women who did not present any major protocol deviations and had valid blood samples.

Study A43598: The FAS included a total of 379 women (YAZ + Metafolin: 285 women; YAZ: 94 women) who took at least one dose of study medication. The PPS comprised 262 women who did not have major protocol deviations and were therefore assessed as suitable for inclusion in the efficacy analysis. For both treatment groups, the mean treatment duration was approximately 21 weeks in the FAS, and 24 weeks in the PPS. The disposition of subjects is presented in Section 6.1.3.

Study A39814: The FAS included all 172 women who received treatment (86 women in each group) and the PPS included 150 women (75 women in each group) who did not have major protocol deviations and were therefore assessed as suitable for inclusion in the pharmacodynamic analysis. The mean treatment duration in the FAS was approximately 23 weeks in the Yasmin + Metafolin group and 24 weeks in the Yasmin + FA group, and 24 weeks in each group of the PPS.

Reviewer's comment:

Yaz and Yasmin are approved products and have been widely marketed for several years in many countries. The US 24-week trial used only YAZ and the European 24+20 week trial used Yasmin, so the amount of safety data for either drug combined with metafolin is limited, but should be adequate as a change in the safety profile is not expected given the addition of only the metafolin to the approved COC.

7.2.2 Explorations for Dose Response

The December 2003 Advisory Committee members agreed that the concept of combining a combination OC with 400 mcg of folic acid was reasonable. The Applicant selected a dose of metafolin that closely approximates the biological activity of 400 mcg of folic acid.

7.2.4 Routine Clinical Testing

Clinical laboratory evaluations were performed in all 4 clinical studies (phases 1 and 3). Depending on the different study design and objectives, laboratory variables were assessed at varying time points during the individual studies. In general, the following laboratory evaluations were performed:

- Long-term US Study A43598: serum chemistry, hematology, coagulation parameters, and urinalysis before and after treatment (after week 24)
- European Study A39814: serum chemistry, hematology, coagulation parameters, and urinalysis at screening, week 24, and follow-up (after week 44)
- Bioequivalence studies A28575 and A27410: hematology, clotting status, serum chemistry, and urinalysis (dip stick) at screening and follow-up

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

YAZ, Yasmin, and folic acid have been used in millions of women for many years, so the safety profile of each has been well-characterized.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in any of the studies included in the development program of YAZ or Yasmin fortified with metafolin.

7.3.2 Nonfatal Serious Adverse Events

In US Study A43598, two treatment-emergent serious adverse events (SAEs) of moderate intensity were experienced by two women in the YAZ + Metafolin group: cervix carcinoma stage 0 (carcinoma in situ in a 30 year old woman) and pneumonia. Study medication was withdrawn from the woman with carcinoma in situ. She recovered/resolved by the end of the study; this SAE was considered by the investigator as possibly related to the study medication. The outcome of the SAE pneumonia was unknown, and the investigator assessed it as being unrelated to the study medication. Three women (ages 25, 25, and 26) taking YAZ + metafolin discontinued because of decreased libido.

In German Study A39814, 16 SAEs were reported for 9 women during this study. Eleven SAEs were reported for 6 women in the Yasmin + Metafolin group. The only SAEs in the active treatment period were acoustic neuroma and impaired healing in a 21 year old woman. Nine SAEs occurred during the second treatment period when the women were taking Yasmin alone: SAEs in period 2 were arthralgia, esophageal food impaction, appendicitis (one each in three different women), abdominal pain lower and hemorrhagic ovarian cyst (both in the same 24 year

old woman), abdominal pain, nausea, diarrhea and cholelithiasis (all four SAEs in a 23 year old woman). In the Yasmin + FA group, five SAEs were reported for three women: SAEs in the first treatment period were pyelonephritis and ulcerative colitis (each SAE in a different woman); SAEs in period 2 were loss of consciousness, hyperventilation, and alcohol poisoning (all three SAEs in the same 23 year old woman). None of the SAEs in either treatment group were considered related to the study medication by either the investigator or the Applicant.

The bioequivalence studies A28575 and A27410 had no reports of SAEs.

Reviewer's comment:

Taken together, none of the SAEs reported in the course of the clinical development program of YAZ or Yasmin fortified with Metafolin gave rise to any new safety concerns compared to the risks already known for the individual OC components in YAZ, Yasmin, or Metafolin (levofolate). It is interesting that 5 of the 11 women who discontinued prematurely while taking YAZ + metafolin did so for decreased libido, depression, or emotional instability. These adverse events, however, are seen with all COCs.

Not all of the women with SAEs were dropped from the trials. See Table 11 and Table 12 for the list of early discontinuations from the two long-term pharmacodynamic studies.

7.3.3 Dropouts and/or Discontinuations

See Subject Disposition in Section 6.1.3 of this review. In the 24-week US study A 43598 (N= 379), 73% completed the study; 4% discontinued because of an adverse event. In the longer (44 week), but smaller (N= 172) European study A39814, 95% completed and 2.3% discontinued because of an adverse event. The discontinuation rates were very similar for both arms of both studies.

7.3.4 Significant Adverse Events

The following two tables show the adverse events that led to premature discontinuation by treatment group in the two long-term studies. SAEs are discussed in Section 7.3.2.

Table 11: Study A43598 Early Discontinuations due to AEs

Treatment	PID no. / RNR (age)	MedDRA preferred term	Premature end of study medication AE text
YAZ + Metafolin	101030 / 10179 (38 years)	Nausea Dizziness	Nausea Dizziness
YAZ + Metafolin	101053 / 10280 (26 years)	Menstrual disorder	Abnormal menstrual bleeding [no further data]
YAZ + Metafolin	103003 / 10196 (30 years)	Cervix carcinoma stage 0	Cervical cancer in situ
YAZ + Metafolin	103097 / 10401 (24 years)	Affect lability	Emotional instability
YAZ + Metafolin	104002 / 10189 (25 years)	Libido decreased Dysmenorrhea Menorrhagia	Decreased libido Increased frequency and intensity of dysmenorrhea Prolonged menstrual flow
YAZ + Metafolin	104006 / 10190 (18 years)	Hypothyroidism	Hypothyroidism
YAZ + Metafolin	106003 / 10218 (24 years)	Genital hemorrhage	Vaginal spotting
YAZ + Metafolin	106026 / 10408 (26 years)	Libido decreased	Decreased libido
YAZ + Metafolin	106044 / 10451 (25 years)	Libido decreased	Decreased libido
YAZ + Metafolin	108101 / 10499 (20 years)	Depressed mood	Depressed mood
YAZ + Metafolin	108139 / 10630 (20 years)	Weight increased	Weight gain
YAZ	104004 / 10211 (20 years)	Migraine	Increase in frequency and uncomplicated migraine
YAZ	108030 / 10506 (29 years)	Systemic lupus erythematosus	Systemic lupus erythematosus
YAZ	108063 / 10521 (29 years)	Abdominal pain Cholelithiasis	Abdominal pain Gallstones

PID no. = patient identification number; RNR = randomization number

Source: Applicant Table 2-12, page 81 of 141 in Summary of Clinical Safety.

Table 12: Study A39814 Early Discontinuations due to AEs

Treatment	PID no. / RNR (age)	Treatment period	MedDRA preferred term	Premature end of study medication AE text
Yasmin + Metafolin	529 / 32 (21 years)	Period 1	Acoustic neuroma	Acusticus neurinoma, left
Yasmin + Metafolin	565 / 54 (28 years)	Period 2	Arthralgia	Pain in the right knee, surgery necessary therefore stop of study medication
Yasmin + Metafolin	681 / 151 (23 years)	Period 2	Cholelithiasis	Biliary sludge
Yasmin + FA	524 / 25 (26 years)	Period 1	Hyperthyroidism	Newly diagnosed hyperthyreosis
Yasmin + FA	903 / 53 (23 years)	Period 2	Pyelonephritis	Pyelonephritis, both sides, due to additional prophylactic treatment (pyelonephritis) with nitrofurantoin
Yasmin + FA	608 / 68 (36 years)	Period 1	Colitis ulcerative	Colitis ulcerosa
Yasmin + FA	703 / 152 (28 years)	Period 1	Basedow's disease	Diagnosis of M. Basedow (with hyperthyreosis)

PID no. = patient identification number; RNR = randomization number. Period 2 is the 20-week "folate elimination" phase when only Yasmin was administered.
Source: Applicant Table 2-13, page 82 of 141 in Summary of Clinical Safety.

Reviewer's comment:

It is unlikely that the AEs listed in the two tables are directly related to the use of the metafolin or folic acid. Weight gain, decreased libido, menstrual symptoms, and cholelithiasis are associated with OC use. No thromboembolic events are noted and there were no deaths in any of the four trials.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In US Study A43598, the most frequently reported AEs by MedDRA System Organ Class (SOC) and decreasing frequency in each treatment group were as follows:

- Infections and infestations in both the YAZ + Metafolin group (30.9%), and the YAZ group (26.6%)
- Investigations in both the YAZ + Metafolin group (11.6%), and the YAZ group (12.8%)
- Reproductive system and breast disorders in the YAZ + Metafolin group (8.4%), and Reproductive system and breast disorders and Respiratory, thoracic and mediastinal disorders the YAZ group (8.5%, respectively)
- Gastrointestinal disorders in the YAZ + Metafolin group (5.6%), and Gastrointestinal disorders, and Nervous system disorders in the YAZ group (7.4%, respectively)
- Nervous system disorders in the YAZ + Metafolin group (4.2%), and Musculoskeletal and connective tissue disorders in the YAZ group (6.4%).

The most frequently reported ADRs [reactions possibly related to the drug] by decreasing frequency in the treatment groups were:

• Reproductive system and breast disorders in the YAZ + Metafolin group (3.2%), and Investigations the YAZ group (5.3%)

• Nervous system disorders in the YAZ + Metafolin group (2.8%), and Nervous system disorders and Reproductive system and breast disorders in the YAZ group (3.2%, respectively).

In European Study A39814, the most frequently reported AEs by MedDRA SOC and decreasing frequency in each treatment group were as follows:

• Infections and infestations in both the Yasmin + Metafolin group (82.6%), and the Yasmin + FA group (87.2%)

• Nervous system disorders in both the Yasmin + Metafolin group (55.8%), and the Yasmin + FA group (61.6%)

• Gastrointestinal disorders in both the Yasmin + Metafolin group (51.2%), and the Yasmin + FA group (57.0%)

• Respiratory, thoracic and mediastinal disorders in both the Yasmin + Metafolin group (38.4%), and the Yasmin + FA group (45.3%)

• Musculoskeletal and connective tissue disorders in both the Yasmin + Metafolin group (27.9%), and the Yasmin + FA group (20.9%).

The most frequently reported ADRs by decreasing frequency in the treatment groups in study A39814 were as follows:

• Reproductive system and breast disorders in both the Yasmin + Metafolin group (12.8%) and the Yasmin + FA group (14.0%)

• Gastrointestinal disorders in the Yasmin + Metafolin group (7.0%); Infections and infestations, and Nervous system disorders in the Yasmin + FA group (3.5%, respectively).

Reviewer's comment:

There were no outstanding differences between the YAZ + Metafolin vs. YAZ alone or Yasmin + Metafolin vs. Yasmin + FA in terms of AEs or ADRs. The label for Beyaz states that "Of 285 women, 4.6% who used YAZ or Beyaz discontinued from the clinical trials due to an adverse event; no reaction leading to discontinuation occurred in more ≥ 1% of women." If menstrual irregularities (menstrual disorder, vaginal hemorrhage, and menorrhagia) are lumped together, then the percentage would be 1.1% (3/285). My final conclusion is that there is no signal that the addition of 0.451 mg levomefolate changes the adverse event profile of YAZ.

7.4.2 Laboratory Findings

7.4.2.1 Potassium and Related Parameters

To assess if there is any relationship between the use of DRSP and serum potassium, several potential aspects related to hyperkalemia were also analyzed, i.e., the role of selected concomitant medications that may result in elevated potassium (e.g., non-steroidal anti-

inflammatory drugs), renal function, and selected cardiovascular AEs as well as renal function evaluated against selected cardiovascular AEs.

No one in any of the 4 studies had post-baseline serum potassium values ≥ 5.5 mmol/L. Mean baseline serum potassium concentrations were similar between the treatment groups in the long-term studies, and comparable with values from the two bioequivalence studies. Maximum and average changes from baseline of serum potassium were minimal, and were comparable between the treatment groups, as well as between the studies.

Almost all women had within-reference range values at baseline that stayed within the reference range post-baseline. Women whose values were outside the reference range mostly had below-reference range values at either or both baseline and post-baseline, and only eight women had values above the reference range (5 women in Study A43598, 3 women in Study A27410).

Serum potassium changes from baseline were also classified into categories (e.g., -1.5 mmol/L ≤ change < -1.0 mmol/L). The majority of women in both long-term studies had a maximum change from baseline in the range of -0.5 mmol/L to < 1.0 mmol/L serum potassium, with comparable proportions of women in both treatment groups. No women who took selected concomitant medication had post-baseline serum potassium values ≥ 5.5 mmol/L.

To evaluate the association between renal function and serum potassium, creatinine clearance rates were calculated and categorized as normal (>80 mL/min), mild (50 to ≤ 80 mL/min), moderate (30 to ≤ 50 mL/min), or severe (≤ 30 mL/min). In all 4 studies, the majority of women had normal renal function that stayed normal at the final examination. Data for the long-term studies showed the following:

- US study A43598: approximately 92% of women in either treatment group had a normal renal function at baseline that stayed normal at the final examination (normal → normal), fewer than 4% of women in either treatment group had a normal renal function at baseline that showed a mild impairment at the final examination (normal → mild), about 2% of women, respectively, had either mild impairment at baseline that was normal at the final examination (mild → normal), or mild impairment at baseline that stayed mildly impaired at the final examination (mild → mild). No one had moderately or severely impaired renal function either at baseline or the final examination.

- European study A39814: transitions in renal function from baseline to cycle 6, and baseline to the final examination, showed very similar percentages in both treatment groups. Through cycle 6, the majority of women (approximately 95%) had normal → normal renal function transitions in both treatment groups, with fewer than 4% of women in the categories normal → mild (1.2%), mild → normal (3.7%), or mild → mild (1.2%). Transitions from baseline to the final examination (~44 weeks) showed a similar trend; the majority were in the normal → normal (94%) category, with fewer than 3% of women in the categories normal → mild, mild → normal, or mild → mild (up to 2.4% for each category). No one had moderately or severely impaired renal function either at baseline, cycle 6 or the final examination.

Mild renal impairment did not affect serum potassium levels, as was observed by comparing maximum serum potassium levels according to baseline creatinine clearance rates. For example,

in Study A43598, a maximum serum potassium level of approximately 4 mmol/L was observed, both for women with normal creatinine clearance and for women with mild renal impairment. Comparable values were observed for both treatment groups in the long-term studies.

Reviewer's comment:

There is no evidence from the two long-term studies that the addition of metafolin or folic acid had an adverse effect on the potassium levels or renal function in the women participating in the studies. The labels for the products (YAZ and Yasmin) clearly address the precautions concerning the potential for hyperkalemia in high-risk women. Women with chronic conditions or diseases with medications that may increase serum potassium should have their potassium level checked during the first treatment cycle with YAZ + metafolin or YAZ + metafolin.

7.4.2.2 Liver Function and Renal Function

The mean values for the parameters of liver function (alkaline phosphatase, gamma glutamyltransferase or GGT, alanine aminotransferase or ALAT, aspartate aminotransferase or ASAT, direct bilirubin, and total bilirubin) and renal function (serum creatinine) were within the limits of the relevant study reference ranges at the time points measured, and were generally comparable between the treatment groups. Overall, all parameters were unchanged at screening compared to the final examination, except for bilirubin, which decreased by about 28% from screening to cycle 6 in both treatment groups in European study A39814. The majority of women (> 75% overall for all liver and renal function parameters) had values within the respective reference ranges at both time points measured. No treatment-related effects were observed, and no clinically relevant changes were observed with a few exceptions in US study A43598 (when 1 woman on YAZ had an increased ALAT; 2 women on YAZ + Metafolin and 2 women on YAZ had increased GGT).

Reviewer's comment:

There is no evidence from the two long-term studies that the addition of metafolin or folic acid had an adverse effect on the parameters of liver function or renal function in the women participating in the studies. In addition, serum electrolytes (chloride, sodium, and potassium) were very stable at the times measurement during the individual studies. Mean values were comparable between the treatment groups and within the limits of the reference ranges for the studies, with the exception of isolated cases in Study A43598 where one woman on YAZ alone had a LFT level above the reference range at the final measurement.

7.4.3 Vital Signs

Vital signs (heart rate, systolic and diastolic blood pressure, and body temperature), height (only US Study A43598) and body weight were measured at screening, and at the final/follow-up examination for the two long-term studies. There were only minimal changes that were comparable between the treatment groups, and no clinically relevant findings.

Reviewer's comment:

I agree with the Applicant's conclusion that no significant changes were noted in the vital signs.

7.4.4 Electrocardiograms (ECGs)

ECG measurements, performed at screening and at the follow-up visit in only the European Study A39814, included an overall interpretation (normal/abnormal) and assessment of the clinical relevance of abnormal findings. ECG changes from screening were reported in 3 women, 2 cases were improvements (abnormal to normal) and 1 case was a new abnormal finding of ventricular extrasystoles, but the woman continued in the study.

Reviewer's comment:

There does not appear to be any signal of concern with the ECG results.

7.4.5 Bleeding Patterns

Evaluation of bleeding patterns:
Bleeding was evaluated based on the subjects' daily diary entries. The length of the reference period was determined as 90 days, in accordance with WHO recommendations. The reference period started on the first day of study medication intake. Treatment was carried out for 6 cycles of 28 days each. Two reference periods were evaluated; Reference Period 1 (Cycles 1, 2, and 3) and Reference Period 2 (Cycles 4, 5, and 6).

The number of bleeding, spotting, and bleeding/spotting days and episodes were calculated for each woman and reference period. A bleeding/spotting-free interval was defined as at least 2 days without bleeding/spotting, preceded and followed by at least 1 bleeding/spotting day. A bleeding/spotting episode was defined as an episode in which the bleeding/spotting was preceded and followed by at least 2 bleeding/spotting-free days and had an intensity of spotting or higher for at least 1 day. A spotting-only episode was defined as an episode in which the spotting was preceded and followed by at least 2 bleed-free days.

For the evaluation of the mean length, maximum length, and range of length of bleeding episodes, only subjects who had any bleeding episodes were included in the statistical evaluations.

Reviewer's Comment:
The method of evaluation of bleeding patterns is acceptable. There were 239 women with evaluable data for Reference Period 1 and 97 women with data for Reference Period 2. Although the data is limited for women actually taking YAZ + Metafolin (Beyaz) for up to 6 months, the final approved label has the following statement in Section 5.9 Bleeding Irregularities:

> ***Data for Beyaz show the average number of episodes of bleeding per reference period (90 days) was 3.2 in Cycles 4-6. The average number of bleeding and/or spotting days with Beyaz was 15.1 days. The intensity of bleeding for Beyaz based on the ratio of spotting-only days versus total bleeding and/or spotting days was 5.2/15.1 days.***

7.4.6 Special Safety Studies/Clinical Trials

There were no special safety studies or clinical trials. The Applicant performed the two bioequivalence and two pharmacodynamic studies that were required and agreed to with the Division.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There is only one approved dose for YAZ and Yasmin, so dose dependency for adverse events is not an issue or a consideration.

7.5.2 Time Dependency for Adverse Events

Most of the common adverse events seen with COCs will subside with time. Common adverse events for hormonal contraceptive products in general and those seen in the clinical trials with YAZ for contraception and the folate trials are listed in the label.

7.5.3 Drug-Demographic Interactions

None were studied.

7.5.5 Drug-Drug Interactions

The two pharmacokinetic studies conducted for this submission (A27410 and A28575) showed that pharmacokinetics of L-5-methyl THF, administered as metafolin, were not influenced by the concomitant administration of DRSP and EE. Concomitant administration of metafolin did not significantly affect the rate and extent of absorption of DRSP and EE. Bioequivalence was demonstrated with regard to DRSP, EE, and Metafolin, the calcium salt of L-5-methyl-THF (for details, see the Clinical Pharmacology review by Doanh Tran, Ph.D.).

According to the Applicant, published data regarding an interaction between oral contraceptives and folic acid is controversial. Oral contraceptive use has not been reported to influence folate status in large-scale population surveys, or in studies in which dietary intake was controlled. A 2003 interaction study by Suetterlin et al. between an oral contraceptive containing a low dose of estrogen and folic acid revealed no influence on folate status. In contrast, a number of early studies of oral contraceptive agents containing high levels of estrogens suggested an adverse effect on folate status. However, this effect has been regarded as mild and unlikely to cause anemia or megaloblastic changes in women who have a good dietary intake of folate and can absorb it properly.

Several drugs have been reported to reduce folate levels and decrease the efficacy of folates by inhibition of the human dihydrofolate reductase (e.g., methotrexate, trimethoprim, sulfasalazine, and triamteren) or by reducing folate absorption (e.g., cholestyramine), or via unknown mechanisms (e.g., antiepileptics such as carbamazepine, phenytoin, and valproic acid).

Folates may modify the pharmacokinetics or pharmacodynamics of certain antifolate drugs, e.g., antiepileptics (such as phenytoin), methotrexate, and pyrimethamine and may result in decreased pharmacological effect of the antifolate drug (mostly reversible if the antifolate dose is adjusted).

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No special carcinogenicity studies were performed. DRSP, EE, and metafolin have been marketed for many years and are considered to be safe and non-carcinogenic. The Division preclinical pharmacology reviewer Leslie McKinney, Ph.D., did not recommend any further studies.

In a meta-analysis based on 20 studies, Fernandez et al. (British J Cancer, 2001) obtained a relative risk for colorectal cancer of 0.82 (95% CI: 0.74-0.92) among ever users of combination oral contraceptives (COCs), suggesting a moderately protective effect of COCs against colorectal cancer. A prospective cohort study published by Lin et al. (Am J Epidemiology, 2007) also demonstrated an inverse association between colorectal cancer and duration of OC use. This agrees with the results of the Nurses Health Study (Martinez et al. Cancer Epidemiology, 1997).

Current data demonstrate that poor folate status is associated with an increased risk for colorectal cancer (CRC). The evidence that high folate intake increases growth of pre-existing tumors is less convincing. Thus the effect of folates on CRC risk remains undetermined and will depend on the relative size of the two potential effects, and of the timing and level of folate intake. In conclusion, the overall effect of YAZ + Metafolin on CRC risk is currently unknown.

Reviewer's comments:

A recent article by Ebbing et al in JAMA[1] presented evidence combining the data from two randomized, blinded, placebo-controlled trials of the association between folic acid and B_{12} treatment and cancer incidence (especially lung cancer), cancer mortality, and all-cause mortality among >6,800 persons with ischemic heart disease in Norway, a country without folic acid fortification. The folic acid dose was 0.8 mg/day, taken by approximately half of the subjects. The Hazard Ratios (95% CI) for the folic acid vs non-folic acid groups were:

- **Cancer incidence: 1.21 (1.03-1.41)**
  - **Lung cancer: 1.59 (0.92-2.75)**
  - **Colorectal cancer: 1.00 (0.59-1.69)**
- **Cancer mortality: 1.38 (1.07-1.79)**
- **All-cause mortality: 1.18 (1.04-1.33)**

An editorial by Drake and Colditz about the article pointed out, however, that in the US (where we have had folic acid fortification since 1998) rates for total cancer incidence and lung cancer have decreased significantly since the late 1990s. They conclude that these US cancer incidence rates do not support a substantial, population-wide adverse effect of the magnitude suggested in the study by Ebbing et al.

Although the lung cancer incidence is higher in this study, it is reassuring that the colorectal incidence is not. At this time, I do not believe that the Beyaz label needs to state the findings of the Ebbing article. If further studies show the same finding, especially in a US population where folate fortification is mandatory, then a change in the approved label may be warranted.

[1] Ebbing et al. Cancer incidence and mortality after treatment with folic acid and vitamin B_{12}. JAMA. 2009;302(19):2119-26.

7.6.2 Human Reproduction and Pregnancy Data

There are postmarketing pregnancy data for women who conceived while taking YAZ and Yasmin; no significant safety signals have been identified concerning pregnancy or newborn outcomes. No clinical trial would be sufficiently powered to demonstrate a reduction in NTD risk due to the relative rarity of this birth defect.

During the trials for this NDA submission, there were no pregnancies on treatment during the US Study A43598. There were three pregnancies that occurred while on treatment in the other studies. All three were electively terminated and no fetal data is available.

- pregnancy during period 2 on treatment with Yasmin alone in German Study A39814 - medical abortion
- pregnancy in period 2 on treatment with YAZ + metafolin in BE Study A28575 - elective abortion
- pregnancy after completion of period 2 in the Yasmin BE Study A27410 - elective abortion

7.6.3 Pediatrics and Assessment of Effects on Growth

On April 14, 2010, the Division met with the Pediatric Review Committee (PeRC) to discuss the Pediatric Research Equity Act (PREA) requirements for this product. After a lengthy discussion the two key recommendations were:

Combination hormonal contraceptives have been considered to be safe for an adolescent population and have not demonstrated any effects on growth that are clinically significant.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There have been no reports of serious ill effects from YAZ or Yasmin overdose, including ingestion by children. Overdosage of YAZ + Metafolin or Yasmin + metafolin may cause nausea and withdrawal bleeding in females and may increase blood levels of potassium or decrease blood levels of sodium. Drospirenone is a spironolactone analogue which has anti-mineralocorticoid properties. Serum concentration of potassium and sodium, and evidence of metabolic acidosis, should be monitored in cases of overdose.

Levomefolate calcium and its metabolites are identical to the folate forms found naturally in foods, which are consumed daily without apparent harm. Levomefolate calcium doses of 17

mg/day (37-fold higher than the levomefolate calcium dose of YAZ + Metafolin) were well tolerated during treatment up to 12 weeks in a sample (N= 25) of hemodialysis patients with markedly elevated homocysteine levels (Bostom et al. June 20, 2000. *Circulation*).

Reviewer's comment:

There were no apparent drug abuse potential or withdrawal and rebound effects demonstrated in the clinical trials for this NDA. In the European study A39814, 80 women each took Yasmin + Metafolin or Yasmin + folic acid for 24 weeks followed by 20 weeks with Yasmin only. No withdrawal adverse events or signals were noted.

7.7 Additional Submissions / Safety Issues

A recent study aimed to investigate the effect of timing, dose, and source of folate during pregnancy on childhood asthma by using data from an Australian prospective birth cohort study (N= 557) from 1998 to 2005. There was a signal for an increased risk (relative risk =1.26 [95% CI 1.08, 1.43]) of asthma at 3.5 years in offspring exposed to high folate levels, especially during late pregnancy in this study[2]. At the 2010 Annual Allergy, Asthma, and Immunology meeting, a poster session[3] showed that "children of mothers with high plasma folate levels during early pregnancy appear to have an increased risk of developing asthma by the age of 3 years; the sample was from the Norwegian Mother and Child Cohort study." Two other studies, one in mice and one conducted by Stephanie London, MD at the National Institute of Environmental Health Sciences (NIEHS) in Durham, NC showed a similar concern. For the YAZ and Yasmin products combined with metafolin, however, two facts must be noted: 1) the amount of metafolin is only 0.451 mg, basically equivalent to the recommended supplementation of 0.4 mg folic acid, and 2) the product will be stopped before or as soon as pregnancy is diagnosed. Prenatal vitamins typically contain 1 mg of folate.

Reviewer's comment:

I do not recommend that a postmarketing requirement or commitment is warranted concerning a risk for childhood asthma.

A 4-month safety update covering March 1 through June 30, 2009 was submitted to the NDA on December 16, 2009. This included a literature review that was conducted to evaluate the published data for DRSP 3mg/ethinyl estradiol 0.02 mg/levomefolate calcium 0.451mg oral tablets (DRSP/EE/Levomefolate) for the reporting interval of March 1, 2009 through June 30, 2009. The Applicant's review of the published literature concluded that there is no new safety information that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling for this NDA 22-532 submission.

A recent Periodic Safety Update Report (PSUR) was submitted on November 5, 2009 for YAZ® (drospirenone 3mg/ethinyl estradiol 0.02 mg) tablets, NDA 21-676. The time period covered by this report is September 7, 2008 through September 6, 2009. No new safety signals were noted in the report.

[2] Whitrow MJ, et al. Effect of Supplemental Folic Acid in Pregnancy on Childhood Asthma: A Prospective Birth Cohort Study. American Journal of Epidemiology. October 2009; 1-8.
[3] London S. Abstract 505, poster at the Annual Meeting of the American Academy of Allergy, Asthma and Immunology, February 28, 2010.

Reviewer's comment:

The label for YAZ was revised in April 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 is consistent with that for YAZ.

I concur with the Applicant's conclusion that no new safety information or signals for drospirenone 3mg/ethinyl estradiol 0.02 mg/ levomefolate calcium 0.451mg oral tablets has been obtained that should be included in the statements regarding contraindications, warnings, precautions, and adverse reactions previously submitted in draft labeling for this product.

8 Postmarket Experience

This combination product is not marketed anywhere in the world; thus, there is no postmarketing experience or data. The reporting interval is based on the cut-off for the review of the clinical-medical literature that was conducted for the NDA, as the Applicant did not have any on-going studies to report.

9 Appendices

9.1 Literature Review/References

The Applicant submitted over 130 references in their entirety. These were read as needed during this review. A couple of additional references are noted in Section 7.7 above.

9.2 Labeling Recommendations

In his 5-06-10 labeling review, Safety Evaluator Richard Abate, RPh, MA, from the Division of Medical Error Prevention and Analysis (DMEPA) recommended that the proposed proprietary name (b) (4) be changed to Beyaz. Furthermore, he recommended that the established name be changed to:

> Drosperinone, Ethinyl Estradiol, and Levomefolate Calcium Tablets and Levomefolate Calcium Tablets
> 3 mg/0.02 mg/0.451 mg and 0.451 mg

On 7-13-10, the Applicant submitted a completely revised label that is in the new PLR format and closely follows the standard combination hormonal contraceptive information found in recently approved COC PLR labels. This was at the Division's recommendation. Following discussions and exchange of proposed label edits between the Applicant and the Division, the final label was agreed to on September 24, 2010. There are no further labeling recommendations.

9.3 Advisory Committee Meeting

In December 2003, an Advisory Committee (AC) meeting was held to discuss the safety and potential clinical benefit associated with combining folic acid and an oral contraceptive into a single combination product. The Committee voted the following on several key questions:

1. Are further increases in folic acid intake, beyond what is available is fortified cereals, likely to result in public health advances in preventing further neural tube defects?
   The vote: Yes- 18, No- 0.
2. Is it necessary to define a subpopulation among women of reproductive age that needs additional folic acid?
   The vote: Yes- 4, No- 14.
3. Are there any safety issues associated with folic acid supplementation targeted at reproductive-age women?
   The vote: Yes- 7, No- 11.
   Some committee members raised the concern that too much folic acid has been associated with masking pernicious anemia (a rare condition) and could also impact the activity of antifolate drugs such as antiepileptics (valproic acid) and methotrexate.
4. Would the benefit of prior folic acid use persist if conception occurs after discontinuation of folic acid?
   The vote: Yes- 12, No- 2, Abstain- 1.
   The members agreed that increased red cell folate levels (following folic acid supplementation) would be maintained for up to 90 days following discontinuation.
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?
   The vote for both questions: Yes- 18, No- 0.
   Many members stated that this dose might not be ideal and that additional studies should be conducted to further define a dose. The members did not provide a recommendation for alternative dosing.

Reviewer's comment:

In essence, the AC meeting members agreed that the concept of combining an OC with 400 mcg of folic acid was reasonable. It would provide a public health advance in preventing neural tube defects in those women who conceive while on the OC or within 90 days following discontinuation of the OC. Based on the results of this AC meeting, Bayer Schering pursued the development plan for both their Yasmin and YAZ products using metafolin as the best form of folic acid supplementation.

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

/s/

DANIEL DAVIS
09/24/2010

LISA M SOULE
09/24/2010

I concur with Dr. Davis' conclusions and recommendation that NDA 22-532 be approved for the primary indication of prevention of pregnancy and the secondary indications of folate supplementation, treatment of PMDD and treatment of moderate acne.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring MD 20993

Tel 301-769-2110
FAX 301-796-9895

M E M O R A N D U M

Date: 7/23/10

From: Snezana Trajkovic, MD, Medical Officer, DDDP

Through: David Kettl, MD, Medical Team Leader, DDDP
Susan Walker, MD, Division Director, DDDP

To: Daniel Davis, MD, Medical Officer, DRUP
Lisa Soule, MD, Medical Team Leader, DRUP
Scott Monroe, MD, Division Director, DRUP

CC: Pamela Lucarelli, RPM, DRUP
LT Dawn Williams, RN, BSN, DDDP
Barbara Gould, CPMS, DDDP

Re: Consult # to DRUP Re: Beyaz NDA 22-532

On June 24, 2010 DRUP requested that the sponsor submit the following:

"Assessment of impact, if any, of levomefolate calcium on the safety and efficacy of Beyaz for the treatment of acne vulgaris and premenstrual dysphoric disorder (PMDD), and final reports of any studies conducted to characterize the safety and efficacy of the proposed combination product for the treatment of acne vulgaris and PMDD."

Conclusion:

The sponsor presented 11 articles in support of their NDA application for Beyaz which includes acne vulgaris as a proposed indication. None of the articles presented in the

submission were trials that evaluated the effects of levomefolate calcium on acne vulgaris, or the potential impact of acne vulgaris on plasma folate levels.

This sponsor submitted literature, and this reviewer's independent literature search, did not result in any relevant studies that evaluated the safety or 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.

Materials Evaluated

This reviewer evaluated sponsor submitted published literature that attempted to assess the impact of treatment with folate (levomefolate calcium, folic acid) on acne vulgaris and PMDD.

An independent literature search and evaluation was also conducted to document any published scientific evidence that could describe the impact of the addition of folate to the approved YAZ product on the treatment of acne vulgaris.

Background

The sponsor submitted NDA 22-532 on August 31, 2009 for drospirenone 3mg/ethinyl estradiol 0.02 mg/levomefolate calcium 0.451mg oral tablets (**Beyaz**) for the additional indication of improvement in folate status in women who elect to use an oral contraceptive to the approved product YAZ.

YAZ is a combination oral contraceptive containing 3 mg of drospirenone (DRSP) and 0.02 mg of ethinyl estradiol. It has been approved for the following indications:

- Prevention of pregnancy in women who elect to use an oral contraceptive (NDA 21-676, approved 3/16/06)

- Treatment of symptoms of premenstrual dysphoric disorder (PMDD), (NDA 21-873, approved 10/04/06), and

- Treatment of moderate *acne vulgaris* in women at least 14 years of age, who have no known contraindications to oral contraceptive therapy and have achieved menarche. YAZ should be used for the treatment of acne only if the patient desires an oral contraceptive for birth control (NDA 22-045, approved 1/26/07).

The sponsor developed the drospirenone 3mg/ethinyl estradiol 0.02mg/ levomefolate calcium (L-mefolate) 0.451mg product under IND 72, 287 which was submitted on March 1, 2007.

Pre-lND meeting was held on September 8, 2005. During the meeting, acceptability of adding L-mefolate instead of folic acid to approved oral contraceptives and the overall clinical program required for approval of a combination drug product that consists of L-mefolate calcium plus the active ingredients of Yasmin was discussed.

A Type C Guidance meeting was held on March 10, 2006 during which DRUP recommended the following studies to be conducted to demonstrate safety and efficacy of L-mefolate:

- "A bioequivalence study of the steroid oral contraceptive with and without Metafolin®.
- An "equivalence" study as described in the Division's response to Question 8, evaluating the pharmacodynamic effects of Metafolin® as compared to folic acid. A non-inferiority trial would not address potential safety concerns that might arise should Metafolin® actually have a greater pharmacodynamic effect than folic acid. Therefore, this should be a typical bioequivalence study, evaluating both upper and lower limits of effect as compared to folic acid.
- A comparative trial showing superiority of treatment with an oral contracetprive + Metafolin® as compared to an oral contraceptive alone, in terms of a clinically relevant change in folate status."

A total of four studies, two bioequivalence studies and two pharmacodynamic studies, were submitted by the sponsor in support of their application.

The two bioequivalence studies were performed in order to demonstrate that the addition of levomefolate calcium has no influence on the rate and extent of absorption of both, estrogen and progestin, and the presence of estrogen and progestin has no influence on the rate and extent of absorption of levomefolate calcium. One study each was performed for Yasmin and YAZ.

The third study is referred to as the "long-tem use of folate study". This study was performed in order to investigate plasma and red blood cell (RBC) folate during a 24-week administration of a fortified oral contraceptive and to demonstrate that the selected dose of 0.451mg levomefolate calcium and 0.4 mg folic acid result in equivalent levels of plasma and RBC folate. Furthermore, the depot effect after cessation of folate supplementation during a 20-week elimination phase was investigated. The oral contraceptive used in this study was Yasmin (3 mg of drospirenone/0.03 mg of ethinyl estradiol).

The forth study, referred to as the "folate benefit study", investigated plasma folate, red blood cell folate and homocysteine levels during a 24-week oral administration of an oral contraceptive with or without levomefolate calcium. This study was conducted to provide

data showing that fortification of an oral contraceptive with levomefolate calcium is clinically beneficial even in women on a folate-fortified diet. The oral contraceptive used in this study was YAZ.

DRUP has preliminarily concluded that clinical trials documenting safety and efficacy for the approved YAZ indications did not need to be conducted if the above bioequivalence/bioavailability studies are deemed successful. Their current preliminary review conclusion is that Beyaz should be approved for the same indications as YAZ is currently approved, including the primary indication for prevention of pregnancy as well as acne and PMDD.

No meetings have been held with DDDP for this product in relation to the acne vulgaris indication, and no formal submission for this application has been received by DDDP.

On June 24, 2010 DRUP requested that the sponsor submits the following: "Assessment of impact, if any, of levomefolate calcium on the safety and efficacy of Beyaz for the treatment of acne vulgaris and premenstrual dysphoric disorder (PMDD), and final reports of any studies conducted to characterize the safety and efficacy of the proposed combination product for the treatment of acne vulgaris and PMDD."

The sponsor submitted summary of 12 individual publications in response to above request. The review of this submission is presented below.

Review:

The sponsor submitted summary of individual publications (12 citations) in support of their NDA 22-532 application. There are three topics covered by the publications: Folic Acid in the Treatment of Acne; Effect of Acne treatment on Plasma Folate, and Folic Acid Influence on Acne Vulgaris.

Folic Acid in the Treatment of Acne

Niren NM, Torok HM. The Nicomide Improvement in Clinical Outcomes Study (NICOS): results of an 8-week trial. Cutis 2006;77(1 Suppl):17-28.

The author of this article discusses treatment of acne vulgaris and signs of aging with products known as "cosmeceuticals" (products that cannot be considered cosmetics or drugs). However, there is no discussion of use of folic acid in treatment of acne vulgaris.

Manela-Azulay M, Bagatin E. Cosmeceuticals vitamins. Clin Dermatol 2009; 27: 469-474.

This was an open label trial of food supplement (nicotinamide / zinc / copper / folic acid) in treatment of acne vulgaris and rosacea. There is no evaluation of folic acid monotherapy on acne vulgaris.

Reviewer's comments:
In neither of the presented citations, the effects of treatment with folic acid on acne vulgaris, were evaluated or discussed.

Effect of Acne Medication on Plasma Folate

The sponsor presented 7 citations:

Chanson A, Cardinault N, Rock E, et al. Decreased plasma folate concentration in young and elderly healthy subjects after a short-term supplementation with isotretinoin. JEADV 2008; 22(1):94-100

Jasim ZF, McKenna KE. Vitamin B12 and folate deficiency anemia associated with isotretinoin treatment for acne. Clin Exper Dermatol 2006;4:599-599.

Jones CC. Megaloblastic anemia associated with long-term tetracycline therapy. Report of a case. Ann Intern Med 1973;78(6):910-2.

Marie I, Girszyn N, Levesque H, Massy N, Senant J. Peripheral neuropathy associated with topical tretinoin therapy. J Intern Med 2009; 39(12):e9-e11.

Polat M, Lenk N, Bingoel S, et al. Plasma homocysteine level is elevated in patients on isotretinoin therapy for cystic acne: a prospective controlled study. J Dermatolog Treat 2008; 19(4):229-32.

Roodsari MR, Akbari MR, Sarrafi-rad N, Saeedi M, Gheisari M, Kavand S. The effect of isotretinoin treatment on plasma homocysteine levels in acne vulgaris. Clin Exper Dermatol 2010; 35:624-626.

Schulpis KH, Karikas GA, Georgala S, Michas T, Tsakiris S. Elevated plasma homocysteine levels in patients on isotretinoin therapy for cystic acne. Int J Dermatol 2001; 40(1):33-36.

Five of seven articles describe the effects of isotretinoin treatment on plasma homocysteine levels in patients with acne vulgaris. One article is a case report of magaloblastic anemia caused by treatment with tetracycline in patient with acne vulgaris. One article is a case report of neuropathy caused by isotretinoin therapy in patient with acne vulgaris.

Reviewer's comments:

None of the articles presented evaluated the effects of folic acid on acne vulgaris. In addition, there is no evaluation of the relationship of folate levels to acne vulgaris.

Folic Acid Influence on Acne Vulgaris

The sponsor presents 2 citations.

Helinski M. [Contribution to the problem of acne vulgaris in women. Therapeutic technics] Beitrag zur Frage der Acne vulgaris bei Frauen [in German]. Behandlungsmethoden.; Z Haut Geschlechtskr 1968;43:648-50.
(English translation is not available)

Kotzman M, Logan AC. Acne vulgaris: Nutritional factors may be influencing psychological sequelae. Med Hypotheses 2007; 69:1080-1084.

First citation was listed but not been provided for review (translation from German not yet available).

Second citation discusses influence of nutritional factors on psychological status of patients with history of depression and acne vulgaris.

Reviewer's comments:
Presented article does not document any effects of folic acid on treatment of acne or the effects of folate deficiency on change in status of acne vulgaris.

Folate and PMDD

The sponsor submitted 1 citation.
Tallova J, Bicikova M, Hill M, Tomandl J, Valentova D. Homocysteine during the menstrual cycle in depressive women. Eur J Clin Invest 203; 33(3):268-273.

This article evaluated homocysteine levels during the menstrual cycle in subjects with depression. There was no evaluation of treatment of PMDD with folic acid. This article will be reviewed by DRUP in support of the proposed PMDD indication.

Conclusion:

The sponsor presented 11 articles in support of their NDA application. None of the articles presented in the submission had studies that evaluated the effects of levomefolate calcium treatment of acne vulgaris, nor any documentation of any effects of acne vulgaris on folate levels.

The entirety of the sponsor's rationale was as follows:

"As a whole, the current literature review supports the scientific and clinical perspective that the addition of metafolin to YAZ (known as Beyaz) has no impact on the safety or efficacy of YAZ with regard to the treatment of acne vulgaris or PMDD. The literature does not reveal any pharmacologic or physiologic mechanism by which metafolin could affect the safety or efficacy of YAZ pharmacotherapy for acne or PMDD"

The absence of any relevant literature neither supports nor repudiates the sponsor's stated conclusion.

This reviewer's independent search of published literature has not resulted in any relevant studies that evaluated safety or efficacy of levomefolate calcium or folate in treatment of acne vulgaris or PMDD. No relevant studies that evaluated effects of folic acid on acne vulgaris were found.

There is a lack of scientific evidence of impact on safety and efficacy of levomefolate calcium or the proposed combination product on treatment of acne vulgaris. Therefore, no meaningful scientific conclusions about safety and efficacy of Beyaz in treatment of acne vulgaris can be drawn.

DDDP Labeling Recommendations:

The sponsor proposed the following labeling to DRUP regarding the **acne** indication for Beyaz, which, if approved by DRUP, will be in PLR format as opposed to Yaz, which is still in the older labeling format. The proposed Beyaz labeling, (b) (4) also includes the same indications as currently listed for Yaz, including the acne indication approved 3/16/06.

Excerpts of the proposed Beyaz label which pertain to the acne indication are presented below. This consult will only note the changes related to the acne indication. They largely mirror the current approved labeling for Yaz. Minor editorial suggested changes to the proposed label are noted below in Reviewer Comments:

1 INDICATION AND USAGE

1.3 Acne

Beyaz is indicated for the treatment of moderate acne vulgaris in women at least 14 years of age, who have no known contraindications to oral contraceptive therapy and have

achieved menarche. Beyaz should be used for the treatment of acne only if the patient desires an oral contraceptive for birth control.

Reviewer's comment: No change from the current approved Yaz label are noted and no edits are recommended for this section of the Beyaz label.

Reviewer's comment: The following section from the Yaz DOSAGE and ADMINISTRATION section has not been repeated in the Beyaz label since it is repetitive in the new labeling format. DDDP agrees with this deletion.

(b) (4)

[redacted]

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Acne Clinical Trials

Two multicenter, double-blind, randomized, placebo-controlled studies, in 536 women aged 14 – 45 with moderate acne vulgaris who took at least one dose of YAZ, evaluated the safety and efficacy during up to 6 cycles.

The most frequent (≥ 1%) treatment-emergent adverse reaction, related with the use of YAZ listed in descending order, included: metrorrhagia, headache, nausea, menorrhagia, emotional lability, breast pain, dysmenorrhea, menstrual disorder, depression, and vomiting.

Reviewer's comments: The current approved label for Yaz lists the adverse events as follows:

The most frequent (≥ 1%) treatment-emergent adverse reaction, related with the use of YAZ listed in descending order, which may or not be drug related, included: upper respiratory infection, metrorrhagia, headache, suspicious Papanicolaou smear, nausea, sinusitis, vaginal moniliasis, flu syndrome, menorrhagia, depression, emotional lability, abdominal pain, gastroenteritis, urinary tract infection, tooth disorder, infection, vomiting, pharyngitis, breast pain, dysmenorrheal, menstrual disorder, accidental injury,

asthenia, sore throat, weight gain, arthralgia, bronchitis, rhinitis, amenorrhea, and urine abnormality.

Reviewer's comments: The Adverse Reactions section has been edited from the current approved Yaz label which included all listed adverse events that "may or may not" have been judged as related to the drug. The current Agency guidance is to list "Adverse Reactions", and have been edited according to an assessment of whether the listed events are likely related to the drug. These changes are acceptable to DDDP.

12.2 Pharmacodynamics

Acne

Acne vulgaris is a skin condition with a multifactorial etiology including androgen stimulation of sebum production. While the combination of ethinyl estradiol and drospirenone increases sex hormone binding globulin (SHBG) and decreases free testosterone, the relationship between these changes and a decrease in the severity of facial acne in otherwise healthy women with this skin condition has not been established. The impact of the antiandrogenic activity of drospirenone on acne is not known.

Reviewer's comment: The text is verbatim from the current Yaz label.

14 CLINICAL STUDIES

14.3 Acne Clinical Trials

In two multicenter, double blind, randomized, placebo-controlled studies, 889 subjects, ages 14 to 45 years, with moderate acne received YAZ or placebo for six 28 day cycles. The primary efficacy endpoints were the percent change in inflammatory lesions, non-inflammatory lesions, total lesions, and the percentage of subjects with a "clear" or "almost clear" rating on the Investigator's Static Global Assessment (ISGA) scale on day 15 of cycle 6, as presented in Table V:

Table V: Efficacy Results for Acne Trials*

	Study 1		Study 2	
	YAZ N=228	Placebo N=230	YAZ N=218	Placebo N=213
ISGA Success Rate	35 (15%)	10 (4%)	46 (21%)	19 (9%)
Inflammatory Lesions	33	33	32	32
Mean Baseline Count	15 (48%)	11 (32%)	16 (51%)	11 (34%)
Mean Absolute (%) Reduction				
Non-inflammatory Lesions	47	47	44	44
Mean Baseline Count	18 (39%)	10 (18%)	17 (42%)	11 (26%)
Mean Absolute (%) Reduction				
Total lesions	80	80	76	76
Mean Baseline Count	33 (42%)	21 (25%)	33 (46%)	22 (31%)
Mean Absolute (%) Reduction				

* Evaluated at day 15 of cycle 6, last observation carried forward for the Intent to treat population

Reviewer's comment: The text is verbatim from the current Yaz label. The table has a mistake in line formatting that as corrected should be identical as the table in Yaz labeling. The numerical values are the same as in the current approved Yaz label.

Corrected Table V:

	Study 1		Study 2	
	YAZ N=228	Placebo N=230	YAZ N=218	Placebo N=213
ISGA Success Rate	35 (15%)	10 (4%)	46 (21%)	19 (9%)
Inflammatory Lesions				
Mean Baseline Count	33	33	32	32
Mean Absolute (%) Reduction	15 (48%)	11(32%)	16 (51%)	11 (34%)
Non-inflammatory Lesions				
Mean Baseline Count	47	47	44	44
Mean Absolute (%) Reduction	18 (39%)	10(18%)	17 (42%)	11 (26%)
Total lesions				
Mean Baseline Count	80	80	76	76
Mean Absolute (%) Reduction	33 (42%)	21(25%)	33 (46%)	22 (31%)

* Evaluated at day 15 of cycle 6, last observation carried forward for the Intent to treat population

There are minor editorial changes to the Patient Prescribing information. DDDP has no further editorial recommendations for the sections related to the acne indication.

The draft Beyaz label should be amended to correct the formatting differences noted above prior to sending to the proposed Beyaz label to the sponsor for negotiation and concurrence.

Snezana Trajkovic, MD
Medical Officer
Division of Dermatology and Dental Products
Office of Drug Evaluations III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22532	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	YAZ Folate

---

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

/s/

SNEZANA TRAJKOVIC
08/30/2010

DAVID L KETTL
08/30/2010

SUSAN J WALKER
08/31/2010

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22-532 **Applicant: Bayer Healthcare** **Stamp Date: 21 August 2009**

Drug Name: YAZ Folate **NDA Type: Standard**

	Content Parameter	Yes	No	NA	Comment
	FORMAT/ORGANIZATION/LEGIBILITY				
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English, or are English translations provided when necessary?	X			
6.	On its face, is the clinical section of the application legible so that substantive review can begin?			X	
	LABELING				
7.	Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56[1] and 201.57 (or 21 CFR Subpart C for OTC products), current divisional and Center policies, and the design of the development package?	X			
	SUMMARIES				
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X 2.7.4			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X 2.7.3			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X 2.5			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	(b)(1)			
	DOSE				
13.	If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: A 27410 and A28575 Study Title: Bioequivalence studies Sample Size: Adequate Arms: Adequate Location in submission: 5.3.1	X			
	EFFICACY				
14.	On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 A 39814 for long-term use of folate. Pivotal Study #2 A43598 for "folate benefit" Indication: increased folate levels with OC use.	X			

[1] http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
	SAFETY				
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[2]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the sponsor submitted the coding dictionary[3] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the sponsor adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
	OTHER STUDIES				
26.	Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	

[2] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[3] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
	PEDIATRIC USE				
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X 1.9.1			
	ABUSE LIABILITY				
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
	FOREIGN STUDIES				
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
	DATASETS				
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
	CASE REPORT FORMS				
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			Each report is > 3,000 pages.
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
	FINANCIAL DISCLOSURE				
38.	Has the applicant submitted the required Financial Disclosure information?	X 1.3.4			
	GOOD CLINICAL PRACTICE				
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X Form 3674			
	CONCLUSION				
40.	From a clinical perspective, is this application fileable? If not, please state why.	X			

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. There are none from the clinical perspective. The Applicant has done the studies that were requested by the Division.

Daniel Davis, MD — 9-30-09 and 11-19-09

Reviewing Medical Officer — Date

Lisa Soule, MD

Clinical Team Leader — Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22532	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	YAZ Folate

---

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

/s/

DANIEL DAVIS
11/19/2009
I made the 2 changes.

LISA M SOULE
11/20/2009
I concur that this NDA is fileable.