(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 September 2014 (18.09.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/143669 A1

(51) International Patent Classification:
A61K 45/06 (2006.01) *A61K 31/57* (2006.01)
A61K 31/513 (2006.01) *A61P 15/00* (2006.01)
A61K 31/565 (2006.01) *A61K 35/00* (2006.01)

(21) International Application Number:
PCT/US2014/027673

(22) International Filing Date:
14 March 2014 (14.03.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/788,821 15 March 2013 (15.03.2013) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2014/143669 A1

(54) Title: COMPOSITIONS FOR USE IN TREATING HEAVY MENSTRUAL BLEEDING AND UTERINE FIBROIDS

(57) Abstract: The present invention relates to the method of treating heavy menstrual bleeding in a subject with or without uterine fibroids and in need of treatment by administering an effective amount of 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-tri-fluoromethyl-benzyl)-4- methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-l-yl]-l-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof, in combination with estrogens and progestogens.

METHODS OF TREATING HEAVY MENSTRUAL BLEEDING

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This claims priority to U.S. Patent Application No. 61/788,821, filed on March 15, 2013, the entire contents of which are fully incorporated herein by reference.

FIELD OF THE INVENTION

[0002] This invention pertains to the use of GnRH receptor antagonists for the treatment of heavy menstrual bleeding in a subject with or without uterine fibroids.

BACKGROUND OF THE INVENTION

[0003] Uterine fibroids (leiomyomata) are the most common benign tumors in women. Uterine fibroids are highly prevalent in women of reproductive age and are identified in more than 50% of women between 35 and 50 years of age. The incidence increases with age and is the most common reason for hysterectomy (Buttram VC Jr, Reiter RC. Uterine leiomyomata: etiology, symptomatology, and management. *Fertil Steril.* 1981;36(4):433-45; Day Baird D, Dunson DB, Hill MC, et al. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. *Am J Obstet Gynecol.* 2003;188(1):100-7).

[0004] The estimated annual direct costs of symptomatic uterine fibroids (surgery, hospital admissions, outpatient visits, and medications) are $4.1 to 9.4 billion. Estimated lost work-hour costs range from $1.55–17.2 billion annually. Obstetric outcomes attributed to fibroid tumors result in a cost of $238 million to $7.76 billion annually. Overall, uterine fibroid tumors were estimated to cost the United States $5.9-34.4 billion annually (Cardozo ER, Clark AD, Banks NK, et al. The estimated annual cost of uterine leiomyomata in the United States. *Am J Obstet Gynecol* 2012;206:211.e1-9).

[0005] Although often asymptomatic, fibroids may cause symptoms severe enough to warrant therapy in 20% to 50% of women. Symptoms associated with fibroids most commonly include heavy or prolonged menstrual bleeding, pelvic pressure and pelvic organ compression, back pain, and adverse reproductive outcomes. Heavy menstrual bleeding (HMB; menorrhagia, defined as greater than 80 mL per menstrual cycle) (The Menorrhagia Research Group. Quantification of menstrual blood loss. *The Obstetrician & Gynaecologist.*

2004;6:88-92) is inconvenient and may lead to iron-deficiency anemia, a key symptom of uterine fibroids and the leading cause of surgical interventions that may include hysterectomy. Other symptoms, in particular pressure symptoms, are largely dependent on the size, number, and location of the tumors.

[0006] Uterine fibroids are highly heterogeneous tumors with variable growth rates and symptomatology. Therefore, the choice of treatment is based on individual symptoms, patient preference, and the desire to preserve either fertility or the uterus, or both. Historically, hysterectomy or myomectomy were preferred treatment options for women with symptomatic uterine fibroids (Stewart EA. Uterine fibroids. *Lancet,* 2001;357:293-8; Myers ER, Barber MD, Gustilo-Ashby T, et al. Management of uterine leiomyomata: what do we really know? *Obstet Gynecol.* 2002:100(1):8-17). However, surgery is also associated with risks such as infections, bleeding complications, thromboembolic effects, scarring/adhesions, and even increased mortality (Maresh MJA, Metcalfe MA, McPherson K, et al. The VALUE national hysterectomy study: description of the patients and their surgery. *Br J Obstet Gynaecol.* 2002;109(3):302-12). The mortality rate for hysterectomy for benign indications is approximately 0.38 per 1,000 cases (Maresh MJA, Metcalfe MA, McPherson K, et al. The VALUE national hysterectomy study: description of the patients and their surgery. *Br J Obstet Gynaecol.* 2002;109(3):302-12). Furthermore, many women opt not to have a hysterectomy for cultural or reproductive reasons. The long-term side effects of hysterectomy may include higher rates of depression in younger women and incontinence in women at least 60 years old (Brown JS, Sawaya G, Thom DH, et al. Hysterectomy and urinary incontinence: a systematic review. *Lancet,* 2000;356:535-39; Carlson KJ, Miller BA, Fowler FJ Jr. The Maine Women's Health Study: I. Outcomes of hysterectomy. *Obstet Gynecol.* 1994;83(4):556-65). As more women delay maternity into their 30s and 40s, there is a growing need for alternatives to surgical treatments, especially hysterectomy. To meet this demand, during the past two decades, many new uterus-sparing therapies have been proposed and studied including semi-invasive procedures, such as uterine artery embolization and magnetic resonance imaging (MRI)-guided high-intensity focused ultrasound ablation therapy as well as nonsurgical, medical treatments. Of note, none of these uterus-sparing methods provide definitive cure, as fibroids often recur following treatment.

[0007] Although the pathogenesis has yet to be fully elucidated, the growth of uterine fibroids is known to be highly dependent on both estrogen and progestogen. This

dependence on ovarian hormones is evidenced by the spontaneous reduction in fibroid size commonly observed after menopause, a natural anovulatory and hypoestrogenic state. On this basis, most medical treatments for women with symptomatic uterine fibroids are aimed at either hormone-blocking or hormone-modulating strategies.

[0008] The ideal medical treatment for symptomatic uterine fibroids, as an alternative to surgical interventions, should provide control of heavy menstrual bleeding, reduce fibroid and uterine volume, improve quality of life, and prove safe and tolerable as a chronic therapy. Unfortunately, currently available medical options provide only short-term improvement of symptoms, and as such, are only indicated prior to surgery or their side-effects limit their long-term use. A safe and effective chronic medical therapy for symptomatic uterine fibroids, as an alternative to hysterectomy or other surgical intervention, has not yet been approved.

[0009] Currently there are no chronic treatments approved for the long term management of heavy menstrual blood loss associated with symptomatic uterine fibroids. However, in the United States, leuprolide acetate (Lupron®) in combination with iron is approved for the preoperative short-term treatment of women with uterine fibroids to improve hematological parameters (Stovall TG. Gonadotropin-releasing hormone agonists: utilization before hysterectomy. *Clin Obstet Gynecol.* 1993;36(3):642-9; Lupron Depot (leuprolide acetate for depot suspension) injection, powder, lyophilized, for suspension [package insert]. North Chicago, IL; Abbott, January 2011; Lethaby A, Vollenhoven B, Sowter MC. Pre-operative GnRH analogue therapy before hysterectomy or myomectomy for uterine fibroids. *Cochrane Database of Syst Rev.* 2009;1:1-97). Beside the preoperative treatment, different medical treatments have been used for the management of heavy menstrual bleeding associated with uterine fibroids that include tranexamic acid, combined oral contraceptives, levonorgestrel intrauterine system (LNG-IUS), high-dose progestins, androgens (danazol), progestogen receptor modulators, GnRH agonists, and GnRH antagonists (*Heavy Menstrual Bleeding.* Welsh A, ed. London: RCOG Press at Royal College of Obstetricians and Gynaecologists; 2007; Stewart A, Cummins C, Gold L, et al. The effectiveness of levonorgestrel-releasing intrauterine system in menorrhagia: a systematic review. BJOG. 2001;108(1):74-86; Lethaby A, Vollenhoven B, Sowter MC. Pre-operative GnRH analogue therapy before hysterectomy or myomectomy for uterine fibroids. *Cochrane Database of Syst Rev.* 2009;1:1-97; Carr BR, Marshburn PB, Weatherall PT, et al. An evaluation of the effect of

gonadotropin releasing hormone analogs and medroxyprogesterone acetate on uterine leiomyomata volume by magnetic resonance imaging: a prospective, randomized, double-blind, placebo-controlled, crossover trial. *J Clin Endocrinol Metab.* 1993;76(5):1217-23; Friedman AM, Daly M, Juneau-Norcross M, et al. A prospective, randomized trial of gonadotropin-releasing hormone agonist plus estrogen progestin or progestin add-back regimens for women with leiomyomata uteri. *J Clin Endocrinol Metab.* 1993;76(6):1439-45; Adamson GD. Treatment of uterine fibroids: current findings with gonadotropin-releasing hormone agonists. *Am J Obstet Gynecol.* 1992;166:746-51; Stovall TG. Gonadotropin-releasing hormone agonists: utilization before hysterectomy. *Clin Obstet Gynecol.* 1993;36(3):642-9). All these treatments are variously effective in reducing heavy menstrual bleeding, but only a few (namely, GnRH agonists, androgens, aromatase inhibitors) also reduce fibroid and uterine volume.

[0010] The antifibrinolytic drug, tranexamic acid has been widely used for more than 2 decades outside the United States for the management of heavy menstrual bleeding and was approved in 2009 in the United States for the management of heavy menstrual bleeding in women with or without uterine fibroids (FDA approves Lysteda to treat heavy menstrual bleeding [press release]. Silver Spring, MD; US Food and Drug Administration, 13 November 2009. Available from http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm190551.htm. Accessed on: 19 June 2012).

[0011] Although combined oral contraceptives (OCs) are widely used for the treatment of women complaining of anovulatory bleeding, to date, there are no high-quality comparative studies supporting their use in heavy menstrual bleeding associated with uterine fibroids. Nevertheless, combined OCs are frequently used for the temporary management of heavy menstrual bleeding. Epidemiological studies indicate that combined OCs are neutral in terms of their effects on fibroid growth or prevalence.

[0012] The levonorgestrel intrauterine system ("LNG-IUS") has been approved for the management of heavy menstrual bleeding in women who use intrauterine contraception as their method of pregnancy prevention. However, LNG-IUS may only be used in women who have no distortion of the uterine cavity. Additionally, oral high-dose progestins are the most commonly prescribed therapy for short-term management of heavy menstrual bleeding not associated with uterine fibroids. However, little evidence supports the use of progestins in

the presence of uterine fibroids and high-dose progestin may stimulate fibroid growth when used continuously as a monotherapy, or in conjunction with a GnRH agonist as add-back therapy (Carr BR, Marshburn PB, Weatherall PT, et al. An evaluation of the effect of gonadotropin releasing hormone analogs and medroxyprogesterone acetate on uterine leiomyomata volume by magnetic resonance imaging: a prospective, randomized, double-blind, placebo-controlled, crossover trial. *J Clin Endocrinol Metab.* 1993;76(5):1217-23; Friedman AM, Daly M, Juneau-Norcross M, et al. A prospective, randomized trial of gonadotropin-releasing hormone agonist plus estrogen progestin or progestin add-back regimens for women with leiomyomata uteri. *J Clin Endocrinol Metab.* 1993;76(6):1439-45). In addition, continuous use of progestins may actually induce breakthrough bleeding and spotting via negative effects on normal endometrial angiogenesis (Hickey M, Dwarte D, Fraser IS. Superficial endometrial vascular fragility in Norplant users and in women with ovulatory dysfunctional uterine bleeding. Hum Reprod 2000;15:1509-14) and may increase endometrial vascular fragility (38 Simbar et al., 2004).

[0013] Clinical data from registration studies with leuprolide acetate (Lupron Depot®) (Lupron Depot® (leuprolide acetate for depot suspension) injection, powder, lyophilized, for suspension [package insert]. and a review of the literature, indicate that GnRH agonists are effective at inducing amenorrhea, improving anemia in women with symptomatic uterine fibroids, and substantially reducing uterine and fibroid volumes. GnRH agonists provide a 30% to 50% reduction in fibroid volume within 3 months of treatment (Carr BR, Marshburn PB, Weatherall PT, et al. An evaluation of the effect of gonadotropin releasing hormone analogs and medroxyprogesterone acetate on uterine leiomyomata volume by magnetic resonance imaging: a prospective, randomized, double-blind, placebo-controlled, crossover trial. *J Clin Endocrinol Metab.* 1993;76(5):1217-23; Friedman AM, Daly M, Juneau-Norcross M, et al. A prospective, randomized trial of gonadotropin-releasing hormone agonist plus estrogen progestin or progestin add-back regimens for women with leiomyomata uteri. *J Clin Endocrinol Metab.* 1993;76(6):1439-45). In addition, the side effects of estrogen deprivation, primarily bone mineral density (BMD) loss and severe hot flushes, limit the use of GnRH agonists. In fact, menopausal symptoms in women with surgically-induced menopause (which is similar to GnRH agonist-induced menopause) are more severe than symptoms in women who undergo menopause naturally (Treatment of menopause-associated vasomotor symptoms: position statement of The North American Menopause Society.

Menopause, 2004:11(1):11-33; Hendrix S. Bilateral oophorectomy and premature menopause. *Am J Med.* 2005;118 (12 Suppl 2):131-5). Furthermore, the effects on the uterus are reversible, gradual regrowth of fibroids occurs within months of treatment cessation.

[0014] Concerns about bone loss and poor tolerability of GnRH agonist monotherapy led to a number of studies whereby various potential add-back therapies were added to these GnRH-agonist regimens. In contrast to the management of endometriosis, there are no FDA-approved add-back therapies for use with GnRH agonists for women with uterine fibroids. Early trials focused on progestin-only add-back therapies, including medroxyprogesterone acetate (15 – 20 mg/day orally) or norethindrone (10 mg/day orally), and there was a reduction of hot flashes but the reduction in uterine or uterine fibroid volume was significantly limited (Carr BR, Marshburn PB, Weatherall PT, et al. An evaluation of the effect of gonadotropin releasing hormone analogs and medroxyprogesterone acetate on uterine leiomyomata volume by magnetic resonance imaging: a prospective, randomized, double-blind, placebo-controlled, crossover trial. *J Clin Endocrinol Metab.* 1993;76(5):1217-23). The effect of progestin-only add-back therapy on uterine bleeding was not reported in these studies, although treatment with high-dose progestins is known to be associated with breakthrough bleeding and spotting.

[0015] Studies with progestogen receptor modulators (mifepristone, asoprisnil, ulipristal acetate) in this population (Chwalisz K, Perez MC, DeManno D, et al. Selective progestogen receptor modulator development and use in the treatment of leiomyomata and endometriosis. Endoc Rev 2005;26(3):423-38), as well as previous experience with high-dose progestins (Carr BR, Marshburn PB, Weatherall PT, et al. An evaluation of the effect of gonadotropin releasing hormone analogs and medroxyprogesterone acetate on uterine leiomyomata volume by magnetic resonance imaging: a prospective, randomized, double-blind, placebo-controlled, crossover trial. *J Clin Endocrinol Metab.* 1993;76(5):1217-23; Friedman AM, Daly M, Juneau-Norcross M, et al. A prospective, randomized trial of gonadotropin-releasing hormone agonist plus estrogen progestin or progestin add-back regimens for women with leiomyomata uteri. *J Clin Endocrinol Metab.* 1993;76(6):1439-45) indicate that uterine fibroids are highly progestogen-dependent. In contrast to other uterine tissues, high doses of progestins were shown to exert proliferative effects on uterine fibroids and these data explain the failure of progestin-based add-back therapy in women with uterine fibroids (Tiltman A.

The effects of progestins on the mitotic activity of uterine fibromyomas. Int J Gynecol Pathol. 1985;4:89-96; Maruo T, Matsuo H, Samoto T. et al. Effects of progestogen on uterine leiomyoma growth and apoptosis. Steroids. 2000;65:585-92). High-dose progestin treatment is also associated with uterine bleeding abnormalities such as breakthrough bleeding and spotting, and systemic side effects, including weight gain and metabolic effects (Hickey M, Dwarte D, Fraser IS. Superficial endometrial vascular fragility in Norplant users and in women with ovulatory dysfunctional uterine bleeding. *Hum Reprod* 2000;15:1509-14; Simbar M, Manconi F, Markham, R, et al. A three-dimensional study of endometrial microvessels in women using the contraceptive subdermal levonorgestrel implant system, norplant. *Micron.* 2004;35:589-95).

[0016] More recently, the effectiveness of low-dose E2 as add-back therapy when used in combination with GnRH agonists was demonstrated in 185 women with heavy menstrual bleeding associated with uterine fibroids (Daniels A, Pike MC, et al; Balance Pharmaceuticals Uterine Fibroids Study Group. Treatment with the GnRH agonist (GnRHa) desorelin (D) and low-dose add-back estradiol (E2) is effective in reducing pain, bleeding, and uterine volume (UV) while maintaining BMD in women with symptomatic uterine fibroids (UF). *Fertil Steril.* 2002;78(3, Suppl 1):O-170). These findings showed that the efficacy (reduction in uterine bleeding and volume) of deslorelin, a GnRH agonist, was maintained when dosed with low-dose transdermal E2, while mitigating significant BMD loss through 6 months of treatment. However, the chronic use of estrogen alone (without a progestin) as add-back therapy is not feasible because of the risk of unopposed estrogen effect on the endometrium that may lead to endometrial hyperplasia.

[0017] Therefore, there is a need in the art for new treatment methods for reducing or managing heavy menstrual blood loss and other symptoms associated with symptomatic uterine fibroids.

BRIEF SUMMARY OF THE INVENTION

[0018] The present invention relates to methods for reducing the volume of menstrual blood loss in a subject with or without uterine fibroids. The present invention also relates to a method for reducing the fibroid and uterine volume and treatment for non-bleeding-related symptoms of uterine fibroids. The methods comprise administering to a subject 300 to 600 mg per day of 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-

benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof, in combination with estrogens and progestogens. In the above methods, the estrogen is selected from the group consisting of estradiol, ethinyl estradiol, and conjugated estrogens, and the progestogen is selected from the group consisting of progesterone, norethindrone acetate, norgestimate, drospirenone, and medroxyprogesterone. For example, in the above methods, the estrogen is estradiol and the progestogens are norethindrone acetate and progesterone.

[0019] Subjects in need of treatment thereof have a volume of menstrual blood greater than 80 mL per menstrual cycle. Once said subjects are treated according to the above methods, these subjects have a volume of menstrual blood loss that is less than 80 mL per menstrual cycle.

[0020] Subjects treated according to the above methods can have uterine fibroids or do not have uterine fibroids.

[0021] Subjects treated according to the above methods can have non-bleeding symptoms related to uterine fibroids ("bulk symptoms") such as pelvic pressure, bloating, pelvic pain, uinary problems, etc.

[0022] In the above methods, the estradiol and norethindrone acetate (which is a progestogen) are administered orally once per day. For example, in one aspect, the estradiol is administered in an amount of about 0.5 mg and the norethindrone acetate is administered in an amount of about 0.1 mg per day. In another aspect, the estradiol is administered in an amount of about 1.0 mg and the norethindrone acetate is administered in an amount of about 0.5 mg per day. Alternatively, the estradiol is administered continuously and the norethindrone acetate is administered once per day during the last 12-14 days of a menstrual cycle.

[0023] In the above methods, the 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof is administered in an amount of about 300 mg per day. Specifically, the 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof is administered twice per day.

[0024] In the above methods, the 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof is administered in an amount of about 400 mg per day. Specifically, the 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof is administered twice per day.

[0025] In the above methods, the 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof is administered in an amount of about 600 mg per day. Specifically, the 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof is administered twice per day.

[0026] In the above methods, the 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid, estrogens, and progestogens are administered daily for at least 28 days. In another aspect, the 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid, estrogens, and progestogens are administered daily for at least 56 days. In yet still another aspect, the 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid, estrogens, and progestogens are administered daily for at least 84 days. In still yet another aspect, the 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid, estrogens, and progestogens are administered daily for at least 168 days. In still yet another aspect, the 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid, estrogens, and progestogens are administered daily for about 168 days to about 1 year.

[0027] The present invention also relates to a method for treating uterine fibroids in a subject in need of treatment. The method comprises administering to the subject 300 to 600

mg per day of 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof, in combination with estrogens and progestogens. For example, in the above method, the estrogen is estradiol and the progestogens are norethindrone acetate and progesterone.

[0028] In the above method, the estradiol and norethindrone acetate are administered once per day. For example, in one aspect, the estradiol is administered in an amount of about 0.5 mg and the norethindrone acetate is administered in an amount of about 0.1 mg per day. In another aspect, the estradiol is administered in an amount of about 1.0 mg and the norethindrone acetate is administered in an amount of about 0.5 mg per day.

[0029] In the above method, the 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof is administered in an amount of about 300 mg per day. Specifically, the 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof is administered twice per day.

[0030] In the above method, the 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof is administered in an amount of about 400 mg per day. Specifically, the 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof is administered twice per day.

[0031] In the above method, the 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof is administered in an amount of about 600 mg per day. Specifically, the 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof is administered twice per day.

[0032] In the above method, the 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid, estrogens, and progestogens are administered daily for at least 28 days. In another aspect, the 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid, estrogens, and progestogens are administered daily for at least 56 days. In yet still another aspect, the 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid, estrogens, and progestogens are administered daily for at least 84 days. In still yet another aspect, the 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid, estrogens, and progestogens are administered daily for at least 168 days. In still yet another aspect, the 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid, estrogens, and progestogens are administered daily for about 168 days to about 1 year.

BRIEF DESCRIPTION OF THE FIGURES

[0033] Figure 1 shows the composite bleeding endpoint (percentage of subjects with blood loss reduction <80 ml/cycle and ≥50% reduction in blood loss compared to baseline) and amenorrhea (no bleeding or spotting) for the study described in Example 1. Figure 1 shows the last observation carried forward (LOCF) for the last 28 days of treatment in all subjects. The composite bleeding endpoint shown on the left was calculated using alkaline hematin data. Amenorrhea was calculated using both alkaline hematin data and a daily bleeding diary data. For each of the Composite Bleeding Endpoint and Amenorrhea bar graphs shown in Figure 1, patients were treated with Elagolix 300 BID (N=30) (first bar on the far left), E600 QD (N=28) (second bar from the left), E300 + estrogen (1.0 mg of estradiol (Estrace®)) and 200 mg progesterone (cyclical Prometrium®) (collectively referred to as "EP") (N=26) (third bar rom the left), E200 BID (N=33) (fourth bar from the left), E400 QD (N=31) (fifth bar from the left), E200 BID + a low dose Activella® (a combination of 0.5 mg estradiol and 0.1 mg northindrone acetate) (referred to as "A") (N=34) (sixth bar from the left), E100 BID (seventh bar from the left) (N=31) and placebo (PBO) (N=49)

(eighth bar from the left (or first on the right)). P values are defined as: ***p<0.001 for Elagolix vs. pooled placebo (PBO; PBO from cohorts 1, 2 & 4). **p<0.01 for Elagolix vs. pooled PBO (PBO from cohorts 1, 2 & 4).

[0034] Figure 2 shows the average total blood loss measured by the alkaline hematin methods during three (3) months of treatment as described in the study in Example 1. Patients were treated with Elagolix 600 QD (N=24), Elagolix 300 BID (N=26), Elagolix 400 QD (N=26), Elagolix 200 BID (N=28), Elagolix 200 BID plus low dose Activella® (a combination of 0.5 mg estradiol and 0.1 mg northindrone acetate), Elagolix 300 BID plus estrogen (1.0 mg of estradiol (Estrace®)) and 200 mg progesterone (cyclical Prometrium®) (collectively referred to as "EP") (N=25); Elagolix 100 BID (N=26) and placebo (PBO) (N=43).

[0035] Figure 3 shows an analysis of the average monthly blood loss (MBL) measured by the alkaline hematin methods during three (3) months of treatment as described in the study in Example 1. Patients were treated with Elagolix 600 QD, Elagolix 300 BID, Elagolix 400 QD, Elagolix 200 BID, Elagolix 200 BID plus low dose Activella® (a combination of 0.5 mg estradiol and 0.1 mg northindrone acetate), Elagolix 300 BID plus estrogen (1.0 mg of estradiol (Estrace®)) and 200 mg progesterone (cyclical Prometrium®); Elagolix 100 BID and placebo. For each of the eight (8) doses shown in Figure 3, 4 bars are shown. The bar farthest to the left shows the average blood loss per cycle measured by AH method in screening (mL). The second bar is the average total MBL from days 6-35 post-baseline (mL). The third bar is the average total MBL from days 36-65 post-baseline (mL). The fourth bar (furthest to the right) is the average total MBL in days 66-95 post-baseline (mL).

[0036] Figure 4 shows an analysis of the mean percentage (%) change from baseline on each of primary fibroid and uterine volume as described in the study in Example 1. For the primary fibroid volume and uterine volume data shown in Figure 4, patients were treated with Elagolix 300 BID (N=30) (first bar on the far left), E600 QD (N=27) (second bar from the left), E300 + estrogen (1.0 mg of estradiol (Estrace®)) and 200 mg progesterone (cyclical Prometrium®) (referred to as "EP") (N=21) (third bar from the left), E200 BID (N=34) (fourth bar from the left), E400 QD (N=27) (fifth bar from the left), E200 BID + a low dose Activella® (a combination of 0.5 mg estradiol and 0.1 mg northindrone acetate) (referred to as "A") (N=32) (sixth bar from the left), E100 BID (seventh bar from the left) (N=28) and placebo (PBO) (N=47) (eighth bar from the left (or first on the right)). P values are defined

as: ***p<0.001 for Elagolix vs. pooled placebo (PBO; PBO from cohorts 1, 2 & 4). **p<0.01 for Elagolix vs. pooled PBO (PBO from cohorts 1, 2 & 4). *p<0.05 for Elagolix vs. pooled placebo (PBO; PBO from cohorts 1, 2 & 4).

[0037] Figure 5 shows an analysis of uterine fibroid symptom severity and quality of life (UFS-QoL) results as described in the study in Example 1. For the symptom severity and Health Related Quality of Life (HRQL) total scores and uterine volume data shown in Figure 5, patients were treated with Elagolix 300 BID (N=28) (first bar on the far left), E600 QD (N=28) (second bar from the left), E300 + estrogen (1.0 mg of estradiol (Estrace®)) and 200 mg progesterone (cyclical Prometrium®) (referred to as "EP") (N=25) (third bar from the left), E200 BID (N=32) (fourth bar from the left), E400 QD (N=30) (fifth bar from the left), E200 BID + a low dose Activella® (a combination of 0.5 mg estradiol and 0.1 mg northindrone acetate) (referred to as "A") (N=30) (sixth bar from the left), E100 BID (seventh bar from the left) (N=29) and placebo (PBO) (N=46) (eighth bar from the left (or first on the right)). P values are defined as: ***p<0.001 for Elagolix vs. pooled placebo (PBO; PBO from cohorts 1, 2 & 4). **p<0.01 for Elagolix vs. pooled PBO (PBO from cohorts 1, 2 & 4). *p<0.05 for Elagolix vs. pooled placebo (PBO; PBO from cohorts 1, 2 & 4).

DETAILED DESCRIPTION OF THE INVENTION

[0038] *Definitions*

[0039] Unless otherwise defined herein, scientific and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. The meaning and scope of the terms should be clear, however, in the event of any latent ambiguity, definitions provided herein take precedent over any dictionary or extrinsic definition. In this application, the use of "or" means "and/or" unless stated otherwise. Furthermore, the use of the term "including", as well as other forms, such as "includes" and "included", is not limiting. With reference to the use of the words "comprise" or "comprises" or "comprising" in this patent application (including the claims), Applicants note that unless the context requires otherwise, those words are used on the basis and clear understanding that they are to be interpreted inclusively, rather than exclusively, and that Applicants intend each of those words to be so interpreted in construing this patent application, including the claims below. For a variable that occurs more than one time in any

substituent or in the compound of the invention or any other formulae herein, its definition on each occurrence is independent of its definition at every other occurrence.

[0040] The term "Elagolix" refers to 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof. Elagolix is an orally active, non-peptide GnRH antagonist and is unlike other GnRH agonists and injectable (peptide) GnRH antagonists. Elagolix produces a dose dependent suppression of pituitary and ovarian hormones in women. Methods of making Elagolix and a pharmaceutically acceptable salt thereof are described in WO 2005/007165, the contents of which are herein incorporated by reference.

[0041] Elagolix or 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid may generally be utilized as the free acid or free base. Alternatively, Elagolix or 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid may be used in the form of acid or base addition salts. Acid addition salts of the free amino compounds of the present invention may be prepared by methods well known in the art, and may be formed from organic and inorganic acids. Suitable organic acids include maleic, fumaric, benzoic, ascorbic, succinic, methanesulfonic, acetic, trifluoroacetic, oxalic, propionic, tartaric, salicylic, citric, gluconic, lactic, mandelic, cinnamic, aspartic, stearic, palmitic, glycolic, glutamic, and benzenesulfonic acids. Suitable inorganic acids include hydrochloric, hydrobromic, sulfuric, phosphoric, and nitric acids. Base addition salts included those salts that form with the carboxylate anion and include salts formed with organic and inorganic cations such as those chosen from the alkali and alkaline earth metals (for example, lithium, sodium, potassium, magnesium, barium and calcium), as well as the ammonium ion and substituted derivatives thereof (for example, dibenzylammonium, benzylammonium, 2-hydroxyethylammonium, and the like). Thus, the term "pharmaceutically acceptable salt" of Elagolix or 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid is intended to encompass any and all acceptable salt forms.

[0042] In addition, Elagolix or 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or salts thereof may also form solvates with water or other organic solvents. Such solvates are similarly included within the scope of this invention.

[0043] The terms "treat", "treating" and "treatment" refer to a method of alleviating or abrogating a disease and/or its attendant symptoms.

[0044] By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0045] "Solvate" of a compound refers to a molecular complex of the solute (the compound) and the solvent.

[0046] The "subject" is defined herein to include animals such as mammals, including, but not limited to, primates (e.g., humans) and the like. In preferred embodiments and aspects, the subject is a human female. In yet another embodiment or aspect, the subject is a premenopausal human female.

[0047] "Effective amount" or a "pharmaceutically-effective amount" in reference to Elagolix or 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid, or salts thereof, or estrogens or progestogens refers to the amount sufficient to induce a desired biological, pharmacological, or therapeutic outcome in a subject.

[0048] *Methods of Reducing or Managing Heavy Menstrual Bleeding Associated with Uterine Fibroids*

[0049] In one embodiment, the present invention relates to methods for reducing or managing heavy menstrual bleeding (HMB) associated with uterine fibroids in subjects in need of treatment thereof. Heavy menstrual bleeding refers to a subject experiencing greater than 80 mL of blood loss per menstrual cycle (a menstrual cycle is typically 28 days). In contrast, women who do not suffer from heavy menstrual bleeding experience about 30-40 mL of blood loss per menstrual cycle. In one aspect, the methods of the present invention can be used to reduce or manage heavy menstrual bleeding in a subject with uterine fibroids to an amount less than 80 mL of blood loss per cycle. In another aspect, the methods of the

present invention can be used to reduce the volume of heavy menstrual bleeding in the subject with uterine fibroids by at least 50% from baseline.

[0050] Methods for analyzing menstrual blood loss are known in the art and include, for example, the alkaline hematin method. The alkaline hematin method is based on the quantitation of menstrual blood collected on sanitary products (Hallberg L., Nilsoon L., Determination of Menstrual Blood Loss. *Scand. J. Clin. Lab. Invest.*, 1964;16:244-248). The method uses a strong alkaline solution to chemically convert the heme from bloodstained sanitary products to alkaline hematin, which is measured colorimetrically. When compared to a subject's serum hemoglobin (Hgb), the volume of blood loss in the menstrual products can be determined.

[0051] **a. Use of Elagolix or a pharmaceutically acceptable salt thereof**

[0052] In one aspect, the methods of the present invention involve reducing or managing heavy menstrual bleeding associated with uterine fibroids in a subject in need of treatment thereof. The methods involve administering to a subject suffering from heavy menstrual bleeding associated with uterine fibroids an effective amount of Elagolix or a pharmaceutically acceptable salt thereof. The effective amount or dose of Elagolix or a pharmaceutically acceptable salt thereof that can be administered to a subject is in the range of 300 to 600 mg. In a further aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 300 mg, 400 mg, or 600 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 300 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 400 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 600 mg per day. The dose can be administered once a day or twice a day.

[0053] **b. Use of Elagolix or a pharmaceutically acceptable salt thereof in combination with Hormone Replacement Therapy**

[0054] In another aspect, the methods of the present invention involve reducing or managing heavy menstrual bleeding associated with uterine fibroids in a subject in need of treatment thereof. The methods involve administering to a subject suffering from heavy menstrual bleeding associated with uterine fibroids an effective amount of Elagolix or a

pharmaceutically acceptable salt thereof in combination with one or more estrogens and progestogens. The administration of a combination of estrogen and progestogens to subjects is often referred to as "hormone replacement therapy" or "add-back therapy". The "hormone replacement therapy" or "add-back therapy" is used to prevent hypoestrogenic symptoms such as bone mineral density loss and vasomotor symptoms. Specifically, it was found that when subjects were treated with an effective amount of Elagolix or a pharmaceutically acceptable salt thereof in combination with the estrogens and progestogens, substantially lower number of subjects reported hot flashes (which are a vasomotor symptom of estrogen deprivation) compared to those treated with Elagolix alone.

[0055] The effective amount or dose of Elagolix or a pharmaceutically acceptable salt thereof that can be administered to a subject is in the range of 300 to 600 mg per day. In a further aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 300 mg, 400 mg, or 600 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 300 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 400 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 600 mg per day. The effective amount or dose can be administered once a day or twice a day. The estrogen and/or progestogens can be administered orally, transdermally or intravaginally.

[0056] Suitable estrogens that can be used include, for example, estradiol, ethinyl estradiol, and conjugated estrogens.

[0057] Suitable progestogens that can be used include, for example, progesterone, norethindrone, norethindrone acetate, norgestimate, drospirenone, and medroxyprogestogen.

[0058] Combined oral formulations, used continuously, containing estogens and progestogens for hormone replacement therapy are known in the art and can also be used in the invention. Suitable formulations include, for example, Activella®, Angeliq®, FemHRT®, Jenteli™, Mimvey™, Prefest™, Premphase®, and Prempro®.

[0059] In one aspect of the invention, the estrogen is estradiol. In another aspect, the dose of estradiol is 0.5 mg. In another embodiment, the dose of estradiol is 1.0 mg. In yet another embodiment, the estradiol is administered once a day.

[0060] In another aspect of the invention, the estrogen is ethinyl estradiol. In another embodiment, the dose of ethinyl estradiol is 2.5 mcg. In yet another embodiment, the dose of estradiol is 5.0 mcg. In still yet another aspect, the ethinyl estradiol is administered once a day.

[0061] In still yet another aspect of the invention, the estrogen is conjugated estrogens. In another embodiment, the dose of conjugated estrogens is 0.3 mg. In still yet another embodiment, the dose of conjugated estrogens is 0.45 mg or 0.625 mg. In still yet another embodiment, the conjugated estrogens is administered once a day.

[0062] In still yet another aspect of the invention, the progestogen is oral progesterone, which is used cyclically (for the last 12 days of the 28-30 day cycle). In another embodiment, the dose of progesterone is 100 or 200 mg.

[0063] In still yet another aspect of the invention, the progestogen is norethindrone or norethindrone acetate. In another aspect, the dose of norethindrone or norethindrone acetate is 0.1 mg. In another aspect, the dose of norethindrone or norethindrone acetate is 0.5 mg. In another embodiment, the dose of norethindrone or norethindrone acetate is 1.0 mg. In yet another aspect, the norethindrone or norethindrone acetate is administered once a day.

[0064] In still yet another aspect of the invention, the progestogen is norgestimate. In another aspect, the dose of norgestimate is 0.09 mg. In still yet another aspect, the norgestimate is administered once a day.

[0065] In still yet another aspect of the invention, the progestogen is medroxyprogesterone. In still yet another aspect of the invention, the dose of medroxyprogesterone is 1.5 mg. In another aspect, the dose of medroxyprogesterone is 2.5 mg or 5 mg. In yet another aspect, the medroxyprogesterone is administered once a day.

[0066] In still yet another aspect of the invention, the progestogen is drospirenone. In another aspect, the dose of drospirenone is 0.25 mg. In still yet another aspect, the dose of drospirenone is 0.5 mg. In yet another aspect, the drospirenone is administered once a day.

[0067] In one aspect of the invention, the dose of Elagolix is 300 mg administered twice a day in combination with 0.5 mg estradiol and 0.1 mg norethindrone acetate.

[0068] In yet another aspect of the invention, the dose of Elagolix is 300 mg administered once or twice a day in combination with 1.0 mg estradiol and 0.5 mg norethindrone acetate.

[0069] In still yet another aspect of the invention, the dose of Elagolix is 400 mg administered once or twice a day in combination with 0.5 mg estradiol and 0.1 mg norethindrone acetate.

[0070] In still yet another aspect of the invention, the dose of Elagolix is 400 mg administered once or twice a day in combination with 1.0 mg estradiol and 0.5 mg norethindrone acetate.

[0071] In still yet another aspect of the invention, the dose of Elagolix is 600 mg administered once or twice a day in combination with 0.5 mg estradiol and 0.1 mg norethindrone acetate.

[0072] In still yet another aspect of the invention, the dose of Elagolix is 600 mg administered once or twice a day in combination with 1.0 mg estradiol and 0.5 mg norethindrone acetate.

[0073] The administration of Elagolix or a pharmaceutically acceptable salt or solvate thereof, and compositions and formulations thereof, may be prior to, immediately prior to, during, immediately subsequent to or subsequent to the administration of the estrogens and progestogens.

[0074] In still yet another aspect, the treatment cycle consist of daily administration of Elagolix and cyclical administration of progestogens in combination with a continuously administered estrogen. For example, the treatment cycle is 3 months or 6 months of daily administration of Elagolix and estrogens and progestogens are administered for the last 12-14 days of each month in order to mimic the normal menstrual cycle and induce regular, light bleeding episodes. In still yet another aspect, the treatment cycle consist of daily administration of Elagolix and estrogens and cyclical administration of progestogens.

[0075] In still yet a further aspect, the treatment cycle consist of daily administration of Elagolix and delayed administration of estrogens and/or progestogens. For example, the treatment cycle is 6 months of daily administration of Elagolix while estrogens and progestogens are administered daily for months 3-6. Alternatively, the treatment cycle is 12 months of daily administration of Elagolix while estrogens and progestogens are administered daily for months 3-12.

[0076] *Methods of Reducing Fibroid Volume in a Subject with Uterine Fibroids*

[0077] In another embodiment, the present invention relates to methods for reducing the fibroid volume in a subject with uterine fibroids. In one aspect, the methods of the present invention can be used to reduce the fibroid volume by greater than or equal to at least about 25%. In another aspect, the methods of the present invention can be used to reduce the fibroid volume in a subject with uterine fibroids. More specifically, the methods of the present invention can be used to reduce the fibroid volume in a subject with uterine fibroids by volume by greater than or equal to at least about 25%. In another aspect, the methods of the present invention are used to reduce the fibroid volume in a subject with uterine fibroids prior to hysterectomy, myomectomy, or uterine artery embolization. Methods for measuring fibroid volume are known in the art and include ultrasound and/or MRI.

[0078] **a. Use of Elagolix or a pharmaceutically acceptable salt thereof**

[0079] In one aspect, the methods of the present invention involve reducing the fibroid volume in a subject with uterine fibroids and in need of treatment thereof. The methods involve administering to a subject suffering with uterine fibroids an effective amount of Elagolix or a pharmaceutically acceptable salt thereof. The effective amount or dose of Elagolix or a pharmaceutically acceptable salt thereof that can be administered to a subject is in the range of 300 to 600 mg per day. In a further aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 300 mg, 400 mg, or 600 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 300 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 400 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 600 mg per day. The dose can be administered once a day or twice a day.

[0080] **b. Use of Elagolix or a pharmaceutically acceptable salt thereof in combination with Hormone Replacement Therapy**

[0081] In another aspect, the methods of the present invention involve reducing the total fibroid volume in a subject with uterine fibroids and in need of treatment thereof. The methods involve administering to a subject suffering with uterine fibroids an effective amount of Elagolix or a pharmaceutically acceptable salt thereof in combination with one or more estrogens and progestogens. The methods involve administering to a subject suffering

from heavy menstrual bleeding associated with uterine fibroids an effective amount of Elagolix or a pharmaceutically acceptable salt thereof in combination with estrogens and progestogens.

[0082] The effective amount or dose of Elagolix or a pharmaceutically acceptable salt thereof that can be administered to a subject is in the range of 300 to 600 mg per day. In a further aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 300 mg, 400 mg, or 600 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 300 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 400 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 600 mg per day. The effective amount or dose can be administered once a day or twice a day. The estrogen and/or progestogens can be administered orally, transdermally or intravaginally.

[0083] Suitable estrogens that can be used include, for example, estradiol, ethinyl estradiol, and conjugated estrogens.

[0084] Suitable progestogens that can be used include, for example, progesterone, norethindrone, norethindrone acetate, norgestimate, drospirenone, and medroxyprogestogen.

[0085] Combined formulations, used continuously, containing estogens and progestogens for hormone replacement therapy are known in the art and can also be used in the invention. Suitable formulations include, for example, Activella®, Angeliq®, FemHRT®, Jenteli™, Mimvey™, Prefest™, Premphase®, and Prempro®.

[0086] In one aspect of the invention, the estrogen is estradiol. In another aspect, the dose of estradiol is 0.5 mg. In another embodiment, the dose of estradiol is 1.0 mg. In yet another embodiment, the estradiol is administered once a day.

[0087] In another aspect of the invention, the estrogen is ethinyl estradiol. In another embodiment, the dose of ethinyl estradiol is 2.5 mcg. In yet another embodiment, the dose of estradiol is 5.0 mcg. In still yet another aspect, the ethinyl estradiol is administered once a day.

[0088] In still yet another aspect of the invention, the estrogen is conjugated estrogens. In another embodiment, the dose of conjugated estrogens is 0.3 mg. In still yet another

embodiment, the dose of conjugated estrogens is 0.45 mg or 0.625 mg. In still yet another embodiment, the conjugated estrogens is administered once a day.

[0089] In still yet another aspect of the invention, the progestogen is progesterone, which is used cyclically (for the last 12 days of the 28-30 day cycle). In another embodiment, the dose of progesterone is 100 or 200 mg.

[0090] In still yet another aspect of the invention, the progestogen is norethindrone or norethindrone acetate. In another aspect, the dose of norethindrone or norethindrone acetate is 0.1 mg. In another aspect, the dose of norethindrone or norethindrone acetate is 0.5 mg. In another embodiment, the dose of norethindrone or norethindrone acetate is 1.0 mg. In yet another aspect, the norethindrone or norethindrone acetate is administered once a day.

[0091] In still yet another aspect of the invention, the progestogen is norgestimate. In another aspect, the dose of norgestimate is 0.09 mg. In still yet another aspect, the norgestimate is administered once a day.

[0092] In still yet another aspect of the invention, the progestogen is medroxyprogesterone. In still yet another aspect of the invention, the dose of medroxyprogesterone is 1.5 mg. In another aspect, the dose of medroxyprogesterone is 2.5 mg or 5 mg. In yet another aspect, the medroxyprogesterone is administered once a day.

[0093] In still yet another aspect of the invention, the progestogen is drospirenone. In another aspect, the dose of drospirenone is 0.25 mg. In still yet another aspect, the dose of drospirenone is 0.5 mg. In yet another aspect, the drospirenone is administered once a day.

[0094] In one aspect of the invention, the dose of Elagolix is 300 mg administered twice a day in combination with 0.5 mg estradiol and 0.1 mg norethindrone acetate.

[0095] In yet another aspect of the invention, the dose of Elagolix is 300 mg administered once or twice a day in combination with 1.0 mg estradiol and 0.5 mg norethindrone acetate.

[0096] In still yet another aspect of the invention, the dose of Elagolix is 400 mg administered once or twice a day in combination with 0.5 mg estradiol and 0.1 mg norethindrone acetate.

[0097] In still yet another aspect of the invention, the dose of Elagolix is 400 mg administered once or twice a day in combination with 1.0 mg estradiol and 0.5 mg norethindrone acetate.

[0098] In still yet another aspect of the invention, the dose of Elagolix is 600 mg administered once or twice a day in combination with 0.5 mg estradiol and 0.1 mg norethindrone acetate.

[0099] In still yet another aspect of the invention, the dose of Elagolix is 600 mg administered once or twice a day in combination with 1.0 mg estradiol and 0.5 mg norethindrone acetate.

[00100] The administration of Elagolix or a pharmaceutically acceptable salt or solvate thereof, and compositions and formulations thereof, may be prior to, immediately prior to, during, immediately subsequent to or subsequent to the administration of the estrogens and progestogens.

[00101] In still yet another aspect, the treatment cycle consist of daily administration of Elagolix and cyclical administration of progestogens in combination with a continuously administered estrogen. For example, the treatment cycle is 3 months or 6 months of daily administration of Elagolix and estrogens and progestogens are administered for the last 12-14 days of each month in order to mimic the normal menstrual cycle and induce regular, light bleeding episodes. In still yet another aspect, the treatment cycle consist of daily administration of Elagolix and estrogens and cyclical administration of progestogens.

[00102] In still yet a further aspect, the treatment cycle consist of daily administration of Elagolix and delayed administration of estrogens and/or progestogens. For example, the treatment cycle is 6 months of daily administration of Elagolix while estrogens and progestogens are administered daily for months 3-6. Alternatively, the treatment cycle is 12 months of daily administration of Elagolix while estrogens and progestogens are administered daily for months 3-12.

[00103] *Methods of Reducing Total Uterine Volume in a Subject with Uterine Fibroids*

[00104] In another embodiment, the present invention relates to methods for reducing the total uterine volume in a subject with uterine fibroids. The "total uterine volume" is the volume of the entire uterus. In one aspect, the methods of the present invention can be used to reduce the total uterine volume by greater than or equal to at least about 25%. In another aspect, the methods of the present invention can be used to reduce the total uterine volume in a subject with uterine fibroids. More specifically, the methods of the present invention can be used to reduce the total uterine volume in a subject with uterine fibroids by greater than or

equal to at least about 25%. Methods for measuring total uterine volume are known in the art and include, ultrasound and/or MRI.

[00105] a. Use of Elagolix or a pharmaceutically acceptable salt thereof

[00106] In one aspect, the methods of the present invention involve reducing the total uterine volume in a subject with uterine fibroids and in need of treatment thereof. The methods involve administering to a subject suffering with uterine fibroids an effective amount of Elagolix or a pharmaceutically acceptable salt thereof. The effective amount or dose of Elagolix or a pharmaceutically acceptable salt thereof that can be administered to a subject is in the range of 300 to 600 mg per day. In a further aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 300 mg, 400 mg, or 600 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 300 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 400 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 600 mg per day. The dose can be administered once a day or twice a day.

[00107] b. Use of Elagolix or a pharmaceutically acceptable salt thereof in combination with Hormone Replacement Therapy

[00108] In another aspect, the methods of the present invention involve reducing the uterine volume in a subject with uterine fibroids and in need of treatment thereof. The methods involve administering to a subject suffering with uterine fibroids an effective amount of Elagolix or a pharmaceutically acceptable salt thereof in combination with one or more estrogens and progestogens. The methods involve administering to a subject suffering from heavy menstrual bleeding associated with uterine fibroids an effective amount of Elagolix or a pharmaceutically acceptable salt thereof in combination with one or more estrogens and progestogens.

[00109] The effective amount or dose of Elagolix or a pharmaceutically acceptable salt thereof that can be administered to a subject is in the range of 300 to 600 mg per day. In a further aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 300 mg, 400 mg, or 600 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a

pharmaceutically acceptable salt or solvate thereof is about 300 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 400 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 600 mg per day. The effective amount or dose can be administered once a day or twice a day. The estrogen and/or progestogens can be administered orally, transdermally or intravaginally.

[00110] Suitable estrogens that can be used include, for example, estradiol, ethinyl estradiol, and conjugated estrogens.

[00111] Suitable progestogens that can be used include, for example, progesterone, norethindrone, norethindrone acetate, norgestimate, drospirenone, and medroxyprogestogen.

[00112] Combined formulations, used continuously, containing estogens and progestogens for hormone replacement therapy are known in the art and can also be used in the invention. Suitable formulations include, for example, Activella®, Angeliq®, FemHRT®, Jenteli™, Mimvey™, Prefest™, Premphase®, and Prempro®.

[00113] In one aspect of the invention, the estrogen is estradiol. In another aspect, the dose of estradiol is 0.5 mg. In another embodiment, the dose of estradiol is 1.0 mg. In yet another embodiment, the estradiol is administered once a day.

[00114] In another aspect of the invention, the estrogen is ethinyl estradiol. In another embodiment, the dose of ethinyl estradiol is 2.5 mcg. In yet another embodiment, the dose of estradiol is 5.0 mcg. In still yet another aspect, the ethinyl estradiol is administered once a day.

[00115] In still yet another aspect of the invention, the estrogen is conjugated estrogens. In another embodiment, the dose of conjugated estrogens is 0.3 mg. In still yet another embodiment, the dose of conjugated estrogens is 0.45 mg or 0.625 mg. In still yet another embodiment, the conjugated estrogens is administered once a day.

[00116] In still yet another aspect of the invention, the progestogen is progesterone, which is used cyclically (for the last 12 days of the 28-30 day cycle). In another embodiment, the dose of progesterone is 100 or 200 mg.

[00117] In still yet another aspect of the invention, the progestogen is norethindrone or norethindrone acetate. In another aspect, the dose of norethindrone or norethindrone acetate is 0.1 mg. In another aspect, the dose of norethindrone or norethindrone acetate is 0.5 mg. In

another embodiment, the dose of norethindrone or norethindrone acetate is 1.0 mg. In yet another aspect, the norethindrone or norethindrone acetate is administered once a day.

[00118] In still yet another aspect of the invention, the progestogen is norgestimate. In another aspect, the dose of norgestimate is 0.09 mg. In still yet another aspect, the norgestimate is administered once a day.

[00119] In still yet another aspect of the invention, the progestogen is medroxyprogesterone. In still yet another aspect of the invention, the dose of medroxyprogesterone is 1.5 mg. In another aspect, the dose of medroxyprogesterone is 2.5 mg or 5 mg. In yet another aspect, the medroxyprogesterone is administered once a day.

[00120] In still yet another aspect of the invention, the progestogen is drospirenone. In another aspect, the dose of drospirenone is 0.25 mg. In still yet another aspect, the dose of drospirenone is 0.5 mg. In yet another aspect, the drospirenone is administered once a day.

[00121] In one aspect of the invention, the dose of Elagolix is 300 mg administered twice a day in combination with 0.5 mg estradiol and 0.1 mg norethindrone acetate.

[00122] In yet another aspect of the invention, the dose of Elagolix is 300 mg administered once or twice a day in combination with 1.0 mg estradiol and 0.5 mg norethindrone acetate.

[00123] In still yet another aspect of the invention, the dose of Elagolix is 400 mg administered once or twice a day in combination with 0.5 mg estradiol and 0.1 mg norethindrone acetate.

[00124] In still yet another aspect of the invention, the dose of Elagolix is 400 mg administered once or twice a day in combination with 1.0 mg estradiol and 0.5 mg norethindrone acetate.

[00125] In still yet another aspect of the invention, the dose of Elagolix is 600 mg administered once or twice a day in combination with 0.5 mg estradiol and 0.1 mg norethindrone acetate.

[00126] In still yet another aspect of the invention, the dose of Elagolix is 600 mg administered once or twice a day in combination with 1.0 mg estradiol and 0.5 mg norethindrone acetate.

[00127] The administration of Elagolix or a pharmaceutically acceptable salt or solvate thereof, and compositions and formulations thereof, may be prior to, immediately prior to, during, immediately subsequent to or subsequent to the administration of the estrogens and progestogens.

[00128] In still yet another aspect, the treatment cycle consist of daily administration of Elagolix and cyclical administration of progestogens in combination with a continuously administered estrogen. For example, the treatment cycle is 3 months or 6 months of daily administration of Elagolix and estrogens and progestogens are administered for the last 12-14 days of each month in order to mimic the normal menstrual cycle and induce regular, light bleeding episodes. In still yet another aspect, the treatment cycle consist of daily administration of Elagolix and estrogens and cyclical administration of progestogens.

[00129] In still yet a further aspect, the treatment cycle consist of daily administration of Elagolix and delayed administration of estrogens and/or progestogens. For example, the treatment cycle is 6 months of daily administration of Elagolix while estrogens and progestogens are administered daily for months 3-6. Alternatively, the treatment cycle is 12 months of daily administration of Elagolix while estrogens and progestogens are administered daily for months 3-12.

[00130] *Methods of Preventing Uterine Fibroid Regrowth or Recurrence after Surgical or Semi-Invasive Intervention*

[00131] In still yet another embodiment, the present invention relates to methods for preventing the regrowth or recurrence of uterine fibroids in a subject after removal of one or more uterine fibroids from the subject by surgical (such as myomectomy) or semi-invasive intervention (such as uterine artery embolization, MRI-guided high-intensity focused ultrasound, etc).

[00132] **a. Use of Elagolix or a pharmaceutically acceptable salt thereof**

[00133] In one aspect, the methods of the present invention involve preventing the regrowth or return of uterine fibroids in a subject after removal of one or more uterine fibroids from the subject by surgical or semi-invasive intervention. The methods involve administering to a subject who has had one or more uterine fibroids removed (such as by surgical or semi-invasive intervention) an effective amount of Elagolix or a pharmaceutically acceptable salt thereof.

[00134] The Elagolix or pharmaceutically acceptable salt thereof can be administered to a subject in need thereof immediately after surgery. "Immediately after surgery" refers to administration of the Elagolix or pharmaceutically acceptable salt thereof 1 day post surgery, 2 days post surgery, 3 days post surgery, 4 days post surgery, 5 days post surgery, 6 days post

surgery or 7 days post surgery. The Elagolix or pharmaceutically acceptable salt thereof can be administered to a subject daily (namely, continuously), post-surgery for a duration of at least 6 months, at least 12 months, at least 18 months, at least 24 months, etc. The effective amount or dose of Elagolix or a pharmaceutically acceptable salt thereof that can be administered to a subject is in the range of 300 to 600 mg per day. In a further aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 300 mg, 400 mg, or 600 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 300 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 400 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 600 mg per day. The dose can be administered once a day or twice a day.

[00135] b. Use of Elagolix or a pharmaceutically acceptable salt thereof in combination with Hormone Replacement Therapy

[00136] In still yet another aspect, the methods of the present invention involve preventing the regrowth or recurrence of uterine fibroids in a subject after removal of one or more uterine fibroids from the subject by surgical or semi-invasive intervention. The methods involve administering to a subject who has had one or more uterine fibroids removed (such as by surgical or semi-invasive intervention) an effective amount of Elagolix or a pharmaceutically acceptable salt thereof in combination with one or more estrogens and progestogens.

[00137] The Elagolix or pharmaceutically acceptable salt thereof in combination with one or more estrogens and progestogens can be administered to a subject in need thereof immediately after surgery. "Immediately after surgery" refers to administration of the Elagolix or pharmaceutically acceptable salt thereof 1 day post surgery, 2 days post surgery, 3 days post surgery, 4 days post surgery, 5 days post surgery, 6 days post surgery or 7 days post surgery. The Elagolix or pharmaceutically acceptable salt thereof can be administered to a subject daily (namely, continuously), post-surgery for a duration of at least 6 months, at least 12 months, at least 18 months, at least 24 months, etc.

[00138] The effective amount or dose of Elagolix or a pharmaceutically acceptable salt thereof that can be administered to a subject is in the range of 300 to 600 mg per day. In a

further aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 300 mg, 400 mg, or 600 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 300 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 400 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 600 mg per day. The effective amount or dose can be administered once a day or twice a day. The estrogen and/or progestogens can be administered orally, transdermally or intravaginally.

[00139] Suitable estrogens that can be used include, for example, estradiol, ethinyl estradiol, and conjugated estrogens.

[00140] Suitable progestogens that can be used include, for example, progesterone, norethindrone, norethindrone acetate, norgestimate, drospirenone, and medroxyprogestogen.

[00141] Combined formulations, used continuously, containing estogens and progestogens for hormone replacement therapy are known in the art and can also be used in the invention. Suitable formulations include, for example, Activella®, Angeliq®, FemHRT®, Jenteli™, Mimvey™, Prefest™, Premphase®, and Prempro®.

[00142] In one aspect of the invention, the estrogen is estradiol. In another aspect, the dose of estradiol is 0.5 mg. In another embodiment, the dose of estradiol is 1.0 mg. In yet another embodiment, the estradiol is administered once a day.

[00143] In another aspect of the invention, the estrogen is ethinyl estradiol. In another embodiment, the dose of ethinyl estradiol is 2.5 mcg. In yet another embodiment, the dose of estradiol is 5.0 mcg. In still yet another aspect, the ethinyl estradiol is administered once a day.

[00144] In still yet another aspect of the invention, the estrogen is conjugated estrogens. In another embodiment, the dose of conjugated estrogens is 0.3 mg. In still yet another embodiment, the dose of conjugated estrogens is 0.45 mg or 0.625 mg. In still yet another embodiment, the conjugated estrogens is administered once a day.

[00145] In still yet another aspect of the invention, the progestogen is progesterone, which is used cyclically (for the last 12 days of the 28-30 day cycle). In another embodiment, the dose of progesterone is 100 or 200 mg.

[00146] In still yet another aspect of the invention, the progestogen is norethindrone or norethindrone acetate. In another aspect, the dose of norethindrone or norethindrone acetate is 0.1 mg. In another aspect, the dose of norethindrone or norethindrone acetate is 0.5 mg. In another embodiment, the dose of norethindrone or norethindrone acetate is 1.0 mg. In yet another aspect, the norethindrone or norethindrone acetate is administered once a day.

[00147] In still yet another aspect of the invention, the progestogen is norgestimate. In another aspect, the dose of norgestimate is 0.09 mg. In still yet another aspect, the norgestimate is administered once a day.

[00148] In still yet another aspect of the invention, the progestogen is medroxyprogesterone. In still yet another aspect of the invention, the dose of medroxyprogesterone is 1.5 mg. In another aspect, the dose of medroxyprogesterone is 2.5 mg or 5 mg. In yet another aspect, the medroxyprogesterone is administered once a day.

[00149] In still yet another aspect of the invention, the progestogen is drospirenone. In another aspect, the dose of drospirenone is 0.25 mg. In still yet another aspect, the dose of drospirenone is 0.5 mg. In yet another aspect, the drospirenone is administered once a day.

[00150] In one aspect of the invention, the dose of Elagolix is 300 mg administered twice a day in combination with 0.5 mg estradiol and 0.1 mg norethindrone acetate.

[00151] In yet another aspect of the invention, the dose of Elagolix is 300 mg administered once or twice a day in combination with 1.0 mg estradiol and 0.5 mg norethindrone acetate.

[00152] In still yet another aspect of the invention, the dose of Elagolix is 400 mg administered once or twice a day in combination with 0.5 mg estradiol and 0.1 mg norethindrone acetate.

[00153] In still yet another aspect of the invention, the dose of Elagolix is 400 mg administered once or twice a day in combination with 1.0 mg estradiol and 0.5 mg norethindrone acetate.

[00154] In still yet another aspect of the invention, the dose of Elagolix is 600 mg administered once or twice a day in combination with 0.5 mg estradiol and 0.1 mg norethindrone acetate.

[00155] In still yet another aspect of the invention, the dose of Elagolix is 600 mg administered once or twice a day in combination with 1.0 mg estradiol and 0.5 mg norethindrone acetate.

[00156] The administration of Elagolix or a pharmaceutically acceptable salt or solvate thereof, and compositions and formulations thereof, may be prior to, immediately prior to, during, immediately subsequent to or subsequent to the administration of the estrogens and progestogens.

[00157] In still yet another aspect, the treatment cycle consist of daily administration of Elagolix and cyclical administration of progestogens in combination with a continuously administered estrogen. For example, the treatment cycle is 3 months or 6 months of daily administration of Elagolix and estrogens and progestogens are administered for the last 12-14 days of each month in order to mimic the normal menstrual cycle and induce regular, light bleeding episodes. In still yet another aspect, the treatment cycle consist of daily administration of Elagolix and estrogens and cyclical administration of progestogens.

[00158] In still yet a further aspect, the treatment cycle consist of daily administration of Elagolix and delayed administration of estrogens and/or progestogens. For example, the treatment cycle is 6 months of daily administration of Elagolix while estrogens and progestogens are administered daily for months 3-6. Alternatively, the treatment cycle is 12 months of daily administration of Elagolix while estrogens and progestogens are administered daily for months 3-12.

[00159] *Methods of Reducing or Managing Heavy Menstrual Bleeding not Associated with Uterine Fibroids*

[00160] In one embodiment, the present invention relates to methods for reducing or managing heavy menstrual bleeding (HMB) in subjects in need of treatment thereof where the heavy menstrual bleeding is not associated with uterine fibroids but is the result of other conditions, such as adenomyosis, hereditary bleeding disorders, idiopathic heavy menstrual bleeding, etc. In one aspect, the methods of the present invention can be used to reduce or manage heavy menstrual bleeding to less than 80 mL of blood loss per cycle. In another aspect, the methods of the present invention can be used to reduce the volume of heavy menstrual bleeding in the subject by 50% from baseline.

[00161] **a. Use of Elagolix or a pharmaceutically acceptable salt thereof**

[00162] In one aspect, the methods of the present invention involve reducing or managing heavy menstrual bleeding associated with conditions other than uterine fibroids in a subject in need of treatment thereof. The methods involve administering to a subject suffering from

heavy menstrual bleeding associated with conditions other than uterine fibroids an effective amount of Elagolix or a pharmaceutically acceptable salt thereof. In one aspect, the subject may not have any uterine fibroids. In another aspect, the subject may have uterine fibroids but the heavy menstrual bleeding is not a result of the uterine fibroids.

[00163] The effective amount or dose of Elagolix or a pharmaceutically acceptable salt thereof that can be administered to a subject is in the range of 300 to 600 mg per day. In a further aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 300 mg, 400 mg, or 600 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 300 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 400 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 600 mg per day. The dose can be administered once a day or twice a day. The estrogen and/or progestogens can be administered orally, transdermally or intravaginally.

[00164] b. Use of Elagolix or a pharmaceutically acceptable salt thereof in combination with Hormone Replacement Therapy

[00165] In another aspect, the methods of the present invention involve reducing or managing heavy menstrual bleeding associated with conditions other than uterine fibroids in a subject in need of treatment thereof. The methods involve administering to a subject suffering from heavy menstrual bleeding associated with conditions other than uterine fibroids an effective amount of Elagolix or a pharmaceutically acceptable salt thereof in combination with one or more estrogens and progestogens. The methods involve administering to a subject suffering from heavy menstrual bleeding associated with uterine fibroids an effective amount of Elagolix or a pharmaceutically acceptable salt thereof in combination with estrogens and progestogens. In one aspect, the subject may not have any uterine fibroids. In another aspect, the subject may have uterine fibroids but the heavy menstrual bleeding is not a result of the uterine fibroids.

[00166] The effective amount or dose of Elagolix or a pharmaceutically acceptable salt thereof that can be administered to a subject is in the range of 300 to 600 mg per day. In a further aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically

acceptable salt or solvate thereof is about 300 mg, 400 mg, or 600 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 300 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 400 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 600 mg per day. The effective amount or dose can be administered once a day or twice a day. The estrogen and/or progestogens can be administered orally, transdermally or intravaginally.

[00167] Suitable estrogens that can be used include, for example, estradiol, ethinyl estradiol, and conjugated estrogens.

[00168] Suitable progestogens that can be used include, for example, progesterone, norethindrone, norethindrone acetate, norgestimate, drospirenone, and medroxyprogestogen.

[00169] Combined formulations, used continuously, containing estogens and progestogens for hormone replacement therapy are known in the art and can also be used in the invention. Suitable formulations include, for example, Activella®, Angeliq®, FemHRT®, Jenteli™, Mimvey™, Prefest™, Premphase®, and Prempro®.

[00170] In one aspect of the invention, the estrogen is estradiol. In another aspect, the dose of estradiol is 0.5 mg. In another embodiment, the dose of estradiol is 1.0 mg. In yet another embodiment, the estradiol is administered once a day.

[00171] In another aspect of the invention, the estrogen is ethinyl estradiol. In another embodiment, the dose of ethinyl estradiol is 2.5 mcg. In yet another embodiment, the dose of estradiol is 5.0 mcg. In still yet another aspect, the ethinyl estradiol is administered once a day.

[00172] In still yet another aspect of the invention, the estrogen is conjugated estrogens. In another embodiment, the dose of conjugated estrogens is 0.3 mg. In still yet another embodiment, the dose of conjugated estrogens is 0.45 mg or 0.625 mg. In still yet another embodiment, the conjugated estrogens is administered once a day.

[00173] In still yet another aspect of the invention, the progestogen is progesterone, which is used cyclically (for the last 12 days of the 28-30 day cycle). In another embodiment, the dose of progesterone is 100 or 200 mg.

[00174] In still yet another aspect of the invention, the progestogen is norethindrone or norethindrone acetate. In another aspect, the dose of norethindrone or norethindrone acetate is 0.1 mg. In another aspect, the dose of norethindrone or norethindrone acetate is 0.5 mg. In another embodiment, the dose of norethindrone or norethindrone acetate is 1.0 mg. In yet another aspect, the norethindrone or norethindrone acetate is administered once a day.

[00175] In still yet another aspect of the invention, the progestogen is norgestimate. In another aspect, the dose of norgestimate is 0.09 mg. In still yet another aspect, the norgestimate is administered once a day.

[00176] In still yet another aspect of the invention, the progestogen is medroxyprogesterone. In still yet another aspect of the invention, the dose of medroxyprogesterone is 1.5 mg. In another aspect, the dose of medroxyprogesterone is 2.5 mg or 5 mg. In yet another aspect, the medroxyprogesterone is administered once a day.

[00177] In still yet another aspect of the invention, the progestogen is drospirenone. In another aspect, the dose of drospirenone is 0.25 mg. In still yet another aspect, the dose of drospirenone is 0.5 mg. In yet another aspect, the drospirenone is administered once a day.

[00178] In one aspect of the invention, the dose of Elagolix is 300 mg administered twice a day in combination with 0.5 mg estradiol and 0.1 mg norethindrone acetate.

[00179] In yet another aspect of the invention, the dose of Elagolix is 300 mg administered once or twice a day in combination with 1.0 mg estradiol and 0.5 mg norethindrone acetate.

[00180] In still yet another aspect of the invention, the dose of Elagolix is 400 mg administered once or twice a day in combination with 0.5 mg estradiol and 0.1 mg norethindrone acetate.

[00181] In still yet another aspect of the invention, the dose of Elagolix is 400 mg administered once or twice a day in combination with 1.0 mg estradiol and 0.5 mg norethindrone acetate.

[00182] In still yet another aspect of the invention, the dose of Elagolix is 600 mg administered once or twice a day in combination with 0.5 mg estradiol and 0.1 mg norethindrone acetate.

[00183] In still yet another aspect of the invention, the dose of Elagolix is 600 mg administered once or twice a day in combination with 1.0 mg estradiol and 0.5 mg norethindrone acetate.

[00184] The administration of Elagolix or a pharmaceutically acceptable salt or solvate thereof, and compositions and formulations thereof, may be prior to, immediately prior to, during, immediately subsequent to or subsequent to the administration of the estrogens and progestogens.

[00185] In still yet another aspect, the treatment cycle consist of daily administration of Elagolix and cyclical administration of progestogens in combination with a continuously administered estrogen. For example, the treatment cycle is 3 months or 6 months of daily administration of Elagolix and estrogens and progestogens are administered for the last 12-14 days of each month in order to mimic the normal menstrual cycle and induce regular, light bleeding episodes. In still yet another aspect, the treatment cycle consist of daily administration of Elagolix and estrogens and cyclical administration of progestogens.

[00186] In still yet a further aspect, the treatment cycle consist of daily administration of Elagolix and delayed administration of estrogens and/or progestogens. For example, the treatment cycle is 6 months of daily administration of Elagolix while estrogens and progestogens are administered daily for months 3-6. Alternatively, the treatment cycle is 12 months of daily administration of Elagolix while estrogens and progestogens are administered daily for months 3-12.

[00187] *Methods of Treating Uterine Fibroids in Subjects in need of treatment thereof*

[00188] In one embodiment, the present invention relates to methods for treating subjects having uterine fibroids and in need of treatment thereof. Subjects having uterine fibroids and treated pursuant to this method may not experience heavy menstrual bleeding but instead exhibit other uterine fibroid symptoms such as pelvic pressure, pelvic pain, bloating, urinary symptoms, etc.

[00189] **a. Use of Elagolix or a pharmaceutically acceptable salt thereof**

[00190] In one aspect, the methods of the present invention involve treating subjects having uterine fibroids that do not exhibit heavy menstrual bleeding but are in need of treatment thereof. The methods involve administering to a subject having uterine fibroids (and that does not exhibit heavy menstrual bleeding) an effective amount of Elagolix or a pharmaceutically acceptable salt thereof. The effective amount or dose of Elagolix or a pharmaceutically acceptable salt thereof that can be administered to a subject is in the range 300 to 600 mg per day. In a further aspect of the invention, the effective amount or dose of

Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 300 mg, 400 mg, or 600 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 300 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 400 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 600 mg per day. The dose can be administered once a day or twice a day. The estrogen and/or progestogens can be administered orally, transdermally or intravaginally.

[00191] b. Use of Elagolix or a pharmaceutically acceptable salt thereof in combination with Hormone Replacement Therapy

[00192] In another aspect, the methods of the present invention treating a subject uterine fibroids in a subject in need of treatment thereof. The methods involve administering to a subject having uterine fibroids (and that does not exhibit heavy menstrual bleeding) an effective amount of Elagolix or a pharmaceutically acceptable salt thereof in combination with estrogens and progestogens. The methods involve administering to a subject suffering from uterine fibroids (and that does not exhibit heavy menstrual bleeding) an effective amount of Elagolix or a pharmaceutically acceptable salt thereof in combination with one or more estrogens and progestogens.

[00193] The effective amount or dose of Elagolix or a pharmaceutically acceptable salt thereof that can be administered to a subject is in the range of 300 to 600 mg per day. In a further aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 300 mg, 400 mg, or 600 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 300 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 400 mg per day. In still yet another aspect of the invention, the effective amount or dose of Elagolix or a pharmaceutically acceptable salt or solvate thereof is about 600 mg per day. The effective amount or dose can be administered once a day or twice a day. The estrogen and/or progestogens can be administered orally, transdermally or intravaginally.

[00194] Suitable estrogens that can be used include, for example, estradiol, ethinyl estradiol, and conjugated estrogens.

[00195] Suitable progestogens that can be used include, for example, progesterone, norethindrone, norethindrone acetate, norgestimate, drospirenone, and medroxyprogestogen.

[00196] Combined formulations, used continuously, containing estogens and progestogens for hormone replacement therapy are known in the art and can also be used in the invention. Suitable formulations include, for example, Activella®, Angeliq®, FemHRT®, Jenteli™, Mimvey™, Prefest™, Premphase®, and Prempro®.

[00197] In one aspect of the invention, the estrogen is estradiol. In another aspect, the dose of estradiol is 0.5 mg. In another embodiment, the dose of estradiol is 1.0 mg. In yet another embodiment, the estradiol is administered once a day.

[00198] In another aspect of the invention, the estrogen is ethinyl estradiol. In another embodiment, the dose of ethinyl estradiol is 2.5 mcg. In yet another embodiment, the dose of estradiol is 5.0 mcg. In still yet another aspect, the ethinyl estradiol is administered once a day.

[00199] In still yet another aspect of the invention, the estrogen is conjugated estrogens. In another embodiment, the dose of conjugated estrogens is 0.3 mg. In still yet another embodiment, the dose of conjugated estrogens is 0.45 mg or 0.625 mg. In still yet another embodiment, the conjugated estrogens is administered once a day.

[00200] In still yet another aspect of the invention, the progestogen is progesterone, which is used cyclically (for the last 12 days of the 28-30 day cycle). In another embodiment, the dose of progesterone is 100 or 200 mg.

[00201] In still yet another aspect of the invention, the progestogen is norethindrone or norethindrone acetate. In another aspect, the dose of norethindrone or norethindrone acetate is 0.1 mg. In another aspect, the dose of norethindrone or norethindrone acetate is 0.5 mg. In another embodiment, the dose of norethindrone or norethindrone acetate is 1.0 mg. In yet another aspect, the norethindrone or norethindrone acetate is administered once a day.

[00202] In still yet another aspect of the invention, the progestogen is norgestimate. In another aspect, the dose of norgestimate is 0.09 mg. In still yet another aspect, the norgestimate is administered once a day.

[00203] In still yet another aspect of the invention, the progestogen is medroxyprogesterone. In still yet another aspect of the invention, the dose of

medroxyprogesterone is 1.5 mg. In another aspect, the dose of medroxyprogesterone is 2.5 mg or 5 mg. In yet another aspect, the medroxyprogesterone is administered once a day.

[00204] In still yet another aspect of the invention, the progestogen is drospirenone. In another aspect, the dose of drospirenone is 0.25 mg. In still yet another aspect, the dose of drospirenone is 0.5 mg. In yet another aspect, the drospirenone is administered once a day.

[00205] In one aspect of the invention, the dose of Elagolix is 300 mg administered twice a day in combination with 0.5 mg estradiol and 0.1 mg norethindrone acetate.

[00206] In yet another aspect of the invention, the dose of Elagolix is 300 mg administered once or twice a day in combination with 1.0 mg estradiol and 0.5 mg norethindrone acetate.

[00207] In still yet another aspect of the invention, the dose of Elagolix is 400 mg administered once or twice a day in combination with 0.5 mg estradiol and 0.1 mg norethindrone acetate.

[00208] In still yet another aspect of the invention, the dose of Elagolix is 400 mg administered once or twice a day in combination with 1.0 mg estradiol and 0.5 mg norethindrone acetate.

[00209] In still yet another aspect of the invention, the dose of Elagolix is 600 mg administered once or twice a day in combination with 0.5 mg estradiol and 0.1 mg norethindrone acetate.

[00210] In still yet another aspect of the invention, the dose of Elagolix is 600 mg administered once or twice a day in combination with 1.0 mg estradiol and 0.5 mg norethindrone acetate.

[00211] The administration of Elagolix or a pharmaceutically acceptable salt or solvate thereof, and compositions and formulations thereof, may be prior to, immediately prior to, during, immediately subsequent to or subsequent to the administration of the estrogens and progestogens.

[00212] In still yet another aspect, the treatment cycle consist of daily administration of Elagolix and cyclical administration of progestogens in combination with a continuously administered estrogen. For example, the treatment cycle is 3 months or 6 months of daily administration of Elagolix and estrogens and progestogens are administered for the last 12-14 days of each month in order to mimic the normal menstrual cycle and induce regular, light bleeding episodes. In still yet another aspect, the treatment cycle consist of daily administration of Elagolix and estrogens and cyclical administration of progestogens.

[00213] In still yet a further aspect, the treatment cycle consist of daily administration of Elagolix and delayed administration of estrogens and/or progestogens. For example, the treatment cycle is 6 months of daily administration of Elagolix while estrogens and progestogens are administered daily for months 3-6. Alternatively, the treatment cycle is 12 months of daily administration of Elagolix while estrogens and progestogens are administered daily for months 3-12.

[00214] *Methods of Practicing the Present Invention*

[00215] In one aspect of the invention, the methods are practiced by administering pharmaceutical compositions containing Elagolix or 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid. For the purposes of administration, 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid may be formulated as pharmaceutical compositions. Pharmaceutical compositions comprise 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid, or a pharmaceutically acceptable salt thereof, or a solvate thereof, and a pharmaceutically acceptable carrier and/or diluent. 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid is present in the composition in an amount which is effective to treat a particular disorder--that is, in an amount sufficient to achieve GnRH receptor antagonist activity, and preferably with acceptable toxicity to the patient.

[00216] All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

[00217] The use of the terms "a" and "an" and "the" and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not

limited to,") unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[00218] Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

EXAMPLES

[00219] Example 1

[00220] This example is a Phase 2a, multicenter, double-blind, placebo-controlled, randomized trial (N=280) with a 3-month treatment duration evaluating the safety and efficacy of Elagolix administered with or without Activella® in premenopausal women with uterine fibroids.

[00221] It evaluates the safety and efficacy of 6 doses of Elagolix (100 mg BID, 200 mg BID, 200 mg BID plus low dose Activella® (a combination of 0.5 mg estradiol and 0.1 mg northindrone acetate), 300 mg BID, 300 mg BID plus 1.0 mg of Estrace and 200 mg cyclical Prometrium (collectively referred to as "EP"), 400 mg QD and 600 QD) versus placebo (PBO) to reduce uterine bleeding associated with uterine fibroids and to reduce fibroid

volume and uterine volume in premenopausal women 20 to 49 years of age with heavy menstrual bleeding (HMB; > 80 mL blood loss per menstrual cycle). The study involved the following six (6) cohorts:

[00222] Cohort 1: Elagolix 200 mg BID or placebo (PBO).

[00223] Cohort 2: Elagolix 300 mg BID or placebo.

[00224] Cohort 3: Elagolix 200 mg BID plus low dose Activella® (a combination of 0.5 mg estradiol and 0.1 mg norethindrone actate).

[00225] Cohort 4: Elagolix 100 mg BID, 400 mg QD or placebo.

[00226] Cohort 5: Elagolix 600 mg QD.

[00227] Cohort 6: Elagolix 300 mg BID plus estrogen (1.0 mg of estradiol (Estrace®)) and 200 mg progesterone (cyclical Prometrium®)) (EP). Estrace® was given daily with Elagolix (continuously) and Prometrium® was given daily for the last 12 days of each 28 day menstrual cycle (cyclical).

[00228] Enrollment

[00229] Preliminary data includes 170 women received at least 1 dose of Elagolix. Overall, 152 women have received Elagolix for at least 2 months and 127 women received Elagolix for 3 months (full treatment duration). The majority of women are black (~80%), with 19% Caucasian. The mean age is 41.9 years (range 28 to 53), and mean body mass index (BMI) is 30.3 kg/m^2.

[00230] The enrollment characteristics are shown in Table 1

[00231] Table 1

Dose (Cohort)	Number of patients								
	E300 BID (2)	**E600 QD (5)**	**E300 BD+EP (6)**	**E200 BID (1)**	**E400 QD (4)**	**E200 BID+A (3)**	**E100 BID (4)**	**PBO* (1, 2, 4)**	**Total**
Randomized	**30**	**30**	**27**	**35**	**32**	**34**	**33**	**50**	**271**
Treated	30	30	27	35	32	34	33	50	271
Completed	26	24	25	28	26	29	26	43	227
Discontinued	4	6	2	7	6	5	7	7	44
Interim	30	30	27	35	32	34	33	50	271

Analysis Set									

[00232] Baseline characteristics are shown in Table 2.

[00233] Table 2

Characteristic	Number of patients								
	E 300 BID n = 30	E 600 QD n = 30	E 300 BID+EP N = 27	E 200 BID n = 35	E 400 QD n = 32	E 200 BID+A n =34	E 100 BID n = 33	PBO n = 50	Total N = 271
Mean Age (yrs.)*	42.6	40.8	41.6	43.1	40.8	40.9	42.1	42.3	41.8
Race White/Black (%)	20/76.7	16.7/80	40.7/55.6	20.0/80.0	15.6/78.1	20.6/76.5	30.3/69.7	24.0/72.0*	23.2/73.8
Mean Weight (Kg)	80.7	82.5	79.4	79.6	86.0	85.7	82.8	82.1	82.4
Mean BMI (kg/m^2)	29	31.1	29.6	29.4	31.7	31.8	30.4	29.9	30.3
Menstrual Blood Loss (mL) – Mean (Median)	208 (186)	216 (179.7)	265.8	333 (193)	210 (192)	245 (177)	261 (210)	336 (190)	237 (163)
Hemoglobin (g/dL) – Mean	11.2	10.8	10.3	10.8	11.0	10.8	10.2	10.4	10.7
Primary Fibroid Volume (cm^3) Mean (Median)	82.7 (47.8)	86.7 (39.5)	148.6 (99.3)	137.9 (55.9)	47 (27)	66 (49)	61 (27)	101.1 (33.2)	90.1 (41.1)
Uterine Volume (cm^3) - Mean (Median)	575 (519)	495.7 (364.4)	658.9 (616.8)	685 (460)	416 (322)	529 (469)	473 (297)	493 (351)	534 (421)

[00234]

- Sex: All female
- * age range 28-53; 15% are > 25 – ≤ 35; 55% are > 35 - ≤ 45; and 30% are > 45
- Note: Asian ethnicity, missing data on race and multi-racial subjects account for remaining % on for race

[00235] Efficacy

There are a number of efficacy endpoints, but a composite endpoint consisting of two bleeding assessments was used to assess one measure of efficacy. It included the percent of subjects who achieved a menstrual blood loss (MBL) volume of < 80 mL at the Final Month (last 28 days of treatment), and also achieved a ≥ 50% reduction in MBL volume from baseline to the Final Month (last 28 days of treatment) as measured by the Alkaline Hematin (AH) method. Eighty-five percent (85%), 97%, and 30% of subjects achieved the composite

bleeding assessment endpoint in the 200 mg BID, 300 mg BID, and placebo groups, respectively ($P < 0.05$ for 200 mg BID versus placebo in cohort 1, and 300 mg BID versus placebo in cohort 2). Eighty-two percent (82%) of subjects in the 200 mg BID + low-dose Activella® (low dose Activella® is a combination of (a combination of 0.5 mg estradiol and 0.1 mg norethindrone acetate) group achieved this composite endpoint. With respect to fibroid and uterine volumes, 63%, 55%, and 29% of subjects achieved a $\geq 25\%$ reduction in fibroid volume and 50%, 68%, and 9% achieved a $\geq 25\%$ reduction in uterine volume in the 200 mg BID, 300 mg BID, and placebo groups, respectively. In the 200 mg BID + low dose group, 53% and 42% of subjects achieved a $\geq 25\%$ reduction in fibroid and uterine volume, respectively. Quality of life (QoL) measures were also determined using the "Responsiveness of the uterine fibroid symptom and health-related quality of life questionnaire" (UFS-QOL) (Harding, Gale, Coyne Karin S., Thompson Christine L., Spies James B, United BioSource Corporation, 7101 Wisconsin Avenue, Suite 600, Bethesda, MD, 20814, USA, Health and Quality Life Outcomes, 2008, 6, page 99).

[00236] The results are summarized in Figures 1-5 as well as Tables 3 and 4 below.

Table 3: Total Menstrual Blood Loss during the Treatment Period Measured by Alkaline Hematin (AH) Method (See, also Figure 2).

Table 3

Dose	Average Total Blood Loss Measured by AH Method During Treatment (in mL)
Elagolix 600 QD (N=24)	69.6
Elagolix 300 BID (N=26)	4.3
Elagolix 400 QD (N=26)	38.4
Elagolix 200 BID (N=28)	47.0
Elagolix 200 BID + Act (N=29)	119.8
Elagolix 300 BID + EP (N=25)	114.5
Elagolix 100 BID (N=26)	198.4
Placebo (PBO) (N=43)	569.7

Table 4: Average monthly Menstrual Blood Loss (MBL) during the Treatment Period Measured by Alkaline Hematin (AH) Method

Table 4:

Dose	Number of subjects (N)	Average Blood Loss Per Cycle Measured by AH Method in Screening (mL)	Average total MBL from days 6-35 post-baseline (mL)	Average Total MBL from Days 36-65 Post-Baseline (mL)	Average Total MBL in Days 66-95 Post-Baseline (mL)
Elagolix 600 QD (N=24)	24	228.7	27.6	35.0	14.9
Elagolix 300 BID (N=26)	26	224.8	0	0	4.3
Elagolix 400 QD (N=26)	26	220.3	14.9	12.4	21.6
Elagolix 200 BID (N=28)	28	287.4	0	5.5	41.5
Elagolix 200 BID + Act (N=29)	29	251.9	26.3	41.5	37.9
Elagolix 300 BID + EP (N=25)	25	253.9	32.7	40.2	46.2
Elagolix 100 BID (N=26)	26	276.4	33.2	100.9	65.4
Placebo (PBO) (N=43)	43	271.2	190.5	194.6	190.3

The results in Tables 3 and 4 and Figures 1-3 show that Elagolix 300 mg BID without add-back therapy provides the maximum inhibition of bleeding (most of women achieved amenorrhea). Elagolix 400 mg QD and 600 mg QD were slightly less effective in this respect. However, these doses were associated with a relatively high percentage of hot flashes (50-62.5% of women reported an adverse event of hot flash). Elagolix 200 mg plus low-dose Activella® (0.5 mg E2/0.1 mg NETA) and elagolix 300 mg BID plus cyclical EP regimen (1 mg E2/ 200 mg progesterone for last 12 days of the cycle) restored HMB to normal levels. Both add-back regimens reduced the rate of hot flashes by approximately 50%.

Figure 4 shows that all Elagolix treatments (with and without add-back therapy) reduced uterine and fibroid volumes within 3 months and Elagolix 300 mg BID showed the strongest effects. Additionally, both add-back therapy regimens did not substantially reduced Elagolix effects on volume reduction. Figure 5 shows that All Elagolix treatments (with or without add-back therapy) showed an improvement in quality of life (QoL) measures compared to placebo.

WHAT IS CLAIMED IS

1. A method for reducing the volume of menstrual blood loss in a subject with or without uterine fibroids, the method comprising administering to the subject 300 to 600 mg per day of 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof, in combination with estrogens and progestogens.

2. The method of claim 1, wherein the estrogen is selected from the group consisting of estradiol, ethinyl estradiol, and conjugated estrogens, and the progestogen is selected from the group consisting of progesterone, norethindrone acetate, norgestimate, drospirenone, and medroxyprogesterone.

3. The method of claims 1 or 2, wherein the estrogen is estradiol and the progestogen is norethindrone acetate.

4. The method of claim 3, wherein the estradiol is administered in an amount of about 0.5 mg and the norethindrone acetate is administered in an amount of about 0.1 mg per day.

5. The method of claim 4, wherein the estradiol and norethindrone acetate are administered once per day.

6. The method of claim 3, wherein the estradiol is administered in an amount of about 1.0 mg and the norethindrone acetate is administered in an amount of about 0.5 mg per day.

7. The method of claim 6, wherein the estradiol and norethindrone acetate are administered once per day.

8. The method of claims 4 or 6, wherein the estradiol is administered continuously and norethindrone acetate are administered once per day during the last 12-14 days of a menstrual cycle.

9. The method of any of claims 1-8, wherein 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof is administered in an amount of about 300 mg per day.

10. The method of claim 9, wherein 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof is administered twice per day.

11. The method of any of claims 1-8, wherein 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof is administered in an amount of about 400 mg per day.

12. The method of claim 11, wherein 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof is administered twice per day.

13. The method of any of claims 1-8, wherein 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof is administered in an amount of about 600 mg per day.

14. The method of claim 13, wherein 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof is administered twice per day.

15. The method of any of claims 1-14, wherein 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-

pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid, estrogens, and progestogens are administered daily for at least 28 days.

16. The method of claim 15, wherein 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid, estrogens, and progestogens are administered daily for at least 56 days.

17. The method of claim 16, wherein 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid, estrogens, and progestogens are administered daily for at least 84 days.

18. The method of claim 17, wherein 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid, estrogens, and progestogens are administered daily for at least 168 days.

19. The method of claim 18, wherein 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid, estrogens, and progestogens are administered daily for about 168 days to about 1 year.

20. The method of claim 1, wherein the volume of menstrual blood loss is less than 80 mL per cycle.

21. The method of claim 1, wherein the subject has uterine fibroids.

22. The method of claim 1, wherein the subject does not have uterine fibroids.

23. A method for treating uterine fibroids in a subject of need of treatment, the method comprising administering to the subject 300 to 600 mg per day of 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-

dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof, in combination with estrogens and progestogens.

24. The method of claim 23, wherein the estrogen is selected from the group consisting of estradiol, ethinyl estradiol, and conjugated estrogens, and the progestogen is selected from the group consisting of progesterone, norethindrone acetate, norgestimate, drospirenone, and medroxyprogesterone.

25. The method of claims 23 or 24, wherein the estrogen is estradiol and the progestogen is norethindrone acetate.

26. The method of claim 25, wherein the estradiol is administered in an amount of about 0.5 mg and the norethindrone acetate is administered in an amount of about 0.1 mg per day.

27. The method of claim 26, wherein the estradiol and norethindrone acetate are administered once per day.

28. The method of claim 25, wherein the estradiol is administered in an amount of about 1.0 mg and the norethindrone acetate is administered in an amount of about 0.5 mg per day.

29. The method of claim 28, wherein the estradiol and norethindrone acetate are administered once per day.

30. The method of any of claims 23-29, wherein 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof is administered in an amount of about 300 mg per day.

31. The method of claim 30, wherein 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof is administered twice per day.

32. The method of any of claims 23-29, wherein 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof is administered in an amount of about 400 mg per day.

33. The method of claim 33, wherein 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof is administered twice per day.

34. The method of any of claims 23-29, wherein 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof is administered in an amount of about 600 mg per day.

35. The method of claim 34, wherein 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid or a pharmaceutically acceptable salt thereof is administered twice per day.

36. The method of any of claims 23-35, wherein 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid, estrogens, and progestogens are administered daily for at least 28 days.

37. The method of claim 36, wherein 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid, estrogens, and progestogens are administered daily for at least 56 days.

38. The method of claim 37, wherein 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-

phenyl-ethylamino)-butyric acid, estrogens, and progestogens are administered daily for at least 84 days.

39. The method of claim 38, wherein 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid, estrogens, and progestogens are administered daily for at least 168 days.

40. The method of claim 39, wherein 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid, estrogens, and progestogens are administered daily for about 168 days to about 1 year.

41. The method of claim 1, wherein the estrogen is estradiol and the progestogen is progesterone.

42. The method of claim 23, wherein the estrogen is estradiol and the progestogen is progesterone.

43. The method of claim 1, wherein the estrogen is estradiol and the progestogen is progesterone.

44. The method of claim 43, wherein the estradiol is administered continuously and the progesterone is administered once per day during the last 12-14 days of a menstrual cycle.

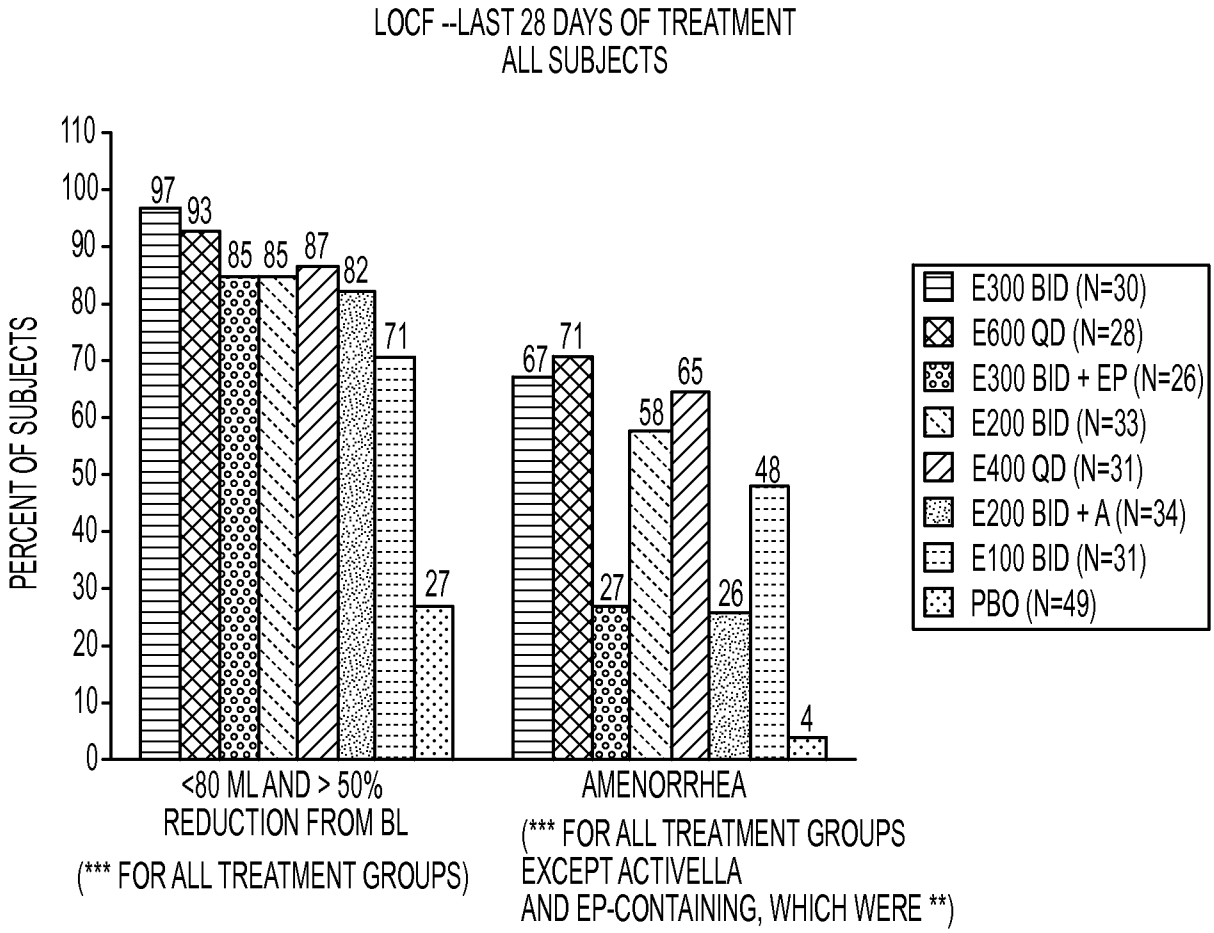
LOCF --LAST 28 DAYS OF TREATMENT
ALL SUBJECTS
PERCENT OF SUBJECTS
110
100
90
80
70
60
50
40
30
20
10
0
97
93
85
85
87
82
71
27
67
71
27
58
65
26
48
4
<80 ML AND > 50%
REDUCTION FROM BL
(*** FOR ALL TREATMENT GROUPS)
AMENORRHEA
(*** FOR ALL TREATMENT GROUPS
EXCEPT ACTIVELLA
AND EP-CONTAINING, WHICH WERE **)
E300 BID (N=30)
E600 QD (N=28)
E300 BID + EP (N=26)
E200 BID (N=33)
E400 QD (N=31)
E200 BID + A (N=34)
E100 BID (N=31)
PBO (N=49)

FIG. 1

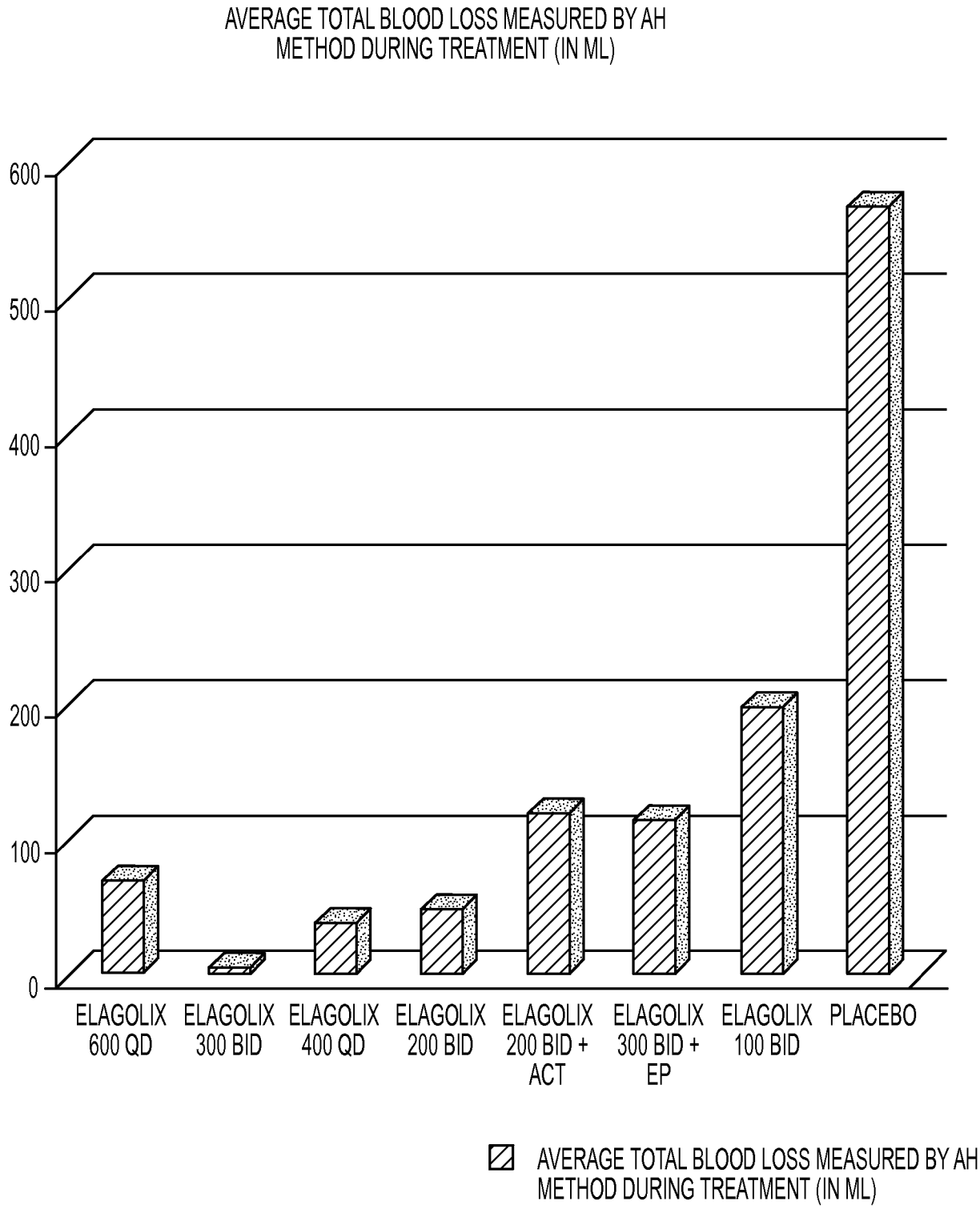
AVERAGE TOTAL BLOOD LOSS MEASURED BY AH METHOD DURING TREATMENT (IN ML)
600
500
400
300
200
100
0
ELAGOLIX 600 QD
ELAGOLIX 300 BID
ELAGOLIX 400 QD
ELAGOLIX 200 BID
ELAGOLIX 200 BID + ACT
ELAGOLIX 300 BID + EP
ELAGOLIX 100 BID
PLACEBO
AVERAGE TOTAL BLOOD LOSS MEASURED BY AH METHOD DURING TREATMENT (IN ML)

FIG. 2

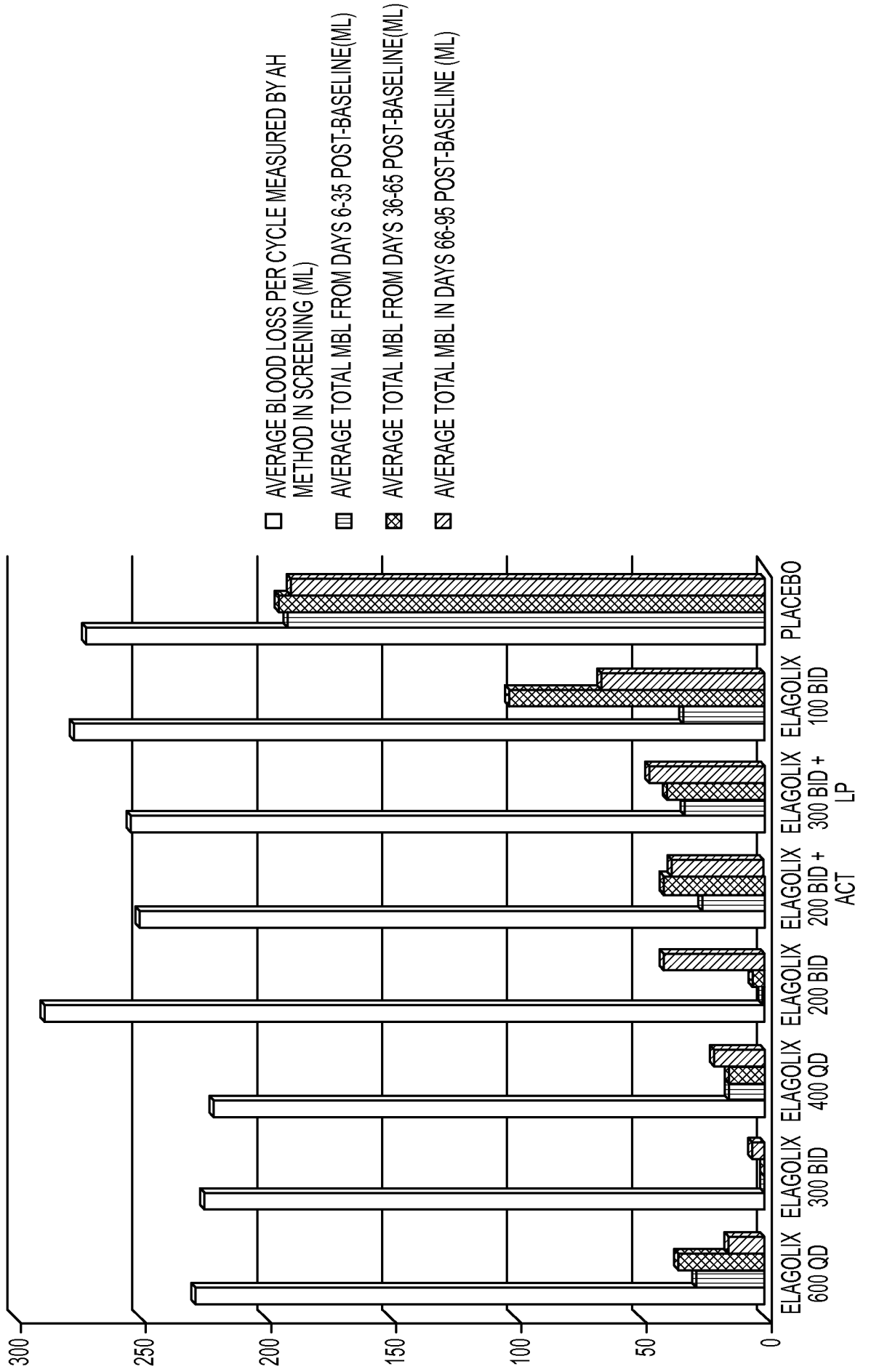
AVERAGE BLOOD LOSS PER CYCLE MEASURED BY AH METHOD IN SCREENING (ML)
AVERAGE TOTAL MBL FROM DAYS 6-35 POST-BASELINE(ML)
AVERAGE TOTAL MBL FROM DAYS 36-65 POST-BASELINE(ML)
AVERAGE TOTAL MBL IN DAYS 66-95 POST-BASELINE (ML)
300
250
200
150
100
50
0
ELAGOLIX 600 QD
ELAGOLIX 300 BID
ELAGOLIX 400 QD
ELAGOLIX 200 BID
ELAGOLIX 200 BID + ACT
ELAGOLIX 300 BID + LP
ELAGOLIX 100 BID
PLACEBO

FIG. 3

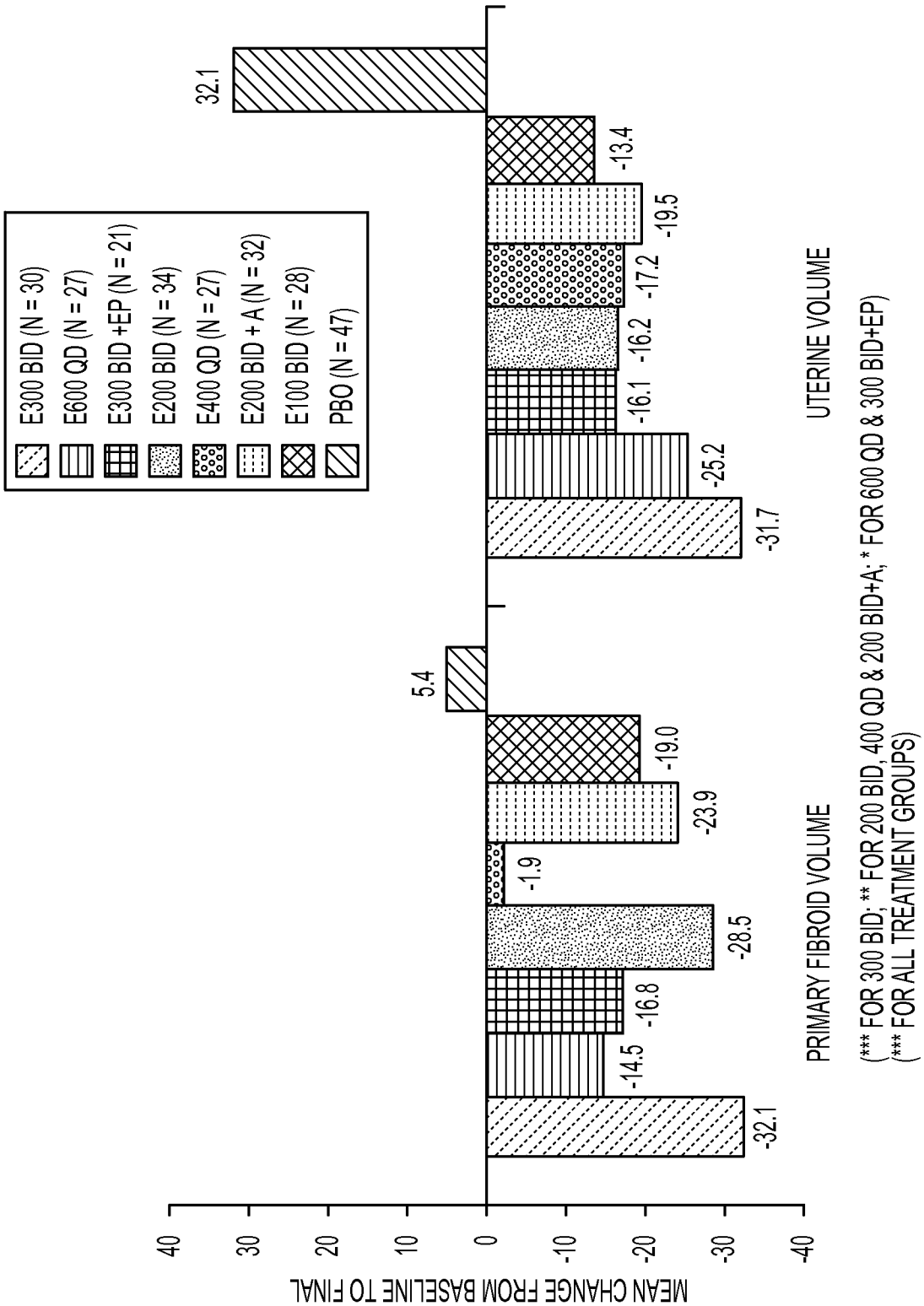
E300 BID (N = 30)
E600 QD (N = 27)
E300 BID +EP (N = 21)
E200 BID (N = 34)
E400 QD (N = 27)
E200 BID + A (N = 32)
E100 BID (N = 28)
PBO (N = 47)
MEAN CHANGE FROM BASELINE TO FINAL
40
30
20
10
0
-10
-20
-30
-40
32.1
-13.4
-19.5
-17.2
-16.2
-16.1
-25.2
-31.7
5.4
-19.0
-23.9
-1.9
-28.5
-16.8
-14.5
-32.1
PRIMARY FIBROID VOLUME
UTERINE VOLUME
(*** FOR 300 BID; ** FOR 200 BID, 400 QD & 200 BID+A; * FOR 600 QD & 300 BID+EP)
(*** FOR ALL TREATMENT GROUPS)

FIG. 4

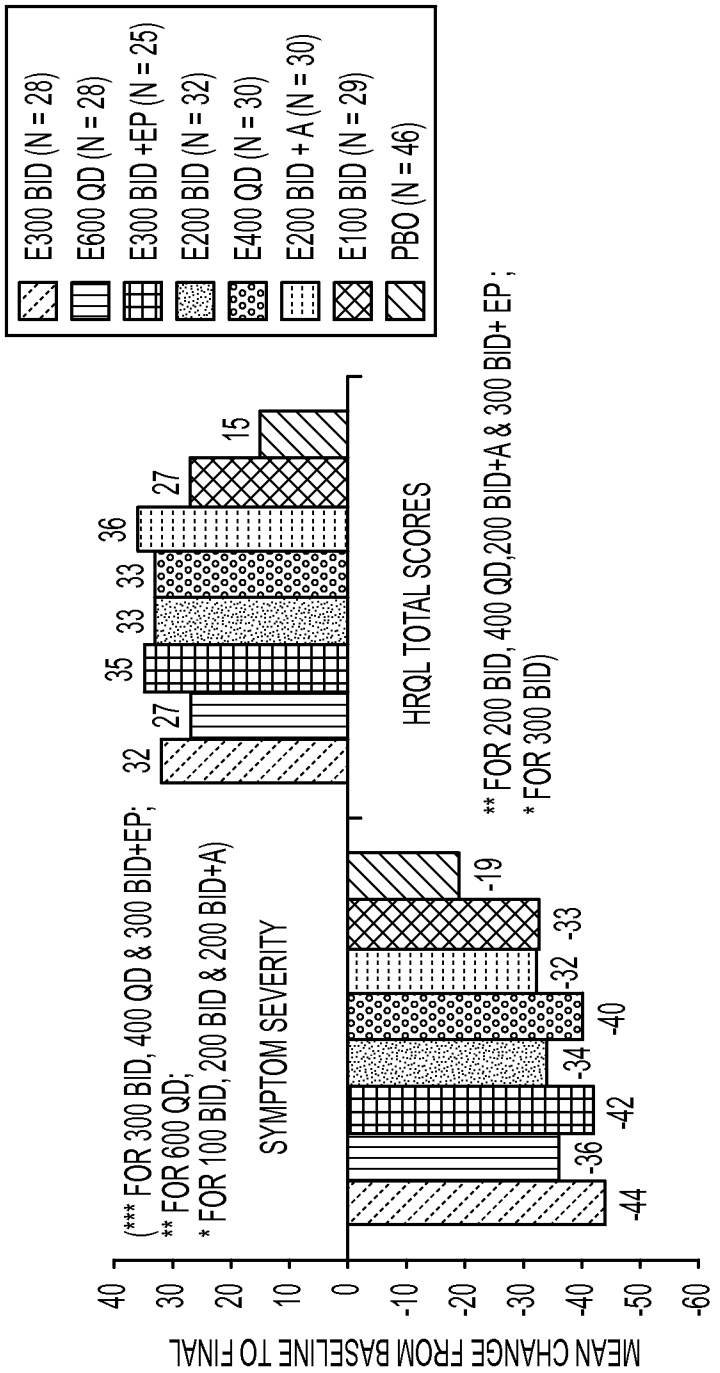
E300 BID (N = 28)
E600 QD (N = 28)
E300 BID +EP (N = 25)
E200 BID (N = 32)
E400 QD (N = 30)
E200 BID + A (N = 30)
E100 BID (N = 29)
PBO (N = 46)
MEAN CHANGE FROM BASELINE TO FINAL
40
30
20
10
0
-10
-20
-30
-40
-50
-60
32
27
35
33
33
36
27
15
-44
-36
-42
-34
-40
-32
-33
-19
SYMPTOM SEVERITY
HRQL TOTAL SCORES
(*** FOR 300 BID, 400 QD & 300 BID+EP;
** FOR 600 QD;
* FOR 100 BID, 200 BID & 200 BID+A)
** FOR 200 BID, 400 QD,200 BID+A & 300 BID+ EP ;
* FOR 300 BID)

FIG. 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/027673

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K45/06 A61K31/513 A61K31/565 A61K31/57 A61P15/00
A61K35/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Anonymous: "NCT01441635 on 2011_09_27: Safety and Efficacy Pre-Menopausal Women With Heavy Uterine Bleeding and Uterine Fibroids", clinicaltrials.gov archive, 27 September 2011 (2011-09-27), pages 1-6, XP055117517, Retrieved from the Internet: URL:http://clinicaltrials.gov/archive/NCT01441635/2011_09_27 [retrieved on 2014-05-12] the whole document ----- -/--	1-22

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 May 2014	27/05/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Haider, Ursula

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	Anonymous: "NCT01817530 on 2013_03_22: Safety and Efficacy in Premenopausal Women With Heavy Menstrual Bleeding (HMB) Associated With Uterine Fibroids (UF)", clinicaltrials.gov archive, 22 March 2013 (2013-03-22), pages 1-4, XP055117520, Retrieved from the Internet: URL:http://clinicaltrials.gov/archive/NCT01817530/2013_03_22 [retrieved on 2014-05-12] the whole document -----	1-22
A	M. SABRY ET AL: "Medical Treatment of Uterine Leiomyoma", REPRODUCTIVE SCIENCES, vol. 19, no. 4, 28 February 2012 (2012-02-28), pages 339-353, XP055117538, ISSN: 1933-7191, DOI: 10.1177/1933719111432867 page 342, right-hand column, paragraph 2 page 343, right-hand column, paragraph 3 - page 344, left-hand column, paragraph 1 -----	23-44
A	MOHAMED SABRY ET AL: "Innovative Oral Treatments of Uterine Leiomyoma", OBSTETRICS AND GYNECOLOGY INTERNATIONAL, vol. 30, no. 1, 1 January 2012 (2012-01-01), pages 44-10, XP055117561, ISSN: 1687-9589, DOI: 10.1016/j.fertnstert.2004.08.004 page 3, right-hand column, paragraph 2 - page 4, paragraph 2 page 5, left-hand column, paragraph 2 -----	23-44