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Running Title: Asoprisnil for Uterine Fibroids

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Abstract

Study question: Can asoprisnil, a selective progesterone receptor modulator, provide clinically meaningful improvements in heavy menstrual bleeding (HMB) associated with uterine fibroids with an acceptable safety profile?

Summary answer: Uninterrupted treatment with asoprisnil for 12 months effectively controlled HMB and reduced fibroid and uterine volume with few adverse events.

What is known already: In a 3-month study, asoprisnil (5, 10, and 25 mg) suppressed uterine bleeding, reduced fibroid and uterine volume, and improved hematological parameters in a dose-dependent manner.

Study design, size, duration: In two phase 3, double-blind, randomized, placebo-controlled, multicenter studies, women received oral asoprisnil 10 mg, asoprisnil 25 mg, or placebo (2:2:1) once daily for up to 12 months.

Participants/materials, setting, methods: Premenopausal women ≥18 years of age in North America with HMB associated with uterine fibroids were included (N=907). The primary efficacy endpoint was the percentage of women who met all 3 predefined criteria at 12 months, or final month for subjects who prematurely discontinued: (1) ≥50% reduction in monthly blood loss (MBL) by menstrual pictogram, (2) hemoglobin concentration ≥11 g/dL or an increase of ≥1 g/dL, and (3) no interventional therapy for uterine fibroids. Secondary efficacy endpoints included changes in other menstrual bleeding parameters, volume of the largest fibroids, uterine volume, and health-related quality of life (HRQL).

Main results and the role of chance: In all, 90% and 93% of women in the asoprisnil 10 mg and 25 mg groups, respectively, and 35% of women in the placebo group met the primary endpoint (P<0.001). Similar results were observed at month 6 (P<0.001). The percentage of

women who achieved amenorrhea in any specified month ranged from 66% to 78% in the asoprisnil 10 mg group and 83% to 93% in the asoprisnil 25 mg group, significantly higher than with placebo (3% to 12%, $P<0.001$). Hemoglobin increased rapidly (by month 2) with asoprisnil treatment and was significantly higher versus placebo throughout treatment. The primary fibroid and uterine volumes were significantly reduced from baseline through month 12 with asoprisnil 10 mg (median changes up to −48% and −28%, respectively) and 25 mg (median changes up to −63% and −39%, respectively) versus placebo (median changes up to +16% and +13%, respectively; all $P<0.001$). Dose-dependent, significant improvements in HRQL (Uterine Fibroid Symptom and Quality of Life instrument) were observed with asoprisnil treatment. Asoprisnil was generally well tolerated. Endometrial biopsies indicated dose- and time-dependent decreases in proliferative patterns and increases in quiescent or minimally stimulated endometrium at month 12 of treatment. Although not statistically significantly different at month 6, mean endometrial thickness at month 12 increased by approximately 2 mm in both asoprisnil groups compared with placebo ($P<0.01$). This effect was associated with cystic changes in the endometrium on MRI and ultrasonography, which led to invasive diagnostic and therapeutic procedures in some asoprisnil-treated women.

Limitations, reasons for caution: Most study participants were black; few Asian and Hispanic women participated. The study duration may have been insufficient to fully characterize the endometrial effects.

Wider implications of the findings: Daily uninterrupted treatment with asoprisnil was highly effective in controlling menstrual bleeding, improving anemia, reducing fibroid and uterine volume, and increasing HRQL in women with HMB associated with uterine fibroids. However,

this treatment led to an increase in endometrial thickness and invasive diagnostic and therapeutic procedures, with potential unknown consequences.

Study funding/competing interest(s): AbbVie Inc. (prior sponsors: TAP Pharmaceutical Products Inc., Abbott Laboratories)

Trial registration number: NCT00152269, NCT00160381 (clinicaltrials.gov)

Trial registration date: September 7, 2005; September 8, 2005

Date of first patient's enrolment: September 12, 2002; September 6, 2002

INTRODUCTION

Uterine fibroids (leiomyomata) are the most common neoplasms in premenopausal women. The cumulative incidence is approximately 80% and 70%, respectively, in black and white women, (Baird et al, 2003), with a two- to three-fold increased risk for development of uterine fibroids in black versus white women (Stewart et al, 2017). Approximately 20% to 50% of premenopausal women with uterine fibroids exhibit symptoms that may require clinical intervention (Buttram and Reiter, 1981); this includes heavy menstrual bleeding (HMB), often associated with iron-deficiency anemia (also called abnormal uterine bleeding due to leiomyoma [AUB-L]) (Munro et al, 2011; Stewart, 2001) and the most common indication for hysterectomy (Carlson et al, 1993).

The treatment of women with uterine fibroids is individualized based on symptoms, age, desire to preserve fertility, and patient preference. Hysterectomy remains the mainstay of treatment of symptomatic uterine fibroids in the United States, accounting for >75% of all procedures (Borah et al, 2016). Alternatives to hysterectomy include myomectomy, uterine artery embolization, magnetic resonance-guided focused ultrasound, and short-term pre-operative pharmacologic treatments (Stewart, 2001).

Uterine fibroids respond to estradiol (E2) and progesterone (Carr et al, 1993). Newer research suggests that progesterone and the progesterone receptor (PR) play a more important role, whereas E2 has a permissive role by stimulating PR synthesis (Bulun, 2013; Chwalisz et al, 2005b). The most compelling evidence of the role of progesterone in uterine fibroid growth and development comes from studies showing that selective PR modulators (SPRMs; eg,

mifepristone, asoprisnil, and ulipristal acetate) suppress uterine bleeding and reduce fibroid volume (Ali and Al-Hendy, 2017; Chwalisz et al, 2007; Donnez et al, 2012a; Eisinger et al, 2003; Wilkens et al, 2008). Ulipristal acetate was approved initially in the EU and Canada as a pre-operative treatment for symptomatic uterine fibroids (Donnez et al, 2012a; Donnez et al, 2012b), and more recently for the long-term management of symptomatic uterine fibroids using an intermittent treatment regimen (Donnez et al, 2014).

Asoprisnil is a highly selective 11β-benzaldoxime-substituted SPRM with mixed PR agonist/antagonist activity (DeManno et al, 2003; Elger et al, 2000). Compared with other SPRMs, including mifepristone and ulipristal acetate, asoprisnil showed a higher degree of progesterone agonist versus antagonist activity in animal models (Elger et al, 2000). In cultured leiomyoma cells, asoprisnil inhibited proliferation and induced apoptosis, without similarly affecting myometrial cells, (Chen et al, 2006; Sasaki et al, 2007) and down-regulated collagen synthesis (Morikawa et al, 2008).

In a phase 1 study, asoprisnil demonstrated dose-dependent suppression of menstrual bleeding without E2 deprivation (Chwalisz et al, 2005a). In a subsequent 3-month, phase 2 study in women with HMB associated with uterine fibroids, asoprisnil (5, 10, and 25 mg) suppressed HMB, reduced fibroid and uterine volume, improved hematological parameters in a dose-dependent manner, and had an acceptable safety and tolerability profile (Chwalisz et al, 2007).

This report presents a pooled analysis of the two phase 3 studies of asoprisnil in women with uterine fibroids and HMB. The objective of these studies was to evaluate the safety and efficacy of two oral doses of asoprisnil (10 mg and 25 mg once daily) compared with placebo over a continuous 12-month treatment period.

MATERIALS AND METHODS

Study Design

This report combines data from two randomized, double-blind, placebo-controlled, parallel-group, multicenter studies (NCT00152269 [Study 1] and NCT00160381 [Study 2], clinicaltrials.gov) conducted in the United States and Canada between September 2002 and January 2005. Both studies had identical protocols except that bone mineral density (BMD) was evaluated in Study 1.

Ethical Approval

The studies were approved by institutional review boards and conducted in accordance with the Declaration of Helsinki, Good Clinical Practice Guidelines, and local and federal laws and regulations. An independent data safety monitoring board (DSMB) and panel of endometrial pathologists regularly reviewed safety.

Study Population

Participants (N=907 randomized) were premenopausal women ≥18 years of age who had regular menstrual cycles, defined as 21 to 42 days, and agreed to use two forms of non-hormonal contraception throughout the studies. The presence of uterine fibroids with at least 1 of the following criteria was documented by ultrasound and magnetic resonance imaging (MRI): 1 submucosal fibroid with diameter ≥2.0 cm, 1 intramural fibroid with diameter ≥3.5 cm, 1 subserosal fibroid with diameter ≥3.5 cm, or multiple small fibroids with uterine volume ≥200 cm^3. HMB was evaluated using a validated semi-quantitative menstrual pictogram (MP) method (Larsen et al, 2013); eligible women had an MP score >80 mL during the screening menstrual cycle or hemoglobin ≤10.5 g/dL at screening and day −1 and had no evidence of malignancy or premalignant changes in screening endometrial biopsies and Pap smears. Study participants were excluded if they were pregnant, were within 3 months postpartum, used an intrauterine device, had a previous myomectomy within 1 year or uterine artery embolization within 6 months of enrollment, or had a history of polycystic ovary syndrome, prolactinomas, or malignancy, or for other reasons **(Supplemental Methods)**.

Efficacy Endpoints

The primary efficacy endpoint was the proportion of women who met all of the following criteria at month 12 or final month for subjects who prematurely discontinued: (1) reduction from baseline of ≥50% in MP score, (2) hemoglobin concentration ≥11 g/dL or increase of ≥1 g/dL from baseline, and (3) no surgical or invasive intervention for uterine fibroids (eg, hysterectomy, myomectomy, and uterine artery embolism) during treatment nor withdrawal from the study with the intention to have such an intervention. This endpoint was designed in consultation with the

United States Food and Drug Administration as a surrogate measure of the avoidance of surgical intervention for HMB. Standardized cotton sanitary protection products (Kotex® Super and Nighttime napkins; Tampax® Regular, Super, and Super Plus tampons) were provided throughout the studies. Secondary efficacy endpoints included the response rate for the primary efficacy endpoint at month 6, monthly MP scores, number of days with bleeding or spotting, monthly rates of amenorrhea (ie, no bleeding during that month), the percentage of participants with suppression of menses (ie, no menses for ≥60 consecutive days during treatment after the end of randomization menses), maintenance of menses suppression, change from baseline in hemoglobin, hematocrit, ferritin, total iron binding capacity, and iron, percentage change from baseline in the volume of each of the two largest fibroids and the uterus at months 6 and 12, and the Uterine Fibroid Symptom and Quality of Life (UFS-QOL)(Spies et al, 2002) and Leiomyoma Symptom Assessment Questionnaire (LSAQ) (Chwalisz et al, 2007). MRI was used to measure fibroid and uterine volume at screening, month 6, month 12, and the month-6 follow-up visit. The primary fibroid was the largest fibroid based on volume.

Safety Evaluation and Endpoints

Adverse events (AEs) were recorded and evaluated throughout the studies. BMD was assessed (Study 1) in the lumbar spine by dual energy x-ray absorptiometry (DXA) at screening and month 12 in a subset of approximately 300 women. A central service (DXA Resource Group, Inc., Worcester, MA, USA) evaluated DXA scans.

Laboratory evaluations, including safety (general, hepatic, renal) and hematology parameters, were conducted at screening, baseline, and every 2 months during the treatment period. Hematology, iron, and select endocrine parameters were also collected at the follow-up month-3 visit. Hormonal parameters (luteinizing hormone [LH], follicle-stimulating hormone [FSH], E2, estrone [E1], progesterone, androstenedione, total and free testosterone, sex hormone binding globulin [SHBG], dehydroepiandrosterone sulfate [DHEA-S], thyroid-stimulating hormone [TSH], thyroxine [T_4], and prolactin) were measured throughout the studies **(Supplemental Table I)**.

Endometrial Assessments

Each endometrial biopsy (from screening, months 6 and 12, and posttreatment month 3) was evaluated by two independent, central pathologists. If their diagnoses were abnormal or discrepant, a third central pathologist provided final arbitration. All readings were conducted blinded to the participant's treatment and to the other pathologist's diagnosis. The endometrial biopsy results were assessed according to diagnostic categories which were developed by the panel of expert endometrial pathologists specifically for asoprisnil clinical trials **(Supplemental Methods)**.

Saline infused sonohysterogram (SIS) was performed in participants with suspected intracavitary lesions on TVU or MRI images at baseline or anytime during the studies. MRI and SIS images were evaluated by blinded, independent central readers (WorldCare Clinical Inc., Cambridge, MA, USA). When indicated, hysteroscopy, dilation and curettage (D&C), and polypectomy were performed to evaluate imaging changes suggestive of a polyp, endometrial thickness ≥19 mm, or

unsatisfactory endometrial biopsies. Tissue samples obtained during these procedures were evaluated by both local and central pathologists.

Randomization

Eligible women (N=907) were randomized using a computer-generated randomization chart with a fixed block size of 5 in a 2:2:1 ratio to receive oral asoprisnil 10 mg (n=370), asoprisnil 25 mg (n=364), or placebo (n=173). Study drug was dispensed in blister packs, each with an attached blinded label. Dosing began within the first 5 days of the onset of the woman's menstrual period and continued once daily for 12 months. Participants, site personnel, and sponsor remained blinded to treatment assignment throughout, including the posttreatment follow-up. At study completion, eligible women could enroll in a 12-month, open-label extension study; women who were ineligible or declined participation in the extension study were followed for 6 months thereafter to allow for the assessment of return to menses and regrowth of leiomyomata. Prohibited medications are listed in **Supplemental Table II**. Hormonal treatment before study initiation required predefined washout periods (2–12 months, depending on the drug). Women with anemia received iron supplementation to normalize hemoglobin and serum ferritin levels.

Statistical Analyses

To calculate the primary endpoint, the modified intent-to-treat (mITT) set was pre-specified in the statistical analysis plan. All women in the mITT set had complete baseline and treatment period data related to calculating the primary endpoint, and either (a) were on treatment for at least 30 days or (b) discontinued prior to day 30 to have surgery for fibroids. In the case of discontinuation to have surgery for fibroids, the woman was considered a non-responder. Pooled

efficacy analyses are presented for this mITT set (placebo, n=153; asoprisnil 10 mg, n=321; asoprisnil 25 mg, n=317).

Pairwise comparisons of the primary and secondary efficacy endpoints at the participant's final visit and 6 months, respectively, were performed using the Fisher exact test, using the Hochberg multiple comparison procedure to control the Type I error rate. Statistical methods for additional efficacy endpoints are noted in the **Supplemental Methods**.

The safety population included all participants who received at least 1 dose of the study drug. Statistical methods for safety analyses are noted in the **Supplemental Methods**. Safety evaluations are unadjusted for multiple comparisons, and nominal *P* values are reported.

A sample size of approximately 375 participants per study (150 participants in each of the asoprisnil 10- and 25-mg arms, respectively, and 75 participants in the placebo arm) would give 90% power to detect a difference between the placebo group and asoprisnil groups assuming rates of 25% and 50%, respectively, for the primary endpoint based on a two-sided α=0.05 significance level.

RESULTS

Study Population

Most participants completed the studies (73%; **Figure 1**). The proportions of women who withdrew were higher in the placebo arm (36%) than in the asoprisnil 10 mg (24%) and 25 mg (26%) arms. AEs were the most common reason besides "other" for discontinuation in the asoprisnil arms in both studies and in the placebo arm for Study 2 (**Figure 1 and Supplemental Table III**). The population in the posttreatment follow-up period included only the 238 women who did not enroll in the extension study.

Most participants were black and were 40 years of age or older (**Table I**). Participant characteristics, fibroid-related characteristics, and hematologic parameters did not differ significantly between groups. Exclusion of randomized patients from primary endpoint analysis due to an MP score ≤80 mL and hemoglobin level >10.5 g/L during screening occurred in small proportions of women in the placebo (6%), asoprisnil 10-mg (5%), and asoprisnil 25-mg (4%) arms.

Efficacy Endpoints

In all, 90% and 93% of women in the asoprisnil 10 mg and 25 mg groups, respectively, met the primary efficacy endpoint compared with 35% of women in the placebo group (P<0.001; **Table II**). Similar results were observed at month 6 (P<0.001; **Table II**).

Menstrual Bleeding Parameters

The mean monthly blood loss (MBL) was consistently and significantly (P<0.001) reduced to <21 mL and <13 mL by asoprisnil 10 and 25 mg, respectively, versus placebo in month 1 through month 12 of treatment (**Figure 2**; **Table II**). There were also significant (P<0.001) reductions in the number of days with bleeding (**Table II**) and bleeding or spotting (**Supplemental Figure 1**) in both asoprisnil groups throughout treatment. Monthly amenorrhea rates **(Figure 3)** and suppression of menses rates **(Table II)** were significantly higher (P<0.001) for both asoprisnil groups. After stopping treatment, 73% to 87% and 53% to 66% of women treated with asoprisnil 10 mg and asoprisnil 25 mg, respectively, experienced return of menses within 1 month across the studies. Mean MBL during the first posttreatment menses was similar to baseline in both the asoprisnil 10-mg and 25-mg groups and placebo, indicating a return toward baseline HMB (**Supplemental Table IV**).

Hematologic and Iron Parameters

Hemoglobin and other hematologic parameters increased rapidly in the asoprisnil groups and were sustained throughout treatment. The mean increases from baseline at month 6 and month 12 were significantly greater (P<0.001) with the asoprisnil groups compared with placebo (**Table III** and **Supplemental Table V**).

Fibroid and Uterine Volume

Compared with baseline, the volume of the primary fibroid was significantly reduced in women receiving asoprisnil (10 or 25 mg) versus placebo at 6 and 12 months (P<0.001; **Figure 4**); this

effect was maintained posttreatment. Median changes from baseline in primary fibroid volume at posttreatment month 6 were up to −45% with asoprisnil 10 mg and −54% with asoprisnil 25 mg versus up to 44% with placebo. Median changes in uterine volume were as large as −28% with asoprisnil 10 mg and −39% with asoprisnil 25 mg at month 6 and month 12 versus 13% with placebo (P<0.001). Uterine volume reductions were substantially maintained posttreatment, especially in the asoprisnil 25-mg group; median changes from baseline in uterine volume at posttreatment month 6 were up to −6% with asoprisnil 10 mg and −29% with asoprisnil 25 mg versus –25% to 50% with placebo.

Patient-Reported Outcomes

The UFS-QOL symptom severity score and health-related quality of life (HRQL) total score at month 6 and month 12 were significantly improved in women treated with asoprisnil versus placebo (P<0.001;**Table II**). All 6 HRQL subscales showed similar results (**Supplemental Tables VI and VII**). Significant improvements in bloating, pelvic pressure, and dysmenorrhea as measured by LSAQ were observed by month 2 for both asoprisnil groups compared with placebo, and these effects were maintained through month 12 (P<0.001; **Supplemental Table VIII**).

Safety and Tolerability

General Safety

The percentage of women who reported ≥1 AE was similar among groups (**Table III**). Hot flush occurred more frequently in the asoprisnil groups and was significantly increased with the 25-mg

dose compared with placebo (14% vs 7%; $P<0.05$). Other AEs were infrequent, but bladder and urethral symptoms and myalgias were significantly increased with asoprisnil treatment, while menstrual symptoms and nonspecific muscle symptoms were decreased, compared with placebo. No pregnancies occurred in asoprisnil-treated women.

Heavy menstrual bleeding (reported as uterine hemorrhage; asoprisnil 10 mg, n=1; asoprisnil 25 mg, n=1) and cholecystitis (asoprisnil 10 mg, n=2) were the only serious AEs experienced by more than one woman in either study. All AEs leading to discontinuation are presented in **Supplemental Table III**. Six women discontinued because of increases in the liver enzymes alanine aminotransferase and/or aspartate aminotransferase (asoprisnil 10 mg, n=2 [starting days 60 and 182]; asoprisnil 25 mg, n=3 [days 56, 61, and 63]; placebo, n=1 [day 115]), one woman because of an increase in gamma-glutamyl transferase (placebo [day 117]), and one woman with a history of Gilbert's syndrome (asoprisnil 10 mg [day 137]) because of isolated increases in total bilirubin. In most women, the increases in liver enzymes were mild (2–3× the upper limit of normal) and transient; none of these events was associated with an increase in total bilirubin or symptoms.

Endometrial Assessments

Endometrial Biopsy Results

Endometrial biopsy results are presented in **Supplemental Table IX**. SPRM-specific categories ("non-physiologic secretory effect" and "secretory pattern, mixed type") were significantly increased with asoprisnil treatment at 6 and 12 months and ranged between 8% to 19% (placebo 1%–4%), with no differences between asoprisnil doses. With asoprisnil treatment, there was a

dose- and time-dependent decrease in the frequency of diagnoses consistent with active proliferation, with "inactive" endometrium being the dominant diagnosis (28%–32%) at month 12 of treatment, compared with placebo (3%). There were two adverse endometrial findings: one woman, who had a history of endometrial hyperplasia, was diagnosed with complex hyperplasia without atypia at the month 6 biopsy (asoprisnil 10 mg), and a second woman (asoprisnil 25 mg) was diagnosed with low-grade endometrial adenosarcoma in an endometrial polyp at month 9. Both of these changes were seen in the setting of an increase in endometrial thickness. Retrospective examination of the baseline MRI images of the woman with adenosarcoma did show a focal endometrial lesion, which suggests a potential pre-existing condition (**Supplemental Tables X and XI**).

In the limited population of women who entered the posttreatment follow-up period, the endometrium of the vast majority of asoprisnil-treated women returned to normal cyclic physiologic patterns by posttreatment month 3 (**Supplemental Table IX**). Only 5% and 2% of women treated with asoprisnil at posttreatment month 3 follow-up were diagnosed with "non-physiologic secretory effect" and "secretory pattern, mixed type," respectively.

Changes in Endometrial Thickness and Texture

There was no significant increase in mean endometrial thickness at months 4 and 8 in both asoprisnil groups compared with placebo when measured with TVU (**Supplemental Table X**). However, there was slight but significant (P<0.01) increase from baseline (approximately 2 mm)

at month 12 in women receiving asoprisnil compared with placebo when measured with MRI **(Supplemental Table XI)**.

The analysis of MRI and TVU images revealed dose- and time-dependent increases in the percentage of women with endometrial thickness ≥19 mm at month 8 and the presence of cystic changes (mostly endometrial cysts and polypoid changes), which somewhat mimicked imaging findings of endometrial hyperplasia (**Supplemental Table XII**). These changes contributed to the notable increase in the rate of invasive diagnostic and therapeutic procedures, including hysteroscopy, D&C, and polypectomy, in the asoprisnil groups (7%–10%) after month 8 compared with the placebo group (0%).

Laboratory Safety Parameters

No clinically meaningful changes in general chemistry, renal, and hepatic parameters were observed with asoprisnil treatment. There was little change in total cholesterol associated with asoprisnil treatment; however, asoprisnil significantly reduced high-density lipoprotein cholesterol in a dose- and time-dependent manner (**Supplemental Table XIII**).

Endocrine and Bone Parameters

A modest, dose-dependent inhibitory effect of asoprisnil on basal FSH and LH was observed at month 12 (**Supplemental Table XIV**). There was a dose-dependent reduction over time in E2 **(Supplemental Figure 2)** and E1 in asoprisnil groups. However, most E2 levels remained in the early follicular phase range. Total testosterone, androstenedione, and SHBG decreased slightly

but significantly more from baseline with either asoprisnil dose versus placebo at 6 and 12 months (**Supplemental Table XIV**). No significant differences in the mean percentage BMD change from baseline to month 12 were observed with asoprisnil treatment compared with placebo (Study 1).

DISCUSSION

In these two randomized, placebo-controlled studies, uninterrupted treatment with asoprisnil for 12 months effectively controlled HMB, improving anemia, quality of life, and non-bleeding symptoms, and reducing the fibroid and uterine volumes in women with HMB and fibroids. The primary endpoint was achieved in ≥90% of women treated with asoprisnil versus 35% of women in the placebo group. The effects were rapid, dose dependent, and maintained during the entire treatment period, with amenorrhea rates ranging between 66% to 93% and low occurrence of breakthrough bleeding or spotting. The effects of asoprisnil on HMB reversed after stopping treatment.

These results are consistent with other SPRMs, including mifepristone and ulipristal acetate (Donnez et al, 2012a; Donnez et al, 2014; Kettel et al, 1994; Murphy et al, 1993), and with earlier asoprisnil studies (Chwalisz et al, 2005a; Chwalisz et al, 2007; Wilkens et al, 2008). However, amenorrhea rates in the present studies seem higher than with ulipristal acetate, particularly in the US population (Soper et al, 2017). This increased efficacy may be related to our hypothesis that asoprisnil controls HMB via a dual mechanism by directly affecting the endometrium and indirectly inhibiting ovulation (Chwalisz et al, 2005a). Subsequent mechanistic

studies have suggested that the endometrial effect of asoprisnil occurs via suppression of the uterine NK cells that regulate the function of spiral arteries (Wilkens et al, 2013).

We also observed significant, progressive reduction in fibroid and uterine volumes, with slow regrowth of uterine fibroids after stopping treatment, that could be due to the selective antiproliferative, proapoptotic effects and inhibition of extracellular matrix formation in uterine fibroids by asoprisnil (Morikawa et al, 2008; Ohara et al, 2007; Sasaki et al, 2007), or other effects including the reduction in uterine blood flow (Wilkens et al, 2008). Similarly, durable reduction of fibroid volume was observed after short-term treatment with ulipristal acetate (Donnez et al, 2014).

Treatment with asoprisnil for up to 12 months was not associated with any general safety issues, including hepatic safety. No cases of liver injury were reported during these placebo-controlled studies. The small increase in the rate of hot flushes (**Table III**) could be attributed to the reduction in E2 levels. The BMD evaluation (Study 1) revealed no significant changes versus placebo at month 12.

At no point throughout the studies did the endometrial biopsy results, which were thoroughly monitored by both the endometrial pathology safety panel and DSMB, raise any safety concerns. The endometrial effects induced by asoprisnil in endometrial biopsies were viewed as unique but benign changes.

In these studies, treatment with asoprisnil was associated with a time-dependent progression of endometrial changes on both endometrial biopsies and images, becoming clinically evident after ≥8 months of treatment (**Supplemental Tables X to XII**), which led to an increase in diagnostic and therapeutic procedures. Both the endometrial biopsy results and textural change on TVU and MRI images seemed to reverse after stopping therapy at month 3 of the follow-up period, with resumption of menses.

A strength of this study is the high percentage of black women, whose disease course is earlier and more severe compared with white women.(Baird et al, 2003; Bulun, 2013; Huyck et al, 2008; Jacoby et al, 2010; Laughlin et al, 2010) Additionally, the HMB was severe, with mean and median MBL of >260 mL and approximately 200 mL, respectively. Additional strengths include use of validated sanitary products for bleeding assessments, thorough endometrial assessments involving expert endometrial pathologists, and the use of MRI to assess changes in fibroid and uterine volumes. A major weakness was limited follow-up data because most patients transferred to the open-label, uncontrolled long-term extension study, described separately.(Diamond et al, 2018) Additionally, hematologic analyses could be confounded by iron supplementation to normalize hemoglobin levels. Finally, although the current sponsor is committed to publication of all its interventional clinical trials conducted in patients, reports of these trials conducted >10 years ago had been delayed for multiple reasons including multiple changes in sponsor and indeterminate development plans. Despite this delay, these data are clinically important because they represent the only studies with an SPRM that used a continuous (uninterrupted) treatment regimen for 12 months.

In summary, asoprisnil treatment was highly effective in controlling bleeding, improving anemia, reducing fibroid and uterine volume, and increasing quality of life in women with HMB associated with uterine fibroids. The safety profile, including hepatic function, was acceptable. However, uninterrupted treatment with the SPRM asoprisnil may pose a safety concern because of the unknown long-term endometrial effects.

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Authors' roles

E. A. Stewart participated in study design, data analysis, and preparation, critical review, and approval of the manuscript.

M. P. Diamond participated in study conduct, data analysis, and preparation, critical review, and approval of the manuscript.

A. R. W. Williams was a member of the independent endometrial pathology consultant panel in these studies. He was involved in drafting, critical review, and approval of the manuscript.

B. R. Carr participated in collection, analysis, and interpretation of the data and in critically reviewing and approving the manuscript.

E. R. Myers participated in interpretation of data and critical review and approval of the manuscript.

R. A. Feldman served as a principal investigator and participated in the conduct of the trials and participated in critical review and approval of the manuscript.

W. Elger proposed the concept of a PR-agonistic PRM. A respective collaboration eventually led to the discovery of asoprisnil and mechanistic insights into its mode of action. (He participated in the analysis of hormonal properties and related findings throughout preclinical and clinical exploration.) He contributed to historical aspects and viewpoints concerning PRM pharmacology for the manuscript and in critical review and approval of the manuscript.

C. Mattia-Goldberg participated in study design, study execution, data clean-up and analysis, and critical review and approval of the manuscript.

B. M. Schwefel participated in analysis and in drafting, critical review, and approval of the manuscript.

K. Chwalisz was the medical director of these studies. He participated in designing and conducting the studies, collection, analysis, and interpretation of the data, and in critical review and approval of the manuscript.

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Data Sharing

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual and trial-level data (analysis data sets), as well as other information (e.g., protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a

research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

Conflict of Interest

E. A. Stewart was a site investigator in the phase 2 study of asoprisnil and consulted for TAP during the design and conduct of these studies while at Harvard Medical School and Brigham and Women's Hospital. She received support from National Institutes of Health grants HD063312, HS023418, and HD074711 and research funding, paid to Mayo Clinic. for patient care costs related to an NIH-funded trial from InSightec Ltd. She consulted for AbbVie, Allergan, Astellas Pharma Inc., Bayer HealthCare AG, Gynesonics, Viteava Pharmaceuticals Inc., GlaxoSmithKline, and Welltwigs. She received royalties from UpToDate and the Massachusetts Medical Society.

M. P. Diamond received research funding for the conduct of the studies paid to the institution, and consulted for AbbVie. He is a stockholder and board and director member of Advanced Reproductive Care. He has also received funding for study conduct paid to the institution from Bayer and ObsEva.

A. R. W. Williams consulted for TAP and Repros Therapeutics Inc. He has current consultancies with PregLem SA, Gedeon Richter, HRA Pharma, and Bayer.

B. R. Carr consulted for and received research funding from AbbVie.

E. R. Myers consulted for AbbVie and Bayer.

R. A. Feldman received compensation for serving as a principal investigator and participating in the conduct of the trial.

W. Elger was co-inventor of several patents related to asoprisnil.

C. Mattia-Goldberg is a former employee of AbbVie and may own AbbVie stock or stock options.

B. M. Schwefel and K. Chwalisz are employees of AbbVie and may own AbbVie stock or stock options.

References

Ali M, Al-Hendy A. Selective progesterone receptor modulators for fertility preservation in women with symptomatic uterine fibroids. *Biol Reprod.* 2017;**97**:337-352.

Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. *Am J Obstet Gynecol.* 2003;**188**:100-107.

Borah BJ, Laughlin-Tommaso SK, Myers ER, Yao X, Stewart EA. Association between patient characteristics and treatment procedure among patients with uterine leiomyomas. *Obstet Gynecol.* 2016;**127**:67-77.

Bulun SE. Uterine fibroids. *N Engl J Med.* 2013;**369**:1344-1355.

Buttram VC, Jr., Reiter RC. Uterine leiomyomata: etiology, symptomatology, and management. *Fertil Steril.* 1981;**36**:433-445.

Carlson KJ, Nichols DH, Schiff I. Indications for hysterectomy. *N Engl J Med.* 1993;**328**:856-860.

Carr BR, Marshburn PB, Weatherall PT, Bradshaw KD, Breslau NA, Byrd W, Roark M, Steinkampf MP. 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**:1217-1223.

Chen W, Ohara N, Wang J, Xu Q, Liu J, Morikawa A, Sasaki H, Yoshida S, Demanno DA, Chwalisz K, et al. A novel selective progesterone receptor modulator asoprisnil (J867) inhibits proliferation and induces apoptosis in cultured human uterine leiomyoma cells in the absence of comparable effects on myometrial cells. *J Clin Endocrinol Metab.* 2006;**91**:1296-1304.

Chwalisz K, Elger W, Stickler T, Mattia-Goldberg C, Larsen L. The effects of 1-month administration of asoprisnil (J867), a selective progesterone receptor modulator, in healthy premenopausal women. *Hum Reprod.* 2005a;**20**:1090-1099.

Chwalisz K, Larsen L, Mattia-Goldberg C, Edmonds A, Elger W, Winkel CA. A randomized, controlled trial of asoprisnil, a novel selective progesterone receptor modulator, in women with uterine leiomyomata. *Fertil Steril.* 2007;**87**:1399-1412.

Chwalisz K, Perez MC, Demanno D, Winkel C, Schubert G, Elger W. Selective progesterone receptor modulator development and use in the treatment of leiomyomata and endometriosis. *Endocr Rev.* 2005b;**26**:423-438.

DeManno D, Elger W, Garg R, Lee R, Schneider B, Hess-Stumpp H, Schubert G, Chwalisz K. Asoprisnil (J867): a selective progesterone receptor modulator for gynecological therapy. *Steroids.* 2003;**68**:1019-1032.

Diamond MP, Stewart EA, Williams ARW, Carr BR, Myers ER, Feldman RA, Elger W, Mattia-Goldberg C, Schwefel BM, Chwalisz K. A 12-month extension study to evaluate the safety and efficacy of asoprisnil in women with heavy menstrual bleeding and uterine fibroids. *Hum Reprod.* 2018:Submitted manuscript.

Donnez J, Tatarchuk TF, Bouchard P, Puscasiu L, Zakharenko NF, Ivanova T, Ugocsai G, Mara M, Jilla MP, Bestel E, et al. Ulipristal acetate versus placebo for fibroid treatment before surgery. *N Engl J Med.* 2012a;**366**:409-420.

Donnez J, Tomaszewski J, Vazquez F, Bouchard P, Lemieszczuk B, Baro F, Nouri K, Selvaggi L, Sodowski K, Bestel E, et al. Ulipristal acetate versus leuprolide acetate for uterine fibroids. *N Engl J Med.* 2012b;**366**:421-432.

Donnez J, Vazquez F, Tomaszewski J, Nouri K, Bouchard P, Fauser BC, Barlow DH, Palacios S, Donnez O, Bestel E, et al. Long-term treatment of uterine fibroids with ulipristal acetate. *Fertil Steril.* 2014;**101**:1565-1573 e1561-1518.

Eisinger SH, Meldrum S, Fiscella K, le Roux HD, Guzick DS. Low-dose mifepristone for uterine leiomyomata. *Obstet Gynecol.* 2003;**101**:243-250.

Elger W, Bartley J, Schneider B, Kaufmann G, Schubert G, Chwalisz K. Endocrine pharmacological characterization of progesterone antagonists and progesterone receptor modulators with respect to PR-agonistic and antagonistic activity. *Steroids.* 2000;**65**:713-723.

Huyck KL, Panhuysen CI, Cuenco KT, Zhang J, Goldhammer H, Jones ES, Somasundaram P, Lynch AM, Harlow BL, Lee H, et al. The impact of race as a risk factor for symptom severity and age at diagnosis of uterine leiomyomata among affected sisters. *Am J Obstet Gynecol.* 2008;**198**:168 e161-169.

Jacoby VL, Fujimoto VY, Giudice LC, Kuppermann M, Washington AE. Racial and ethnic disparities in benign gynecologic conditions and associated surgeries. *Am J Obstet Gynecol.* 2010;**202**:514-521.

Kettel LM, Murphy AA, Morales AJ, Yen SS. Clinical efficacy of the antiprogesterone RU486 in the treatment of endometriosis and uterine fibroids. *Hum Reprod.* 1994;**9 Suppl 1**:116-120.

Larsen L, Coyne K, Chwalisz K. Validation of the menstrual pictogram in women with leiomyomata associated with heavy menstrual bleeding. *Reprod Sci.* 2013;**20**:680-687.

Laughlin SK, Schroeder JC, Baird DD. New directions in the epidemiology of uterine fibroids. *Semin Reprod Med.* 2010;**28**:204-217.

Morikawa A, Ohara N, Xu Q, Nakabayashi K, DeManno DA, Chwalisz K, Yoshida S, Maruo T. Selective progesterone receptor modulator asoprisnil down-regulates collagen synthesis in cultured human uterine leiomyoma cells through up-regulating extracellular matrix metalloproteinase inducer. *Hum Reprod.* 2008;**23**:944-951.

Munro MG, Critchley HO, Fraser IS, Group FMDW. The FIGO classification of causes of abnormal uterine bleeding in the reproductive years. *Fertil Steril.* 2011;**95**:2204-2208, 2208 e2201-2203.

Murphy AA, Kettel LM, Morales AJ, Roberts VJ, Yen SS. Regression of uterine leiomyomata in response to the antiprogesterone RU 486. *J Clin Endocrinol Metab.* 1993;**76**:513-517.

Mutter GL, Bergeron C, Deligdisch L, Ferenczy A, Glant M, Merino M, Williams AR, Blithe DL. The spectrum of endometrial pathology induced by progesterone receptor modulators. *Mod Pathol.* 2008;**21**:591-598.

Ohara N, Morikawa A, Chen W, Wang J, DeManno DA, Chwalisz K, Maruo T. Comparative effects of SPRM asoprisnil (J867) on proliferation, apoptosis, and the expression of growth factors in cultured uterine leiomyoma cells and normal myometrial cells. *Reprod Sci.* 2007;**14**:20-27.

Sasaki H, Ohara N, Xu Q, Wang J, DeManno DA, Chwalisz K, Yoshida S, Maruo T. A novel selective progesterone receptor modulator asoprisnil activates tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-mediated signaling pathway in cultured

human uterine leiomyoma cells in the absence of comparable effects on myometrial cells. *J Clin Endocrinol Metab.* 2007;**92**:616-623.
Soper D, Lukes AS, Gee P, Kimble T, Kroll R, Mallick M, Chan A, Sniukiene V, Shulman LP, Liu J. Ulipristal acetate (UPA) treatment of symptomatic uterine fibroids (UF): VENUS II subgroup analyses by race and BMI. *Fertil Steril.* 2017;**108**:e28.
Spies JB, Coyne K, Guaou Guaou N, Boyle D, Skyrnarz-Murphy K, Gonzalves SM. The UFS-QOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata. *Obstet Gynecol.* 2002;**99**:290-300.
Stewart EA. Uterine fibroids. *Lancet.* 2001;**357**:293-298.
Stewart EA, Cookson CL, Gandolfo RA, Schulze-Rath R. Epidemiology of uterine fibroids: a systematic review. *BJOG.* 2017;**124**:1501-1512.
Wilkens J, Chwalisz K, Han C, Walker J, Cameron IT, Ingamells S, Lawrence AC, Lumsden MA, Hapangama D, Williams AR, et al. Effects of the selective progesterone receptor modulator asoprisnil on uterine artery blood flow, ovarian activity, and clinical symptoms in patients with uterine leiomyomata scheduled for hysterectomy. *J Clin Endocrinol Metab.* 2008;**93**:4664-4671.
Wilkens J, Male V, Ghazal P, Forster T, Gibson DA, Williams AR, Brito-Mutunayagam SL, Craigon M, Lourenco P, Cameron IT, et al. Uterine NK cells regulate endometrial bleeding in women and are suppressed by the progesterone receptor modulator asoprisnil. *J Immunol.* 2013;**191**:2226-2235.
Williams AR, Critchley HO, Osei J, Ingamells S, Cameron IT, Han C, Chwalisz K. The effects of the selective progesterone receptor modulator asoprisnil on the morphology of uterine tissues after 3 months treatment in patients with symptomatic uterine leiomyomata. *Hum Reprod.* 2007;**22**:1696-1704.

Table I. Demographics and Baseline Characteristics (All Randomized Participants)

Characteristic	Study 1 and Study 2 (N=907)		
	Placebo (n=173)	Asoprisnil 10 mg (n=370)	Asoprisnil 25 mg (n=364)
Race or ethnicity, n (%)			
Black	98 (56.6)	180 (48.6)	186 (51.1)
White	64 (37.0)	162 (43.8)	148 (40.7)
Hispanic	10 (5.8)	24 (6.5)	17 (4.7)
Asian	0	2 (0.5)	6 (1.6)
Other	1 (0.6)	2 (0.5)	7 (1.9)
Mean (SD) age, y	42.0 (5.6)	42.8 (5.2)	43.1 (5.6)
Mean (SD) BMI, kg/m^{2}[a]	29.9 (6.92)	29.3 (6.44)	29.4 (6.46)
Mean (SD) primary fibroid volume, cm^{3}[b]	168.7 (238.1)	189.2 (294.5)	155.2 (187.6)
Primary fibroid location, n (%)[b]			
Intramural	102 (68.0)	216 (63.9)	196 (58.9)
Pedunculated submucosal	1 (0.7)	3 (0.9)	2 (0.6)
Pedunculated subserosal	3 (2.0)	1 (0.3)	1 (0.3)
Submucosal	28 (18.7)	92 (27.2)	104 (31.2)
Subserosal	16 (10.7)	26 (7.7)	30 (9.0)
Mean (SD) uterine volume, cm^{3}[c]	542.8 (430.5)	656.6 (546.6)	588.6 (454.1)
Mean (SD) MP total score, mL[d]	283.6 (293.3)	263.8 (213.3)	283.3 (260.4)
Anemic, n (%)[e]	71 (41.5)	151 (41.7)	196 (55.1)
Mean (SD) hemoglobin, g/dL[e]	12.0 (1.7)	12.0 (1.8)	11.8 (1.7)

BMI=body mass index; MP=menstrual pictogram.
[a]Placebo, n=171; asoprisnil 10 mg, n=364; asoprisnil 25 mg, n=362.
[b]Placebo, n=150; asoprisnil 10 mg, n=338; asoprisnil 25 mg, n=333.
[c]Asoprisnil 10 mg, n=366; asoprisnil 25 mg, n=362.
[d]Placebo, n=171; asoprisnil 10 mg, n=363; asoprisnil 25 mg, n=359.
[e]Placebo, n=171; asoprisnil 10 mg, n=362; asoprisnil 25 mg, n=356. Hemoglobin <12 g/dL was considered to indicate anemia.

Table II. Efficacy Outcomes (mITT Population)

	Study 1 and Study 2				
Outcome	**Placebo (n=153)**	**Asoprisnil 10 mg (n=321)**	***P* Values**	**Asoprisnil 25 mg (n=317)**	***P* Values**
	Primary endpoint response rate, n/M (%)				
Month 6	44/153 (29)	291/321 (91)	<0.001[a]	294/315 (93)	<0.001[a]
Month 12	53/153 (35)	288/321 (90)	<0.001[a]	295/317 (93)	<0.001[a]
	Monthly MP score: Mean change from baseline, mL (SD)				
Month 6	−112.3 (246.43) n=119	−250.7 (194.97) n=288	<0.001[b]	−296.9 (265.60) n=283	<0.001[b]
Month 12	−106.0 (270.70) n=98	−256.2 (201.62) n=254	<0.001[b]	−303.5 (284.49) n=233	<0.001[b]
	Number of days with bleeding: Mean change from baseline, days (SD)				
Month 6	−1.1 (3.62) n=119	−6.2 (3.59) n=288	<0.001[b]	−7.0 (3.40) n=283	<0.001[b]
Month 12	−1.4 (3.56) n=97	−6.4 (3.78) n=254	<0.001[b]	−7.0 (3.86) n=233	<0.001[b]
	Suppression of menses, n/M (%)				
Treatment period	14/151 (9)	281/315 (89)	NC	294/305 (96)	NC
	Maintenance of suppression of menses after initial suppression, n/M (%)				
Treatment period	8/151 (5)	228/315 (72)	NC	265/305 (87)	NC
	Hemoglobin: Mean change from baseline, g/dL (SD)				
Month 6	0.3 (1.35) n=109	1.6 (1.66) n=259	<0.001[b]	1.7 (1.63) n=255	<0.001[b]
Month 12	0.0 (1.40) n=86	1.6 (1.72) n=222	<0.001[b]	1.8 (1.75) n=214	<0.001[b]
	UFS-QoL symptom severity score: Mean change from baseline (SD)				
Month 6	−15.5 (22.47) n=120	−37.0 (21.51) n=276	<0.001[b]	−46.2 (21.49) n=271	<0.001[b]
Month 12	−13.6 (23.91)	−39.3 (19.72)	<0.001[b]	−46.9 (20.60)	<0.001[b]

	n=94	n=239		n=230	
	UFS-QoL HRQL total score: Mean change from baseline (SD)				
Month 6	19.8 (25.08) n=114	37.6 (24.65) n=271	<0.001[b]	44.1 (23.44) n=268	<0.001[b]
Month 12	13.7 (23.84) n=92	39.8 (23.63) n=236	<0.001[b]	46.5 (23.97) n=226	<0.001[b]

M=number of participants included in the primary endpoint analysis per given subcategory; HRQL=health-related quality of life; mITT=modified intent-to-treat; MP=menstrual pictogram; NC=not calculated; UFS-QoL=Uterine Fibroid Symptom and Quality of Life.

[a]*P*<0.001 statistically significant difference vs placebo using the Hochberg multiple comparison procedure with an initial critical *P*=0.05 (from the Fisher exact test).

[b]*P*<0.001 statistically significant difference vs placebo using the Hochberg multiple comparison procedure with an initial critical *P*=0.05 (from the contrasts within the framework of the analysis of covariance model with baseline as a covariate and treatment as a fixed factor).

Table III. Most Frequently Reported Adverse Events (Safety Population)

MedDRA High-Level Term	**Study 1 and Study 2**		
MedDRA preferred terms	**Placebo (n=173), n (%)**	**Asoprisnil 10 mg, (n=370) n (%)**	**Asoprisnil 25 mg, (n=364) n (%)**
Total participants with ≥1 adverse event, n (%)	145 (84)	337 (91)	321 (88)
Upper respiratory tract infections	44 (25)	92 (25)	94 (26)
Acute sinusitis, laryngitis, nasopharyngitis, pharyngitis, rhinitis, sinusitis, tonsillitis, upper respiratory tract infection			
Headaches NEC	44 (25)	102 (28)	92 (25)
Headache, sinus headache, tension headache			
Musculoskeletal and connective tissue signs and symptoms NEC	31 (18)	84 (23)	70 (19)
Back pain, chest wall pain, flank pain, musculoskeletal discomfort, musculoskeletal stiffness, neck pain, nodule on extremity, pain in extremity, sensation of heaviness, shoulder pain			
Peripheral vascular disorders NEC	12 (7)	35 (9)	52 (14)[a]
Flushing, hot flush			
Nausea and vomiting symptoms	20 (12)	48 (13)	32 (9)
Nausea, vomiting			
Vulvovaginal signs and symptoms	16 (9)	36 (10)	39 (11)
Genital pruritus female, postcoital bleeding, vaginal burning sensation, vaginal discharge, vaginal lesion, vaginal odour, vaginal pain, vulvovaginal discomfort, vulvovaginal dryness			
Breast signs and symptoms	10 (6)	39 (11)	24 (7)
Breast discharge, breast discomfort, breast engorgement, breast pain, breast swelling, breast tenderness, nipple pain			
Gastrointestinal and abdominal pains (excluding oral and throat)	15 (9)	35 (9)	39 (11)
Abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness			
Joint-related signs and symptoms	8 (5)	29 (8)	22 (6)
Arthralgia, joint stiffness, joint swelling, temporomandibular joint syndrome			
Fungal infections NEC	8 (5)	15 (4)	25 (7)
Fungal infection, onychomycosis, vaginal mycosis			
Influenza viral infections	10 (6)	31 (8)	24 (7)

Influenza			
Menstruation and uterine bleeding NEC	12 (7)	5 (1)[b]	4 (1)[b]
Dysmenorrhaea			
Muscle-related signs and symptoms NEC	10 (6)	8 (2)[a]	6 (2)[a]
Muscle fatigue, muscle spasm, muscle tightness, muscle twitching			
Pain and discomfort NEC	8 (5)	25 (7)	21 (6)
Chest pain, pain			
Bacterial infections NEC	12 (7)	20 (5)	25 (7)
Cellulitis, upper respiratory tract infection bacterial, vaginitis bacterial			
Bladder and urethral symptoms	3 (2)	29 (8)[c]	23 (6)[a]
Bladder spasm, dysuria, micturition urgency, pollakiuria, stress incontinence, urge incontinence, urinary incontinence			
Flatulence, bloating, and distension	5 (3)	22 (6)	23 (6)
Abdominal distension, flatulence			
Muscle pains	3 (2)	21 (6)[a]	23 (6)[a]
Myalgia			
Upper respiratory tract signs and symptoms	3 (2)	22 (6)[a]	14 (4)
Nasal discomfort, pharyngolaryngeal pain, rhinorrhea, throat irritation, throat tightness			
Asthenic conditions	7 (4)	15 (4)	20 (5)
Asthenia, fatigue, malaise			
Oedema NEC	9 (5)	12 (3)	9 (2)
Generalized oedema, oedema, oedema peripheral, pitting oedema			
Reproductive tract signs and symptoms NEC	8 (5)	20 (5)	14 (4)
Genital rash, hydrometra, pelvic pain, premenstrual syndrome			

MedDRA=Medical Dictionary for Regulatory Activities; NEC=not elsewhere classified.

Most frequent was defined as those high-level terms reported by ≥5% of participants in any treatment group. Includes all adverse events from the start of the study drug through 30 days postdosing.

[a]$P<0.05$ statistical significance vs placebo, using the Fisher exact test.

[b]$P<0.001$ statistical significance vs placebo, using the Fisher exact test.

[c]$P<0.01$ statistical significance vs placebo, using the Fisher exact test.

Figure Legends

Figure 1. Participant flow diagram. ASO 10=asoprisnil 10 mg once daily; ASO 25=asoprisnil 25 mg once daily; PBO=placebo.

Figure 2. Mean menstrual pictogram score in mL (modified intent-to-treat population). BL=baseline. *P<0.001 statistically significant difference for asoprisnil 10 mg or 25 mg vs placebo for change from baseline using the Hochberg multiple comparison procedure with an initial critical P=0.05 (from the Fisher exact test). Error bars represent 2 × the standard error of the mean.

Figure 3. Percentage of women with incremental amenorrhea by month (modified intent-to-treat population). *P<0.001 statistically significant difference for asoprisnil 10 mg or 25 mg vs placebo using the Hochberg multiple comparison procedure with an initial critical P=0.05 (from the Fisher exact test).

Figure 4. Median percentage change in volume of the largest fibroid (modified intent-to-treat population). *P<0.001 statistically significant difference vs placebo using the Hochberg multiple comparison procedure with an initial critical P=0.05 (from the Kruskal-Wallis large-sample approximation test).

Figure 1

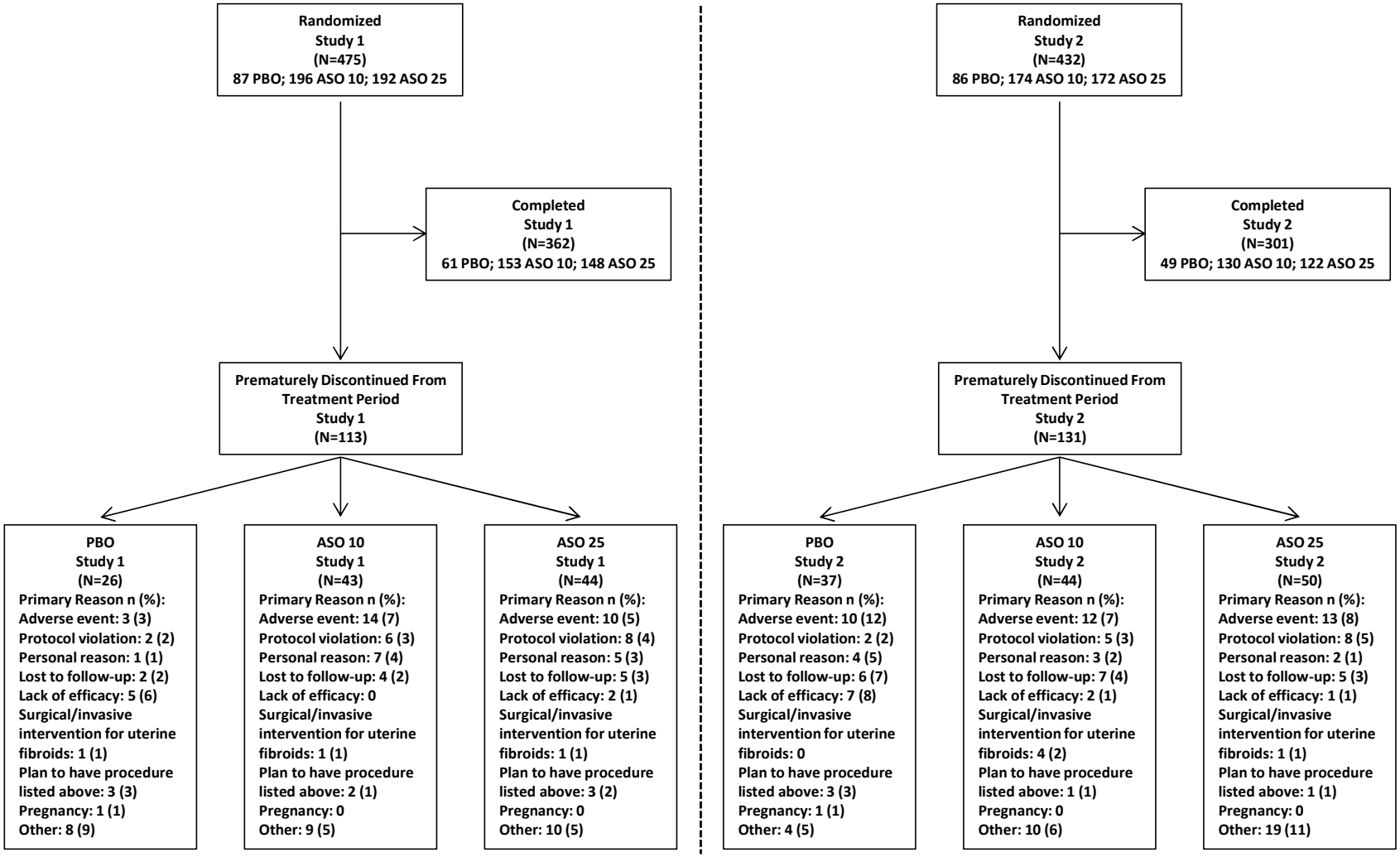

Randomized
Study 1
(N=475)
87 PBO; 196 ASO 10; 192 ASO 25
Completed
Study 1
(N=362)
61 PBO; 153 ASO 10; 148 ASO 25
Prematurely Discontinued From Treatment Period
Study 1
(N=113)
PBO
Study 1
(N=26)
Primary Reason n (%):
Adverse event: 3 (3)
Protocol violation: 2 (2)
Personal reason: 1 (1)
Lost to follow-up: 2 (2)
Lack of efficacy: 5 (6)
Surgical/invasive intervention for uterine fibroids: 1 (1)
Plan to have procedure listed above: 3 (3)
Pregnancy: 1 (1)
Other: 8 (9)
ASO 10
Study 1
(N=43)
Primary Reason n (%):
Adverse event: 14 (7)
Protocol violation: 6 (3)
Personal reason: 7 (4)
Lost to follow-up: 4 (2)
Lack of efficacy: 0
Surgical/invasive intervention for uterine fibroids: 1 (1)
Plan to have procedure listed above: 2 (1)
Pregnancy: 0
Other: 9 (5)
ASO 25
Study 1
(N=44)
Primary Reason n (%):
Adverse event: 10 (5)
Protocol violation: 8 (4)
Personal reason: 5 (3)
Lost to follow-up: 5 (3)
Lack of efficacy: 2 (1)
Surgical/invasive intervention for uterine fibroids: 1 (1)
Plan to have procedure listed above: 3 (2)
Pregnancy: 0
Other: 10 (5)
Randomized
Study 2
(N=432)
86 PBO; 174 ASO 10; 172 ASO 25
Completed
Study 2
(N=301)
49 PBO; 130 ASO 10; 122 ASO 25
Prematurely Discontinued From Treatment Period
Study 2
(N=131)
PBO
Study 2
(N=37)
Primary Reason n (%):
Adverse event: 10 (12)
Protocol violation: 2 (2)
Personal reason: 4 (5)
Lost to follow-up: 6 (7)
Lack of efficacy: 7 (8)
Surgical/invasive intervention for uterine fibroids: 0
Plan to have procedure listed above: 3 (3)
Pregnancy: 1 (1)
Other: 4 (5)
ASO 10
Study 2
(N=44)
Primary Reason n (%):
Adverse event: 12 (7)
Protocol violation: 5 (3)
Personal reason: 3 (2)
Lost to follow-up: 7 (4)
Lack of efficacy: 2 (1)
Surgical/invasive intervention for uterine fibroids: 4 (2)
Plan to have procedure listed above: 1 (1)
Pregnancy: 0
Other: 10 (6)
ASO 25
Study 2
(N=50)
Primary Reason n (%):
Adverse event: 13 (8)
Protocol violation: 8 (5)
Personal reason: 2 (1)
Lost to follow-up: 5 (3)
Lack of efficacy: 1 (1)
Surgical/invasive intervention for uterine fibroids: 1 (1)
Plan to have procedure listed above: 1 (1)
Pregnancy: 0
Other: 19 (11)

Figure 2

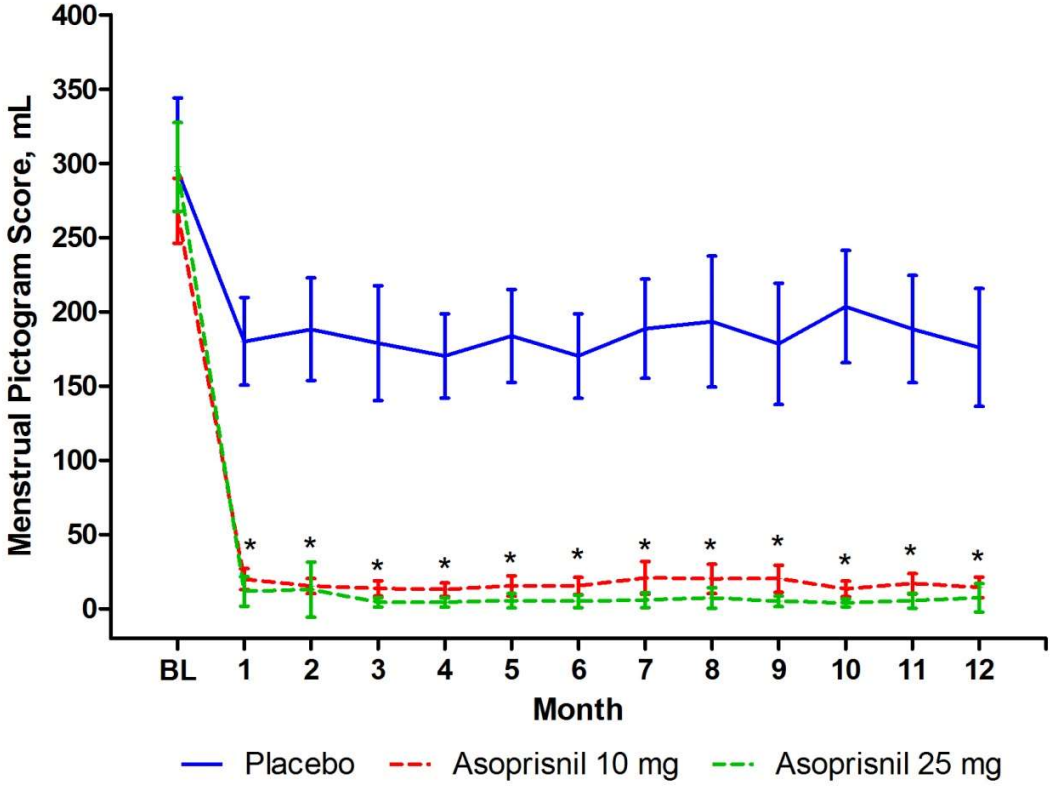

Menstrual Pictogram Score, mL
400
350
300
250
200
150
100
50
0
BL
1
2
3
4
5
6
7
8
9
10
11
12
Month
Placebo
Asoprisnil 10 mg
Asoprisnil 25 mg

Figure 3

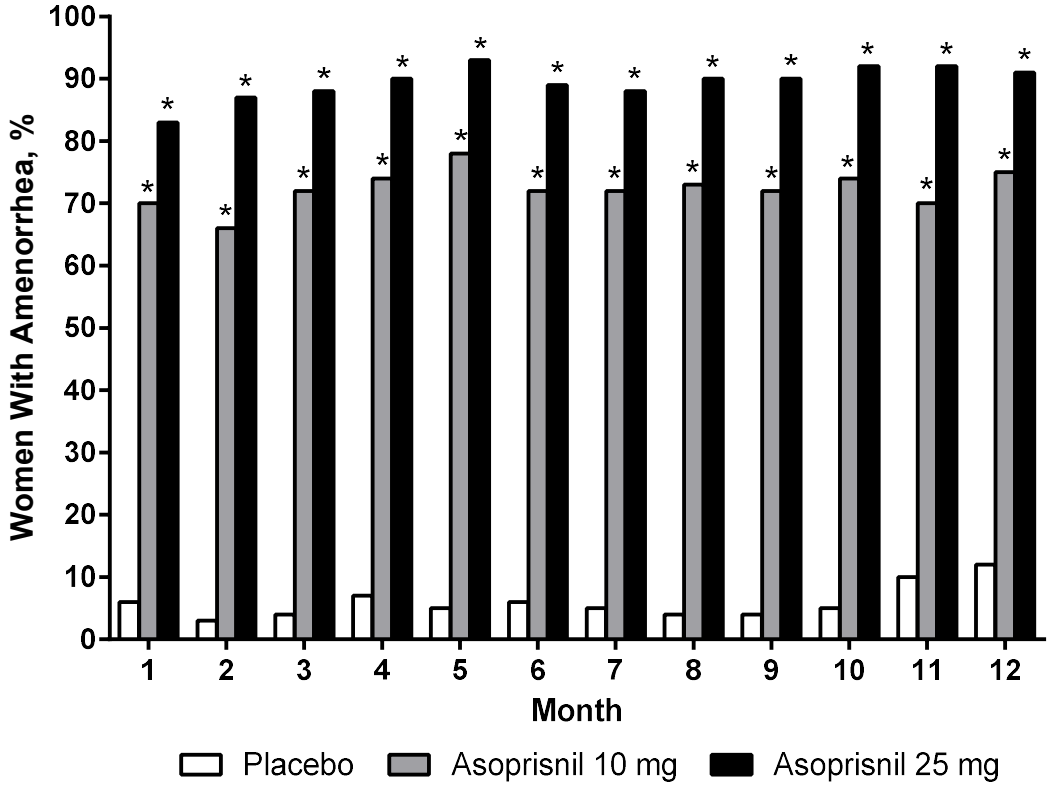
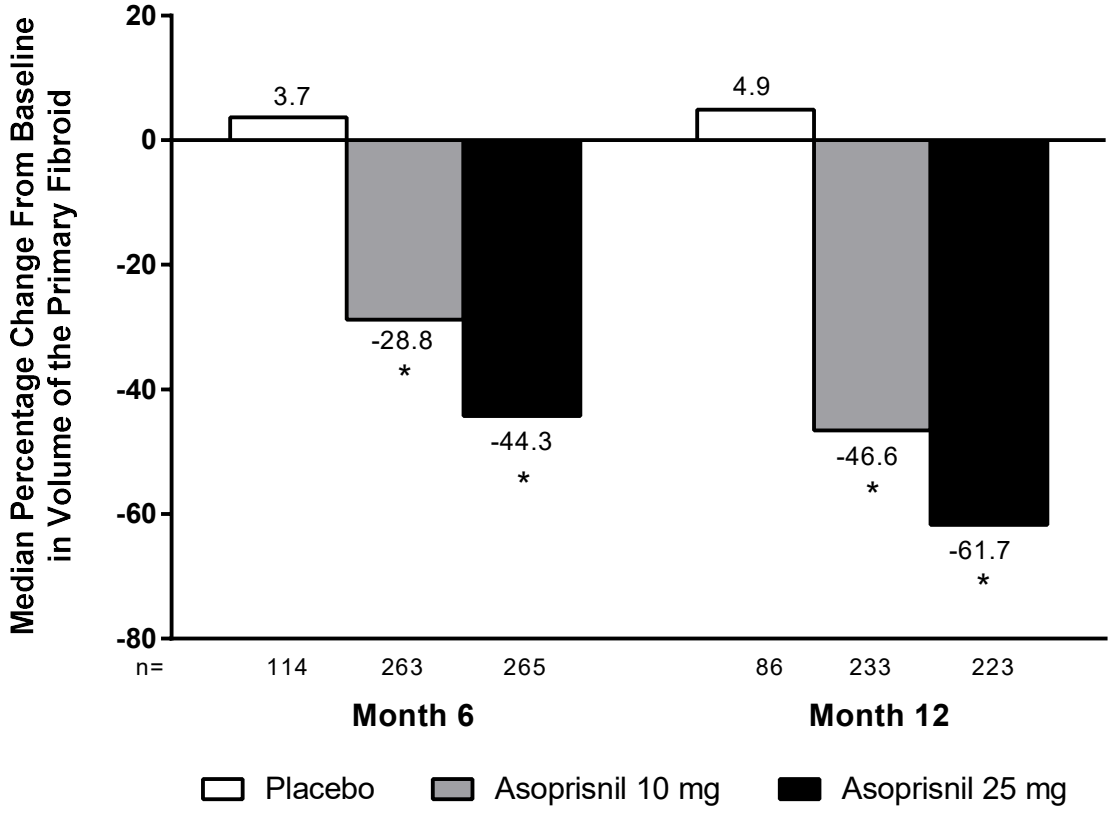

Women With Amenorrhea, %
100
90
80
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
8
9
10
11
12
Month
Placebo
Asoprisnil 10 mg
Asoprisnil 25 mg

Figure 4


Median Percentage Change From Baseline in Volume of the Primary Fibroid
20
0
-20
-40
-60
-80
3.7
-28.8
*
-44.3
*
4.9
-46.6
*
-61.7
*
n=
114
263
265
86
233
223
Month 6
Month 12
Placebo
Asoprisnil 10 mg
Asoprisnil 25 mg

Supplemental Methods

Study Population

Additional exclusion criteria were the presence of intracavitary pedunculated fibroids or endometrial polyps (assessed via saline-infusion sonohysterogram) in participants with suspected intracavitary lesions on transvaginal ultrasound [TVU] or MRI), hemoglobin <8 g/dL on day −1, and in Study 1, a bone mineral density T-score at or below −2.5 at screening.

Endometrial Assessments

The diagnostic dictionary included two morphologic patterns that were considered specific for selective progesterone receptor modulator effects. “Non-physiologic secretory pattern” referred to endometrial glands in which weak secretory changes were seen that were variable and incomplete, with basally oriented epithelial cell nuclei and minimal or no evidence of proliferation. “Secretory pattern – mixed type” referred to glands with non-physiological secretory activity as above, with additional evidence of proliferative activity (less marked basal orientation of epithelial cell nuclei, and more than 1 mitosis per 20 gland profiles). In both patterns, the stroma showed a variable degree of partial secretory differentiation. These categories were used in previous studies with asoprisnil (Chwalisz et al, 2005a; Chwalisz et al, 2007; Williams et al, 2007), and were later included as part of the progesterone receptor modulator associated endometrial changes (PAEC) spectrum (Mutter et al, 2008).

Statistical Analyses

The mean change from baseline in monthly menstrual pictogram (MP) scores, number of days with bleeding, and bleeding or spotting each month were analyzed using an analysis of

covariance (ANCOVA) model. Changes in hemoglobin levels were analyzed using a 1-way ANCOVA with treatment as a factor and baseline level as a covariate. Uterine Fibroid Symptom and Quality of Life and Leiomyoma Symptom Assessment Questionnaire total and subscale scores were analyzed using the generalized Cochran-Mantel-Haenszel mean score test with baseline score as strata. The percentage change in fibroid and uterine volume was analyzed with a 1-way Kruskal-Wallis analysis with treatment as a factor; percentages of participants with incremental amenorrhea were compared using the Fisher exact test. Most efficacy analyses were based on changes from baseline to the last assessment, ie, using the last observation carried forward (LOCF) methodology.

AEs and endometrial biopsy results for all participants were summarized by treatment group; pairwise between-group comparisons were performed using the Fisher exact test. Endometrial thickness, hematology, chemistry, urinalysis, and endocrine parameters were summarized descriptively; changes from baseline to each study visit were analyzed using an analysis of variance (ANOVA) model with treatment as a fixed factor, and pairwise comparisons were assessed within this model.

References

<<At submission, this section will be provided with its own bibliography.>>

Tables in Supplemental Material

Supplemental Table XIV. Mean Hormone and SHBG at Baseline and 6 and 12 Months (All Participants)

Supplemental Table I. Safety Evaluations

Procedure/assessment	Screening	Predose Day –1	Months 2 and 4	Month 6	Months 8 and 10	Month 12	Month 3 Follow-up
Clinical laboratory (including total iron-binding capacity)	X	X	X	X	X	X	X[a]
Lipid profile	X	X	—	X	—	X	—
Endocrine panel 1[b]	X	X	X	X	X	X	—
Endocrine panel 2[c]	X	X	—	X	—	X	—
Endocrine panel 3[d]	—	—	—	—	—	—	X
Cortisol	X	—	—	—	—	X	—
MRI	—	X[e]	—	X	—	X	X[f]
TVU	X[g]	—	X[h]	—	X[i]	—	X
BMD (Study 1 only)	X	—	—	—	—	X	—
Endometrial biopsy	X[j]	—	—	X	—	X	X[f]

BMD=bone mineral density; MRI=magnetic resonance imaging; TVU=transvaginal ultrasound.
[a]Hematology and iron assessments only.
[b]Endocrine panel 1 included estrone, estradiol, androstenedione, dehydroepiandrosterone sulfate, total and free testosterone, and sex hormone binding globulin.
[c]Endocrine panel 2 included prolactin, luteinizing hormone, follicle-stimulating hormone, thyroid-stimulating hormone, and thyroxine.
[d]Endocrine panel 3 included progesterone, estradiol, total and free testosterone, and sex hormone binding globulin.
[e]Performed between day –30 and day –14.
[f]Performed at month 6 follow-up visit
[g]Screening ultrasound was performed and reviewed before scheduling baseline MRI, and if needed, could have included an abdominal view to assess leiomyoma size and location.
[h]Month 4 only.
[i]Month 8 only.
[j]Screening biopsy performed at least 21 days before day –1.

Supplemental Table II. Medications Not Permitted in the Studies

Gonadotropin-releasing hormone agonists
Progestogens
Estrogens
Oral contraceptives
Antiestrogens
Chronic glucocorticoids during screening, treatment, and follow-up
Synthetic prostaglandin E1 analogs during treatment and follow-up, until cessation of the first posttreatment menses
Cytochrome P450 3A4 inhibitors and osteoporosis treatments during treatment

E1=estrone; GnRH=gonadotropin-releasing hormone; P450=cytochrome P450.

Any women receiving GnRH analogs before enrollment required at least 6 months washout (9 months for 3-month depot formulations of leuprorelin and goserelin acetate) before treatment with asoprisnil. Participants previously receiving progesterone preparations required 2 months washout before treatment with asoprisnil.

Supplemental Table III. Adverse Events Leading to Premature Study Discontinuation (Safety Analysis Set)

Treatment	MedDRA Preferred Term	Relationship to Study Drug (by Investigator)	Severity	Day of Onset
Study 1				
Placebo	Pain in extremity	Unlikely	Moderate	101
	Pain	Unlikely	Moderate	111
Placebo	Uterine haemorrhage	Not related	Severe	111
Placebo	Adnex uteri mass	Unlikely	Moderate	118
Placebo	Depression	Possible	Moderate	223
Asoprisnil 10 mg	Migraine	Possible	Severe	163
Asoprisnil 10 mg	Pain in extremity	Possible	Moderate	1, 39
	Anxiety	Possible	Moderate	5
	Depression	Possible	Moderate	5
	Insomnia	Possible	Moderate	5
	Pruritus	Possible	Mild	5
	Bursitis	Not related	Moderate	39
Asoprisnil 10 mg	Abdominal pain	Unlikely	Severe	56
Asoprisnil 10 mg	Abdominal distension	Possible	Moderate	82[a]
	Gastric disorder	Possible	Moderate	82[a]
Asoprisnil 10 mg	Stress incontinence[b]	Not related	Severe	124

Asoprisnil 10 mg	Migraine	Possible	Severe	31
Asoprisnil 10 mg	Weight increased	Definite	Moderate	124
Asoprisnil 10 mg	Ovarian cyst ruptured	Probable	Moderate	152 (0)[c]
Asoprisnil 10 mg	Endometrial hypertrophy	Possible	Moderate	136
Asoprisnil 10 mg	Malignant melanoma[b]	Not related	Severe	70
Asoprisnil 10 mg	Liver function test abnormal	Probable	Mild	60
Asoprisnil 10 mg	Nausea	Probable	Severe	1
Asoprisnil 10 mg	Uterine polyp	Possible	Moderate	231
Asoprisnil 10 mg	Vomiting	Possible	Moderate	1
	Nausea	Possible	Moderate	1
Asoprisnil 25 mg	Bone density decreased	Probable	Mild	193
Asoprisnil 25 mg	Uterine leiomyoma[d]	Unlikely	Moderate	187
Asoprisnil 25 mg	Acne	Not related	Mild	1
	Chloasma	Possible	Mild	63
Asoprisnil 25 mg	Hot flush	Unlikely	Severe	8
Asoprisnil 25 mg	Gastroenteritis viral	Possible	Moderate	68
Asoprisnil 25 mg	Hot flush	Probable	Severe	14
Asoprisnil 25 mg	Vaginal discharge	Probable	Mild	68
	Bone pain	Possible	Moderate	82

	Headache	Probable	Mild	82
	Influenza like illness	Possible	Moderate	82
Asoprisnil 25 mg	Weight increased	Possible	Mild	32
Asoprisnil 25 mg	Hepatic enzyme increased	Unlikely	Moderate	56
Asoprisnil 25 mg	Endometrial sarcoma[b]	Probable	Severe	282
Asoprisnil 25 mg	Intervertebral disc protrusion	Not related	Moderate	185[a]
Study 2				
Placebo	Ovarian cyst	Not related	Mild	128
Placebo	Libido decreased	Not related	Mild	49
	Weight fluctuation	Not related	Mild	49
Placebo	Gamma-glutamyl transferase increased	Unlikely	Moderate	117
Placebo	Body temperature increased	Probable	Mild	5
Placebo	Liver function test abnormal	Probable	Moderate	115
Placebo	Adnexa uteri cyst	Possible	Mild	186
Placebo	Abdominal pain lower	Possible	Severe	65
Placebo	Headache	Possible	Moderate	1

	Dizziness	Unlikely	Mild	4
	Menorrhagia	Unlikely	Mild	4
	Pelvic pain	Possible	Moderate	4
	Syncope	Unlikely	Moderate	6
	Insomnia	Unlikely	Mild	8
Placebo	Carbohydrate antigen 125 increased	Not related	Mild	261
Placebo	Asthma[b]	Unlikely	Severe	392
Placebo	Abdominal distension	Possible	Mild	98 (2)[c]
Asoprisnil 10 mg	Breast cancer in situ	Not related	Moderate	128
Asoprisnil 10 mg	Blood bilirubin increased	Not related	Mild	137
Asoprisnil 10 mg	Endometrial hyperplasia	Possible	Mild	176
Asoprisnil 10 mg	Headache	Possible	Moderate	69
	Paraesthesia	Possible	Mild	69
	Vision blurred	Possible	Mild	69
Asoprisnil 10 mg	Anorexia	Unlikely	Mild	4
	Chest discomfort	Unlikely	Mild	4
	Paraesthesia	Unlikely	Mild	4
Asoprisnil 10 mg	Headache	Probable	Moderate[e]	17, 42, 54, 58, 60

	Nausea	Probable	Moderate	17, 42, 54, 58
Asoprisnil 10 mg	Uterine leiomyoma[b]	Not related	Severe	52 (3)[c]
Asoprisnil 10 mg	Acne	Probable	Moderate	8
	Dry skin	Probable	Moderate	8
	Hair texture abnormal	Probable	Moderate	8
	Breast tenderness	Probable	Severe	13
	Asthenia	Possible	Mild	38
	Libido decreased	Probable	Severe	38
	Vulvovaginal dryness	Probable	Severe	38
Asoprisnil 10 mg	Urinary tract infection	Unlikely	Mild	6
Asoprisnil 10 mg	Ovarian cyst	Possible	Moderate	112
Asoprisnil 10 mg	Pancreatitis[b]	Possible	Severe	161
Asoprisnil 10 mg	Liver function test abnormal	Possible	Moderate	182
Asoprisnil 10 mg	Hypertension	Unlikely	Moderate	141
Asoprisnil 25 mg	Liver function test abnormal	Definite	Moderate	61
Asoprisnil 25 mg	Depression	Probable	Severe	1
	Fatigue	Probable	Severe	1
Asoprisnil 25 mg	Hepatic enzyme increased	Probable	Mild	63

Asoprisnil 25 mg	Headache	Not related	Mild	1
Asoprisnil 25 mg	Endometrial disorder	Possible	Moderate	124
Asoprisnil 25 mg	Mood swings	Definite	Moderate	14
	Alopecia	Definite	Moderate	21
Asoprisnil 25 mg	Upper respiratory tract infection	Unlikely	Mild	175
Asoprisnil 25 mg	Muscle contractions involuntary	Possible	Mild	38
	Palpitations	Possible	Mild	38
Asoprisnil 25 mg	Dyspepsia	Possible	Mild	9
	Diarrhea	Unlikely	Mild	306 (1)[c]
Asoprisnil 25 mg	Vaginal haemorrhage	Unlikely	Severe	222
Asoprisnil 25 mg	Endometrial hyperplasia	Probable	Moderate	269
Asoprisnil 25 mg	Breast tenderness	Probable	Mild	261
Asoprisnil 25 mg	Fatigue	Possible	Moderate	162

[a]Estimated.
[b]Serious adverse event.
[c]Number in parentheses represents the number of days relative to the last dose of study drug.
[d]Described as “growing fibroid.”
[e]Mild on day 60.

Supplemental Table IV. MP Score During the First Follow-Up Menses (mITT Population)

Parameter	Study 1			Study 2		
	Placebo (n=14)	Asoprisnil 10 mg (n=43)	Asoprisnil 25 mg (n=24)	Placebo (n=22)	Asoprisnil 10 mg (n=29)	Asoprisnil 25 mg (n=35)
Baseline, mean (SD)	236.0 (176.5)	191.5 (138.6)	255.1 (212.6)	265.1 (164.0)	191.2 (122.9)	193.4 (149.0)
Follow-up,[a] mean (SD)	227.4 (460.6)	207.4 (240.6)	116.8 (183.0)	209.1 (203.8)	215.4 (333.8)	203.0 (361.5)
Follow-up,[a] median (min, max)	102.3 (7.0, 1815.0)	127.0 (3.0, 923.0)	89.5 (3.0, 930.0)	188.5 (9.0, 921.0)	92.0 (10.0, 1508.0)	102.0 (7.0, 1897.0)
Change from baseline to follow-up, mean (SD)	−8.6 (467.8)	15.9 (226.0)	−138.3 (205.9)	−56.0 (185.1)	24.2 (352.2)	9.6 (322.6)
P value for change from baseline, asoprisnil vs placebo[b]		0.978	0.182		0.509	0.601

Max=maximum; min=minimum; mITT=modified intent to treat; MP=menstrual pictogram.

[a]Follow-up menses is the first menses after the last dose.

[b]*P* values are for pairwise comparisons from contrasts within the framework of an analysis of covariance model.

Supplemental Table V. Hematologic Parameters (mITT Population)

Parameter	Study 1 and Study 2		
	Placebo (n=153)	**Asoprisnil 10 mg (n=321)**	**Asoprisnil 25 mg (n=317)**
Hematocrit: Mean change from baseline, % (SD)			
Month 6	0.4 (3.7) n=109	2.8 (4.3)[a] n=256	3.4 (4.1)[a] n=252
Month 12	0.2 (3.4) n=86	3.2 (4.2)[a] n=220	3.8 (4.3)[a] n=213
Ferritin: Mean change from baseline, ng/mL (SD)			
Month 6	0.3 (41.0) n=109	20.6 (47.9)[a] n=268	19.1 (50.7)[a] n=258
Month 12	−4.4 (45.2) n=89	28.4 (52.5)[a] n=233	31.0 (57.9)[a] n=226
Total iron-binding capacity: Mean change from baseline, µg/dL (SD)			
Month 6	9.8 (38.8) n=110	−22.3 (39.7)[a] n=261	−18.9 (40.1)[a] n=260
Month 12	2.7 (38.6) n=89	−35.4 (38.3)[a] n=231	−35.5 (43.0)[a] n=227
Iron: Mean change from baseline, µg/dL (SD)			
Month 6	15.7 (59.5) n=110	34.1 (55.0)[a] n=261	27.4 (60.6)[a] n=260
Month 12	14.0 (56.8) n=89	34.8 (51.7)[a] n=231	25.8 (58.0)[a] n=227

mITT=modified intent-to-treat.

[a]$P<0.001$ statistically significant difference vs placebo using the Hochberg multiple comparison procedure with an initial critical $P=0.05$ (from the analysis of covariance model).

Supplemental Table VI. Change from Baseline in UFS-QoL Individual Symptom Scores (mITT Population)

Symptom	Study 1 and Study 2		
	Placebo (n=120)	**Asoprisnil 10 mg (n=276)**	**Asoprisnil 25 mg (n=271)**
Heavy bleeding: Mean change from baseline			
Month 6	−0.9 n=120	−2.7[a] n=276	−3.0[a] n=271
Month 12	−0.7 n=94	−2.8[a] n=239	−3.0[a] n=230
Passing blood clots: Mean change from baseline			
Month 6	−0.9 n=120	−2.5[a] n=276	−2.6[a] n=271
Month 12	−0.6 n=94	−2.5[a] n=239	−2.7[a] n=230
Fluctuation in the duration of menstrual period: Mean change from baseline			
Month 6	−0.4 n=119	−1.1[a] n=275	−1.8[a] n=271
Month 12	−0.5 n=93	−1.4[a] n=238	−1.8[a] n=230
Fluctuation in the length of monthly cycle: Mean change from baseline			
Month 6	−0.4 n=120	−1.2[a] n=275	−1.6[a] n=270
Month 12	−0.4 n=94	−1.3[a] n=239	−1.6[a] n=230
Tightness or pressure in pelvic area: Mean change from baseline			
Month 6	−0.7 n=118	−1.4[a] n=275	−1.9[a] n=270
Month 12	−0.7 n=92	−1.4[a] n=239	−1.9[a] n=229
Frequent daytime urination: Mean change from baseline			
Month 6	−0.5	−0.9[a]	−1.3[a]

	n=120	n=275	n=269
Month 12	−0.4 n=92	−0.9[a] n=239	−1.2[a] n=228
Frequent nighttime urination: Mean change from baseline			
Month 6	−0.4 n=119	−0.8[a] n=275	−1.1[a] n=270
Month 12	−0.4 n=94	−0.8[a] n=240	−1.0[a] n=227
Fatigue: Mean change from baseline			
Month 6	−0.8 n=120	−1.3[a] n=276	−1.6[a] n=270
Month 12	−0.7 n=94	−1.5[a] n=240	−1.7[a] n=229

mITT=modified intent-to-treat; UFS-QoL=Uterine Fibroid symptom and Health Related Quality of Life questionnaire.
[a]*P*<0.001 statistically significant difference vs placebo analyzed using the Hochberg multiple comparison procedure with an initial critical *P*=0.05 (from the generalized Cochran-Mantel-Haenszel mean score test with baseline scores as strata).
Score 1=Not at all; 2=A little bit; 3=Somewhat; 4=A great deal; 5=A very great deal.

Supplemental Table VII. Change from Baseline in UFS-QoL HRQL Subscale Scores (mITT Population)

Subscale	Study 1 and Study 2		
	Placebo (n=153)	**Asoprisnil 10 mg (n=321)**	**Asoprisnil 25 mg (n=317)**
Concern: Mean change from baseline (SD)			
Month 6	21.3 (30.2) n=120	51.6 (31.0)[a] n=275	59.7 (28.6)[a] n=273
Month 12	16.4 (28.5) n=94	52.5 (29.7)[a] n=240	61.7 (28.7)[a] n=230
Activities: Mean change from baseline (SD)			
Month 6	18.9 (28.3) n=120	39.8 (28.3)[a] n=275	46.4 (27.5)[a] n=273
Month 12	11.7 (27.0) n=94	41.9 (27.7)[a] n=240	48.9 (28.0)[a] n=230
Energy/Mood: Mean change from baseline (SD)			
Month 6	20.2 (26.6) n=120	33.7 (26.1)[a] n=275	39.8 (26.5)[a] n=273
Month 12	13.5 (25.6) n=94	36.2 (25.1)[a] n=240	42.0 (26.4)[a] n=230
Control: Mean change from baseline (SD)			
Month 6	18.9 (26.8) n=120	32.6 (27.8)[a] n=276	38.0 (26.2)[a] n=273
Month 12	12.9 (27.3) n=94	33.8 (25.6)[a] n=240	39.2 (26.5)[a] n=230
Self-Conscious: Mean change from baseline (SD)			
Month 6	19.2 (30.0) n=120	32.0 (29.2)[a] n=276	42.1 (31.2)[a] n=273
Month 12	16.3 (26.1) n=94	35.1 (31.0)[a] n=240	46.4 (32.0)[a] n=230
Sexual function: Mean change from baseline (SD)			
Month 6	14.8 (34.3)	29.6 (36.1)[a]	32.1 (34.2)[a]

	n=114	n=272	n=268
Month 12	12.0 (38.7) n=92	31.2 (34.7)[a] n=236	36.0 (35.6)[a] n=226

HRQL=health-related quality of life; mITT=modified intent-to-treat; UFS-QoL=Uterine Fibroid symptom and Health Related Quality of Life questionnaire.

[a]*P*<0.001 statistically significant difference vs placebo analyzed using the Hochberg multiple comparison procedure with an initial critical *P*=0.05 (from the contrasts within the framework of the analysis of covariance model with baseline as a covariate and treatment as a fixed factor).

Scores can range from 0 to 100. For symptom severity: 0=distressed not at all, 100=distressed a very great deal. For other subscales: 0=Quality of life affected all of the time, 100=Quality of life affected none of the time.

Supplemental Table VIII. Change from Baseline in Leiomyoma Symptom Assessment Questionnaire Scores (mITT Population)

Symptom	Study 1 and Study 2		
	Placebo (n=149)	**Asoprisnil 10 mg (n=308)**	**Asoprisnil 25 mg (n=306)**
Bloating: Mean change from baseline			
Month 2	−0.35 n=149	−0.62[a] n=307	-0.79[a] n=306
Month 4	−0.35 n=137	−0.73[a] n=295	−0.87[a] n=290
Month 6	−0.41 n=120	−0.77[a] n=278	−0.99[a] n=271
Month 12	−0.43 n=93	−0.81[a] n=239	−1.03[a] n=235
Pelvic pressure: Mean change from baseline			
Month 2	−0.40 n=149	−0.79[a] n=308	−1.05[a] n=306
Month 4	−0.45 n=137	−0.85[a] n=296	−1.11[a] n=290
Month 6	−0.43 n=120	−0.83[a] n=278	−1.18[a] n=271
Month 12	−0.46 n=93	−0.87[a] n=239	−1.20[a] n=235
Dysmenorrhea: Mean change from baseline			
Month 2	−0.50 n=149	−1.19[a] n=308	−1.41[a] n=305
Month 4	−0.50 n=137	−1.25[a] n=296	−1.44[a] n=289
Month 6	−0.54 n=120	−1.23[a] n=278	−1.47[a] n=270
Month 12	−0.45	−1.22[a]	−1.43[a]

	n=93	n=239	n=234

mITT=modified intent-to-treat.
[a]*P*<0.001 statistically significant difference vs placebo analyzed using the Hochberg multiple comparison procedure with an initial critical *P*=0.05 (from the generalized Cochran-Mantel-Haenszel mean score test with baseline scores as strata).
Visit and baseline scores are from a 4-point grading scale: 0=None or not applicable; 1=Mild; 2=Moderate; 3=Severe.

Supplemental Table IX. Endometrial Biopsy Results at Baseline, Month 6, and Month 12 (Safety Analysis Set)

	Study 1 and Study 2		
Diagnostic Category Diagnostic Subcategory	**Placebo** **n/N (%)**	**Asoprisnil 10 mg** **n/N (%)**	**Asoprisnil 25 mg** **n/N (%)**
Normal quiescent or minimally stimulated endometrium			
Atrophy			
Baseline	0/171	0/362	0/363
Month 6	0/135	0/312	2/301 (1)
Month 12	0/110	0/281	1/272 (<1)
Inactive			
Baseline	2/171 (1)	1/362 (<1)	7/363 (2)
Month 6	4/135 (3)	60/312 (19)[a]	60/301 (20)[a]
Month 12	3/110 (3)	79/281 (28)[a]	88/272 (32)[a]
Endometrial epithelium without intact glands and stroma			
Baseline	0/171	3/362 (1)	3/363 (1)
Month 6	0/135	3/312 (1)	2/301 (1)
Month 12	0/110	1/281 (<1)	2/272 (1)
Inactive pattern with disordered glandular architecture			
Baseline	0/171	0/362	0/363
Month 6	0/135	1/312 (<1)	0/301
Month 12	0/110	2/281 (1)	2/272 (1)
Inactive pattern with abundant stromal component			
Baseline	1/171 (1)	0/362	1/363 (<1)
Month 6	0/135	3/312 (1)	5/301 (2)
Month 12	0/110	12/281 (4)[b]	13/272 (5)[b]
Category subtotal			
Baseline	3/171 (2)	4/362 (1)	11/363 (3)
Month 6	4/135 (3)	67/312 (21)[a]	69/301 (23)[a]
Month 12	3/110 (3)	94/281 (33)[a]	106/272 (39)[a]
Normal secretory phase or non-physiologic secretory patterns			

Cycling/physiologic			
Baseline	80/171 (47)	152/362 (42)	127/363 (35)[c]
Month 6	34/135 (25)	11/312 (4)[a]	2/301 (1)[a]
Month 12	35/110 (32)	13/281 (5)[a]	2/272 (1)[a]
Non-physiologic secretory effect			
Baseline	3/171 (2)	8/362 (2)	23/363 (6)[b]
Month 6	1/135 (1)	47/312 (15)[a]	58/301 (19)[a]
Month 12	4/110 (4)	30/281 (11)[b]	21/272 (8)
Secretory pattern, mixed type (mixed secretory and proliferative changes)			
Baseline	11/171 (6)	17/362 (5)	9/363 (2)[b]
Month 6	5/135 (4)	42/312 (13)[a]	36/301 (12)[c]
Month 12	3/110 (3)	23/281 (8)	30/272 (11)[c]
Menstrual			
Baseline	1/171 (1)	4/362 (1)	3/363 (1)
Month 6	4/135	0/312[c]	0/301[c]
Month 12	2/110 (2)	1/281 (<1)	0/272
Category subtotal			
Baseline	95/171 (56)	181/362 (50)	162/363 (45)[b]
Month 6	44/135 (33)	100/312 (32)	96/301 (32)
Month 12	44/110 (40)	67/281 (24)[c]	53/272 (19)[a]
Proliferative phase or non-physiologic proliferative endometrium			
Weakly proliferative			
Baseline	10/171 (6)	14/362 (4)	17/363 (5)
Month 6	9/135 (7)	58/312 (19)[a]	51/301 (17)[c]
Month 12	0/110	34/281 (12)[a]	25/272 (9)[a]
Mild to strongly proliferative patterns (active proliferation)			
Baseline	51/171 (30)	120/362 (33)	137/363 (38)
Month 6	52/135 (39)	34/312 (11)[a]	10/301 (3)[a]
Month 12	43/110 (39)	19/281 (7)[a]	7/272 (3)[a]
Proliferative pattern with dominant breakdown/stromal collapse			
Baseline	5/171 (3)	23/362 (6)	15/363 (4)
Month 6	11/135 (8)	3/312 (1)[a]	2/301 (1)[a]

Month 12	4/110 (4)	1/281 (<1)[b]	3/272 (1)
Disordered proliferative pattern			
Baseline	1/171 (1)	1/362 (<1)	3/363 (1)
Month 6	2/135 (1)	10/312 (3)	14/301 (5)
Month 12	0/110	6/281 (2)	8/272 (3)
Category subtotal			
Baseline	67/171 (39)	158/362 (44)	172/363 (47)
Month 6	74/135 (55)	105/312 (34)[a]	77/301 (26)[a]
Month 12	47/110 (43)	60/281 (21)[a]	43/272 (16)[a]
Reactive and inflammatory states (endometritis, infections, metaplasia)			
Endometritis, acute			
Baseline	1/171 (1)	0/362	0/363
Month 6	0/135	1/312 (<1)	0/301
Month 12	0/110	1/281 (<1)	0/272
Endometritis, chronic			
Baseline	0/171	3/362 (1)	5/363 (1)
Month 6	0/135	2/312 (1)	0/301
Month 12	1/110 (1)	1/281 (<1)	2/272 (1)
Endometritis, granulomatous			
Baseline	0/171	0/362	0/363
Month 6	0/135	0/312	0/301
Month 12	0/110	0/281	0/272
Epithelial metaplasia, ciliated (tubal) type			
Baseline	1/171 (1)	0/362	0/363
Month 6	0/135	0/312	0/301
Month 12	0/110	0/281	0/272
Epithelial metaplasia, ciliated and eosinophilic types			
Baseline	1/171 (1)	0/362	3/363 (1)
Month 6	0/135	0/312	0/301
Month 12	0/110	0/281	0/272
Category subtotal			
Baseline	3/171 (2)	3/362 (1)	8/363 (2)
Month 6	0/135	3/312 (1)	0/301

Month 12	1/110 (1)	2/281 (1)	2/272 (1)
Polyp (Uterine)			
Endometrial polyp, atrophic type			
Baseline	0/171	0/362	0/363
Month 6	0/135	1/312 (<1)	0/301
Month 12	0/110	1/281 (<1)	0/272
Endometrial polyp, functional type			
Baseline	0/171	2/362 (1)	0/363
Month 6	0/135	3/312 (1)	1/301 (<1)
Month 12	0/110	0/281	2/272 (1)
Endometrial polyp, hyperplastic type			
Baseline	0/171	0/362	0/363
Month 6	0/135	0/312	1/301 (<1)
Month 12	0/110	1/281 (<1)	1/272 (<1)
Endometrial polyp, not otherwise specified			
Baseline	0/171	1/362 (<1)	0/363
Month 6	0/135	1/312 (<1)	4/301 (1)
Month 12	0/110	3/281 (1)	4/272 (1)
Category subtotal			
Baseline	0/171	3/362 (1)	0/363
Month 6	0/135	5/312 (2)	6/301 (2)
Month 12	0/110	5/281 (2)	7/272 (3)
Endometrial hyperplasia			
Complex hyperplasia (no atypia)			
Baseline	0/171	0/362	0/363
Month 6	0/135	1/312 (<1)	0/301
Month 12	0/110	0/281	0/272
Endometrial benign tumor or cervical disease including dysplasias/CIS			
Baseline	0/171	0/362	0/363
Month 6	0/135	0/312	1/301 (<1)
Month 12	0/110	2/281 (1)	0/272
Endometrial and other malignancies			
Baseline	0/171	0/362	0/363
Month 6	0/135	0/312	1/301 (<1)

Month 12	0/110	0/281	0/272
Unsatisfactory tissue for diagnosis			
Baseline	3/171 (2)	13/362 (4)	10/363 (3)
Month 6	12/135 (9)	31/312 (10)	51/301 (17)[b]
Month 12	15/110 (14)	51/281 (18)	61/272 (22)

P values are from Fisher exact test. Patients could have findings in more than 1 category.
[a]*P*≤0.001 vs placebo.
[b]*P*≤0.05 vs placebo.
[c]*P*≤0.01 vs placebo.

Supplemental Table X. Endometrial Thickness by TVU (Safety Analysis Set)

	Study 1 and Study 2		
Parameter	**Placebo (n=173)**	**Asoprisnil 10 mg (n=370)**	**Asoprisnil 25 mg (n=364)**
Baseline endometrial thickness, mean (SD), mm	8.6 (4.0) n=154	8.4 (4.2) n=331	8.8 (4.5) n=323
Visit endometrial thickness, mean (SD), mm			
Month 4	8.0 (3.6) n=123	8.0 (4.6) n=279	7.8 (4.5) n=265
Month 8	8.4 (4.5) n=108	9.3 (6.3) n=260	9.4 (6.6) n=257

TVU=transvaginal ultrasound.
Each dose of asoprisnil was tested versus placebo for change from baseline, and there were no statistically significant differences based on a pairwise comparison from contrasts within the framework of the 1-way analysis of variance model.

Supplemental Table XI. Endometrial Thickness by MRI (Safety Analysis Set)

	Study 1 and Study 2		
Parameter	**Placebo (n=173)**	**Asoprisnil 10 mg (n=370)**	**Asoprisnil 25 mg (n=364)**
Baseline endometrial thickness, mean (SD), mm	7.8 (4.1) n=173	7.5 (3.7) n=366	8.0 (4.4) n=363
Visit endometrial thickness, mean (SD), mm			
Month 6	6.8 (3.3) n=139	7.1 (4.6) n=311	7.4 (6.5) n=304
Month 12	6.9 (3.0) n=104	9.6 (8.7)[a] n=274	9.7 (8.2)[a] n=256

MRI=magnetic resonance imaging.
[a]$P<0.01$ vs placebo for change from baseline (pairwise comparison from contrasts within the framework of the 1-way analysis of variance model).

Supplemental Table XII. Endometrial Texture by MRI Images (All Participants With Follow-Up Data)

	Study 1 and Study 2		
Diagnosis	**Placebo n=25 n/N (%)**	**Asoprisnil 10 mg n=61 n/N (%)**	**Asoprisnil 25 mg n=59 n/N (%)**
Endometrial cysts			
Screening	0/25	0/60	0/59
Month 6	0/18	4/52 (8)	5/46 (11)
Month 12	0/10	6/45 (13)	7/33 (21)
Follow-up month 6	0/19	1/42 (2)	0/37
Subendometrial cysts			
Screening	3/25 (12)	4/60 (7)	7/59 (12)
Month 6	1/18 (6)	5/52 (10)	2/46 (4)
Month 12	1/10 (10)	7/45 (16)	2/33 (6)
Follow-up month 6	1/19 (5)	2/42 (5)	1/37 (3)
Endometrial heterogeneity suggestive of polyp			
Screening	0/25	0/60	0/59
Month 6	0/18	3/52 (6)	5/46 (11)
Month 12	0/10	8/45 (18)	7/33 (21)
Follow-up month 6	0/19	1/42 (2)	0/37
Endometrial heterogeneity suggestive of polyp or cyst			
Screening	0/25	0/60	0/59
Month 6	0/18	4/52 (8)	6/46 (13)
Month 12	0/10	9/45 (20)	7/33 (21)
Follow-up month 6	0/19	1/42 (2)	0/37

MRI=magnetic resonance imaging.

Supplemental Table XIII. Mean Serum Lipids at Baseline and 6 and 12 Months (All Participants)

	Study 1			Study 2		
Lipid	Placebo (n=87)	Asoprisnil 10 mg (n=196)	Asoprisnil 25 mg (n=192)	Placebo (n=86)	Asoprisnil 10 mg (n=174)	Asoprisnil 25 mg (n=172)
Total Cholesterol, mg/dL						
Baseline, mean (SD)	188.4 (40.1) n=85	190.2 (33.6) n=189	188.5 (34.9) n=189	193.7 (35.5) n=82	185.8 (34.4) n=171	184.1 (29.4) n=164
Month 6, mean (SD)	194.1 (41.5) n=67	191.9 (33.2) n=163	186.7 (32.7) n=161	205.4 (40.8) n=60	190.6 (30.7) n=138	183.2 (28.7)[a] n=135
Month 12, mean (SD)	196.0 (37.8) n=56	196.5 (34.1) n=131	194.1 (36.3) n=138	200.6 (34.1) n=43	195.9 (31.6) n=118	190.9 (28.8) n=110
HDL, mg/dL						
Baseline, mean (SD)	55.4 (14.7) n=85	56.3 (15.7) n=189	55.7 (14.2) n=189	55.8 (13.1) n=82	55.8 (13.9) n=170	56.8 (14.7) n=164
Month 6, mean (SD)	56.1 (15.4) n=67	54.1 (14.9)[b] n=163	50.3 (13.6)[b] n=161	56.1 (11.1) n=60	53.3 (12.4)[a] n=137	50.4 (12.8)[b] n=135
Month 12, mean (SD)	54.4 (12.3) n=56	52.3 (15.0)[c] n=131	47.2 (12.5)[b] n=138	54.9 (11.9) n=43	50.9 (12.3)[c] n=118	48.0 (12.6)[b] n=110
LDL, mg/dL						
Baseline, mean (SD)	112.5 (37.0) n=85	110.5 (28.6) n=186	110.2 (31.1) n=188	113.9 (32.1) n=81	108.1 (31.5) n=169	105.7 (26.9) n=164
Month 6, mean (SD)	117.3 (38.9) n=66	116.9 (30.6) n=162	117.1 (29.3)[d] n=161	129.1 (38.4) n=60	115.9 (28.1) n=137	112.8 (27.2) n=135
Month 12, mean (SD)	121.7 (33.3) n=56	123.6 (29.4) n=130	125.5 (31.5)[d] n=136	126.6 (30.9) n=43	122.6 (30.2) n=118	122.9 (25.9) n=110
Triglyceride, mg/dL						
Baseline, mean (SD)	102.8 (57.4) n=85	121.3 (84.0) n=189	114.2 (74.9) n=189	118.4 (84.5) n=82	112.7 (76.5) n=171	108.1 (66.7) n=164
Month 6, mean (SD)	103.1 (78.1) n=67	105.0 (58.9) n=163	96.2 (51.8)[d] n=161	100.7 (48.7) n=60	108.1 (67.0) n=138	99.9 (60.1) n=135

Month 12, mean (SD)	99.6 (54.5) n=56	102.5 (61.0) n=131	102.6 (68.2) n=138	95.7 (47.6) n=43	112.1 (63.6)[a] n=118	99.6 (51.2) n=110

HDL=high-density lipoprotein; LDL=low-density lipoprotein.
P values derived from pairwise contrasts within the framework of a 1-way analysis of variance model.
[a]*P*<0.005, relative to placebo for change from baseline.
[b]*P*<0.001, relative to placebo for change from baseline.
[c]*P*<0.01, relative to placebo for change from baseline.
[d]*P*<0.05, relative to placebo for change from baseline.

Supplemental Table XIV. Mean Hormone and SHBG at Baseline and 6 and 12 Months (All Participants)

	Study 1			Study 2		
Hormone	**Placebo (n=87)**	**Asoprisnil 10 mg (n=196)**	**Asoprisnil 25 mg (n=192)**	**Placebo (n=87)**	**Asoprisnil 10 mg (n=196)**	**Asoprisnil 25 mg (n=192)**
Thyroxine (T_4), µg/dL						
Baseline, mean (SD)	7.9 (1.1) n=85	7.8 (1.3) n=189	8.0 (1.5) n=185	7.6 (1.3) n=81	8.0 (1.4) n=170	7.8 (1.4) n=163
Month 6, mean (SD)	7.9 (1.2) n=67	7.4 (1.4)[a] n=160	7.2 (1.3)[b] n=160	7.7 (1.7) n=60	7.6 (1.3)[c] n=138	7.4 (1.3)[a] n=134
Month 12, mean (SD)	7.7 (1.1) n=56	7.4 (1.4) n=131	7.3 (1.4)[c] n=138	7.6 (1.7) n=43	7.6 (1.4) n=118	7.4 (1.3) n=110
TSH, µIU/mL						
Baseline, mean (SD)	1.8 (1.3) n=85	1.8 (1.2) n=189	1.8 (1.31) n=186	2.0 (2.7) n=82	1.8 (1.8) n=171	1.7 (1.2) n=163
Month 6, mean (SD)	1.8 (1.3) n=67	1.9 (1.5) n=161	1.9 (1.4) n=161	1.8 (1.5) n=60	1.6 (0.9) n=138	1.9 (2.1) n=134
Month 12, mean (SD)	2.0 (2.2) n=56	1.8 (1.4) n=131	2.0 (1.5) n=139	2.2 (2.2) n=43	1.8 (1.7) n=118	1.9 (1.5) n=110
Cortisol, µg/dL						
Baseline, mean (SD)	11.8 (4.9) n=86	11.0 (4.9) n=195	11.2 (4.9) n=181	11.8 (5.4) n=84	12.3 (4.9) n=174	11.8 (5.1) n=172
Month 12, mean (SD)	10.5 (4.3) n=56	9.9 (4.1) n=131	9.2 (4.0)[c] n=139	10.7 (4.2) n=43	9.8 (4.2) n=117	10.1 (4.4) n=111
DHEA-S, µg/dL						
Baseline, mean (SD)	79.7 (43.0) n=84	80.2 (45.7) n=189	76.7 (44.7) n=188	72.2 (36.5) n=82	85.4 (45.6) n=171	82.6 (47.4) n=164
Month 12, mean (SD)	70.6 (35.8) n=56	76.0 (42.3) n=134	73.9 (40.9)[c] n=143	71.4 (40.0) n=44	84.8 (47.2) n=120	82.6 (44.4) n=113
Prolactin, ng/mL						
Baseline, mean (SD)	15.3 (8.3) n=85	15.2 (9.5) n=189	15.4 (9.0) n=185	16.0 (13.6) n=81	15.9 (8.6) n=170	15.3 (7.8) n=163

Month 6, mean (SD)	16.5 (7.7) n=67	16.7 (12.3) n=161	13.6 (7.7)[d] n=160	16.3 (13.0) n=60	15.2 (9.1) n=138	14.0 (8.0) n=135
Month 12, mean (SD)	17.2 (8.7) n=56	15.2 (9.2) n=131	12.4 (6.3)[b] n=138	19.9 (11.3) n=43	15.5 (8.3)[b] n=118	12.7 (8.0)[b] n=110
FSH, mIU/mL						
Baseline, mean (SD)	9.7 (5.7) n=85	11.4 (7.4) n=190	9.8 (6.1) n=187	9.2 (7.5) n=82	9.4 (5.8) n=171	11.8 (9.0) n=164
Month 6, mean (SD)	9.4 (10.2) n=67	7.2 (6.9)[b] n=163	6.5 (5.2)[a] n=161	8.8 (8.3) n=60	7.3 (10.1) n=139	5.9 (3.6)[b] n=134
Month 12, mean (SD)	9.6 (12.6) n=56	9.1 (11.3) n=131	6.9 (6.9) n=139	5.8 (3.6) n=43	8.3 (11.5) n=118	7.2 (6.5) n=111
Luteinizing Hormone, mIU/mL						
Baseline, mean (SD)	5.5 (4.2) n=85	5.7 (4.7) n=190	5.1 (4.0) n=187	5.1 (6.0) n=82	5.3 (3.9) n=171	6.6 (8.7) n=164
Month 6, mean (SD)	10.7 (13.1) n=67	7.1 (9.2)[d] n=163	5.6 (4.5)[d] n=161	9.6 (13.0) n=60	8.2 (16.6) n=139	6.1 (5.0)[c] n=134
Month 12, mean (SD)	10.1 (12.2) n=55	7.6 (8.8)[c] n=129	5.4 (4.7)[a] n=137	7.9 (10.2) n=43	7.3 (8.4) n=117	5.8 (4.0)[c] n=110
Total Testosterone, ng/dL						
Baseline, mean (SD)	21.1 (8.9) n=84	19.2 (7.8) n=189	20.1 (7.4) n=188	21.1 (10.6) n=81	22.7 (9.5) n=170	20.8 (9.8) n=165
Month 6, mean (SD)	28.3 (17.0) n=67	21.9 (8.7)[b] n=164	19.3 (8.0)[b] n=162	27.8 (14.6) n=60	23.1 (11.0)[b] n=138	19.0 (7.9)[b] n=137
Month 12, mean (SD)	28.8 (19.2) n=57	20.7 (7.9)[b] n=134	18.6 (7.5)[b] n=143	28.9 (14.3) n=44	22.9 (11.0)[b] n=120	19.1 (7.6)[b] n=113
Androstenedione, ng/dL						
Baseline, mean (SD)	90.5 (34.1) n=84	81.8 (32.0) n=191	85.9 (33.6) n=186	87.3 (32.7) n=83	94.8 (36.8) n=170	89.6 (35.8) n=165
Month 6, mean (SD)	103.3 (47.3) n=67	96.5 (30.1) n=164	91.2 (36.4) n=162	107.4 (47.1) n=59	101.7 (43.0)[c] n=139	91.8 (36.2)[c] n=136
Month 12, mean (SD)	99.5 (41.4) n=57	89.5 (30.6) n=135	84.8 (38.0) n=142	112.5 (44.7) n=44	97.6 (37.3)[d] n=121	93.1 (37.8)[d] n=113
SHBG, nmol/L						

Baseline, mean (SD)	92.5 (43.8) n=84	88.1 (41.4) n=190	91.7 (45.5) n=188	87.6 (42.5) n=81	94.2 (48.7) n=170	95.0 (53.1) n=165
Month 6, mean (SD)	98.2 (52.3) n=67	68.8 (38.7)[b] n=165	50.8 (24.5)[b] n=162	84.2 (36.5) n=60	68.0 (34.7)[b] n=139	51.1 (28.8)[b] n=137
Month 12, mean (SD)	96.4 (50.0) n=57	69.8 (36.4)[b] n=134	50.0 (26.4)[b] n=143	85.1(39.5) n=44	65.9 (32.6)[b] n=121	50.3 (26.8)[b] n=113

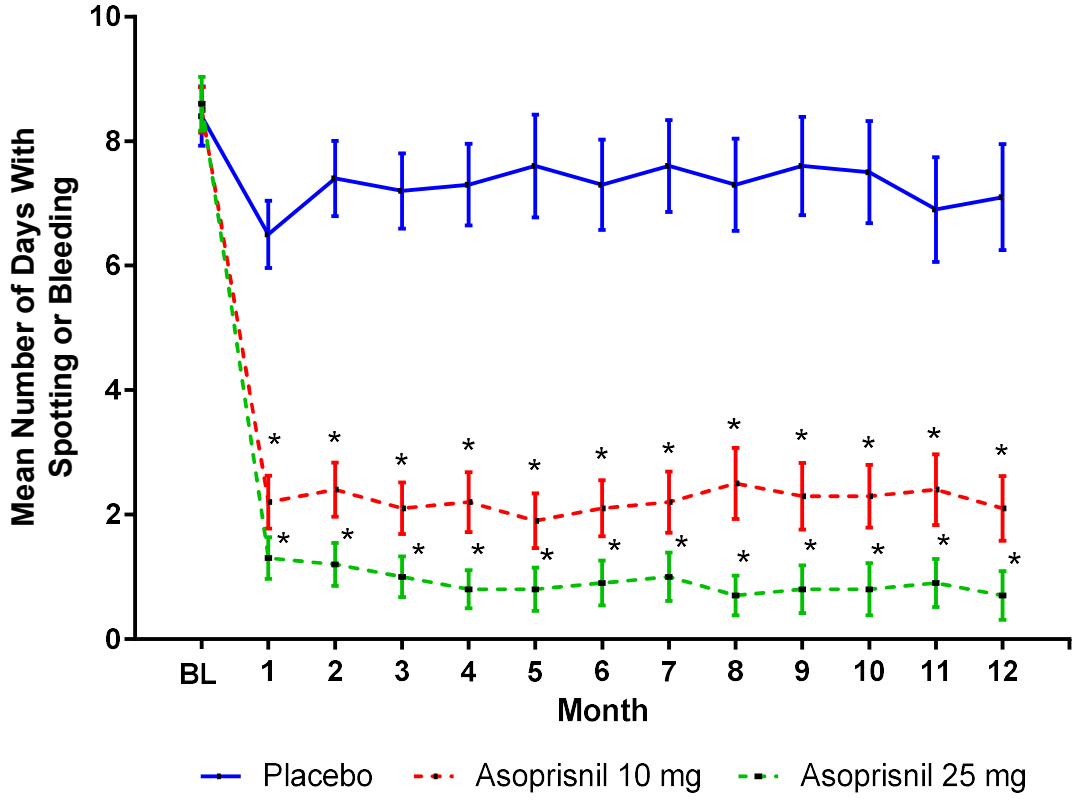
DHEA-S=dehydroepiandrosterone sulfate; FSH=follicle-stimulating hormone; SHBG=sex hormone binding globulin; TSH=thyroid-stimulating hormone.
P values derived from pairwise contrasts within the framework of a 1-way analysis of variance model.
[a]*P*<0.01, relative to placebo for change from baseline.
[b]*P*<0.001, relative to placebo for change from baseline.
[c]*P*<0.05, relative to placebo for change from baseline.
[d]*P*<0.005, relative to placebo for change from baseline.

Supplemental Figure Legends

Supplemental Figure 1. Mean number of days with spotting or bleeding (intent-to-treat population). BL=baseline. Error bars represent 2 × the standard error of the mean. *P<0.001 statistically significant difference for asoprisnil 10 mg or 25 mg vs placebo for change from baseline using the Hochberg multiple comparison procedure with an initial critical P=0.05 (from the Fisher exact test).

Supplemental Figure 2. Mean estradiol (E2) values over time (all participants). LLN=lower limit of normal; ULN=upper limit of normal. *P<0.001, **P<0.01, and ***P<0.05 vs placebo for change from baseline (pairwise comparison from contrasts within the framework of the 1-way analysis of variance model). Error bars represent 2 × the standard error of the mean.

Supplemental Figure 1.



Supplemental Figure 2.