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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

TEVA WOMEN'S HEALTH, INC., Plaintiff/Counterclaim-Defendant, v. LUPIN, LTD., LUPIN PHARMACEUTICALS, INC., Defendants/Counterclaim-Plaintiffs.	Civil Action No. 10-00603(PGS)(DEA) Civil Action No. 10-01235(PGS)(DEA) Consolidated **NOTICE OF APPEAL**
TEVA WOMEN'S HEALTH, INC., Plaintiff/Counterclaim Defendant, v. MYLAN INC., MYLAN PHARMACEUTICALS INC., and FAMY CARE LTD., Defendants/Counterclaim Plaintiffs.	

Notice is hereby given that plaintiff Teva Women's Health, Inc. ("TWH") hereby appeals to the United States Court of Appeals for the Federal Circuit from the Judgment entered in this

action on June 29, 2012 (D.I. 290, Ex. A) finding TWH's U.S. Patent No. 7,320,969 ("'969 patent," Ex. B) invalid as obvious and, on that basis alone, denying TWH's claim that the filing of Defendants' Abbreviated New Drug Application Nos. 91-467 and 20-0492 infringed the '969 patent, as well as all orders and decisions giving rise to that Judgment, including without limitation the Court's June 29, 2012 Opinion (D.I. 289, Ex. C).

Date: July 26, 2012

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EXHIBIT A

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

TEVA WOMEN'S HEALTH, INC., Plaintiff, v. LUPIN, LTD. et al., Defendants.	Civil Action No.: 10-603 (PGS) ORDER

SHERIDAN, U.S.D.J.

This action having been opened to the Court, and the Court having heard the testimony of witnesses, and considered the briefs and arguments of counsel, and for the reasons set forth in its Opinion, and for good cause having been shown;

IT IS on this 29th day of June, 2012;

ORDERED AND ADJUDGED that claim 19 of U.S. Patent No. 7,320,969 is invalid as obvious in view of the prior art under 35 U.S.C. § 103; and it is further

ORDERED that the suit is dismissed with prejudice and without costs to either party and the case is closed.

s/Peter G. Sheridan
PETER G. SHERIDAN, U.S.D.J.

June 29, 2012

EXHIBIT B

US007320969B2

(12) **United States Patent**
Bell et al.

(10) **Patent No.: US 7,320,969 B2**
(45) **Date of Patent: Jan. 22, 2008**

(54) **ORAL CONTRACEPTIVES TO PREVENT PREGNANCY AND DIMINISH PREMENSTRUAL SYMPTOMATOLOGY**

(75) Inventors: **Robert G. Bell**, Palm Harbor, FL (US); **Carole Ben-Maimon**, Merion, PA (US); **Beata Iskold**, Livingston, NJ (US)

(73) Assignee: **Duramed Pharmaceuticals, Inc.**, Cincinnati, OH (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 422 days.

(21) Appl. No.: **10/309,313**

(22) Filed: **Dec. 4, 2002**

(65) **Prior Publication Data**

US 2003/0139381 A1 Jul. 24, 2003

Related U.S. Application Data

(60) Provisional application No. 60/335,807, filed on Dec. 5, 2001.

(51) **Int. Cl.**
A61K 31/56 (2006.01)

(52) **U.S. Cl.** **514/170**; 514/171; 514/182

(58) **Field of Classification Search** 514/171, 514/649, 170, 182
See application file for complete search history.

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(57) **ABSTRACT**

This invention relates to a method of preventing pregnancy and treating PMS including PMDD. More particularly, the invention relates to a method, which involves administering one of several combination oral contraceptive regimens in combination with an antidepressant and a kit containing the same.

19 Claims, No Drawings

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ORAL CONTRACEPTIVES TO PREVENT PREGNANCY AND DIMINISH PREMENSTRUAL SYMPTOMATOLOGY

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 60/335,807, filed Dec. 5, 2001, the disclosure of which is hereby incorporated herein by reference.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to oral contraceptives that prevent pregnancy and diminish or eliminate premenstrual symptomatology, including PMS and PMDD, and to a method of preventing pregnancy and diminishing or eliminating premenstrual symptomatology, including PMS and PMDD.

2. Background Art

The human menstrual cycle involves a repetitive sequence of hormonal changes that result in episodic uterine bleeding. Normally, each menstrual cycle has a mean interval of 21 to 35 days, conventionally beginning with the first day of menstrual flow and ending on the day before the next onset of bleeding. Duration of the menstrual flow is usually 2 to 6 days with loss of 20 to 60 ml of blood.

The menstrual cycle is divided into follicular and luteal phases, each corresponding to changes occurring in the ovary. These phases may also be described as proliferative or secretory, corresponding to changes observed in the uterine endometrium. Variations in the length of the cycle are usually due to alterations in the follicular phase, because the luteal phase length remains relatively constant at 12 to 16 days.

During the follicular phase, several primary follicles are recruited for further growth and development. Granulosa cells in primary follicles posses follicle stimulating hormone (FSH) and estradiol receptors. Upon FSH stimulation, granulosa cells produce aromatase. This enzyme converts the androgens androstenedione and testosterone, made in response to luteinizing hormone (LH) by thecal cells, to estrone and estradiol, respectively. Granulosa cells respond to estradiol by undergoing mitosis to increase the number of granulosa cells and estradiol production. By day 7 of the cycle, one enlarging primary follicle is selected by unknown processes to be the follicle that will release the oocyte at ovulation.

The midcycle rise in plasma estradiol stimulates the large midcycle LH surge. This midcycle LH surge triggers resumption of meiosis within the oocyte and luteinization of the granulosa cells within the preovulatory follicle. Immediately before ovulation, the outer follicular wall begins to dissolve and an oocyte is released approximately 24 to 36 hours from the onset of the LH surge.

After ovulation, granulosa cells and the surrounding theca cells enlarge, accumulate lipid, and become transformed into lutein cells. This begins the luteal phase of the menstrual cycle. These cells form a new vascularized structure called the corpus luteum, which secretes estradiol and progesterone. LH maintains the corpus luteum during the luteal phase and, acting via the adenyl cyclase system, stimulates progesterone production. If pregnancy does not occur, lutein cells degenerate, and diminished hormone secretion precedes menstruation. Menstruation is immediately followed by the onset of another menstrual cycle.

Because endometrial proliferation serves to prepare the uterus for an impending pregnancy, manipulation of hormones and of the uterine environment can provide contraception. For example, estrogens are known to decrease FSH secretion by feedback inhibition. Under certain circumstances, estrogens can also inhibit LH secretion, once again by negative feedback. Under normal circumstances, the spike of circulating estrogen found just prior to ovulation induces the surge of gonadotropic hormones that occurs just prior to and results in ovulation. High doses of estrogen immediately post-coitally also can prevent conception probably due to interference with implantation.

Progestins can also provide contraception. Endogenous progesterone after estrogen is responsible for the progestational changes of the endometrium and the cyclic changes of cells and tissue in the cervix and the vagina. Administration of progestin makes the cervical mucus thick, tenacious and cellular which is believed to impede spermatozoal transport. Administration of progestin also inhibits LH secretion and blocks ovulation in humans.

The most prevalent form of oral contraception is a pill that combines both an estrogen and a progestin, a so-called combined oral contraceptive preparation. Alternatively, there are contraceptive preparations that comprise progestin only. However, the progestin-only preparations have a more varied spectrum of side effects than do the combined preparations, especially more breakthrough bleeding. As a result, the combined preparations are the preferred oral contraceptives in use today (Sheth et al., *Contraception* 25:243 (1982)).

In establishing an estrogen-progestin regimen for oral contraceptives, two principal issues must be confronted. First, efficacy must be maintained and second, there must be avoidance of further erosion in the control of endometrial bleeding. In general, even the lowest dose oral contraceptive products commercially available have demonstrated efficacy but the overall instances of bleeding control problems have increased as the doses were reduced, as manifested both in breakthrough bleeding (untimely flow or spotting) or withdrawal amenorrhea during the "pill free" week (expected menses).

During the luteal phase of the menstrual cycle, as many as 75% of women with regular menstrual cycles experience some symptoms of premenstrual syndrome (PMS), a recurring, cyclical disorder involving behavioral, emotional, social and physical symptoms (Steiner et al., *Annu. Rev. Med.* 48:447-455 (1997)). Behavioral, emotional and social symptoms include, but are not limited to, irritability, mood swings, depression, hostility and social withdrawal. Physical symptoms include, but are not limited to, bloating, breast tenderness, myalgia, migraines or headaches and fatigue. True PMS only occurs during the luteal phase of the menstrual cycle, with a symptom-free period during the follicular phase. The etiology of PMS is still unknown.

A subgroup of women with PMS, about 2-9%, exhibit symptoms that are primarily related to a severe mood disorder. In these women, the diagnosis of Premenstrual Dysphoric Disorder (PMDD), which is defined in the Fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) can be applied. According to the DSM-W, a woman with PMDD must have at least five premenstrual symptoms during the luteal phase, with at least one of the symptoms being an emotional or "core" symptom. The core symptoms must be irritability, anger, mood swings, tension or depression (and interfere with daily activities),

and must be confirmed by a prospective daily rating for at least two cycles. Three to five percent of women with PMS report to have PMDD.

There is also a subgroup of women who experience severe PMS, which accounts for about 20% of the PMS population. These women experience severe emotional symptoms that do not fall under the strict criteria of PMDD as defined in DSM-IV but require medical attention.

Symptoms of PMDD may begin at any age after menarche, but the average age at onset appears to be around 26 years and several researchers found that symptoms, such as estrogen withdrawal symptoms, associated with the premenstrual phase gradually become worse, and perhaps more protracted, over time. It has been suggested that worsening could occur because of the recurring increases and decreases in ovarian hormones. This is supported by data from other cultures: when menstruation is infrequent, premenstrual symptoms are rare. It is also supported by data associating low parity with the risk of PMDD. Low parity yields a greater number of hormonal cycles, and, thus, a woman has more exposure to and withdrawal from massive amounts of progesterone. Further, several studies find lower rates of premenstrual symptoms among users of oral contraceptives, again suggesting that briefer exposure to peaks and troughs of endogenous progesterone is protective against PMDD (Yonkers, K., *J. Clin. Psychiatry* 58(Suppl. 14):4-13 (1997)).

Suppression of ovulation has been an important rationale for the use of hormonal treatments for PMS. One method of inhibiting ovulation is by using oral contraceptives (OCs). Combination oral contraceptives inhibit ovulation by suppressing gonadotropins, follicle stimulating hormone (FSH) and luteinizing hormone (LH). To date, only two controlled studies of the oral contraceptive treatment of PMS have been published. The results indicate that combination oral contraceptives effectively reduce physical symptoms (especially breast pain and bloating), but the response on the relief of psychological symptoms has been less clear.

Therapeutic interventions for women who meet the criteria for PMDD include selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants and anxiolytics, as well as the antidepressant alprazolam (XANAX®). These interventions have demonstrated efficacy with minimal side effects. Recent investigations of SSRI have also demonstrated success at low doses.

Antidepressants that are active at serotonin receptors include clomipramine (ANAFRANIL®), fluoxetine (PROZAC®), paroxetine (PAXIL®), sertraline (ZOLOFT®), nefazodone (SERZONE®), fenfluramine (PONDIMIN®) and venlafaxine (EFFEXOR®).

The only approved product today for the treatment of PMDD is the SSRI fluoxetine hydrochloride (SARAFEM®). The effectiveness of fluoxetine for the treatment of PMDD was established in four randomized, placebo-controlled trials. Fluoxetine at a daily dose of either 20 mg or 60 mg proved to be superior to placebo in reducing symptoms (Steiner et al., *New Engl. J Med.* 332:1529-34 (1995)). However, the combination of oral contraceptive and fluoxetine was not examined, as women who were taking oral contraceptives were excluded from the trial.

It is the object of the present invention to provide estrogen-progestin combinations and/or regimens for oral contraceptive use, including estrogen-progestin combinations and/or regimens that contain an antidepressant, to concurrently diminish or eliminate premenstrual symptoms (PMS) including PMDD. Two regimens are proposed, the so-called 28-day regimen and the 91-day regimen. The 28-day regimen will allow women the option of maintaining the customary 13 menstrual cycles per year while diminishing or alleviating premenstrual symptoms (PMS) including PMDD. The 91-day regimen will allow women the option of maintaining only 4 menstrual cycles per year while diminishing or alleviating premenstrual symptoms (PMS) including PMDD. Thus, the 91-day regimen enhances compliance by involving fewer stop/start transitions per year and also results in less blood loss, and hypothetically, will diminish premenstrual symptoms, including PMDD. Having fewer menstrual intervals can also enhance lifestyles and convenience. This and other objects of the invention will become apparent to those skilled in the art from the following detailed description.

BRIEF SUMMARY OF THE INVENTION

This invention relates to female oral contraceptives that will prevent pregnancy and treat PMS including PMDD. This invention further relates to a method of preventing pregnancy and treating PMS including PMDD, by avoiding complete withdrawal of estrogen at the end of the treatment period, or between treatment periods, by administering oral contraceptives. Premenstrual symptoms are rare when menstruation is infrequent. Further, users of oral contraceptives have lower rates of premenstrual symptoms, again suggesting that briefer exposure to peaks and troughs of endogenous progesterone is protective against PMDD. More particularly, the invention relates to a method of preventing pregnancy, which involves administering one of two combination oral contraceptive regimens. Additionally, the invention relates to a method of preventing pregnancy, which involves administering one of two combination oral contraceptive regimens that contain an antidepressant.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to oral contraceptives that will prevent pregnancy and diminish or eliminate PMS including PMDD. Methods of using these oral contraceptives to prevent pregnancy and diminish or eliminate PMS including PMDD are also provided. More particularly, the methods involve administering one of several combination oral contraceptive regimens. Importantly, these regimens do not contain pill-free or placebo intervals.

One embodiment of the invention is the so-called twenty-eight day regimen that allows women the option of maintaining 13 menstrual cycles per year. In accordance with the present invention, a women in need of contraception and treatment of PMS including PMDD, is administered a combined dosage form of estrogen and progestin, preferably monophasicly, for 21 to 26 consecutive days, preferably about 22-25 days, followed by administration of low-dose estrogen for 2 to 10 days, preferably about 3-7 days, more preferably about 2-7 days, in which the daily amounts of estrogen and progestin are equivalent to about 5-50 μg of ethinyl estradiol and about 0.025 to 10 mg, preferably about 0.05 to 1.5 mg, of levonorgestrel, respectively.

In a preferred embodiment, women will be administered an oral contraceptive on days 1 through 21 of the menstrual cycle containing 150 μg levonorgestrel and 30 μg ethinyl estradiol, followed by a dosage form on days 22-28 of the cycle, which contains 30 μg ethinyl estradiol. A typical administration schedule is illustrated in Table 1. Thus, in a 28-day regimen schedule, there are about 13 treatment and menstrual cycles per year.

TABLE 1

Administration schedule for a 28-day regimen

Days	Hormone	Antidepressant
1-21	150 μg levonorgestrel and 30 μg ethinyl estradiol	none
22-28	30 μg ethinyl estradiol	none

In another embodiment of the invention, a women in need of contraception and treatment of PMS including PMDD, is administered a combined dosage form of estrogen and progestin, preferably monophasicly, for 21 to 26 consecutive days, preferably about 22-25 days, followed by administration of low-dose estrogen for 2 to 10 days, preferably about 3-7 days, more preferably about 2-7 days, in combination with the antidepressant fluoxetine hydrochloride, in which the daily amounts of estrogen and progestin are equivalent to about 5-50 μg of ethinyl estradiol and about 0.025 to 10 mg, preferably about 0.05 to 1.5 mg, of levonorgestrel, respectively, and the fluoxetine hydrochloride is in an amount of about 5-120 mg. Oral contraceptives with initial doses of fluoxetine at either 5 mg or 10 mg/day can be started to avoid any activating side effects that may lead to noncompliance. The dose can then be increased as needed. Fluoxetine can also be given intermittently during the late luteal phase, which is typically 1-2 weeks before menses. In addition, a one-time or once-weekly dose of about 90 mg of fluoxetine can be administered.

In a preferred embodiment, women will be administered an oral contraceptive on days 1 through 21 of the menstrual cycle containing 150 μg levonorgestrel and 30 μg ethinyl estradiol, followed by a dosage form on days 22-28 of the cycle, which contains 20 mg fluoxetine hydrochloride and 30 μg ethinyl estradiol. A typical administration schedule is illustrated in Table 2. Thus, in a 28-day regimen schedule, there are about 13 treatment and menstrual cycles per year.

TABLE 2

Administration schedule for a 28-day regimen with an antidepressant

Days	Hormone	Antidepressant
1-21	150 μg levonorgestrel and 30 μg ethinyl estradiol	none
22-28	30 μg ethinyl estradiol	20 mg fluoxetine hydrochloride daily OR a one-time dose of 90 mg fluoxetine hydrochloride OR a once-weekly dose of 90 mg fluoxetine hydrochloride

An additional embodiment of the invention is a long-term regimen that allows women the option of limiting their menstrual periods to about four times per year. In accordance with the present invention, a women in need of contraception and treatment of PMS including PMDD, is administered a combined dosage form of estrogen and progestin, preferably monophasicly, for 60 to 110 consecutive days, preferably about 81 to 89 days, followed by administration of estrogen for 2 to 10 days, preferably about 5 to 8 days, in which the daily amounts of estrogen and progestin are equivalent to about 5-50 μg of ethinyl estradiol and about 0.025 to 10 mg, preferably about 0.05 to 1.5 mg, of levonorgestrel, respectively.

In a preferred embodiment, the 91-day regimen, women will be administered an oral contraceptive on days 1 through 84 of the menstrual cycle containing 150 μg levonorgestrel and 30 μg ethinyl estradiol, followed by a dosage form on days 85-91 of the cycle, which contains 30 μg ethinyl estradiol. A typical administration schedule is illustrated in Table 3. Thus, in a 91-day regimen, there are only four treatment and menstrual cycles per year.

TABLE 3

Administration schedule for a 91-day regimen

Days	Hormone	Antidepressant
1-84	150 μg levonorgestrel and 30 μg ethinyl estradiol	none
85-91	30 μg ethinyl estradiol	none

In an additional embodiment of the invention, a women in need of contraception and treatment of PMS including PMDD, is administered a combined dosage form of estrogen and progestin, preferably monophasicly, for 60 to 110 consecutive days, preferably about 81 to 89 days, followed by administration of low-dose estrogen and fluoxetine hydrochloride for 2 to 10 days, preferably about 5 to 8 days, in which the daily amounts of estrogen and progestin are equivalent to about 5-50 μg of ethinyl estradiol and about 0.025 to 10 mg, preferably about 0.05 to 1.5 mg, of levonorgestrel, respectively, and the fluoxetine hydrochloride is in an amount of about 5-120 mg. Oral contraceptives with initial doses of fluoxetine at either 5 mg or 10 mg/day can be started to avoid any activating side effects that may lead to noncompliance. The dose can then be increased as needed. Fluoxetine can also be given intermittently during the late luteal phase, which is typically 1-2 weeks before menses. In addition, a one-time or once-weekly dose of about 90 mg of fluoxetine can be administered.

In a preferred embodiment, women will be administered an oral contraceptive on days 1 through 84 of the menstrual cycle containing 150 μg levonorgestrel and 30 μg ethinyl estradiol, followed by a dosage form on days 85-91 of the cycle, which contains 30 μg ethinyl estradiol and 20 mg fluoxetine hydrochloride. A typical administration schedule is illustrated in Table 4. Thus, in a 91-day regimen, there are only four treatment and menstrual cycles per year.

TABLE 4

Administration schedule for a 91-day regimen with an antidepressant

Days	Hormone	Antidepressant
1-84	150 μg levonorgestrel and 30 μg ethinyl estradiol	none
85-91	30 μg ethinyl estradiol	20 mg fluoxetine hydrochloride daily OR a one-time dose of 90 mg fluoxetine hydrochloride OR a once-weekly dose of 90 mg fluoxetine hydrochloride

The estrogens which may be employed as a component in the regimens of this invention may be any of those conventionally available. Typically, the estrogen may be selected from the group comprising synthetic and natural estrogens, including steroidal and nonsteroidal estrogens. The synthetic estrogens may be selected from, for example, ethinyl estradiol, ethynodiol diacetate, mestranol and quinestranol. Particularly of interest are 17α-ethinyl estradiol and esters and ethers thereof. The preferred estrogen is 17α-ethinyl estradiol. The natural estrogens may include, for example, con-

jugated equine estrogens, esterified estrogens, 17β-estradiol, estradiol valerate, estrone, piperazine estrone sulphate, estriol, estriol succinate and polyestrol phosphate.

The progestin component may be any progestationally active compound. Thus, the progestin may be selected from progesterone and its derivatives such as, for example, 17-hydroxy progesterone esters, 19-nor-17-hydroxy progesterone esters, 17α-ethinyltestosterone and derivatives thereof, 17α-ethinyl-19-nor-testosterone and derivatives thereof, norethindrone, norethindrone acetate, ethynodiol diacetate, dydrogesterone, medroxy-progesterone acetate, norethynodrel, allylestrenol, lynoestrenol, fuingestanol acetate, medrogestone, norgestrienone, dimethiderome, ethisterone, cyproterone acetate, levonorgestrel, dl-norgestrel, d-17α-acetoxy-13β-ethyl-17α-ethinyl-gon-4-en-3-one oxime, cyproterone acetate, gestodene, desogestrel and norgestimate. The preferred progestin is levonorgestrel.

The weight ratio of the active ingredients, e.g., ethinyl estradiol and levonorgestrel, is at least 1:45 and preferably at least 1:50. The preferable amount of ethinyl estradiol is about 10-50 μg and the preferable amount of levonorgestrel is about 0.15-1.5 mg. Other estrogens vary in potency from ethinyl estradiol. For example, 30 μg of ethinyl estradiol is roughly equivalent to 60 μg of mestranol or 2 g of 17β-estradiol. Likewise, other progestins vary in potency from levonorgestrel. Thus, 1 mg of levonorgestrel is roughly equivalent to about 3.5 mg of norethindrone acetate, or 1 mg of desogestrel and 3-ketodesogestrel or about 0.7 mg of gestodene. The values given above are for ethinyl estradiol and levonorgestrel and if a different estrogen or progestin is employed, an adjustment in the amount based on the relative potency should be made. The correlations in potency between the various estrogens and progestins are known. See for example European Patent Application No.0 253 607, which is hereby incorporated in its entirety by reference hereto.

The preferred antidepressant is fluoxetine hydrochloride although other antidepressants can be employed. For example, the antidepressants alprazolam (XANAX®), clomipramine (ANAFRANIL®), paroxetine (PAXIL®), sertraline (ZOLOFT®), nefazodone (SERZONE®), fenfluramine (PONDIMIN®) and venlafaxine (EFFEXOR®) can also be used. The daily amounts of these antidepressants can vary, depending on the antidepressant used, from 0.75 to 2 mg, 10 to 20 mg or 50 to 100 mg.

Each of the described regimens will prevent pregnancy and additionally diminish or eliminate debilitating premenstrual symptomatology.

Other useable estrogens include the esters of estradiol, estrone and ethinyl estradiol such as the acetate, sulfate, valerate or benzoate, conjugated equine estrogens, agnostic anti-estrogens, and selective estrogen receptor modulators. The formulations of the invention may be administered orally, preferably in tablet form, parenterally, sublingually, transdermally, intravaginally, intranasally or buccally. The method of administration depends on the types of estrogens and progestins used in the formulation, as well as the amounts per unit dosage. Most estrogens are orally active and that route of administration is therefore preferred. Methods for transdermal administration including the associated methods for manufacturing such systems are well known in the art. In this connection, reference may be had to U.S. Pat. Nos. 4,752,478, 4,685,911, 4,438,139 and 4,291,014, which are hereby incorporated in their entirety by reference hereto.

Pharmaceutical formulations or preparations containing the formulations of the invention and a suitable carrier can be solid dosage forms which includes tablets, dragees, capsules, cachets, pellets, pills, powders or granules; topical dosage forms which include solutions, powders, fluid emulsions, fluid suspensions, semi-solids, ointments, pastes, creams, gels or jellies, foams and controlled release depot entities; transdermals, vaginal rings, buccal formulations; and parenteral dosage forms which includes solutions, suspensions, emulsions or dry powder comprising an effective amount of estrogen, progestin and antidepressant as taught in this invention.

It is known in the art that active ingredients can be contained in such formulations in addition to pharmaceutically acceptable diluents, fillers, disintegrants, binders, lubricants, surfactants, hydrophobic vehicles, water soluble vehicles, emulsifiers, buffers, humectants, moisturizers, solubilizers, preservatives and the like. The means and methods for administration are known in the art and an artisan can refer to various pharmacologic references for guidance. For example, "Modem Pharmaceutics", Banker & Rhodes, Marcel Dekker, Inc. (1979); "Goodman & Gilman's The Pharmaceutical Basis of Therapeutics", 6th Edition, MacMillan Publishing Co., New York (1980), or Remington's Pharmaceutical Sciences, Osol, A., ed., Mack Publishing Company, Easton, Pa. (1980) can be consulted.

Generally speaking, the formulations are prepared according to conventionally known procedures in accordance with the method of administration. Thus, the active ingredients are prepared according to known methods in a pharmaceutically acceptable form for administration. These ingredients, in their required quantities are combined with the appropriate pharmaceutical carriers such as additives, vehicles and/or flavor ameliorating substances. These substances may be referred to as diluents, binders and lubricants. Gums, starches and sugars are also common terms. Typical of these types of substances or excipients are pharmaceutical grades of mannitol, lactose starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate and the like. The active ingredient(s) may comprise from about 0.01% by weight to about 99.99% by weight of the total formulation and the remainder comprises the pharmaceutically acceptable carrier. The percentage of active ingredient(s) may vary according to the delivery system or method of administration and is chosen in accordance with conventional methods known in the art.

In the oral form of the formulation, the contraceptive preparations are preferably produced in the form of a kit or package, with the daily dosages arranged for proper sequential administration. Thus, in another aspect, the present invention also provides a pharmaceutical package which contains combination-type contraceptives in multiple dosage units in a synchronized, fixed sequence, wherein the sequence or arrangement of the dosage units corresponds to the stages of daily administration.

For example, the pharmaceutical formulations may be provided in kit form containing for the 28-day regimen at least about 18, and preferably at least about 21 tablets, and up to 26 tablets, intended for ingestion on successive days. Preferably administration is daily for at least 21 days using tablets containing both the estrogen and the progestin and then for at least 7 days using tablets containing only estrogen. In another preferred embodiment, administration is daily for at least 21 days using tablets containing both the estrogen and the progestin and then for at least 7 days using tablets containing both estrogen and an antidepressant, e.g., fluoxetine hydrochloride. For the long-term regimen, the pharmaceutical formulation may be provided in kit form containing at least about 60, and preferably at least about 81

to 89 tablets, and up to 110 tablets, intended for ingestion on successive days. Preferably administration is daily for at least 84 days using tablets containing both the estrogen and the progestin and then for at least 7 days using tablets with only estrogen. In another preferred embodiment, administration is daily for at least 84 days using tablets containing both the estrogen and the progestin and then for at least 7 days using tablets with both estrogen and an antidepressant, e.g., fluoxetine hydrochloride.

Efficacy of the 28-day and 91-day regimens on premenstrual symptomatology are measured by psychometric scales that include self-administered Visual Analogue Scales (VAS) and a prospective daily symptoms chart or diary to evaluate psychological and somatic symptoms. Total score of the psychological and somatic symptoms is computed. The VAS measures tension, irritability, dysphoria, sleeping and eating patterns, headache, bloating, pain and breast tenderness and weight gain symptoms.

In order to further illustrate the present invention, specific examples are set forth below. It will be appreciated, however, that these examples are illustrative only and are not intended to limit the scope of the invention.

EXAMPLES

Example 1

Multicenter Randomized Phase III Clinical Trial to Evaluate Two Continuous Oral Contraceptive Regimens in Women Diagnosed with Premenstrual Syndrome (PMS) and Premenstrual Dysphoric Disorder (PMDD)

Clinical Design and Summary

In a multicenter, randomized, clinical trial the efficacy and safety of three combination oral contraceptives regimens in the prevention of pregnancy in sexually active women, ages 18 through 40 years, will be evaluated. Patients will be randomized in a 1:1:1 fashion to one of the following regimens:

- Levonorgestrel 150 μg/ethinyl estradiol (EE) 30 μg administered once daily for 84 days as a combination oral tablet followed by ethinyl estradiol 30 μg administered once daily for 7 days (DP3-84/30);
- Levonorgestrel 150 μg/ethinyl estradiol 30 μg administered once daily for 84 days as a combination oral tablet followed by ethinyl estradiol 10 μg administered once daily for 7 days (DP3-84/10); or
- Levonorgestrel 150 μg/ethinyl estradiol 30 μg administered once daily for 25 days as a combination oral tablet followed by ethinyl estradiol 30 μg administered once daily for 3 days (DP3-25/30).

Patients randomized to either DP3-84/30 or DP3-84/10 will receive 4 cycles of study drug. Patients randomized to DP3-25/30 will receive 13 cycles of study drug. All patients will receive approximately 1 year of therapy.

The study coordinator or designated personnel will register the patient. Patients will be randomly assigned to one of the treatment regimens. The treatment group assignment will not be revealed to the patient prior to signing of the informed consent.

All patients, regardless of randomization, will initiate study OC therapy on the first Sunday following the beginning of their menstrual period ("Sunday starters") and will remain as Sunday starters throughout the study. Each of the dose packs will be dispensed with an abbreviated patient information sheet and a more detailed patient package insert (PPI).

All patients will complete and download information entered into an electronic diary. Assessments will include study drug compliance, use of additional forms of contraception, bleeding patterns, weight, assessment of the incidence and severity of menstrual related symptoms and medication taken to relieve these symptoms. Information will be self-recorded on the electronic diary via a series of pre-programmed questions.

Two hundred (200) patients in each treatment arm are targeted to complete the study. Pregnancy rate will be calculated using data from those patients age 18 to 35. Patients age 36 through 40 will also be enrolled.

Patient Eligibility

Inclusion Criteria

Patients must meet the following criteria to be included in the study:

1. Sexually active adult females (age 18 through 40), of child bearing potential, in a heterosexual relationship, at risk for pregnancy, who are in good health and who
   have a history of OC use for an interval of at least three successive cycles with regular withdrawal bleeding (bleeding during the pill-free interval or during the first three days of the subsequent cycle) prior to enrollment (Continuous Users)
   OR
   have no prior history OC use (Fresh-Starts)
   OR
   have no history of OC use in the 6 months prior to enrollment (Prior Users)
2. Negative urine pregnancy test.
3. Signed informed consent.
4. Agree to use study oral contraceptive therapy as their primary birth control method (BCM).

Exclusion Criteria:

Patients will be excluded from the study if any of the following criteria are met:

1. History of hypersensitivity to estrogen or progestin components of OCs.
2. History of alcohol or drug abuse which, in the opinion of the investigator, makes the patient unfit for participation in the study.
3. Active smoker age >34 years.
4. Chronic use of any medication that may interfere with the efficacy of oral contraceptives.
5. History of being HIV or Hepatitis C positive.
6. History of persistent noncompliance with any chronic medication.
7. History of having received injectable hormone therapy (e.g., Depo-Provera® (Pharmacia and Upjohn)) within the 10 months prior to enrollment or having a progestin-releasing intrauterine device (IUD) in place within 3 months prior to enrollment or has had a contraceptive implant removed within one month prior to enrollment or has received any other form of hormonal contraception within 3 months prior to enrollment.
8. Routine concomitant use of additional forms of contraception (IUD, diaphragm, contraceptive sponge) with the exception of condoms.
9. Patients who have had recent surgical or medical abortion, miscarriage, or vaginal or cesarean delivery must have had at least two normal menstrual cycles prior to enrollment.
10. History of abnormal bleeding (breakthrough or withdrawal bleeding that lasts ≧10 consecutive days or exces-

sive spotting that lasts ≧10 consecutive days) while on conventional oral contraceptives.

11. History of thromboembolic disorder, vascular disease, cerebral vascular or coronary artery disease.
12. Uncontrolled or untreated hypertension (systolic BP ≧140 mmHg and diastolic BP ≧90 mmHg on more than two occasions).
13. Known or suspected carcinoma of the breast, endometrial carcinoma or known or suspected estrogen dependent neoplasia.
14. Undiagnosed abnormal genital bleeding.
15. History of hepatic adenomas or carcinomas.
16. History of cholestatic jaundice of pregnancy or jaundice with prior OC use.
17. Known or suspected pregnancy or currently breastfeeding.
18. Hyperlipidemia requiring active treatment with antihyperlipidemic agents.
19. History of diabetes mellitus, glucose intolerance or gestational diabetes.
20. History of abnormal laboratory value at screening
21. Any clinically significant abnormal finding or condition on history, screening, physical exam, pelvic exam or any laboratory finding which contraindicates the use of oral contraceptives.
22. Has participated in any clinical investigation within the 30 days prior to enrollment.
23. Has donated or had a loss of more than 500 cc of blood within the 30 days prior to enrollment.

Treatment Regimen

Description of Study Medication

DP3-84/30

All tablets in the DP3-84/30 regimen; 84 tablets each containing 150 μg levonorgestrel/30 μg EE and 7 tablets each containing 30 μg of EE will be white unembossed tablets. One combination tablet will be taken each day for 84 days followed by 7 days of EE tablets in 91-day cycles repeated consecutively for approximately one year (4 cycles). Each DP3-84/30 dose kit will be packaged in a 3-part fold-out white blister card pack where each of the first two blister packs has 28 active tablets each and the third blister pack has 28 active tablets and 7 ethinyl estradiol tablets (35 tablets total) for each 91-day cycle.

Each blister card pack will be sealed into a foil pouch, which will be labeled with a patient-specific label. Each foil pouch will contain an oxygen absorber. At each clinic visit one foil pouch, a patient information sheet, a PPI and a child resistant pouch will be dispensed.

DP3-84/10

All tablets in the DP3-84/10 regimen; 84 tablets each containing 150-μg levonorgestrel/30-μg EE and 7 tablets each containing 10 μg of EE will be white unembossed tablets. One combination tablet will be taken each day for 84 days followed by 7 days of EE tablets in 91-day cycles repeated consecutively for approximately one year (4 cycles). Each DP3-84/10 dose kit will be packaged in a 3-part fold-out white blister card pack where each of the first two blister packs has 28 active tablets each and the third blister pack has 28 active tablets and 7 ethinyl estradiol tablets (35 tablets total) for each 91-day cycle.

Each blister card pack will be sealed into a foil pouch, which will be labeled with a patient-specific label. Each foil pouch will contain an oxygen absorber. At each clinic visit one foil pouch, a patient information sheet, a PPI and a child resistant pouch will be dispensed.

DP3-25/30

All tablets in the DP3-25/30 regimen; 25 tablets each containing 150-μg levonorgestrel/30-μg EE and 3 tablets each containing 30 μg of EE will be white unembossed tablets. One combination tablet will be taken each day for 25 days followed by 3 days of EE tablets in 28-day cycles repeated consecutively for approximately one year (13 cycles). Each DP3-25/30 blister card will have 25 active tablets followed by 3 ethinyl estradiol tablets (28 tablets total) for each 28-day cycle.

Each blister card will be sealed into a foil pouch, which will be labeled with a patient-specific label. Each foil pouch will contain an oxygen absorber. At clinic visits one through three, 3 foil pouches, a patient information sheet, a PPI and a child resistant pouch will be dispensed. At clinic visit four, 4 foil pouches, a patient information sheet, a PPI and a child resistant pouch will be dispensed.

All patients, regardless of randomization, will be instructed to initiate OC therapy on the first Sunday following the beginning of their menstrual period ("Sunday starters"). Patients will be instructed to take their study medication at the same time each day. Day 1 of the study will be defined as the first day of study medication.

Administration

Designated personnel will dispense all study drugs. All study medications must be kept in a secured area at temperature ranging from approximately 15-25° C. (59-77° F.). All patients will be instructed to take one tablet per day at approximately the same time each day. All patients will be "Sunday starters"; that is all patients will begin study drug therapy on the first Sunday following the start of their previous menstrual cycle or completion of prior oral contraceptive regimens. All patients enrolled in the study will maintain Sunday starts for each successive cycle.

The end-of-study evaluation will take place 1 week following completion of withdrawal menses following the last cycle of study OC therapy. At the clinic visit during which patients receive the final supply of study medication, they will be counseled to use an alternative method of birth control during the interval between when they have finished study medication until they have completed the final study visit.

Patients randomized to DP3-84/30 or DP3-84/10 will receive a 13-week supply (single cycle) of study drug at each clinic visit during Weeks 13, 26 and 39. Patients randomized to DP3-25/30 will receive a 12-week supply (three-cycles) of study drug at the initiation of the study and at clinic visits during Weeks 12 and 24. During the clinic visit at Week 36 patients randomized to DP3-25/30 will receive 16-week supply (four cycles) of study medication.

Examinations/Tests

TABLE 5

	Study Schedule			
Parameter	Screening	Visit 1	Visits 2-4[a]	Completion of Therapy
Informed consent	X			
Medical and contraceptive history	X			
Physical exam including pelvic exam	X			X
Weight, vital signs	X	X	X	X
Pap smear	X			X
Randomization		X		

TABLE 5-continued

Parameter	Study Schedule: Screening	Visit 1	Visits 2-4[a]	Completion of Therapy
Clinical laboratory tests[b]	X			X
Urine pregnancy test[c]	X	X	X	X
Study drug distribution[d]		X	X	
Electronic diary distribution		X		
Study drug compliance measurement			X	X
Adverse event recording			X	X

[a]Patients randomized to DP3-84/30 or DP3-84/10 will be seen at Weeks 13, 26 and 39. Patients randomized to DP3-25/30 will be seen at Weeks 12, 24, and 40.
[b]Clinical laboratory tests include CBC, serum chemistry, lipid profile, urinalysis
[c]Repeated on Visit 1 if the screening was completed more than 2 weeks prior to enrollment
[d]For patients randomized to DP3 25/30, three (3) cycle supply will be dispensed at Weeks 12 and 24; a four (4) cycle supply will be dispensed at Week 40.

Study Procedures by Visit

Screening and Enrollment

Patients will sign informed consent. Prior to enrollment, within four weeks prior to initiation of study therapy, all patients will undergo a screening evaluation that will include prior medical and contraceptive history, smoking history, physical examination including pelvic exam and Pap smear, vital signs and weight, and clinical laboratory tests including complete blood count (CBC), serum chemistry, lipid profile, urinalysis, and urine pregnancy test.

All clinical laboratory evaluations (blood and urine) will be tested by a central laboratory. All investigators will be provided with a laboratory manual that outlines sampling and shipping procedures.

If the screening evaluation is completed more than two weeks prior to the initiation of study therapy, the urine pregnancy test must be repeated at Visit 1. Patients with a report of an abnormality on Pap smear will be disqualified for enrollment unless investigator decides the results are not clinically significant and will not interfere with conduct of the study. Investigator's decision must be documented. Patients who have had a normal Pap smear within the three months prior to enrollment in the study will not be required to have the test repeated. A copy of the results must be available in the patient's medical record. Any patient with a report of insufficient cells must have the test repeated and documented as normal prior to enrollment. Patients will then be enrolled in the study.

Visit 1

Visit 1 will take place during the final week of the menstrual cycle prior to beginning study therapy (i.e., during menses for those patients not taking oral contraceptives or during Week 4 for those patients taking oral contraceptives). During Visit 1 patients will be randomized to one of the following treatment groups:

DP3-84/30; levonorgestrel 150 μg/EE 30 μg for 84 days+ EE 30 μg for 7 days

OR

DP3-84/10; levonorgestrel 150 μg/EE 30 μg for 84 days+ EE 10 μg for 7 days

OR

DP3-25/3; levonorgestrel 150 μg/EE 30 μg for 25 days+ EE 30 μg for 3 days

The treatment regimen assignment will be ascertained by randomization via Interactive Voice Response System (IVRS). The treatment group assignment will not be revealed to the patient prior to signing of the informed consent.

A urine pregnancy test will be re-administered to those women who were screened more than two weeks prior to Visit 1. Study medication will be dispensed with patient instructions. An electronic diary will be given to each patient. Each patient will be trained regarding the use and care of the electronic diary. Patients will be instructed to take each dose of study medication and to complete all diary entries at approximately the same time each day.

Visits 2-4

All visits should take place within seven days prior to completion of study medication for that cycle. Any visit that takes place prior to the final week of the cycle will be recorded as a protocol deviation. Any visit that takes place following the final week of the cycle resulting in a lapse in study medication intake will be recorded as a protocol violation and will result in the patient being withdrawn from the study. Any visit that takes place following the final week of the cycle but does not result in a lapse in study medication (e.g., the patient received an emergency supply of study medication) will be recorded as a protocol deviation.

Patients randomized to either DP3-84/30 or DP3-84/10 will be seen at Weeks 13, 26 and 39. Patients randomized to DP3-25/30 will be seen at Weeks 12, 24 and 36. During these visits, patients will be queried regarding adverse events, concomitant medications, change in smoking history, and compliance. Vital signs and weight will be recorded. A urine pregnancy test will be conducted. Used study medication will be returned and counted by the study pharmacist or designated personnel.

Completion of Therapy

The end-of-study evaluation will take place 1 week following completion of last cycle of the study drug. Patients will be counseled to use birth control during the interval between when they have finished study medication until they have completed the final study visit. Patients will undergo physical exam, including pelvic exam and pap smear. Vital signs and weight will be recorded. Blood and urine samples for clinical laboratory tests including CBC, serum chemistry, lipid profile, urinalysis and urine pregnancy test will be obtained. Used study medication cards will be returned and counted by the study pharmacist or designated personnel. Patients will be queried regarding adverse events, concomitant medications, change in smoking history and compliance. The electronic diary will be returned.

Post-Study Visit

After study completion/withdrawal, patients will be followed via a phone call for occurrence of pregnancy and until the menstrual cycle returns to normal. The patient based on the cycle pattern prior to the study entry will determine return to normal menstrual cycle. The minimum period of follow up will be 3 months. Patients who decide to use a contraceptive method that regulates/alters menstrual cycle after study completion/withdrawal will be followed for 3 months via a phone call.

Only those patients who have an on-going serious adverse event that has not resolved or those who become pregnant during the course of the study will be followed via clinic visits after completion of the study. Patients with on-going serious adverse events will be followed until the event has

been satisfactory managed or resolved. Patients who are pregnant will be followed for eight weeks following delivery or termination of the pregnancy. Infants' health assessment will be followed for eight weeks following delivery. This follow-up may be in the form of a written report from a family physician, obstetrician or pediatrician. All serious adverse events that occur in the three months following discontinuation of therapy will be reported. SAEs that occur at any time after study completion/discontinuation will be reported if investigator determines it is drug-related.

Early Termination

Any patient who withdraws or is withdrawn from the study must return the investigational medication and electronic diary and will be required to complete all procedures for the final visit. All patients will be followed via a phone call for 3 months for the occurrence of pregnancy and until the menstrual cycle return to normal. All patients will be followed via a phone call for three months for the occurrence of serious adverse events.

Examinations and Procedures

Physical Exam, Medical and Gynecologic History

A complete physical and gynecologic exam, including PAP smear, will be performed at screening and at the completion of therapy or upon early withdrawal from the study. Any patient with an abnormal Pap smear will be disqualified for enrollment unless investigator decides the results are not clinically significant and will not interfere with conduct of the study. The Investigators decision must be documented. Patients who have had a Pap smear reported as within normal limits within the three months prior to enrollment in the study will not be required to have the test repeated. A copy of the results must be available in the patient's medical record. Any patient with a report of insufficient cells must have the test repeated and documented by the investigator as within normal limits prior to enrollment.

Laboratory Safety Tests

Clinical laboratory tests will be performed at screening and at the completion of therapy or upon early withdrawal. All clinical laboratory tests will be done at one central laboratory. Laboratory tests will include CBC, serum chemistry, lipid profile, urinalysis, and urine pregnancy test. In addition, urine pregnancy tests will be conducted at every clinic visit and at the completion of therapy or upon early withdrawal from the study. All urine pregnancy tests will be performed using the Sure Step® Pregnancy Test kit (Applied Biotech, Inc.).

Pregnancy

All patients will be followed for the occurrence of pregnancy for three months following completion of the study. This follow-up may be in the form of a telephone call. All pregnancies that occur during the course of the study or in the three months following completion of the study will be dated using ultrasound to establish the gestational age of the fetus. Patients who become pregnant during the course of the study due to method failure will be followed for eight weeks following delivery or termination of the pregnancy. Infants' health assessment will be followed for eight weeks following delivery. This follow-up may in the form of a documented telephone conversation with associated pediatrician or written report from the associated pediatrician.

Electronic Diaries

Patients will be asked to complete electronic diaries. The diary will be programmed to ask specific questions related to the study compliance, bleeding pattern and occurrence of symptoms that are commonly associated with the hormone fluctuation during the menstrual cycle. The questions will address dosage, compliance, bleeding pattern and hormone-related symptoms either on the scale from 0-3 or using 10 cm Visual Analogue Scale (VAS).

Hand-held data acquisition devices will be used to collect patient responses. The electronic diary will provide patients with a menu-driven, graphical interface to enter diary information (as well as objective data) using a hand-held stylus. Data entry will be electronic and key fields must be completed properly before allowing patient to finish the report. Each report will be downloaded by dial-up network connection.

The electronic diary will incorporate an alarm to remind the patient when to complete their reports. Alarm times will be set by the site and can be specific to the patient preference. The patient will be instructed to complete a diary on a daily basis. Retrospective data entry will not be allowed; reports cannot be completed for previous days. Once each question is completed the patient will confirm the response and will not be permitted to return to that question for modification.

Information on the hormone-related symptoms to be collected is from the Calendar of Premenstrual Experiences (COPE) and Diagnostic and Statistical Manual of Mental Disorders Forth Edition (DSM-IV).

The validity and reliability of the COPE instrument was assessed by Mortola, et al., *Obstet. Gynecol.* 89:179-83 (1990), who administered it throughout two consecutive ovulatory cycles to 36 rigidly screened women with PMS and to 18 controls. The validity of the visual analogue scales applied to the psychological symptoms associated with the PMDD has been previously documented.

Treatment Modifications Based on Toxicity

No significant toxicity is expected from the study medication. However, if the patient develops any symptoms or any abnormal laboratory parameter attributed to the drug, which are considered by the patient and/or physician to be of unacceptable severity, then the study medication should be discontinued.

Concomitant Medications

Patients will be queried regarding concomitant medication use at monthly phone calls and quarterly clinic visits. All concomitant medication use (both prescription and over-the-counter (OTC), including herbal medications and nutritional supplements) must be reported during the study, and recorded on the patient's Case Report Form (CRF).

Patients who require the initiation of chronic therapy with drugs that are known to interact with OCs will be withdrawn from the study. Patients who require intermittent therapy with drugs known to interact with OCs (e.g. antibiotic therapy) will remain in the study and will receive counseling regarding the need for additional contraceptive protection during the entire cycle. Patients will be provided with the list of medications that are know to interact with OC and will be instructed to notify study coordinator as soon as medication is prescribed to receive proper counseling. Notification and counseling can be conducted via the phone and must be documented in the patient's CRF. Those cycles in which drugs known to interact with OC therapy are taken will not be used in the calculation of the pregnancy rate.

The use of emergency contraceptive pills ("morning after pills") is prohibited in the study. Data from any patient who utilizes contraceptive pills others than those provided for the study will not be included in the calculation of the pregnancy rate for that cycle.

Adverse Event Reporting

An Adverse Event (AE) is any reaction, side effect, or other undesirable event that occurs in conjunction with the

use of a drug, biological product or diagnostic agent in humans, whether or not the event is considered drug related.

A serious adverse event (SAE) is one that meets any one of the following criteria:

Fatal or life threatening

Requires or prolongs inpatient hospitalization

Results in persistent or significant disability/incapacity

Congenital anomaly

The term "life threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. Medical and scientific judgment should be exercised in deciding whether an important medical event is serious. Although the event may not be immediately life threatening, fatal, or result in hospitalization, it should be considered serious when it jeopardizes the patient, or requires an intervention to prevent a serious outcome as defined above.

The AE reporting period for this study begins at the Enrollment Visit and ends at the final clinic visit. The SAE reporting period will continue for 3 month after the final clinic visit. All SAEs will be followed through resolution or until investigator assesses the SAE as chronic or stable.

A preexisting condition (i.e., a disorder present before the AE reporting period started and noted on the pretreatment medical history/physical form) should not be reported as an AE unless the condition worsens or episodes increase in frequency during the AE reporting period.

During the study AEs will be recorded through monthly phone calls and quarterly clinic visits. A call-in number will be provided to the patients who wish to report an adverse event between the scheduled phone calls and clinic visits.

Example 2

Multicenter Randomized Phase III Clinical Trial to Evaluate Two Continuous Oral Contraceptive Regimens in Combination with Fluoxetine Hydrochloride in Women Diagnosed with Premenstrual Syndrome (PMS) and Premenstrual Dysphoric Disorder (PMDD)

Overview of the Study Design

In a three-arm, parallel, randomized, multicenter, placebo-controlled, double-blinded study, the efficacy and safety of continuous oral contraceptive therapy as a ninety-one day regimen (84 days active combination therapy followed by low dose estrogen for 7 consecutive days (DP3-91)), or as a twenty-eight day regimen (21 day active combination therapy followed by low dose estrogen for 7 consecutive days (DP3-28)), in combination with fluoxetine hydrochloride administered for approximately 6 consecutive months to women diagnosed with PMS and/or PMDD who desire contraception, will be evaluated.

A cohort of approximate 40-100 patients enrolled in each of the study arms will undergo endometrial biopsy (to test incidence of hyperplasia and carcinoma) prior to the initiation of study drug therapy and at the conclusion of the study or withdrawal.

Efficacy of the 28-day and 91-day regimens on premenstrual symptomatology will be measured by psychometric scales that include self-administered Visual Analogue Scales (VAS) and a prospective daily symptoms chart to evaluate psychological and somatic symptoms. The VAS measures tension, irritability, dysphoria, sleeping and eating patterns, headache, bloating, pain and breast tenderness and weight gain symptoms. Total score of the psychological and somatic symptoms will be computed. The patient and blind observer will also complete the PMTS at each visit.

Study Population

Females ages 18 through 49 who are fluent in English and capable of giving informed consent, without contraindication to the use of oral contraceptives and selective serotonin reuptake inhibitors (SSRIs), and meet the criteria for PMS including PMDD as defined in the diagnostic and statistical manual of mental disorders (DSM-IV). All patients will be counseled at the beginning of the study and at each study visit to use an alternative form of contraception. All patients will be followed for the occurrence of pregnancy during the course of the study. Patients who become pregnant during the course of the study will be followed for eight weeks following delivery or termination of the pregnancy. Infants will be followed for eight weeks following delivery.

Dosage

Patients will be randomized to one of the following:

(1) Ninety-one day oral contraceptive therapy with ethinyl estradiol (DP3-91) and fluoxetine hydrochloride administered for two cycles where each cycle consists of: 150 μg levonorgestrel and 30 μg ethinyl estradiol (days 1-84 of the first cycle and days 92-175 of the second cycle, 30 μg ethinyl estradiol (days 85-91 of the first cycle and days 176-182 of the second cycle), 20 mg fluoxetine hydrochloride (days 1-182), and placebo to preserve blinding (days 183-196);

(2) Twenty-eight day oral contraceptive therapy with ethinyl estradiol (DP3-28) administered for 7 cycles where each cycle consists of: 150 μg levonorgestrel and 30 μg ethinyl estradiol (days 1-21 for seven cycles), 30 μg ethinyl estradiol (days 22-28 for seven cycles), and 20 mg fluoxetine hydrochloride (days 1-196); or

(3) Fluoxetine hydrochloride administered daily for 196 days: 20 mg fluoxetine hydrochloride per day (days 1-196) or placebo to preserve blinding (days 1-196).

Study Management

The study will utilize electronic case report forms and remote system management. Each investigator will be provided a programmed laptop computer dedicated to the study. This system allows the investigator to download and view patient diary data during clinic visits and also allows for rapid data queries by the study monitors. The system will also allow real-time on-line tracking of study site accrual rates, serious adverse events, pregnancies and study progress.

Outcomes Measurement Scales

The primary outcome will be defined as reduction in symptoms of PMS including PMDD as measured by the mean scores on Visual Analogue Scales (VAS) and the Premenstrual Tension Syndrome Scale (PMTS). The VAS will measure tension, irritability, dysphoria, sleeping and eating patterns, headache, bloating, pain and breast tenderness symptoms. Patients will be prompted to rate how they feel each day using 100 mm scales in which the descriptors range from "no symptoms" (0 mm) to "severe or extreme symptoms" (100 mm). The PMTS consists of a 36 item scale that will be completed by the patient and a 10-item scale completed by the blinded observer. Both scales rate premenstrual symptoms for a particular day; the total score can range from 0 (no symptoms) to 36 (all symptoms present and severe).

The secondary outcome will be defined as reduction in symptoms of PMS including PMDD as measured by the sub-score of somatic symptoms on VAS. The VAS will measure headache, bloating, pain and breast tenderness and weigh gain symptoms. Patients will be prompted to rate how they feel each day using 100 mm scales in which the descriptors range from "no symptoms" (0 mm) to "severe symptoms" (100 mm). In addition to information recorded

in paper diaries, a standardized questionnaire will be used to determine whether the patient had any side effects.

Statistical Analysis

For the primary analysis, the mean of the VAS scales will be derived to obtain a single VAS score, which evaluates composite psychological and symptomatic outcomes. Mean percent reduction from baseline at the luteal phase will be compared using an analysis of covariance (ANCOVA) approach that evaluates the effects of the treatment group, center and treatment-by-center interaction, after adjusting for the effect of the baseline VAS score. All statistical tests will be two-sided at the 0.05 level of significance. Pairwise comparisons will be made for each active treatment to placebo. Secondary analyses will include a set of statistical tests for the PMTS and 10-item blinded observer-based measures.

Application of the compounds, compositions and methods of the present invention for the medical or pharmaceutical uses described can be accomplished by any clinical, medical, and pharmaceutical methods and techniques as are presently or prospectively known to those skilled in the art. It will therefore be appreciated that the various embodiments which have been described above are intended to illustrate the invention and various changes and modifications can be made in the inventive method without departing from the spirit and scope thereof.

What is claimed is:

1. A method of contraception in a female in need thereof, the method comprising administering to the female a dosage comprising a combination of estrogen and progestin for a period of 81 to 89 consecutive days, followed by administration of a dosage consisting essentially of estrogen for a period of 2 to 8 consecutive days,

wherein the estrogen that is administered in combination with progestin for the period of 81 to 89 consecutive days is administered in a daily amount equivalent to about 10 μg to about 50 μg of ethinyl estradiol,

the estrogen that is administered for the period of 2 to 8 consecutive days is administered in a daily amount equivalent to about 5 μg to about 10 μg of ethinyl estradiol, and

the progestin that is administered for the period of 81 to 89 consecutive days is administered in a daily amount of about 150 μg of levonorgestrel.

2. The method of claim **1**, wherein the estrogen that is administered for the period of 81 to 89 consecutive days is administered in a daily amount equivalent to about 10 μg to about 30 μg of ethinyl estradiol.

3. The method of claim **1**, wherein the estrogen that is administered for the period of 81 to 89 consecutive days is administered in a daily amount equivalent to about 30 μg of ethinyl estradiol.

4. The method of claim **1**, wherein the estrogen that is administered for the period of 2 to 8 consecutive days is administered in a daily amount equivalent to about 10 μg of ethinyl estradiol.

5. The method of claim **1**, wherein the dosage comprising the combination of estrogen and progestin is administered for at least 84 consecutive days.

6. The method of claim **1**, wherein the dosage consisting essentially of estrogen is administered for a period of 5 to 8 consecutive days.

7. The method of claim **6**, wherein the dosage consisting essentially of estrogen is administered for at least 7 consecutive days.

8. The method of claim **1**, wherein the dosage comprising the combination of estrogen and progestin is administered for 84 consecutive days, and the dosage consisting essentially of estrogen is administered for 7 consecutive days.

9. The method of claim **1**, wherein the estrogen is ethinyl estradiol.

10. The method of claim **1**, wherein an antidepressant is administered (i) in combination with the dosage consisting essentially of estrogen for the period of 2 to 8 consecutive days, (ii) intermittently, (iii) one time, or (iv) once weekly.

11. The method of claim **10**, wherein the combination of the dosage consisting essentially of estrogen and the antidepressant that is administered for the period of 2 to 8 consecutive days is administered for a period of 5 to 8 consecutive days.

12. The method of claim **11**, wherein the antidepressant administered in combination with the estrogen for the period of 5 to 8 consecutive days is administered in a daily amount equivalent to about 5 mg to about 120 mg of fluoxetine hydrochloride.

13. The method of claim **10**, wherein a one-time dose of the antidepressant is administered in combination with the dosage consisting essentially of estrogen.

14. The method of claim **10**, wherein the antidepressant is fluoxetine hydrochloride.

15. The method of claim **1**, wherein the dosage comprising the combination of estrogen and progestin that is administered for the period of 81 to 89 consecutive days, and the dosage consisting essentially of estrogen that is administered for the period of 2 to 8 consecutive days, are administered orally.

16. The method of claim **1**, wherein the dosage comprising the combination of estrogen and progestin that is administered for the period of 81 to 89 consecutive days, and the dosage consisting essentially of estrogen that is administered for the period of 2 to 8 consecutive days, are administered transdermally.

17. A method of contraception in a female in need thereof, the method comprising administering to the female a dosage comprising a combination of estrogen and progestin for a period of 84 consecutive days, followed by administration of a dosage consisting essentially of estrogen for a period of 7 consecutive days,

wherein the estrogen that is administered in combination with progestin for the period of 84 consecutive days is orally administered monophasicly in a daily amount of about 10 μg to about 50 μg of ethinyl estradiol,

the estrogen that is administered for the period of 7 consecutive days is orally administered monophasicly in a daily amount of about 10 μg of ethinyl estradiol, and

the progestin that is administered in combination with estrogen for the period of 84 consecutive days is orally administered monophasicly in a daily amount of about 150 μg of levonorgestrel.

18. A method of contraception in a female in need thereof, the method comprising administering to the female a dosage comprising a combination of estrogen and progestin for a period of 84 consecutive days, followed by administration of a dosage consisting essentially of estrogen for a period of 7 consecutive days,

wherein the estrogen that is administered in combination with progestin for the period of 84 consecutive days is orally administered monophasicly in a daily amount of about 10 μg to about 30 μg of ethinyl estradiol,

the estrogen that is administered for the period of 7 consecutive days is orally administered monophasicly in a daily amount of about 10 μg of ethinyl estradiol, and

the progestin that is administered in combination with estrogen for the period of 84 consecutive days is orally administered monophasicly in a daily amount of about 150 μg of levonorgestrel.

19. A method of contraception in a female in need thereof the method comprising administering to the female a dosage comprising a combination of estrogen and progestin for a period of 84 consecutive days, followed by administration of a dosage consisting essentially of estrogen for a period of 7 consecutive days,

wherein the estrogen that is administered in combination with progestin for the period of 84 consecutive days is orally administered monophasicly in a daily amount of about 30 μg of ethinyl estradiol,

the estrogen that is administered for the period of 7 consecutive days is orally administered monophasicly in a daily amount of about 10 μg of ethinyl estradiol, and

the progestin that is administered in combination with estrogen for the period of 84 consecutive days is orally administered monophasicly in a daily amount of about 150 μg of levonorgestrel.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

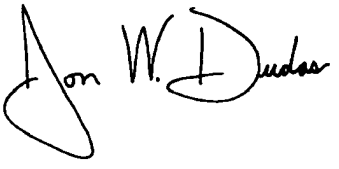
PATENT NO. : 7,320,969 B2
APPLICATION NO. : 10/309313
DATED : January 22, 2008
INVENTOR(S) : Bell et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 21, claim 19, line 1, please delete "A method of contraception in a female in need thereof" and insert therein --A method of contraception in a female in need thereof,--.

Signed and Sealed this

Thirteenth Day of May, 2008



JON W. DUDAS
Director of the United States Patent and Trademark Office

EXHIBIT C

NOT FOR PUBLICATION

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

TEVA WOMEN'S HEALTH, INC., Plaintiff, v. LUPIN, LTD. et al., Defendants.	Civil Action No.: 10-603 (PGS) OPINION

SHERIDAN, U.S.D.J.

This case is a patent infringement action arising under the Hatch-Waxman Act involving Teva Women's Health, Inc.'s (Teva) oral contraceptive (OC) Seasonique.[1] Teva owns the patent-in-suit, U.S. Patent No. 7,320,969 ("the '969 patent"). The '969 patent, entitled "Oral contraceptives to prevent pregnancy and diminish premenstrual symptomology," was issued on January 22, 2008. Teva's predecessors-in-interest to the '969 patent include Duramed and Barr.[2]

Teva alleges that defendants Lupin Ltd. and Lupin Pharmaceuticals, Inc. (collectively, "Lupin") and defendants Mylan Inc., Mylan Pharmaceuticals, Inc., and Famy Care Ltd. (collectively, "Mylan") infringed on Claim 19 of the '969 patent. Claim 19 of the '969 patent discloses an extended OC regimen that administers unopposed estrogen during the traditionally hormone free

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1 While Seasonique and similar FDA-approved products are trademarked, in this opinion the Court refrains from using such marks for the sake convenience.

2 There is a lawsuit captioned *Duramed Pharmaceuticals v. Watson Laboratories*, Case No. 08-116 (D. Nev.) which involves the same patent and remains pending in Nevada. Although the parties knew of this other case, none of the parties sought to consolidate matters.

interval (HFI). The remaining claims of the '969 patent are not at issue. While the patent was issued on January 22, 2008, the critical date for the claimed invention is December 5, 2001.

Both Defendants have stipulated that the filing of their respective Abbreviated New Drug Applications (Lupin's ANDA No. 91-467 and Mylan's ANDA No. 20-0492) infringed Claim 19 of Teva's '969 patent if that claim is found valid. The only issue presented at trial was the Defendants' affirmative defense that Claim 19 of the '969 patent is invalid as obvious in view of the prior art under 35 U.S.C. § 103.

For organizational purposes this opinion will be presented in the following manner: (1) standard of review, (2) description of the patent, (3) the level of ordinary skill in the art, (4) overview of the menstrual cycle and OCs, (5) the prior art, (6) inventor's testimony, (7) secondary considerations, and (8) evaluation of the evidence.

1. Standard of Review

Generally, a patent is presumed valid and each patent claim is presumed valid independently of the validity of other claims. 35 U.S.C. § 282. "The presumption of validity is based on the presumption of administrative correctness of actions of the agency charged with examination of patentability." *Applied Materials, Inc. v. Advanced Semiconductor Materials Am., Inc.*, 98 F.3d 1563, 1569 (Fed. Cir. 1996). Thus, the '969 patent is presumed valid and claim 19 is also presumed to be valid.

To defeat this presumption, Defendants have raised the affirmative defense of obviousness, based on 35 U.S.C. § 103(a):

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the

> prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Defendants have "[t]he burden of establishing invalidity of a patent or any claim thereof with clear and convincing evidence." 35 U.S.C. § 282; *Microsoft Corp. v. i4i Ltd.*, 131 S.Ct. 2238, 2242 (2011); *see also Polaroid Corp. v. Eastman Kodak Co.*, 789 F.2d 1556, 1558 (Fed. Cir. 1986). The U.S. Supreme Court has defined "clear and convincing evidence" as evidence that places in the Court, as factfinder, in an "abiding conviction that the truth of its factual contentions are highly probable." *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984) (internal quotation marks omitted). The burden of persuasion remains with Defendants and does not shift to Teva, the patent holder. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1534 (Fed. Cir. 1983); *Jones v. Hardy*, 727 F.2d 1524, 1528 (Fed. Cir. 1984).

Decades ago, the Supreme Court set forth a roadmap on determining obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). The Court stated:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or non-obviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or non-obviousness, these inquiries may have relevancy.

Id. In 2007, the Supreme Court reaffirmed the *Graham* test in *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 415 (2007), and applied the *Graham* roadmap within *KSR Int'l Co.* Justice Kennedy

writing for the majority, reaffirmed *Graham*'s "functional approach," which "set forth a broad inquiry and invited courts, where appropriate, to look at any secondary considerations that would prove instructive." *Id.* The Court reasoned that "[g]ranting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, in the case of patents combining previously known elements, deprive prior inventions of their value or utility." *Id.* at 419.

Justice Kennedy found that "[c]ommon sense teaches . . . that familiar items may have obvious uses beyond their primary purposes, and in many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.* at 420. Similarly, a "combination of elements [that are] 'obvious to try'" may be sufficient to show obviousness. *Id.* at 421. The Supreme Court reasoned that where there is a "finite number of identified, predictable solutions, a person of ordinary skill [in the art] has good reason to pursue [them]." *Id.* This "is likely the product not of innovation but of ordinary skill and common sense." *Id.* The principles of *KSR* have been applied in pharmaceutical cases. *See, e.g., Takeda Chemical Indus. v. Alphapharm*, 492 F.3d 1350 (Fed. Cir. 2007). Here, the Court will follow the *Graham* and *KSR* standard.

2. Description of the Patent

Claim 19 of the '969 patent claims a method of contraception that administers a regimen of 84 days of a combination pill containing 150 mcg of a specific progestin (levonorgestrel) together with 30 mcg of a specific estrogen (ethinyl estradiol ("EE")), followed by precisely 7 consecutive days of a different pill containing 10 mcg of estrogen (EE) administered on its own without any progestin ("unopposed estrogen"). (T. 71, 21 through T. 72, 8).

The language of Claim 19 is set forth below:

> A method of contraception in a female in need thereof, the method comprising administering to the female a dosage comprising a combination of estrogen and progestin for a period of 84 consecutive days, followed by administration of a dosage consisting essentially of estrogen for a period of 7 consecutive days, wherein the estrogen that is administered in combination with progestin for the period of 84 consecutive days is orally administered monophasicly in a daily amount of about 30 mcg of [EE], the estrogen that is administered for the period of 7 consecutive days is orally administered monophasicly in a daily amount of about 10 mcg of [EE], and the progestin that is administered in combination with estrogen for the period of 84 consecutive days is orally administered monophasicly in a daily amount of about 150 mcg of levonorgestrel.

(JTX-1, col. 21, 5 – col. 22, 10). Claim 19 covers the Seasonique OC regimen. (T. 8, 5-10). The alleged invention is a combined OC product which eliminates the usual HFI, and fills that 7 day HFI with unopposed estrogen, and does so, as part of an extended-regimen. (T. 524, 14-19) (T. 525, 25 through T. 526, 3). The invention "prevent[s] pregnancy and diminish or eliminate premenstrual symptomology, including PMS and PMDD." (JTX-1, col. 1, ll. 15-20).

Dr. Kurt T. Barnhart, expert for the Lupin defendants,[3] explained that PMS (Premenstrual Syndrome) means "there are symptoms associated with their menstrual period, breast tenderness, cramps, among other things; some women are bothered by them to a degree that they actually affect their daily life, and that syndrome is called premenstrual syndrome." (T. 76, 11-15). Dr. Barnhart continued that "a subset of those women have so much effect where they reach a psychiatric disorder where it affects their mood, where it's categorized and diagnosed as premenstrual dysphoric disorder [(PMDD)]."(T. 76, 16-22). Hence, these are disorders which may be alleviated by the '969 patent.

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[3] Dr. Barnhart is currently a professor of obstetrics and gynecology, and a professor of epidemiology, at the University of Pennsylvania, and serves as assistant dean for the school of medicine for clinical research operations. (T. 49, 8-13) (LTX-128 at 2).

3. The level of ordinary skill in the art

35 U.S.C. § 103 requires that obviousness be determined from the perspective of "a person having ordinary skill in the art" ("PHOSITA") to which said subject matter pertains." 35 U.S.C. § 103(a). "The person of ordinary skill in the art is a hypothetical person who is presumed to know the relevant prior art." *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995) (citations omitted). One of the factors the Court may consider when determining the level of ordinary skill in the art is the background of the inventors. *Daiichi Sankyo Co., Ltd. v. Apotex, Inc.*, 501 F.3d 1254, 1256 (Fed. Cir. 2007).

The parties essentially agree on the scope of the background of a PHOSITA, but they disagree on whether a PHOSITA should include a nurse practitioner. In discussing the ordinary level of skill in the art, Dr. Barnhart testified that "the level of ordinary skill is relatively high in the circumstance." (T. 78 3-4). Dr. Barnhart based this conclusion on the '969 patent, which is directed not only to the prevention of pregnancy but also the prevention of side effects. (T. 78, 4-8). According to Dr. Barnhart, a PHOSITA would be a person having a graduate medical degree – such as an M.D., Ph.D., or Pharm.D., or equivalent – as well as several years of experience in the research and development of OC pills to be able to understand how one puts a protocol together and understands the criteria for success of a study protocol. (T. 78, 19 through T. 79, 5). Similar to Dr. Barnhart, Dr. Bruce Richard Carr, expert for the Mylan defendants,[4] defined a PHOSITA as an

[4] Dr. Carr has been a tenured professor of obstetrics and gynecology at the University of Texas, Southern Medical Center in Dallas, since 1984. (T. 785, 18-24) (MylanTX-3259 at 1). Dr. Carr is also a fellowship director at the Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, at the University of Texas, Southern Medical Center in Dallas, which he has held since 1987. (T. 785, 17-24) (MylanTX-3259 at 1).

individual who has a basic science degree in biochemistry or pharmacology, a Ph.D., and experience in developing contraceptives or modifying contraceptive regimens. (T. 797, 4-8). Dr. Carr also testified that a PHOSITA could be an M.D. or a D.O. who has experience in conducting clinical trials or who has extensive experience in prescribing OC pills. (T. 797, 8-10). Dr. Patricia Sulak, expert for Teva,[5] defined a PHOSITA as someone who utilizes OCs in his practice, a definition that includes nurse practitioners. (T. 986, 18-20). Dr. Sulak admitted, however, that in evaluating the skill level of a PHOSITA for this case, she did not consider the levels of education or the background of the inventors. (T. 1157, 14-17). Dr. Sulak also testified that her opinion on obviousness would not change if the Court adopted the level of skill in the art proposed by Drs. Barnhart and Carr. (T. 986, 25 through T. 987, 7). Likewise, Drs. Barnhart and Carr testified that their opinions on obviousness would not change if the Court adopted Dr. Sulak's proposed level of skill in the art. (T. 83, 23 through T. 84, 3) (T. 798, 9-12).

The Court rejects Dr. Sulak's definition because a nurse practitioner does not possess the skills necessary to put a protocol together of an OC with combined doses of estrogen and progestin supplemented with seven days of an unopposed estrogen. Hence, a PHOSITA would be a person having a graduate medical degree, such as an M.D., Ph.D., or Pharm.D. as well as several years experience in the research and development of OC pills.

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[5] Dr. Sulak has a medical degree and specializes in obstetrics and gynecology. (T. 7, 16-19) (T. 8, 15 through T. 9, 20). She completed her residency at Walter Reed Army Medical Center. (T. 9, 18-20). Dr. Sulak's primary research focus throughout her professional career has been on OC regimens, and particularly on modifying the standard 21/7 OC regimen. (T. 10, 3-4).

4. Overview of the Menstrual Cycle and Oral Contraceptives

By way of background, some facts about the menstrual cycle are critical to understanding the claim. The menstrual cycle starts in a part of the brain called the hypothalamus with the secretion of gonadotropin releasing hormone (GnRH), which stimulates the pituitary gland. (T. 16, 8- 13). The pituitary gland in turn produces two other hormones: follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which act on the ovaries. (T.16, 15-17). This causes the ovaries to release a mature egg (ovulation) and, in the process, the ovaries produce two additional hormones: estrogen, and after ovulation occurs, progestin. (T. 16, 19-22). The hormones that are released during the menstrual cycle have effects throughout the entire body as well as on the reproductive system. (T. 16, 25 through T. 17, 3). Since the hormones act throughout the body in the blood stream, liver, and brain, health problems can be created. (T. 19, 23 through T. 20, 15). The hormones released by the ovaries causes the lining of the uterus (orendometrium) to thicken. This thickening is essential to conception, because a fertilized egg must implant in the endometrium to receive nourishment during pregnancy. (T. 17, 5-12). The estrogen also thins the cervical mucus, which allows sperm to move easily through the cervix to fertilize the egg. (T. 17, 15-18). The maturation and release of the egg, the thickening of the endometrium, and the thinning of the cervical mucus, all happen simultaneously. (T. 17, 25 through T. 18, 6). An OC works by disrupting the natural menstrual cycle. (T. 19, 4-7). Dr. Sulak testified that since OCs "contain estrogen and progestin, they sort of fake the body into thinking its pregnant, and the hormone levels remain high and that inhibits ovulation." The OCs "provide negative feedback; and messes up the hypothalamus and the pituitary." (T. 19, 7-12). Parenthetically, OCs prevent pregnancy in three ways: (1) prevention of

ovulation; (2) thinning the lining of the uterus to prevent implantation of a fertilized egg, and (3) by thickening the cervical mucus to impede sperm mobility. (T. 19, 17-22).

Using hormones to inhibit ovulation has been relatively common since the 1960s, and combination OC products have been on the market in the United States since that time. (T. 19, 25 through T. 20, 23). However, the overall process of designing an OC is complex because the efficacy of the OC considers both objective and subjective concerns. (T. 19, 23 through T. 20, 15). This requires balancing of several considerations such as efficacy, safety (e.g., increased risks of cancer or clotting conditions), side effects, and acceptability to patients and health care providers. (T. 19, 23 through T. 20, 15).

Millions of women have been, and currently are, taking OC products. (Stip. Fact ¶23). Since their introduction, OC regimens have historically consisted of a combination pill containing both an estrogen and a progestin, taken daily for 21 days, followed by a 7 day HFI. (T. 20, 16 through T. 21, 21). During the 7 day HFI, the lack of hormones cause an artificially induced menstrual bleed. (T. 21, 8-21).

OC regimens following this 28 day cycle (21/7 regimens) were designed to mimic a woman's natural cycle. (T. 21, 13-16). This standard regimen was well understood and accepted by patients. (T. 21, 17-21).

During the 1960s, the high doses of hormones in the OC pills caused some unanticipated health concerns, such as risk of cancer, heart attacks, strokes, and blood clots along with other "nuisance" side effects such as breast tenderness, bloating, and headaches. (T. 22, 6 through T. 23, 15). To resolve these problems, manufacturers of OCs lowered the dosage of hormones contained in the OC pills. (T. 23, 10-15). As a result of 30 years of research (1960 to 1992) the estrogen

component of OCs was reduced by 75-80%, while the progestin component was reduced by 90%. (JTX-58 at 365). Lowering the dosage of hormones in the pills successfully reduced major complications, but it required substantial development work. Dr. Barnhart testified that it took nearly 10 years to learn that even the 50 mcg EE pills had safety risks. (T. 136, 23 through T. 137, 9). In light of this history, Dr. Barnhart admitted that a person having ordinary skill in the art (PHOSITA) designing a new OC regimen would "clearly" want to use the lowest effective dose. (T. 139, 10-15). While lower doses of hormones in the OC pills generally lessened suppression of the ovary, lower dose OC regimens remained very effective in preventing pregnancy due to other "backup" mechanisms (i.e., the thinning of the endometrium) and the thickening of the cervical mucus. (T. 24, 15-13). Despite these advances, during the 1990s, new problems arose with the lower hormone dosage in the combination pills, particularly problems associated with the traditional 7 day HFI. (T. 23, 18-24). Lower dose OCs have been associated with hormone withdrawal symptoms, such as headaches, breast tenderness, bloating, and swelling, as well as increased breakthrough bleeding.[6] These side effects often caused patients to discontinue usage. As a result, in the 1990s, researchers began to study methods for reducing side effects associated with the HFI.

5. The Prior Art

In this case, the Defendants contend that Teva's alleged invention was obvious. That is, Defendants argue that the research, studies and articles published prior to the alleged invention (prior

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[6] Breakthrough bleeding is the unanticipated shedding of the endometrium (resulting in bleeding) that occurs while a woman is taking estrogen-plus progestin combination pills. (T. 25, 17 through T. 26, 8). This is in contrast to withdrawal bleeding, which is the bleed that occurs during the traditional HFI. (T. 46, 1-6).

art) make the alleged invention obvious. Accordingly, the prior art shows that extending a traditional contraceptive regimen of 21 days of estrogen/progestin combination to a 84 day regimen, and replacing the traditional 7 day HFI interval with seven days of unopposed estrogen, would reduce hormone withdrawal symptoms. On the other hand, Teva argues that the 84 day regimen and the use of 7 days of unopposed estrogen went against the current trend of reducing the amount of hormones prescribed in OCs. Therefore, in order to review the merits of both arguments, the Court must consider the prior art. Presented below will be a summary of the prior art published before the introduction of the '969 Patent, together with commentary of the experts who testified at trial.

The prior art was presented by three experts at trial; namely, Dr. Patricia Sulak for Teva, Dr. Kurt Barnhart for Lupin, and Dr. Bruce Carr for Mylan.

The testimony of the experts conflicted with each other. For instance, in discussing what was known about extended OC regimens, Dr. Sulak's testimony was different from that of Dr. Barnhart and Dr. Carr. Dr. Sulak opined that there was little information about the extended regimen of 84 days plus 7 days of unopposed estrogen (84/7). In speaking with Dr. Carole Ben-Maimon, lead inventor of the Seasonique regimen, prior to the clinical research being undertaken, Dr. Sulak advised "we had no data on adding estrogen only to all seven days of an OC regimen." (T. 32, 13-16). Further, Dr. Sulak emphasized to Dr. Ben-Maimon that "there's definitely no data with adding it to an extended regimen, not even a 21 day regimen." (T. 32, 22 through T. 33, 1). Dr. Sulak testified that at the time of the clinical research she advised Dr. Ben-Maimon as to the extended regimen with seven days of estrogen: "could it make it worse, yeah, could it make it better, . . . I said we're really just guessing since we didn't have any data to go by." (T. 33, 5-9).

Dr. Barnhart's testimony at trial utilized a demonstrative chart which broke down the alleged invention into two parts (A and B). Subpart A concerned writings about extended regimens, and subpart B highlighted use of estrogen only instead of a 7 day HFI. (T. 71, 21 through T 72, 20). Dr. Barnhart's conclusion simply combined the articles from A and B to show that the invention was obvious. Since the experts' views of the prior art are entirely different, the PHOSITA's viewpoint on the prior art is reviewed below.

1. Silverberg

Steven G. Silverberg & Edgar L. Makowski, *Endometrial Carcinoma in Young Women Taking Oral Contraceptive Agents*, 46 J. Obstetrics & Gynecology 5 (1975) ("Silverberg") (PTX-268), written in the 1970's, addressed the concern about endometrial cancer from unopposed estrogen used in OCs. (T. 1031, 5-11). Dr. Sulak relied on these findings in her discussion of safety concerns related to unopposed estrogen. (*See, e.g.,* T. 1168:17-1169:2).

2. Gambrell

R. Don Gambrell, Jr., *Clinical Use of Progestin in Menopausal Patient, Dosage and Duration,* 27 J. Reprod. Med. 531 (1982) ("Gambrell") (LTX-175) was an article relied on by Dr. Barnhart for the proposition that administering progestin alleviates endometrial cancer risk in women receiving unopposed estrogen, because progestin counteracts and reverses any increase in hyperplasia. (T. 237, 9-13). Specifically, Dr. Barnhart testified that this article demonstrates "that even women that have hyperplasia, if you give progestin for as little as five to 10 days, you can completely reverse that process in 95 percent of patients." (T. 238, 18-21).

3. Guillebaud

John Guillebaud, *The Forgotten Pill—and the Paramount Importance of the Pill-Free Week*, 12 Brit. J. Fam. Plan. 35 (1987) ("Guillebaud") (Mylan TX-3315) was an article relied on by Dr. Carr for the proposition that extended cycles were performed "off label" by many physicians as early as 1987. (T. 815, 16-18). On cross, Dr. Carr testified that Guillebaud does not discuss complete elimination of the pill-free week. (T. 869, 4-22).

4. Kovacs

In Gabor T. Kovacs et al., *A Trimonthly Regimen for Oral Contraceptives*, 19 Brit. J. Fam. Plan. 274 (1994) ("Kovacs") (JTX-21), Dr. Kovacs undertook a study to determine the acceptability and efficacy of a trimonthly regimen (12 weeks) of OCs, comprised of 84 days of estrogen/progestin combination pills followed by one week of HFI regimen. From January 1989 through June 1992, many women (203) entered the study. According to Kovacs, the purpose was to challenge the usual concept of administering 21 days of hormones followed by 7 hormone free days. Kovacs noted that there is "no physiological reason" for a woman to have a monthly cycle, but the OC "mimicked the natural 28 day cycle to promote acceptability." This study compared itself to a 1977 Edinburgh study where researchers recommended that women return to their usual regimen (21/7) due to the side effects. The difference was that in the Edinburgh study, the OC was a 50 mcg EE and in this study 30 mcg pills were utilized. In the Kovacs study, only 29% of the respondents completed the 12 month study period while 70% discontinued mainly due to breakthrough bleeding, breast tenderness, headaches, nausea, weight gain and bloating. Although Dr. Kovacs concluded that "it was disappointing" that only 29% of the women completed the 12 month study, he found two primary causes for discontinuance (1) women often change OC regimens; and (2) completing a

calendar year was onerous in light of side effects such as breakthrough bleeding. As a result of the study, Dr. Kovacs "suggested" that this extended regimen may be considered so long as the recipient is counseled about the possibility of breakthrough bleeding. Dr. Kovacs believed that such counseling would promote better compliance.

Dr. Sulak testified that the extended regimen of 84 days of active pills plus a 7 day HFI was not supported by this article. Due to the large number of drop-outs, Dr. Sulak found no one "would deem this article as a success" to support an extended regimen. Since Dr. Kovacs "described his results as disappointing," (T. 989, 7-11), Dr. Sulak concluded it was "unsuccessful" due to the "high dropout rate." (T. 991, 18-21). Dr. Sulak noted she had never "seen a drop out rate of 71%" (T. 991, 20-22); and the primary reason for dropouts was breakthrough bleeding. (T. 992, 1). Hence, according to Dr. Sulak, this article taught away from employing extended regimens.

5. Szarewski

Anne Szarewski & John Guillebaud, *Contraception: A User's Handbook* (1994) ("Szarewski") (JTX-52) is a handbook written by two family planning doctors that "provide[s] up-to-date . . . information about the many different methods of contraception" in use as of the 1994 publication date. (JTX-52 at 1, 3)[7]. In a chapter titled "Practical Aspects of Taking the Combined Pill," Szarewski discussed "tricycling." (JTX-52 at 93). According to Szarewski, tricycling "means taking three, or sometimes four, packets [of active pills] in a row before having a pill-free week" or taking a placebo. (JTX-52 at 93). Szarewski stated that "[w]omen who suffer side-effects related to the pill-free week, for example headaches which occur only or mostly at that time, may be advised

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[7] The numbers for exhibits correspond to the exhibit numbers, not the internal numbers of the document.

to try [tricycling], to reduce the frequency of headaches. Similarly, it can also be useful for women who have heavy and/or painful withdrawal bleeds" to reduce the number of menstrual periods. (JTX-52 at 93). Szarewski also stated that tricycling still includes "a few pill-free weeks rather than none at all," and he cautions that the health advantages of this procedure are, at the time of publication, unknown. (JTX-52 at 93).

At trial, Dr. Barnhart testified that "this [reference] discloses how to make an extended regimen and the motivation to do it." (T. 124, 24-25). Dr. Barnhart also stated that the packets referred to in Szarewski are each 21 days long, and that taking 4 packets would lead to an extended regimen of 84 days. (T. 124, 14-16). According to Dr. Barnhart, some women were using this method for years, "and even in my practice" tricycling occurred. (T. 124, 1-3). Dr. Barnhart also opined that a PHOSITA could combine this regimen "with the other references I mentioned to combine [tricycling] with . . . putting estrogen in the [HFI]" which attacks the novelty the '969 patent. (T. 125: 1, 3). On cross-examination however, Dr. Barnhart admitted that elsewhere in the book, the authors state that breakthrough bleeding can be remedied by increasing the strength of the progestin in the combination pill, rather than by adding estrogen to the HFI as the '969 patent taught. (T. 362, 1 through T. 363, 3).

Dr. Sulak testified that the Szarewski book should not even be considered prior art. (T. 999, 15-21). Within the Szarewski book (JTX-52), there is a short section on tricycling "which is using three or four packs followed by [an HFI]." (T. 998, 21-22). Although Dr. Sulak agreed that a PHOSITA "might have" relied on the book to support use of the extended regimen, (T. 999, 1-5), Dr. Sulak concluded that the book contained no supporting data which a PHOSITA would consider to be a problem. (T. 999, 11-21). Dr. Sulak further testified that "a person of ordinary skill in the

art is really going to rely on data, not some mentioning, oh, you know, this is something that might be tried." (T. 999, 11-13). In summary, Dr. Sulak minimized the value of Szarewski, stating that there is "no data and they're just describing a concept." (T. 999, 20-21).

6. Sulak 1997

In Patricia J. Sulak et al., *Extending the Duration of Active Oral Contraceptive Pill to Manage Hormone Withdrawal Symptoms*, 89 J. Obstetrics. & Gynecology 179 (1997) ("Sulak 1997") (JTX-11) Plaintiff's expert, Dr. Sulak, sought to determine whether extending the number of "consecutive active" OCs will decrease the frequency of menstrual cycle related problems. Dr. Sulak involved 50 women who had menstrual related problems and had symptoms during the HFI into her study. Each patient was permitted to extend the number of consecutive active OCs to delay menstrual related symptoms while under the care of a physician and/or a nurse practitioner. The purpose of the study was to determine whether better counseling would improve compliance with the extended regimen. The results were 74% of patients (37 women) stabilized on extended regimens of 6 to 12 weeks, while 26% of patients (13 women) either discontinued OCs or returned to the standard bleeding and/or headaches. Dr. Sulak concluded that "delaying menses by extending the number of consecutive days of active pills is well tolerated and efficacious," because it reduces the frequency of menstrual related symptoms. Moreover, Dr. Sulak found that "extending the duration of active pills may be an underused method of management for patients with menstrual-related disorders."

Dr. Sulak's testimony at trial was somewhat different from this abstract because the abstract sounds positive in nature, but her trial testimony was negative as to the success of extend oral contraceptive regimens. Dr. Sulak enrolled a population of women who had significant

complications during the menstrual cycle, and by working with them on a step by step basis, she was attempting to "make the 84 days a success." (T. 995, 1-3). Although 32% of the population completed the extended regimen, Dr. Sulak testified "I did not think this was the answer and pursued a different direction, and actually abandoned" this concept of an extended regimen. Dr. Sulak stated:

> When it became apparent to me in my clinical practice and after doing the study and looking at the literature, that, you know, asking women to do 12 weeks and a week off, that's not going to work for the majority of them. I started pursuing a flexible regimen where women didn't have to go that long.

In Dr. Sulak's opinion, the Kovacs article plus this article (Sulak 1997) did not teach that an extended regimen would be beneficial. In fact, Dr. Sulak believed that the two articles together "taught away" from the extended regimen because of menstrual related problems extending the regimen and Kovac's disappointing drop out rate. (T. 997).

7. Fauser

In Bart C. J. M. Fauser & Arne M. Van Heusden, *Manipulation of Human Ovarian Function: Physiological Concepts and Clinical Consequences*, 18 Endocrine Rev. 71 (1997) ("Fauser") (LTX-173), Dr. Fauser reviewed new information related to the regulation of human follicle development. Dr. Fauser noted that:

> Due to ongoing concern regarding the potential for side effects and long-term health hazards, doses of combined estrogen/progestin steroid contraceptive pills have been decreased continuously since their introduction in the 1960s. It has been noticed subsequently that tolerance for omission of pill intake, especially around the pill-free interval, has diminished substantially in women using regimens presently on the market. Modest suppression of pituitary gonadotropin secretion during pill intake and recovery of FSH release during the pill-free week creates a situation resembling the early follicular phase of the normal menstrual cycle and allows for substantial residual ovarian activity.

After reviewing a significant number of other abstracts and reports, Dr. Fauser concluded:

> Presently available, low-dose steroid contraception is characterized by extensive residual ovarian activity and reduced tolerance for omission of pill intake. The endocrine profile and follicle growth dynamics in pill users during and shortly after the pill-free interval are compared with the normal menstrual cycle. Alternative strategies for contraceptive development to improve the safety margin can be postulated on the basis of this comparison.

More specifically, Dr. Fauser proffered some alternative strategies for safer contraceptive developments which should be considered. Chiefly, he recommended that (a) the 7 day HFI be reduced in length, (i.e. five days); or (b) HFI's be reduced in frequency (i.e. once every 2 to 3 months); and (c) low does of estrogen may be continued during the HFI without interference with bleeding patterns.

8. Killick

S. R. Killick et al., *Ovarian Activity in Women Taking an Oral Contraceptive Containing 20 mcg Ethinyl Estradiol and 150 mcg Desogestrel: Effects of Low Estrogen Doses During the Hormone-Free Interval*, Am. J. Obstetrics & Gynecology S18-S24 (July 1998) ("Killick") (JTX-23) is an article that examined the effects on women of taking low doses of EE during the traditional HFI. (JTX-23 at S18). In particular, the article examined the effect of the Mircette brand contraceptive regimen, a regimen involving 150 mcg desogestrel, a progestin, and 20 mcg EE as a combination OC for a 21 day period followed by 5 days of 10 mcg of EE. (JTX-23 at S18). These effects were determined "[i]n a randomized, double-blind study [of] healthy women," who received either a placebo or 10 mcg EE for the first 5 days of each 7 day HFI. (JTX-23 at S18-S19). Importantly, the study measured (1) ovarian follicular development through the use of

ultrasonographic evaluations, and (2) cycle control,[8] or the ability to minimize breakthrough bleeding, through self-reporting by the subjects. (JTX-23 at S19-S20).

Dr. Barnhart described Killick as "setting out in a scientific way . . . the rationale of putting estrogen in the [HFI]." (T. 172, 9-12). In reviewing Killick, Dr. Barnhart examined the results of the underlying study. In regard to the ultrasonographic evaluation of ovarian follicular development, Dr. Barnhart testified that the differences between the Mircette group and the placebo group were "substantial and clear." (T. 175, 17-19). Relying on data within the article (tables 2 and 3), Dr. Barnhart testified that there is "no question to someone reading this that the effects are in the direction you want them to be, in the order of magnitude you want them to be and they're bordering on statistical significance." (T. 176, 24 through T. 177, 4). Dr. Barnhart did note, however, that these results did fall short of the "scientific standard of statistical significance." (T. 175, 10-16) (T. 176, 19-24). When asked whether these results would have motivated a PHOSITA to add unopposed estrogen to a pill-free interval , Dr. Barnhart testified: "I think reading that data alone would provide a very strong evidence." (T. 177, 5-9). Dr. Barnhart also reviewed the authors' comments on this study. (T. 177, 9 through T. 178, 18). In Killick, the authors concluded that "[t]he results of this study appear to validate the rationale for the administration of 10 mcg EE during the last 5 days of the 7-day nominally hormone-free interval of the Mircette regimen." (JTX-23 at S24). Dr. Barnhart testified that this conclusion provides "probably the most persuasive evidence" of whether a PHOSITA would be motivated to add unopposed estrogen to the pill-free interval. (T. 177, 5-12).

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[8] As explained by Dr. Barnhart, "cycle control is having a woman bleed when she's supposed to bleed during the pill-free interval, and have a minimum of breakthrough bleeding at a different time in the cycle." (T. 178, 20-22).

In regard to Killick's results relating to cycle control, Dr. Barnhart testified that "the cycle control was acceptable, even though they didn't have enough information to claim that was either better or worse than others." (T. 180, 6-12).

Dr. Sulak testified that the Killick article concluded that the Mircette regimen did not represent a statistically significant improvement in terms of ovarian follicular development. (T. 1003, 13-18). Killick specifically states that "[b]ecause of the low failure rate and the multiple anti-fertility effects of OCs, the clinical significance of these findings is uncertain." (JTX-23 at S22). According to Dr. Sulak, this language "means that you cannot draw any conclusions . . . at least . . . any clinically meaningful outcomes." (T. 1004, 12-15). Dr. Sulak also pointed out that any discussion in Killick of the broader concept of contraceptive efficacy is constrained by the omission of any results related to alternate mechanisms of contraceptive action, such as the thinning of the lining or the thickening of cervical mucous. (T. 1006, 15 through T. 1008, 21). Dr. Sulak testified that the Killick study did not include enough patients to thoroughly evaluate contraceptive efficacy. (T. 1005, 5-7). In regard to cycle control, Dr. Sulak testified that the study concluded that "there was no difference in bleeding, between the two groups." (T. 1005, 8-15). Finally, Dr. Sulak concluded that there was no suggestion in the Killick article to change Mircette by replacing the two days of the HFI with unopposed estrogen. (T. 1006, 7-10).

9. Mircette Article

Am. Health Consultants, *Shortened Pill-Free Interval Delivered by New 20 mcg Pill*, 7 Contraceptive Tech. Update 85 (1998) ("Mircette Article") (LTX-121) is an article that announced Mircette's debut. (LTX-121 at 85). Notably, the Mircette Article is not a peer-reviewed article; rather, it is a summary of findings and updates of those in the field." (T. 181, 5-8). According to the

article, the Mircette regimen received FDA approval in April 1998. (LTX-121 at 85). The article details the Mircette regimen, which "uses a patent dosing regimen with 20 mcg of [EE] and 150 mcg of desogestrel for days one through 21, followed by two days of placebo pills, and closed with five days of 10 mcg pills of [EE]." (LTX-121 at 85-86). The article also states that Mircette achieves "[g]ood cycle control," and points out that "only 12% of patients experienced breakthrough bleeding or spotting." (LTX-121 at 86). The article also includes excerpts of interviews with Sara Berga, "a well-known obstetrician and gynecologist in the field of contraception," (T. 183, 6-7); and John Guillebaud, a "professor of family planning and reproductive health in London." (T. 184, 1-3) (LTX-121 at 85-87).

Dr. Barnhart testified that the Mircette Article would have provided a PHOSITA with motivation to both add unopposed estrogen to the pill-free interval and extend a regimen up to 84 days. (T. 186, 10 through T. 187, 2). According to Dr. Barnhart, the Mircette Article states that Mircette is "safe and effective, . . . dispelling any potential concerns that it wouldn't be a safe or effective contraception." (T. 184, 13-15). Dr. Barnhart also testified that the Mircette Article shows (1) the application of estrogen during the pill-free interval can minimize unwanted symptoms, including headaches, (T. 184, 15-20); and (2) that the trend in OCs during this time period was to start with the lowest efficacious dose of estrogen. (T. 184, 23-25). In reviewing the comments of Ms. Berga and Mr. Guillebaud, Dr. Barnhart testified that both experts found that "the five days of [EE] used in Mircette, ought to oppose the effect of any follicle stimulating hormone in promoting the growth of the follicle in these women who are close to ovulation at the end of the pill-free interval." (T. 184, 3-7 (reviewing LTX-121 at 86)). Finally, Dr. Barnhart discussed a section of the

Mircette Article identifying those women who might benefit from the Mircette regimen. (T. 184, 21 through T. 185, 14). In pertinent part, the Mircette Article states:

> Another set of women who may be served by Mircette's dosing regimen are those who have had a "breakthrough pregnancy" on an ultra-low dose[9] regimen, Guillebaud suggests. Those women also could achieve contraception by "tricycling" any OC, which is the practice of taking three to four pills packs in a row, followed by a four-day pill-free interval.

(LTX-121 at 87). According to Dr. Barnhart, this reference shows that there are two different strategies—applying unopposed estrogen to the pill-free interval and tricycling—and that these strategies may be complementary. (T. 185, 25 through 186, 2). Specifically, Dr. Barnhart stated that this reference shows that "[o]ne could add estrogen in a pill-free interval, or one could extend the regimen to up to 84 days as is also claimed in the '969 patent." (T. 186, 2-5).

In response, Dr. Sulak, who was a consultant to the developers of Mircette, asserted that a PHOSITA would never have relied on the Mircette Article because the Mircette Article lacked any statistically significant data about the actual effects of the unopposed estrogen in the Mircette regimen. (T. 1044, 3-12). Dr. Sulak also pointed out that neither the Mircette Article nor the Mircette regimen described therein discusses the use of unopposed estrogen for all seven days of the HFI. (T. 1044, 13-16). Hence, according to Dr. Sulak, a PHOSITA would not have seen this article as evidence to eliminate the HFI completely.

10. Mircette Study Group Article

Mircette Study Group, *An open-label, multicenter, noncomparative safety and efficacy study of Mircette, a low-dose estrogen-progestin oral contraceptive*, Am. J. Obstetrics & Gynecology S2-8

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[9] Dr. Barnhart testified that an "ultra low dose" constitutes any dose below 30 mcg. (T. 185, 17-20).

(July 1998) ("Mircette Study Group Article") (LTX-231) is an article evaluating the primary efficacy and safety of Mircette. (LTX-231 at S2) ("Mircette Study Group"). Importantly, the Mircette Study Group was "open-label," which means the patients were not blinded (T. 188, 15-16); "multicenter," which means that the study was conducted at more than one center, (T. 188, 16-17); and "non-comparative," which means that the Mircette regimen was not compared directly to another regimen, but administered to a large group of subjects who then cataloged their experiences. (T. 188, 17-23) (LTX-231 at S-3). The study involved the participation of "1200 healthy female subjects, between the ages of 18 and 50 years, . . . with regular menstrual cycles and at risk for pregnancy." (LTX-231 at S-3). Unlike the Killick article which provided a "mechanistic study" of the Mircette regimen, the Mircette Study Group is a "summary article" written by Mircette's developers who conducted a "larger stud[y] which show[s] the general contraceptive efficacy in a lot more women." (T. 188, 3-10). According to Dr. Sulak, who participated in the administration of this study, "this article . . . describes the results of the clinical trial . . . which we used so Mircette [could] get FDA approval." (T. 1042, 25 through T. 1043, 1). In discussing the results of the underlying study, the Mircette Study Group article stated "[a]bsence of withdrawal bleeding occurred in 5.5% of total cycles and intermenstrual bleeding occurred in 12.0% of total cycles." (LTX-231 at S2). Furthermore, the Mircette Study Group states as its conclusion that "[t]he study confirmed that Mircette is a safe and efficacious OC that is well tolerated." (T. LTX-231 at S2).

At trial Dr. Barnhart agreed with the study's stated conclusion that Mircette is safe and efficacious. (T. 190, 4-9) (T. 193, 16 through T. 194, 2). In doing so, Dr. Barnhart stressed that the Mircette Study Group article comports with his overarching discussion of the history of OCs, a history in which the doses have progressively decreased since the 1960's. (T. 190, 13-25).

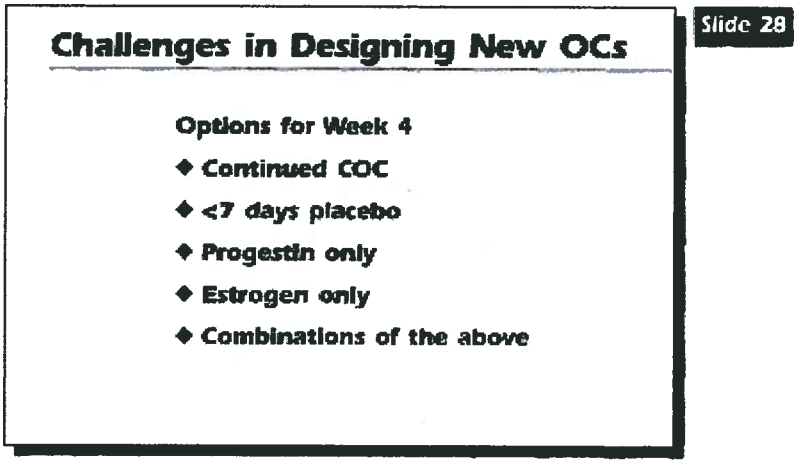
According to Dr. Barnhart, "[t]he question [the Mircette Study Group] want[s] to answer is whether estrogen dosage can be reduced while maintaining this follicular suppression and good cycle control." (T. 191, 1-3). Dr. Barnhart interpreted the Mircette Study Group article as answering this question in the affirmative, and concluded that a PHOSITA would have interpreted the article as demonstrating both an improvement in follicle growth and cycle control. (T. 192, 17-25). Additionally, Dr. Barnhart highlighted a portion of the Mircette Study Group that cited the Sulak 1997 article. This portion of the Mircette Study Group article stated: "[Sulak 1997] demonstrated that extending the duration of active OC pills resulted in a lower incidence of menstrual problems, similar to the results of this study." (LTX-231 at S7). Dr. Barnhart read this sentence as including the "two primary suggestions of how to improve menstrual symptoms." (T. 196, 24-25). Ultimately, Dr. Barnhart determined that (1) these suggestions were "well-known possibilities," and (2) a PHOSITA would have known that they "may be complementary in terms of improving the pill." (T. 197, 2-4).

In response Dr. Sulak limits the findings of the Mircette Study Group because it provides no teachings regarding the use of unopposed estrogen for seven days of the HFI. (T. 1043, 14-19). Thus, according to Dr. Sulak, the results and conclusions of the Mircette Study Group are of little value to the PHOSITA. (T. 1043, 7-19).

11. Organon Speaker Slide Kit

Organon, Oral Contraception: State of the Art, Speaker's Slide Kit, (Mar. 5-7, 1999) ("Organon Speaker Slide Kit") (LTX-201) is a printout provided by Organon Inc, the developers of Mircette, to the participants of the Contraception Presentation Meeting, a meeting held from March 5-7, 1999 in Orlando, Florida. (LTX-201 at 1-2) (T. 229, 10-20). Dr. Barnhart attended the meeting

with about one-hundred other participants. (T. 229, 7-12). According to Dr. Barnhart, Organon devised the meeting to gather health practitioners, disseminate information about the state of the art of contraception, and then encourage said experts to disseminate said information through lectures about family planning. (T. 229, 10-20). At slide 28, the Organon Speaker Slide Kit states:



Traditionally the 4th week of oral contraceptive cycles has contained 7 days of inactive tablets. Potential modifications of the 4th week include:

- The use of combination oral contraceptive tablets for part or all of the 4th week.
- The use of active pills for part or all of the week such that the number of inactive tablets is reduced to less than the usual 7.
- Administration of only progestin during part or all of the 4th week.
- Administration of only estrogen for part or all of the 4th week.

(LTX-201 at 6). Dr. Sulak reviewed this slide at trial. (T. 1114, 13 through T. 1116, 10). During her review, Dr. Sulak testified that "Continued COC" refers to "extended regimens." (T. 114, 24 through T. 1115, 3). Dr. Sulak conceded, by the terms of this slide, any combination of the above options may be feasible and it could be claiming elimination of the HFI, (T. 115, 9 through 1115, 14); but she said that this interpretation of slide 28 was "confusing" since it would be impossible to

combine many of the above options based on the scope of the slide; and Dr. Sulak concluded that the slide, to be more accurate, should be limited to the fourth week. (T. 116, 3-7).

12. The '032 Patent[10]

U.S. Patent No. 5,898,032 ("the '032 patent") (JTX-53) titled "Ultra Low Dose Oral Contraceptives with Less Menstrual Bleeding and Sustained Efficacy," was issued on Apr. 27, 1999. (JTX-53 at cover). The parties agree that the claims in the '032 patent cover the Seasonale regimen. (Pl.'s Responses to Def.'s Proposed Findings of Fact ¶ 48). The Seasonale regimen is an extended regimen OC that provided for the administration of a combination pill for 84 days followed by seven days of placebo pills. (LTX-226 at 58) (T. 115, 23 through T. 116, 1). The parties admit that the Seasonale product contains the same dosage and number of days for the first interval (i.e., 84 days of a combination dose of 30 mcg EE and 150 mcg levonorgestrel) as Seasonique. (Stip. Fact ¶ 31). However the FDA did not approve Seasonale for sale in the United States until 2003, (Stip. Fact ¶ 29), and Seasonale is therefore not in the prior art. (Stip. Fact ¶ 36) (Def.'s Responses to Pl.'s Proposed Findings of Fact ¶ 8). In the section titled "Summary of the Invention," the '032 patent states:

> This invention relates to a method of female contraception which is characterized by a reduced number of withdrawal menses per year. More particularly, it relates to a method of female contraception which involves administering, preferably monophasicly,[11] a combination of estrogen and progestin for 60-110 consecutive days followed by 3-10 days of no administration, in which the daily amounts of the estrogen and progestin are equivalent to about 5-35 mcg of [EE] and about 0.025-10 mg of norethindrone acetate, respectively.

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10 The '032 patent covers the Seasonale regimen.

11 According to Dr. Barnhart, "[m]onophasic means that the combination of the estrogen/ progestin is the same throughout the duration you use, ..." (T. 118, 4-5).

(PTX-53, col. 3, ll. 34-44).

Dr. Barnhart testified that the '032 patent is the basis for the '969 Patent because it discloses (1) the duration of the '969 patent, (2) the dose of the '969 patent, and (3) a rationale for "developing an extended regimen of estrogen and progestin" as a means of "improving the pill in terms of efficiency, improving non-contraceptive benefits or even reducing side effects." (T. 116, 25 through T. 117, 8). Dr. Barnhart also testified that the '032 patent includes "very specific examples that are identical to Claim 19 [of the '969 patent]." (T. 119, 24 through T. 120, 4). Dr. Barnhart conceded that the '032 patent lists "norethindrone acetate," not "levonorgestrel," as the preferred progestin (T. 120, 8-10); however Dr. Barnhart pointed out that levonorgestrel is referenced as a potential progestin, (T. 120, 19-21) (PTX-53, col. 4, ll. 1-2), and the '032 patent even provides a "conversion factor" which enables a PHOSITA to convert to the correct dosage of levonorgestrel. (T. 120, 12-18). Dr. Barnhart also emphasized that, as both parties have stipulated, the '032 patent covers the Seasonale regimen (T. 116, 6-7), and the Seasonale regimen contains the same dosage and duration as the first interval of Seasonique. (T. 115, 23 through 116, 1).[12]

On cross examination, Dr. Barnhart conceded three additional points. First, the precise dose of levonorgestral prescribed in the '969 patent (150 mcg) does not appear in the '032 patent. (T. 366, 6-7). Second, while the '032 patent includes a range of "5-35 mcg of [EE]," (PTX-53, col. 3, ll. 41-42), the "preferable amount of [EE] is about 10-20 mcg" (PTX-53, col. 3, ll. 62-63), which is less than the highest dose taught by the '969 patent (30 mcg). (T. 366, 9-19). Third, the '032 patent claims to provide enhanced control of endometrial bleeding, (T. 367 2-3) (PTX-53, col. 3, ll. 22-25); but a PHOSITA would not have any motivation to modify the '032 patent to address the issue of breakthrough bleeding. (T. 368, 9-19).

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[12] Dr. Carr corroborated Dr. Barnhart's conclusions. (T. 804, 24 through T. 805, 19).

In response, Dr. Sulak testified that Kovacs and Sulak 1997 would have taught away from relying on the '032 patent to use an extended regimen of 84 days of combination pills. (T. 997, 13-19). Dr. Sulak also pointed out that the '032 patent lacks any statistically significant data about whether a particular extended regimen would work. (T. 997, 20-22).

13. Rosenberg

Rosenberg et al., *Efficacy, Cycle Control, and Side Effects of Low and Lower-Dose Oral Contraceptives: A Randomized Trial of 20 mcg and 35 mcg Estrogen Preparations*, 60 Contraception 321 (1999) ("Rosenberg") (JTX-10) is offered by Teva as proof that the prior art taught away from the claimed invention. (T. 1143, 5-9). Rosenberg reported the results of a head-to-head comparative study of three OCs: Alesse, Ortho Tri-Cyclen, and Mircette. (JTX-10 at 321). All three of these OCs are standard-length (28-day) regimens with a 21-day first interval and a 7-day second interval. (JTX-10 at 322). The doses and duration of the three OCs compared in Rosenberg are as follows:

Brand	**Manufacturer**	**First Interval (21 days)**	**Second Interval (7 days)**
Alesse	Wyeth-Ayerst	20 mcg EE 100 mcg levonorgestrel	Hormone-free
Mircette	Organon	20 mcg EE 150 mcg desogestrel	Days 22-23: Hormone-free Days 24-28: 10 mcg EE
Ortho Tri-Cyclen	Ortho Pharmas	Days 1-7 35 mcg EE 180 mcg norgestimate Days 8-14 35 mcg EE 215 mcg norgestimate Days 15-21 35 mcg EE 250 mcg norgestimate	Hormone-free

(JTX-10 at 322). The results were obtained from 463 subjects gathered from 15 separate study sites distributed across the United States. (JTX-10 at 321, 328). One OC was randomly assigned to each subject, and the subjects were to use the product for six cycles. (JTX-10 at 322). The study was funded by Organon, makers of Mircette. (JTX-10 at 328). The study was designed to compare efficacy, estrogenic side effects, and cycle control between oral contraception preparations with 20 mcg of estrogen during the first interval (like Alesse and Mircette) and those with 35 mcg of estrogen (like Ortho Tri-Cyclen). (JTX-10 at 321).

At trial Dr. Barnhart concluded that even though the Rosenberg article was offered by Teva as proof that the prior art taught away from the claimed invention, the Rosenberg article actually supports the rationale for combining an extended regimen with unopposed estrogen. (T. 259, 2-6). According to Dr. Barnhart, Rosenberg "gets the same story about the need for a better pill, it gives the same story about what we might expect when we lower the dose, and it actually evaluates a clinically approved contraception." (T. 258, 6-9). Along the same lines Dr. Barnhart concluded that Rosenberg would certainly not have taught a PHOSITA to avoid adding unopposed estrogen in place of the HFI. (T. 257, 8-13). In support of his conclusion, Dr. Barnhart relied on Rosenberg's efficacy results.[13] (T. 249, 8 through T. 254, 25). In reviewing these results, Dr. Barnhart concluded that the study showed "a clear trend towards a lower pregnancy rate for Mircette compared to Tri-Cyclen." (T. 249, 13-15). Dr. Barnhart admitted that Rosenberg's authors concluded that there was no difference between the efficacy of the regimens because of the size of the study, but he remained

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[13] To the extent Dr. Barnhart relied on Rosenberg's results on cycle control, the Court finds the value of such analysis eroded by Dr. Barnhart's reexamination of the results during cross-examination. *Compare* (T. 251, 15 through T. 253:12) *with* (T. 421, 8 through T. 429, 8).

certain that "someone reading this paper would have recognized there was a trend towards a lower pregnancy rate" in OCs that added unopposed estrogen during the second interval. (T. 249, 16-18). Dr. Barnhart also relied on the final sentence of the Discussion section of the Rosenberg article, which states: "Subject to additional work to confirm and extend our findings, this study suggests that 20 [mcg OCs] represents a logical and beneficial progression of the trend toward [oral contraception] with lower estrogen doses." (JTX-10 at 328) (T. 255, 23 through T. 256, 3).

Dr. Carr agreed with Dr. Barnhart on the point that there was nothing in Rosenberg that would discourage or lead a PHOSITA away from combining the teachings of extended regimens and unopposed estrogen. (T. 835, 10-15). However Dr. Carr disagreed with Dr. Barnhart's analysis of Rosenberg's efficacy results. (T. 885, 17-22). According to Dr. Carr, there were too few subjects to perform a reliable study; therefore, Rosenberg's efficacy results were inherently unreliable. (T. 885, 17-22).

Dr. Sulak testified that Rosenberg showed that there were no benefits to the unopposed estrogen in Mircette. (T. 1033, 1-4). On the efficacy issue, Dr. Sulak agreed with Dr. Carr that the sample size was too small to provide meaningful results. (T. 1035, 1-6). Specifically with regard to cycle control, Dr. Sulak testified:

> [W]hat [the study] showed, was that actually the progestin matters. Mircette has a lower incidence . . . in the first couple of cycles, but there was no improvement. That Mircette contains desogestrel, and Alesse contains levonorgestrel, and because there are different progestins, it's hard to compare bleeding. But in this trial over time, if that addition of the estrogen to the [HFI], if it actually does something to breakthrough bleeding, then – after the first month you should start seeing improvement in that pill, and you should see improvement over the other – the other 20 microgram pill.

> And just the opposite occurred. The bleeding profile in Mircette actually got worse in the fourth cycle, whereas Alesse is getting better. So you saw – unfortunately they actually saw the opposite of what we would have liked to have seen, if that estrogen did anything.

(T. 1036, 7-22). Dr. Sulak relied on these results for her conclusion that a PHOSITA would not have been encouraged to use unopposed estrogen in the HFI. (T. 1041, 10-11).

14. The '749 Patent

U.S. Patent No. 6,027,749 ("the '749 patent") titled "Pharmaceutical Combined Preparation, Kit and Method for Hormonal Contraception" was issued on February 22, 2000. (LTX-233 at cover). At the heart of the patent is a two-stage OC preparation in which the first stage involves a combined OC containing estrogen and progestin and the second stage includes unopposed estrogen.[14] (LTX-233 at cover). By the terms of the patent, the range of this regimen varies between a minimum of 30 days (25 days of combined OC and 5 days of unopposed estrogen) and a maximum of 91 days (84 days of combined OC and 7 days of unopposed estrogen). (LTX-233 at cover) (LTX-233, col. 4, ll.19-29). Notably, the '749 patent describes a large number of potential doses and ingredients. (LTX-233, col. 4, ll. 19 – col. 7, l. 4). The parties agree that there is no evidence that any of the regimens described in the patent were tested, nor is there any evidence that the owner of the patent attempted to bring any of these regimens to market. (T. 400, 23 through T. 401, 19) (T. 866, 20 through T. 867, 8) (T. 1052, 17-18).

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[14] In the abstract, the combination includes "oestrogen" and "gestagen." (LTX-233 at cover). During trial, the experts explained that these terms are equivalent to "estrogen" and "progestin," respectively. (T. 102, 6-20) (T. 1046, 23-24).

At trial Dr. Barnhart provided two conclusions related to the '749 patent: (1) the '749 patent disclosed the Seasonique regimen (i.e., 84 days of combination pills (150 mcg levonorgestrel plus 30 mcg EE) followed by 7 days of unopposed estrogen (10 mcg EE)); and (2) the '749 patent, in conjunction with prior art as a whole, taught toward the Seasonique regimen. (T. 101, 09 through T. 113, 19) (T. 269, 16 through T. 272, 14). In support of this first conclusion, Dr. Barnhart cited duration information located in column 4 ("the first stage comprises a . . . maximum of 84 daily unit doses, . . . the second stage comprises 7 daily unit doses,") (LTX-233, col. 4, 19-29) (T. 102, 21 through T. 104, 8); hormone selection information located in column 6 ("[p]referably, in all embodiments of the invention the oestrogen of the first hormone component is . . . ethynyloestradiol and . . . the gestagen is . . . levonorgestrel, . . . and also the oestrogen of the second hormone component is . . . ethynyloestradiol . . .) (LTX-233, col. 6, ll 9-25) (T. 105, 6 through T. 106, 1), and the dosing information located in column 6 ("[a]ccording to an especially preferred embodiment the second hormone component contains as oestrogen ethynyloestradiol in an amount of from 0.01 to 0.015 mg[15] in each daily unit dose") (LTX-233, col. 6, ll. 56-69) (T. 104, 9 through 105, 5). Dr. Barnhart also cited example 5 of the '749 patent which Dr. Barnhart testified "is almost exactly the regimen called out in the '969 patent." (T. 106, 24-25). In support of the second conclusion, Dr. Barnhart testified that even though the '749 patent disclosed thousands of possible regimens, the patent still directed a PHOSITA toward the Seasonique regimen. On the issue of hormone selection, Dr. Barnhart testified that some hormones are more likely to be selected by a PHOSITA than others, whether because of common usage, (T. 105, 11-13 (stating that EE is the only listed estrogen that

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[15] The parties agree that these amounts correspond to "10-to-15 mcg" of EE. (T. 104, 23 through T. 105, 1).

is "commonly used")), or because they are listed as "preferred" within the patent. (T. 106, 2-7 (noting that the patent lists "gestodene" and "levonorgestral" as the preferred progestins)). On the issue of duration, Dr. Barnhart testified that the duration of an OC cycle is meant to correspond to a "memorable calendar event," and often this event is a calendar week. (T. 103, 13-25).[16] Based on this understanding, Dr. Barnhart concluded that the obvious duration for the first stage of any extended regimen would be a multiple of one week (e.g., 12 weeks (84 days); 13 weeks (91 days)) (T. 103, 15-21); and the obvious duration for the second stage of the regimen would be a full week, as opposed to the "5, 6, or 7" days disclosed in the patent (LTX-233 at cover) (T. 104, 4-9). Dr. Barnhart further testified that a PHOSITA would have arrived at the Seasonique regimen by combining the '749 patent with other articles of prior art, particularly Kovacs, (T. 112, 16-23) or the '032 patent (T. 115, 2-15). Dr. Barnhart concluded that a PHOSITA would be motivated to combine such articles because the '749 patent itself listed a great number of benefits to employing the regimens disclosed in the '749 patent, including efficacy and cycle control. (T. 107, 8 through T. 109, 7) (T. 111, 21 through T. 112, 11) (LTX-233, col. 9, 33 – col. 10, 4).

On cross, Dr. Barnhart conceded that the '749 patent disclosed a list of estrogens, progestins, dosages, and durations (T. 394, 18-22). Dr. Barnhart claimed however that by winnowing the list down to the reasonable options, "[t]here's only a handful of progestins and a handful of estrogens, and in reality only a handful of doses." (T. 394, 21-24).[17] Dr. Barnhart also conceded that the '749

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16 According to Dr. Barnhart "it's really a matter of convenience and advertising and how we sell the product, there is no material difference between that time period, other than what you think will resonate with somebody when they're taking it." (T. 103, 13-25).

17 For example, Dr. Barnhart testified that "in the field . . . you consider [EE] doses in increments of five." (T. 395, 21-23). Dr. Sulak agreed with this particular assessment. (T. 1084, 24

patent includes preferred ranges for both EE and levongestrel that exclude the doses described in the '969 patent. *Compare* (LTX-233, col. 6, ll. 38-42 (max preferred dose of levonorgestrel is 125 mcg)) *with* (JTX-001, col. 22, ll. 7-10 (150 mcg of levonorgestrel)) (T. 396, 10-16); *compare* (LTX-233, col. 6, ll. 32-36 (max preferred dose for the first phase of EE is 25 mcg)) *with* (JTX-001, col. 22, ll. 1-2 (30 mcg of EE)) (T. 403, 13-16). Dr. Barnhart claimed however that other disclosures in the '749 patent would direct a PHOSITA to the doses disclosed in the '969 patent. (T. 403, 17-25). Furthermore, Dr. Barnhart reiterated that any disclosures absent in the '749 could be found elsewhere in the prior art. (T. 404, 14-18).

Dr. Carr's testimony corroborated Dr. Barnhart's testimony. (T. 806, 60 through T. 811, 24). However Dr. Carr was also able to provide a clear citation within the '749 patent to Microgynon, a 28 day European OC that prescribes the same dosages in the combined pill as the Seasonique regimen. (T. 807, 11-15) (T. 459, 16-19). According to Dr. Carr, the patent discloses that the Microgynon regimen can be used as the basis for the combined pill in an extended regimen. (T. 807, 17-23). Such a formulation would result, according to Dr. Carr, in the formulation "found in the claim 19 of the '969 patent." (T. 807, 20-23). On cross-examination, Dr. Carr reviewed the number of possible regimens disclosed in the '749 patent and arrived at a minimum of 1,800 permutations. (T. 861, 1 through T. 866, 19).

Dr. Sulak drew two conclusions from the '749 patent: (1) that the '749 did not disclose the Seasonique regimen, (T. 1045, 8-20), and (2) that the '749 patent actually taught away from the Seasonique regimen. (T. 1054, 16-19). Dr. Sulak cited three primary reasons for her conclusions:

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through T. 1085, 1).

> [T]his patent has a lot of problems; number one is the regimen, there's no specific regimen that's identified. And there are in fact a broad range of regimens, none of which include Seasonique.
>
> And second of all, the dosage range of the estrogens and progestins are multiple and wide. And third, they have a list of advantages that are claimed, that data as of 2001 would have [disproved].[18]

(T. 1045, 7-14). Dr. Sulak based these conclusions on the broad ranges of doses, durations, and hormones included in the'749 patent. (T. 1045, 24 through T. 1046, 24). Dr. Sulak also noted, as both Dr. Barnhart and Dr. Carr conceded, the '749 patent includes a ranges for EE and levonorgestrel that exclude the doses prescribed in the '969 patent (T. 1050, 1 through T. 1051, 5). Dr. Sulak also pointed out that the patent specifically discusses the prevention of hormone fluctuations, particularly in the estrogen. (T. 1047, 21 through T. 1048, 25). From this language Dr. Sulak determined that the inventors were "try[ing] to not have a big difference in the estrogen level between the combination pills, and . . . the estrogen only pills." (T. 1049, 10-16). Dr. Sulak concluded that such a formulation would preclude the regimen disclosed in the '969 patent as the '969 regimen includes 30 mcg of estrogen in the combination pill and 10 mcg of estrogen during the traditional HFI. (JTX-001, col. 22, ll. 1-6) (T. 1049, 17-23).

On cross-examination, Dr. Sulak conceded that the '749 patent discloses only continuous regimens that include a second stage of unopposed estrogen with no hormone-free days. (T. 1083, 14 through T. 1084, 9). Dr. Sulak also admitted that the '749 patent discloses both extended regimens and that application of unopposed estrogen during the traditionally HFI. (T. 1085, 13-18).

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[18] The data Dr. Sulak referred to is the Mircette data contained in the Rosenberg article. (T. 1045, 15-18).

15. Sulak Feb. 2000

In Patricia J. Sulak et al., *Hormone Withdrawal Symptoms in Oral Contraceptive Users*, 95 Obstetrics & Gynecology 261 (2000) ("Sulak Feb. 2000") (JTX-47) Dr. Sulak sought to gauge the frequency and severity of hormone related symptoms in OC users; and most particularly to compare the data of such symptoms during use of the active pill with the HFI. There were 262 participants in the study who may be broken down into several categories—26 participants had no previous OC use; 43 were prior OC users, and 193 are current OC users. Each participant was prescribed a 21 day hormone combination pill and a 7 day HFI. Each participant maintained a daily diary wherein each recorded pelvic pain, bleeding, headaches, analgesic user, nausea, vomiting, bloating or swelling, and breast tenderness. The results of the study showed that all symptoms were significantly worse during the seven day HFI than during the 21 days of hormone containing pills. Headaches, pain, breast tenderness, and bloating or swelling were all significantly worse during the HFI. This finding led Sulak to conclude that in order to achieve greater compliance with a regimen,

(a) "Shortening the HFI from 7 to 4 to 5 days could provide greater ovarian suppression and decrease the number of days of symptoms;"

(b) Adding estrogen during the HFI (7 days) may also better ovarian suppression and decrease symptoms wherein Sulak cites to Mircette which reduced the HFI to 2 days with 5 days of unopposed estrogen; and

(c) Overcoming problems during HFI could be managed by extending the number of active weeks before the HFI.

In her testimony, Dr. Sulak placed this reference into context. According to Dr. Sulak, the February 2000 study was "the first to find out what the hormone withdrawal symptoms are, and how

common they occur and how frequently they occur." (T. 1001, 11-15). Dr. Sulak's conclusions (above) were in the context of Mircette, and Dr. Sulak explained that "referring to Mircette whether those symptoms can be reduced, has not been evaluated it hadn't been studied." (T. 1001, 18-22). Dr. Sulak contends that her February 2000 study agrees with the Killick study where there was some follicular suppression in Mircette observed but "clinical significance of these [Killick's] findings is uncertain." (T. 1004, 5-11), and she emphasized Killick "can't draw any clinical meaningful outcomes." Hence, according to Dr. Sulak, the Mircette regimen (21 days of active pills, five days of estrogen and 2 days of HFI) did not provide any significant data to support the alleged invention here.

16. Sulak Aug. 2000

In Patricia J. Sulak, *Maximizing OC Benefits with Patent-Specific Schedules*, OBG Mgmt. 46-59 (Aug. 2000) ("Sulak Aug. 2000") (LTX-226), Dr. Sulak commented that women on OC regimen (21/7) "find only limited relief from their menstrual difficulties." Since the 21/7 regimen "mimicked the familiar natural cycle" it made the OC more acceptable and reassuring to women; but Dr. Sulak contended that adherence to this natural cycle should be abolished, and an alternative regimen may relieve side effects for a greater period of time. Dr. Sulak recommended to "tweak" the 21 days of active pills "many times" and "simultaneously shortening the" HFI from 7 to 4 or 5 days in order to decrease the side effects. Dr. Sulak concludes:

> Despite the significant reduction in the hormone content of OCs since their introduction, associated side effects — most commonly nausea, and vomiting, breakthrough bleeding and spotting, headaches, bloating or swelling and breast tenderness — still negatively affect patient acceptance of and compliance with a drug that provides tremendous contraceptive and non-contraceptive benefits. However, physicians can minimize those drawbacks simply by tweaking the flawed 21/7 schedule.

17. The Mircette Approval Package

The Medical Officer's Review of the Mircette FDA Application No. 20-713 ("Mircette Approval Package") (JTX-9) is an article of prior art offered by Teva as proof that the prior art taught away from the claimed invention. (T. 1143, 5-9). The Mircette Approval Package contains both the Center for Drug Evaluation and Research's official approval of Mircette as well as supporting documents. (JTX-9). Notably, the Mircette Approval Package describes three studies: one pivotal study used to determine the contraceptive efficacy of Mircette and two smaller studies that assessed Mircette's impact on follicular development and bleeding patterns. (JTX-9 at 3). Mircette was approved for marketing on April 22, 1998. (JTX-9 at initial page 2). The Mircette Approval Package became available on March 8, 2001, and is prior art to the '969 patent. (Stip. Fact ¶ 60).

Dr. Barnhart concluded that, contrary to Teva's assertions, the Mircette Approval Package actually teaches towards the '969 patent. (T. 260, 7-19). Dr. Barnhart came to this conclusion because the approval package "discloses the safety data regarding the unopposed estrogen as effect[ing] the endometrium, in that it discloses there was a study performed evaluating this, with absolutely no cases of endometrial hyperplasia or cancer." (T. 260, 3-6). Dr. Barnhart further testified that the approval package "would have actually given people confidence that Mircette, because it was FDA approved based on the data submitted, that it was clearly a safe effective contraception." (T. 260, 11-14). Dr. Barnhart conceded that the FDA asked the makers of Mircette to supply additional data regarding cancer and hyperplasia once the drug was marketed and sold; however, Dr. Barnhart stressed that Mircette was nonetheless approved as a safe and effective form of contraception. (T. 260, 20-22).

Dr. Sulak testified that the Mircette Approval Package concludes that "there's no proven benefit of Mircette over other pills." (T. 1037, 22-23). During trial, Dr. Sulak read the following language from the approval package:

> While the product appears effective, the studies failed to show that the addition of EE on days 24-28 improves follicular suppression or cycle control compared with not administering EE during this time. The risk of endometrial hyperplasia that theoretically ensues from the addition of five days of unopposed estrogen has not been adequately evaluated.

(JTX-9 at 33). From this language Dr. Sulak concluded that a PHOSITA would not have believed that the use of unopposed estrogen during a traditionally HFI would yield any advantages. (T. 1038, 20 through T. 1039, 2).

6. Inventor's Testimony

Dr. Carole Ben-Maimon testified about her role in creating the invention. In 2001, Dr. Ben-Maimon became president of Barr Research (T. 475, 5). Barr had several contraceptive products which had some "significant unmet medical needs." (T. 481, 22-24). Dr. Ben-Maimon specifically addressed the Seasonale product. She noted that it was an extended regimen of 84 days and 7 days of placebo. (T. 482, 21-22), and the dose approved by the FDA was 20 mcg of EE and 100 mcg of levonorgestrel. However, Seasonale did not move forward in the marketplace "because it had just unacceptable bleeding patterns, women were spotting pretty much continuously throughout the cycle." (T. 485, 5-9). As Dr. Ben-Maimon recalled, "Seasonale had bleeding problems in the first three cycles . . . , but at least for the first three cycles there was a significant amount of bleeding and spotting during the active pill phase which is very undesirable for women." (T. 486, 8-14). As a result of the bleeding problems, Dr. Ben-Maimon was seeking a solution. Dr. Ben-Maimon read some of the prior art, including the Kovacs and Sulak (1997) articles regarding breakthrough

bleeding and extended regimens. (T. 490, 13-14). She noted that the Kovacs article had a "large number of dropouts, and women just didn't tolerate the extended regimens." (T. 491, 16-17). According to Ben-Maimon, neither article provided a solution. (T. 493, 15-17).

As a result, she decided "actually to work on the [HFI]; [because] everyone had been working on the combination pill period, lowering the doses, but we decided to work on the [HFI]." (T. 550, 17-22). Hence, the alleged invention was an 84 day extended regimen with a combined pill of 30 mcg EE and 150 mg of levonorgestrel plus seven days of unopposed estrogen of 10 mg of EE. According to Dr. Ben-Maimon, the invention was not predictable "because nobody had ever done it." (T 527, 10-12),and common wisdom was that if you didn't have a break [from hormones] there was risks of endometrial cancer," due to no withdrawal bleed. (T. 529,22 through T. 530, 20)

Since Dr. Ben-Maimon "had a lot of training in" endocrinology and nephrology she had "always been aware of the fact that a little in the hormone area . . . may do more than you think." (T 555, 13-20). She proposed the 10 mcgs of unopposed estrogen replacing the HFI period. In addition, Dr. Ben-Maimon knew the FDA "liked the lowest effective dose," and felt the 10 mcg was worth pursuing. (T. 555, 20-24). Although her medical experience was the basis for suggesting to propose the 10 mcg of unopposed estrogen, Dr. Ben-Manion had read the Rosenberg article which discussed the Mircette regimen (T. 528, 20 through T. 529, 5). In addition, she had discussed the matter with Dr. Sulak (T 552, 10) and was aware of prior art where unopposed estrogen replaced part of the HFI. (T. 541, 20). Her co-inventors (Bell and Iskold) were critical of the low dose of unopposed estrogen. They thought the dose of unopposed estrogen should be 30 mcgs. As a result, Barr sought approval from the FDA to perform clinical tests on two regimens that had different amounts of unopposed estrogen.

7. Secondary Considerations

The parties have presented evidence on the following objective indicia of nonobviousness: (1) long-felt unmet need, (2) failure of others, (3) skepticism, (4) unexpected results, (5) praise, and (6) copying. The parties have agreed not to present evidence for or against obviousness with respect to the secondary factor of commercial success. (T. 980, 20 through T. 982, 2). The Court will analyze each of the secondary considerations in turn.

(1) Long-felt unmet need

Extended regimens were known since the 1970's. (T. 338, 23-25). While such regimens had multiple benefits, (T. 93, 15-19), the major disadvantage of such regimens was breakthrough bleeding. (T. 93, 19-22) (T. 991, 19 through T. 992, 1). Teva claims that the absence of an FDA-approved extended regimen with an acceptable bleeding profile represented a long-felt, unmet need. (Teva COL ¶ 186). Dr. Carr specifically testified that he agreed with this position at trial. (T. 912, 1-5). Defendants challenge this assertion, claiming that extended regimens were known about and available at least since 1994, (T. 340, 13-15) (JTX-21 at 274), and the bleeding profile of such regimens were acceptable to at least some women. (T. 340, 2-3). Defendants also cite to the Federal Circuit for the proposition that "[w]here the differences between the prior art and the claimed invention are as minimal as they are here, . . . it cannot be said that any long-felt need was unsolved." *Geo M. Martin Co. v. Alliance Mach. Sys. Int'l, LLC*, 618 F.3d 1294, 1304 (Fed. Cir. 2010).

(2) Failure of others

As of December 5, 2011, the critical date of the '969 patent, no extended regimens had been approved by the FDA. (T. 340, 16-22). Teva cites *Pfizer, Inc. v. Teva Pharmaceuticals USA, Inc.*, 460 Supp. 2d 655 (D.N.J. 2006), for the proposition that "[g]etting to market after securing FDA

approval is the inevitable corollary of solving the problem where there is an unmet need. Therefore, not getting to market with FDA approval is an appropriate benchmark for failure." *Pfizer*, 460 Supp. 2d at 662. According to Teva, all those who tried to create an extended OC with an acceptable bleeding profile—i.e., the Kovacs study, the Sulak 1997 article, the '749 patent—had failed. (Teva COL ¶ 182). Conversely Defendants assert that, for the reasons stated in their discussion of said prior art, neither Kovacs nor Sulak 1997 nor the '749 patent was a failure. (Defs.' FOF Reply ¶¶ 633-38). Furthermore, Defendants note that, while no extended regimens had FDA approval as of the critical date, the patent for Seasonale (the first FDA-approved extended regimen) was approved prior to the critical date. (JTX-053) (T. 115, 7 through T. 116, 1). Finally Defendants assert that "[a] commercialized product is not necessary for a PHOSITA to prescribe the regimen disclosed in the '749 patent, and therefore met the need in the art." (Defs' FOF Reply ¶ 637); *see also Geo*, 618 F.3d at 1304.

(3) Skepticism

Dr. Ben-Maimon testified that during the development of the Seasonique regimen, her proposal for a 91-day regimen including 84 days of combination pills followed by 10 mcg of unopposed estrogen—the regimen that would ultimately become Seasonique—was met with skepticism by the development team. (T. 524, 6-9) (T. 543, 20 through T. 544, 25). Dr. Ben-Maimon also testified that outside experts consultants, including Dr. Sulak and Dr. Andy Anderson,[19] were skeptical of her proposed regimen. (T. 571, 21 through T. 572, 20). Dr. Ben Maimon testified that "there was a lot of cynicism being conveyed to me about whether the [10 mcg] would have any effect

[19] Dr. Anderson is one of the leading experts in the OC field. (T. 483, 7-9).

at all." (T. 572, 14-16). Additionally, the FDA, when contacted about the proposed testing of the Seasonique regimen, stated that they "cannot . . . predict or anticipate the results" of the proposed regimen. (JTX-51 at TWH_LOSEA0159462). The FDA also stated that the Seasonique regimen was "anticipated to affect menses in such a way that women may not menstruate at all or may have irregular spotting/bleeding." (JTX-51 at TWH_LOSEA0159462).

According to Defendants, Dr. Ben-Maimon's testimony illustrates that Teva had no concerns that the addition of EE to the traditionally hormone-free interval could be problematic. (Defs' FOF ¶ 469) (T. 542, 18 through T. 552, 25). Defendants instead claim that "[t]he internal debate within [Teva's] predecessor did not concern whether the 10 mcg dosage would work. Rather, it was whether the 10 [mcg] dosage would work better than the 30 [mcg] dosage." (Defs' FOF ¶ 469). Regarding the comments of the FDA, at trial Dr. Barnhart disagreed with the assertion that the FDA's requirement to perform clinical testing on Seasonique constituted skepticism. (T. 295, 21-24). According to Dr. Barnhart, "the FDA requires a very high standard of proof before it will give a claim for a product. . . . The fact that the FDA says 'prove it,' is in my mind a completely different question." (T. 296, 1-15). Dr. Carr agreed with this interpretation. (T. 823, 4-9).

(4) Unexpected Results

After discussing the Seasonique regimen with the FDA, Teva's predecessor conducted efficacy and safety testing for both the 30 mcg and 10 mcg versions of Seasonique. (T. 569, 1-7). These tests, which ran for more than one year, "showed that the 10 mcg dose was effective in preventing pregnancy and had better bleeding patterns," including breakthrough bleeding and withdrawal bleeding, "than the 30 mcg dose." (T. 569, 5-13). Dr. Ben-Maimon was surprised and pleased by these results because she was "bucking the trend," and because the results showed that

the 10 mcg dose she championed was superior to the 30 mcg dose. (T. 569, 18-25). Ultimately, the PTO relied on the results of these tests in allowing the '969 patent. (JTX-2 at 2420) (T. 585, 16-25). Subsequently, Teva's predecessor performed a cross-study comparison of Seasonique and Seasonale. (T. 1059, 3-17) (PTX-311). The comparison showed that "the bleeding profile with Seasonique is somewhat better than Seasonale." (T. 1059, 18-21). The results of the cross-study comparison ultimately led to the FDA approving Seasonique. (T. 585, 19 through T. 586, 15). However, Dr. Ben-Maimon conceded that the cross study comparison was inadequate to permit any claims of clinical significance of the seven days of unopposed estrogen. (T. 777, 4-8).

(5) Praise

After distributing the testing data, Dr. Ben-Maimon received an email from Dr. Andrew Kaunitz, a member of the Seasonique advisory board. (T. 573, 13 through 574, 1). Dr. Kaunitz stated that Seasonique is an "innovative OC formulation" representing the "direction of the future." (PTX-377) (T. 579, 20-24). Additionally, in an article titled *The Clinical Rationale for Menses-Free Contraception* (PTX-359) Dr. Barnhart wrote: "[R]ecently, addition of 10 [mcg] [EE] per day to the previously hormone-free 7 days successfully improved cycle control and sharply decreased spotting in subsequent cycles." (PTX-359 at 1177) (T. 435, 18-22).

(6) Copying

There is no doubt that the Defendants seek to copy Seasonique. (Lupin Stip. of Infringement) (Mylan's Stip. of Infringement). Additionally, there is no debate that a third company, Watson Laboratories, Inc., seeks to copy Seasonique.[20]

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[20] *See* fn 2 (*Duramed Pharms. v. Watson Labs.*, Case No. 08-116 (D. Nev.)).

8. Evaluation of the Evidence

As initially set forth in the prior art section, Dr. Sulak's opinions were far different than those of Dr. Barnhart and Dr. Carr. The Court must determine which witness is most credible. The Court will focus on Dr. Sulak.

Dr. Sulak found her 1997 article and Kovacs article to teach away from the use of extended regimens. This may have been true to Dr. Sulak, but tricycling packets of OC as stated in Szarewski was part of the art, and widely adopted within doctors' practices. It is difficult to ignore the practice of tricycling packets when it was commonly used. Dr. Sulak's testimony that "it was just a concept" and that the Szarewski article should be discounted because it did not contain significant data is a faulty conclusion. As a result, Dr. Sulak's testimony is discounted on this point.

With regard to the Mircette articles (Killick, the Mircette Article, and the Mircette Study Group) and Rosenberg, Dr. Sulak criticizes them because the results did not reach significant statistical data, and therefore could not be relied upon by a PHOSITA. To the contrary, Drs. Barnhart and Carr believed these articles showed very positive results and Mircette was actively prescribed based on the FDA approval. It appears to this Court that the Mircette findings would have encouraged a PHOSITA to utilize the Mircette teaching, that is to reduce the HFI from 7 to 2 days using unopposed estrogen. Hence, the weight of Dr. Sulak's testimony is discounted on this point.

In reviewing the prior art as a whole and discounting Dr. Sulak's testimony, Dr. Carr and Dr. Barnhart were more believable as to the state of the prior art. They argue the prior art shows the obviousness of the '969 patent, and the Court agrees.

In reaching a decision of obviousness, the Court seeks to guard against use of hindsight. *See Shushank, Generic Pharmaceutical Patent and FDA Law* § 1.38 p. 39 (2010). In the Court's view,

Dr. Ben-Maimon's role is akin to a person who is within the definition of a PHOSITA. As a result, her testimony can be likened to that of the PHOSITA, and assist in determining whether improper use of hindsight occurred in deciding the case. The issue is whether Dr. Ben-Maimon's decision was a brainstorm or an act of common sense. Dr. Ben-Maimon is a medical doctor and her work experience included oversight of clinical testing. In addition, she reviewed the prior art including Sulak, Kovacs, Mircette, Rosenberg and the Seasonable patent, all things a PHOSITA might have done. Furthermore, as President of Barr Research, she was responsible for finding a market for the Seasonale product in light of the breakthrough bleeding issues (market pressure). There were limited solutions available—i.e., increasing or decreasing the dose of two known hormones and whether to include the use of the Mircette teachings to reduce the number of days of HFI. In addition, Dr. Ben-Maimon knew the 84 day extended regimen was for women who had PMS and PMDD for whom extended regimens were often prescribed. In light of all the evidence, it was obvious to try to eliminate the HFI in light of Mircette's promising results for the target group. To eliminate the HFI was only 2 more days! In that light, the creation of '969 patent was more common sense than a brainstorm. It is more like fitting the pieces of a puzzle together. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 420 (2007). Any PHOSITA would have reached the same conclusion as Dr. Ben-Maimon.[21]

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[21] The Court thus determines that the evidence of prima facie evidence is strong, and any evidence brought by Teva regarding secondary considerations are substantially outweighed. *See Tokai Corp. v. Easton Enterprises, Inc.*, 632 F.3d 1358, 1371 (Fed. Cir. 2011).

Conclusion

In reviewing all of the evidence, the prior art, the inventor's testimony, and the secondary factors, the Court finds that the Defendants presented clear and convincing evidence that the '969 patent is obvious. An appropriate form of order will follow shortly.

s/Peter G. Sheridan
PETER G. SHERIDAN, U.S.D.J.

June 29, 2012