In addition to the estrogen receptor, the progesterone receptor plays an important role in the growth of uterine fibroids. Several selective progesterone receptor modulators (SPRMs) have been evaluated for medical treatment of uterine fibroids and, because of safety issues, some molecules were stopped during clinical development. However, in 2012, ulipristal acetate received the approval for a pre-surgical treatment of uterine fibroids. Clinical trials with ulipristal acetate for long-term medical treatment of uterine fibroids are ongoing. This review article describes the action of SPRMs at the progesterone receptor level and the mechanism of action on the fibroid tissue. A review of the published clinical trials is performed, including the current evidence of efficacy on uterine fibroid symptom management, size reduction and tolerability. The therapeutic potential of SPRMs for uterine fibroids is discussed.

**KEYWORDS:** asoprisnil • estrogen receptor • GnRH-agonist • mifepristone • progesterone receptor • progesterone receptor modulators • SPRM • telapristone acetate • ulipristal acetate • uterine fibroids

Uterine fibroids are the most frequent tumor of the female genital tract with an increasing frequency during the women’s fertile years with a prevalence of 20–77% depending on the population and method of assessment [1–3]. Its incidence increases with increasing age and the life time risk for women to develop uterine fibroids is 70% [4]. Uterine fibroids are more frequent and appear at an earlier age in black women, whereas the incidence of fibroids in Asian or Hispanic women is comparable to the incidence in Caucasian women [1,2,4]. The majority of women with uterine fibroids remain asymptomatic but some women have symptoms of uterine fibroids that may warrant therapy. The most frequent symptoms attributable to uterine fibroids are abnormal uterine bleeding, pelvic pressure or pain and an impacted reproductive function [5]. These symptoms lead to a significantly worse health related quality of life (HRQoL) when compared to women without fibroids [6]. The most common symptom of uterine fibroids, in other words, heavy menstrual bleeding, is associated with an annual cost of US$1692/woman because of work loss and increased use of health care resources [7]. One-third of the patients with diagnosed fibroids will finally decide for surgery [8]. Fibroids constitute the leading indication for hysterectomy in the USA [9].

Traditionally, estrogen has been considered the major promoter of fibroid growth and there is significant biochemical evidence to support its influence on fibroid size. However there is also an increasing evidence to suggest that not only estrogen stimulates fibroid growth but that progesterone has important biologic effects on fibroids. Consequently, progesterone receptor (PR) antagonists or modulators are becoming an interesting target for research in the medical treatment of uterine fibroids [10].

Since the accidental discovery of mifepristone (RU486) by Roussel-Uclaf in the early 1980s, several other PR ligands have been identified. Mifepristone which was initially discovered when searching for a pure glucocorticoid antagonist revealed to be a strong progesterone antagonist with anti-glucocorticoid properties and with a progesterone agonistic activity in presence of protein kinase A activators (cAMP) [11].
Additional selective progesterone receptor modulators (SPRMs) with strong anti-progesterone activities have been developed by Bayer Schering AG (onapristone [ZK 137316] and lonaprisan [ZK 230211]). It was of particular importance to develop progesterone antagonists with little or no glucocorticoid activity, such as ulipristal acetate (CDB-2914) and telapristone acetate (CDB-4124) [12]. These molecules showed more agonist activity than onapristone, lonaprisan or mifepristone while still being mostly antagonistic at the PR level. Some SPRMs are classified as being PR ligands with a more pronounced agonistic activity. The ‘J-series’ of SPRMs, of which asoprisnil (J-867) is the best known representative, were specifically designed to have low anti-glucocorticoid receptor activity and with little or no abortifacient effect [13]. New SPRMs are currently under development including non-steroidal SPRMs such as CP8863 and CP8947 which should not produce anti-glucocorticoid related adverse effects [14]. Attempts are also being made to develop PR-A or PR-B specific molecules [15].

Only a few SPRMs were selected for clinical development and to date only two SPRMs have reached the market. Ulipristal acetate is the only SPRM which is currently marketed in the indication for uterine fibroids. This article reviews the current knowledge about the potential of SPRMs as therapy for uterine fibroids.

SPRM & the PR

Progesterone is one of the key players in the female reproductive function. Its main role is the establishment and maintenance of pregnancy by preparing the endometrium for implantation, regulating the implantation process and following the successful implantation of the blastocyst, reducing the uterine contractility. The withdrawal of progesterone in the physiological menstrual cycle leads to changes in the endometrial extracellular matrix paralleled by constriction of spiral arteries which results in the occurrence of menstruation. In the uterus, progesterone regulates the growth and differentiation of endometrial and myometrial cells, and is therefore a counter player to estrogen. Progesterone may have inhibitory and stimulatory effects on cell proliferation.

The effects of progesterone on target tissues are mediated by the PR, which belongs to the nuclear receptor family. The relationship between the agonistic and antagonistic activities of SPRMs on the PR is still being elucidated. Progesterone is the physiological ligand of the PR.

Two main PR isoforms exist, PR-A and PR-B and these are transcribed from two promoters on a single gene and have distinct functions depending on the cell type and transcriptional context. When binding to progesterone agonists and antagonists, PR-A can function as a repressor of other steroid receptors including PR-B, the estrogen receptor (ER), androgen receptor (AR), mineralocorticoid receptor and glucocorticoid receptor. In the absence of progesterone, the PR is inactive and bound by heat shock proteins (HSP). Progesterone and its agonists lead to a conformational change, release from HSPs, dimerization of the PR which will bind to a specific progesterone response element sequence of the DNA and finally lead to gene transcription, with or without the association of co-factors (Figure 1). Progesterone receptor antagonists induce an altered conformation in the receptor that is transcriptionally inactive, owing to the association of co-repressors instead of co-activators or to inhibition of binding to co-activators [16]. SPRMs are synthetic compounds which compete at the PR binding site displaying a mixed agonist-antagonist activity on the PR and when bound, also lead to dimerization and binding to the progesterone response element sequence but induce an intermediate conformation allowing the receptors to interact with both co-activators and/or co-repressors.

Whether an SPRM acts more as an antagonist or agonist depends on its structure and how it alters PR conformation leading to exposure or inactivation of particular binding domains which affect the association of co-repressors and/or co-activators with the PR. This is, in turn, impacted by the presence of co-regulators in a particular cell type and by the ratio of co-activators and co-repressors. The activity of an SPRM varies with tissue type and physiological context (e.g., pregnancy) and may be different from one cell type to another. For instance, SPRMs suppress the estrogen-driven proliferation of glandular epithelium in the endometrium of menstruating primates, which is a function of native progesterone, but do not antagonize estrogenic effects in the oviduct and vagina [13,16–20].

Progesterone receptors are known to be upregulated in uterine fibroids compared with the adjacent myometrium at the mRNA and protein levels [21]. Progesterone receptor A and B contents are higher in fibroids than in the adjacent myometrium with a significant dominance of PR-A over PR-B [18–22] and it has been demonstrated that in vitro, SPRMs cause apoptosis of uterine fibroid cells but not of myometrial cells [23]. No correlation between binding affinity and the agonist-antagonist activity of SPRMs has been demonstrated [24].

It might have been expected, that the antagonistic action of SPRMs at the PR level would have led to an unopposed estrogenic stimulation resulting in increased proliferative action on the endometrial glands, especially as SPRMs do not bind to the ER. It has been demonstrated on human and non-human primate endometrial cells that low-dose, chronic administration of mifepristone results in the upregulation of the ER and AR and the downregulation of the PR [25–27]. If mifepristone is combined with estradiol, it results in further upregulation of the ER and PR in the epithelium, expression of the AR in these cells and further upregulation of all three receptors in the stroma. The increase of the AR is suspected to lead to an enhancement of androgen action in the endometrium. As androgens suppress estrogen-dependent endometrial proliferation, the increase of the AR in the endometrial glands could be an explanation for the paradoxical anti-proliferative action of SPRMs and explain why anti-progestins block the proliferative action of estradiolon endometrial glands. This is further supported by the fact that flutamide, an AR antagonist, abolishes the anti-proliferative effect of SPRMs on the endometrium and increases the mitotic index and endometrial thickness.
The potential of selective progesterone receptor modulators for the treatment of uterine fibroids

Uterine fibroids

Uterine fibroids are benign, monoclonal and smooth muscle tumors of the uterus. Estrogen has long been considered as the major growth stimulant for uterine fibroids. Progesterone has equally important biological effects on fibroids and clinical observations that have traditionally supported the estrogen hypothesis may equally support the hypothesis that progesterone is an important factor involved in the fibroid pathogenesis: similar to estrogen, progesterone concentrations are subject to cyclic elevation over the menstrual cycle and to a significant increase during pregnancy. During menopause, both estrogen and progesterone concentrations are decreased [25]. Furthermore, the EGF seems to be involved in the regulation of

effects of estrogen mediated by the ER in the glands might then be counteracted by direct effects of androgens mediated by the AR in the same cells [28,29].

Asoprisnil demonstrates a greater agonist activity and tends consequently to interact less with pregnancy. In non-human primate models, it demonstrated anti-proliferative effects on the endometrium [13].

Ulipristal acetate and telapristone acetate are potent anti-progestins in vitro and in vivo. Both molecules bind with high affinity to rabbit uterine PR and recombinant human PR-A and PR-B (rhPR-A and rhPR-B). Because of the reduced anti-glucocorticoid activities compared with mifepristone they are excellent candidates for chronic administration [12].

Figure 1. Activation of the progesterone receptor by progesterone and SPRMs. (A) Binding of progesterone to the inactive receptor complex induces a conformational change, which leads to HSP dissociation, receptor dimerization, DNA binding and recruitment of co-activators to facilitate communication with the basal transcription apparatus. (B) SPRM may act as agonists at the progesterone receptor which will activate the transcription comparably to progesterone. In case of an antagonistic action, the SPRM competes with agonists for binding at the PR and induces a conformational change which allows a more potent recruitment of co-repressors. The precise conformational change induced at the PR, and consequently the balance of interaction with co-activators and co-repressors depends upon the identity of the individual SPRM. In addition, the activity of each SPRM varies with tissue type and is influenced by the ratio of co-activators and co-repressors in each cellular environment.


Data taken from [44,78].

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fibroid growth as under gonadotropin-releasing hormone (GnRH) agonist therapy a remarkable reduction in uterine EGF-binding sites could be demonstrated [30]. Treatment with progesterone increases EGF and Bcl-2 protein expression, but inhibits IGF-I and TNF expression in cultured fibroid cells thus suggesting that progesterone has a direct action on uterine fibroid growth: to stimulate the fibroid cell growth and survival through upregulating EGF and Bcl-2 protein expression as well as downregulating TNF expression and to inhibit fibroid cell growth through downregulating IGF-I expression in those cells. Progesterone seems to act in combination with estradiol to stimulate the proliferative potential of cultured leiomyoma cells through the induction of EGF and its receptor EGFR [28–31]. In consequence, despite the dual actions of progesterone on the growth of fibroids, the net effect of progesterone on fibroid cells is likely to favor fibroid cell growth through the augmentation of cell proliferation and the inhibition of apoptosis. Evidence from clinical studies suggests that synthetic progestins stimulate fibroid growth whereas such as mifepristone, have opposite effects [32].

**SPRMs & their mechanism of action on uterine fibroids**

**SPRMs & uterine fibroid size reduction**

Currently, the mechanism of action of SPRMs in treating uterine fibroids is not fully elucidated. *In vitro* studies aiming to investigate the mechanism of action of SPRMs in uterine fibroid reduction show that progesterone stimulates fibroid cell proliferation whereas SPRMs such as asoprisnil, telapristone acetate and ulipristal acetate inhibit the proliferative processand induce apoptosis selectively in fibroid cells by downregulating anti-apoptotic factors [23,33,34], anti-fibrotic activity [35] and reducing or blocking growth factor expression [36–38]. The SPRM CP8947 has also been recently shown to inhibit fibroid cell proliferation without adversely affecting the endometrium or the myometrium [14]. For the time being, the apoptotic effect *in vivo* has been confirmed only with ulipristal acetate in a small 12-week study comparing surgically removed fibroids after ulipristal acetate therapy with fibroids having undergone pre-treatment with a GnRH agonist or no pre-treatment [39].

Other mechanisms of action of SPRMs may contribute to their efficacy in decreasing the size of uterine fibroids and reducing the associated heavy blood loss, such as a direct effect on uterine blood vessels which has been demonstrated *in vivo* for asoprisnil and mifepristone [40,41].

**SPRMs & control of uterine bleeding**

It has to be recognized that the interest of SPRM treatment in the indication of uterine fibroids is not only related to its decrease in fibroid size, but even more importantly because of its impressive reduction of uterine bleeding and its control of ovulation and the menstrual bleeding. For all SPRMs, a high rate of bleeding control is reported with frequent occurrence of amenorrhea. The amenorrhea has been suggested to be either due to a direct effect on the endometrium [42] or at least in part due to anovulation [17–43]. However, the exact mechanism of action by which daily SPRM dosing inhibits ovulation and leads to amenorrhea is not yet entirely clear [44]. Single dose SPRM treatment in the follicular phase or around the LH peak can delay ovulation and follicular maturation as demonstrated for ulipristal acetate and mifepristone [45–48]. Chronic low-dose SPRM treatment leads to anovulation and induction of amenorrhea in most women; 5 or 10 mg of ulipristal acetate can inhibit ovulation and lead to amenorrhea without reducing endogenous estrogen secretion [49]. Asoprisnil has shown to suppress the menstrual bleeding from doses of 10 mg/day or more; however, ovulation was controlled only with a dose of 50 mg twice daily [49]. Despite the suppression of ovulation, endogenous estradiol concentrations remain at physiological levels [43,44]. The effects of the drug on menstruation are reversible and for ulipristal acetate it has been demonstrated that when ulipristal acetate treatment is stopped, menstrual cycles generally resume within 4 weeks.

**SPRMs & the endometrium**

It is known that SPRMs have a very distinct effect on the endometrium, which may be directly linked to its effect on bleeding control. Early reports described endometrial thickening and pathologists have observed glands with dilatation. Now described as Progesterone receptor modulator Associated Endometrial Changes (PAEC) [50], these changes were, in early studies, originally interpreted as simple endometrial hyperplasia, as the architecture of PAEC has similarities to simple endometrial hyperplasia and as these new features could not be categorized in existing classification systems. Eisinger reported hyperplasia after 6 months of treatment in 14% of women receiving mifepristone 10 mg for uterine fibroids [51].

In 2006, the Division of Cancer Treatment and the Office of Women’s Health of the National Cancer Institute and the NIH Office of Research on Women’s Health convened a panel of pathologists to evaluate endometrial changes associated with four different SPRMs. All of the pathologists had been involved in clinical development of SPRM and previously been exposed to endometrial specimens after SPRM exposure. The pathologists were blinded to treatment, dose and treatment regimen [24]. The panel of pathologists found that the appearance of cystically-dilated glands was a frequent architectural finding after SPRM exposure. In its simplest form, scattered cysts were only moderately dilated, comparable to a disordered proliferative endometrium as seen because of unopposed estrogen effect in case of anovulation. Instead of the proliferative lining, which can be seen with hyperplasia, the glands were only weakly mitotic or sometimes secretory. The endometrial appearances seemed to differ by agent, the applied dose and the administration schedule. The panel concluded that the endometrium could neither be classified as proliferative nor secretory, hence termed these findings as PAEC [50]. Judged as a benign condition, PAEC is characterized by an inactive and weakly proliferating epithelium associated with asymmetry of stromal and epithelial growth resulting in prominent cystically-dilated glands with admixed estrogen (mitotic) and progestin
(secretory) epithelial effects. The diagnosis of PAEC is a constellation of histologic features that, taken together, are characteristic, however, none of the features is unique and consequently may be seen in patients who have not been treated previously with SPRMs. In earlier publications on SPRMs, cases of hyperplasia were reported, however, many of these cases were later observed to be cystic glandular dilatation. Cystic dilatation of endometrial glands and an irregular architecture lined by inactive gland cells and compact, non-decidualized stroma are nowadays recognized as common features of PAEC and do not occur in physiological states [24–22].

Under physiological conditions, the intermittent progesterone during the luteal phase of the menstrual cycle opposes the otherwise mitogenic effects of estrogens. The pharmacological effects of SPRMs are, however, neither purely antagonistic nor restricted only to the PR but may exert anti-estrogenic effects through either partial PR agonist activity or through up-regulation of the androgen receptor response. These SPRM effects are evident as dose-dependent suppression of estrogen-induced mitotic activity and appearance of glandular secretory changes.

The absence of proliferative features in the endometrial biopsies in combination with an observed thickening of the endometrium raises the hypothesis that the frequently described cystic glandular dilatation under SPRM treatment may be at the origin of the observed thickening of the endometrium when performing ultrasound or MRI examinations. The thickening of the endometrium is assumed to be due to the fluid accumulation in glands which are otherwise weakly proliferative or not proliferative at all. This hypothesis was supported by a study by Croxatto et al., in which no hyperplasia was observed in women taking 1 mg/day mifepristone, although 25% of these women experienced increased endometrial thickness and 34% experienced increased dilated glands [53].

**Therapeutic potential of SPRMs**

Owing to their pharmacological properties, SPRMs were mainly tested in indications which are supposed to have a relation to the role of progesterone, mainly in gynecological and oncological indications. Only few SPRMs have been tested or are under development in the indication of uterine fibroids. Ulipristal acetate is the only molecule which has received marketing authorization for a pre-surgical 3-month treatment of uterine fibroids. Three other SPRMs have been tested for the indication of uterine fibroids: mifepristone [5455], asoprisnil [49] and telapristone acetate [56]. Table 1 indicates the clinical trials and selected results which have been performed with mifepristone and other SPRMs in the indication of uterine fibroids to date. All SPRMs have consistently decreased fibroid and/or uterine volume and significantly reduced uterine bleeding and/or even induced amenorrhea.

**Mifepristone**

In most literature, mifepristone is designated as a pure PR antagonist according to its reaction in the McPhail test; however, mifepristone was found to have some agonist action in other tests [11] and should, therefore, be considered as an SPRM with strong antagonistic properties. In general, it has proven difficult to pin down the exact agonist or antagonist actions of individual SPRMs because results of *in vitro* studies have not always matched results *in vivo* and tests in animal models (e.g., the McPhail test). As progesterone effects can be species-specific, effects in animal models may not necessarily reflect the expected activity in man [57].

Mifepristone was initially developed as an abortifacient drug owing to its strong progesterone antagonist properties. This indication, its moral implications and the possible negative consequences for the developing company inhibited its further clinical development. However, mifepristone was tested in several indications in the frame of a clinical trial. We identified 13 published clinical trials in uterine fibroid patients which have been performed with mifepristonedoses from 2.5 to 50 mg (Table 1). Only four of those were double-blind, placebo-controlled clinical trials with 30–124 subjects [55,58–60] and one small trial was leuprolide acetate-controlled, but with an open-label design [40]. In the placebo-controlled trials, mifepristone daily doses ranged from 5 to 25 mg or 50 mg every other day. In all four trials, mifepristone demonstrated a significant effect on menstrual bleeding. Reduction of fibroid size was reported in three trials ranging from -28 to -30.2% reaching statistical significance in two trials. Uterine fibroid volume reduction was reported in all four trials ranging from 0 to -47% and reaching significance in two trials. Because of the limited number of subjects in double-blind, placebo- or active-controlled trials, the authors concluded, however, that the current evidence on the clinical efficacy of mifepristone in the treatment of uterine fibroids is still limited.

**Telapristone acetate**

Telapristone acetate (CDB 4124) which is considered as an SPRM with a strong antagonistic activity at the PR was initially tested by the National Institute of Child Health and Human Development (NICHD) and further developed by Repros Therapeutics in the indications of endometriosis, uterine fibroids and anemia associated with uterine fibroids. A clinical Phase III program in uterine fibroids and anemia associated with uterine fibroids was ongoing, when the US FDA requested to stop the entire development program because of cases of suspected drug induced liver toxicity. After a full clinical hold in 2009, the company restarted with dose-finding studies and performs currently clinical trials in the treatment of endometriosis with an intravaginal formulation exposing subjects to much lower doses. Despite different company press releases about successful study completion with telapristone acetate in the uterine fibroid population, only one small placebo and GnRH agonist controlled clinical trial was published to date and is included in Table 1. In this clinical study, 40 subjects were distributed to five groups comparing three different strengths of telapristone acetate (12.5, 25 and 50 mg) against its controls [56]. Based on subject diary information, all telapristone acetate groups showed an efficient control of uterine
Table 1. Summary table of clinical trials with selective progesterone receptor modulators in uterine fibroid patients. Efficacy and safety results.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Type</th>
<th>Treatment groups</th>
<th>Subjects treated (n)</th>
<th>Fibroid volume % CFB</th>
<th>Uterine volume % CFB</th>
<th>Amenorrhea at end point</th>
<th>Endometrial changes</th>
<th>Endometrial thickening</th>
<th>Hot flashes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mifepristone</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Murphy et al. (1993)</td>
<td>OL</td>
<td>50 mg</td>
<td>10</td>
<td>3 m: -49%</td>
<td>NR</td>
<td>3 m: 100%</td>
<td>NR</td>
<td>NR</td>
<td>40%</td>
</tr>
<tr>
<td>Reinsch et al. (1994)</td>
<td>R, OL, c</td>
<td>25 mg 3.75 mg LA</td>
<td>8</td>
<td>NR</td>
<td>3 m: -32% -54%</td>
<td>NR</td>
<td>Not investigated</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Eisinger et al. (2003)</td>
<td>R, OL</td>
<td>5 mg 10 mg</td>
<td>6 m:</td>
<td>NR</td>
<td>6 m: -48% -49%</td>
<td>6 m: 61% 65%</td>
<td>Simple hyperplasia</td>
<td>NR</td>
<td>6 m: 45% 55%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12 m subgroup:</td>
<td></td>
<td>12 m (subgroup):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8</td>
<td></td>
<td>52% 53%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eisinger et al. (2005)</td>
<td>R, OL</td>
<td>5 mg 10 mg</td>
<td>6 m:</td>
<td>NR</td>
<td>6 m: 41% 0%</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12 m subgroup:</td>
<td></td>
<td>3 m:</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td></td>
<td>-11%</td>
<td></td>
<td></td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td>Fiscella et al. (2006)</td>
<td>R, DB, Plc</td>
<td>5 mg placebo</td>
<td>22</td>
<td>NR</td>
<td>6 m: -47% +10% (p = significant)</td>
<td>6 m: 41% 0% (p = significant)</td>
<td>Cystic glandular dilatation</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Carbonell Esteve et al. (2008)</td>
<td>R, DB</td>
<td>5 mg 10 mg</td>
<td>50</td>
<td>3 m:</td>
<td>3 m:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 mg</td>
<td></td>
<td>-57% -45%</td>
<td>-36% -40%</td>
<td>Simple hyperplasia</td>
<td>NR</td>
<td>10.0% 20.4%</td>
</tr>
<tr>
<td>Eisinger et al. (2009)</td>
<td>R, OL</td>
<td>5 mg 10 mg</td>
<td>6 m:</td>
<td>NR</td>
<td>3 m:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
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<td>12 m subgroup:</td>
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<td></td>
<td></td>
<td>8</td>
<td></td>
<td>52% 53%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bagaria et al. (2009)</td>
<td>R, DB, Plc</td>
<td>5 mg placebo</td>
<td>20</td>
<td>3 m:</td>
<td>3 m:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 mg</td>
<td></td>
<td>-30.2% +0.5</td>
<td>-26.6% +0.2</td>
<td>Hyperplasia 63.2% 0%</td>
<td>NR</td>
<td>No</td>
</tr>
<tr>
<td>Engman et al. (2009)</td>
<td>R, DB, Plc</td>
<td>50 mg (every other day)</td>
<td>14</td>
<td>3 m:</td>
<td>3 m:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>placebo</td>
<td></td>
<td>-28%</td>
<td>No reduction</td>
<td>Cystic glandular dilatation 62.5% (mifepristone)</td>
<td>NR</td>
<td>Around 50%</td>
</tr>
<tr>
<td>Esteeve et al. (2012)</td>
<td>R, DB</td>
<td>5 mg 10mg</td>
<td>86</td>
<td>6 m:</td>
<td>6 m:</td>
<td>6 m: at 3 m:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>85</td>
<td></td>
<td>-39.1% -48.1%</td>
<td>-27.2% -30.3%</td>
<td>26.8% 42.9%</td>
<td>Yes (significant towards baseline reversible)</td>
<td></td>
</tr>
</tbody>
</table>

Shaded rows indicate placebo or active controlled clinical trials. C: Controlled; DB: Double-blind; LA: Leuprolide acetate; NR: Not reported; NS: Non significant; Plc: Placebo; OL: Open-label; R: Randomized; S: Significant.
<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Type</th>
<th>Treatment groups</th>
<th>Subjects treated (n)</th>
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<th>Uterine volume % CFB</th>
<th>Amenorrhea at end point</th>
<th>Endometrial changes</th>
<th>Endometrial thickening</th>
<th>Hot flashes</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mifepristone? (cont.)</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbonell et al. (2012)</td>
<td>R</td>
<td>2.5 mg</td>
<td>71</td>
<td>3 m: -38.7%</td>
<td>3 m: -9.6%</td>
<td>3 m: 84.0%</td>
<td>Yes</td>
<td></td>
<td>37.1%</td>
<td>[76]</td>
</tr>
<tr>
<td></td>
<td>5 mg</td>
<td>75</td>
<td></td>
<td>54.3%</td>
<td>-24.3%</td>
<td>92.0%</td>
<td></td>
<td>24.1%</td>
<td></td>
<td></td>
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<tr>
<td>Carbonell et al. (2013a)</td>
<td>R, DB, Plc</td>
<td>5 mg placebo</td>
<td>62</td>
<td>3 m: -28.5%</td>
<td>3 m: -22.7%</td>
<td>3 m: 93.1%</td>
<td>Yes (significant towards placebo)</td>
<td></td>
<td>24.5%</td>
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<td></td>
<td></td>
<td>+ 1.8% (p = 0.031)</td>
<td>+ 2.6% (p = 0.034)</td>
<td>4.3% (p &lt; 0.001)</td>
<td></td>
<td>2.4%</td>
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<tr>
<td>Carbonell et al. (2013b)</td>
<td>R, DB</td>
<td>5 mg</td>
<td>34</td>
<td>9 m: -52.2%</td>
<td>9 m: -33.4%</td>
<td>3 m: 100%</td>
<td>3 m: 100%</td>
<td>3 m: 100%</td>
<td>24.5%</td>
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<tr>
<td></td>
<td>10 mg</td>
<td>35</td>
<td></td>
<td>-65.8%</td>
<td>-38.5%</td>
<td>97.1%</td>
<td></td>
<td>80%</td>
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<tr>
<td>Carbonell et al. (2013)</td>
<td>R</td>
<td>2.5 mg</td>
<td>110</td>
<td>3 m: -27.9%</td>
<td>3 m: -18.2%</td>
<td>3 m: 78.3%</td>
<td>3 m: 37.9%</td>
<td>3 m: reversible</td>
<td>24.2%</td>
<td></td>
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<tr>
<td></td>
<td>5 mg</td>
<td>110</td>
<td></td>
<td>-46.4%</td>
<td>-22.1%</td>
<td>93.6%</td>
<td></td>
<td>15.6%</td>
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<tr>
<td><strong>Telapristone acetate</strong></td>
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<tr>
<td>Wiehle et al. (2008)</td>
<td>R, DB, Plc</td>
<td>12.5 mg</td>
<td>6</td>
<td>3 m: -17.9%</td>
<td>NR</td>
<td>3 m: majority in amenorrhea on telapristone acetate, superior to LA in month 1 and 2, comparable to LA in month 3 and 4</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>[56]</td>
</tr>
<tr>
<td></td>
<td>25 mg</td>
<td>6</td>
<td></td>
<td>-40.3%</td>
<td>NR</td>
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<td></td>
<td>50 mg</td>
<td>5</td>
<td></td>
<td>-32.6%</td>
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<td></td>
<td>Lupron</td>
<td>5</td>
<td></td>
<td>-10.6% (p = 0.05 for 25 and 50mg)</td>
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<tr>
<td></td>
<td>placebo</td>
<td>6</td>
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<td><strong>Asoprisnil</strong></td>
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<tr>
<td>Chwalisz et al. (2007)</td>
<td>R, DB, Plc</td>
<td>5 mg</td>
<td>33</td>
<td>3 m: -36% (25 mg)</td>
<td>3 m: -14% (S)</td>
<td>3 m: 16%</td>
<td>3 m: No</td>
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<td>3%</td>
<td></td>
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<td></td>
<td>10 mg</td>
<td>29</td>
<td></td>
<td>-4% (NS)</td>
<td>-9%</td>
<td>36%</td>
<td></td>
<td>10%</td>
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</tr>
<tr>
<td></td>
<td>25 mg</td>
<td>36</td>
<td></td>
<td>-14% (S)</td>
<td>-7%</td>
<td>36%</td>
<td></td>
<td>8%</td>
<td></td>
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<tr>
<td></td>
<td>placebo</td>
<td>31</td>
<td></td>
<td>+1% (S for 5 and 25mg)</td>
<td>+1%</td>
<td>70%</td>
<td></td>
<td>0%</td>
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</tbody>
</table>

Shaded rows indicate placebo or active controlled clinical trials.
C: Controlled; DB: Double-blind; LA: Leuprolide acetate; NR: Not reported; NS: Non significant; Plc: Placebo; OL: Open-label; R: Randomized; S: Significant.
<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Type</th>
<th>Treatment groups</th>
<th>Subjects treated (n)</th>
<th>Fibroid volume % CFB</th>
<th>Uterine volume % CFB</th>
<th>Amenorrhea at end point</th>
<th>Endometrial changes</th>
<th>Endometrial thickening</th>
<th>Hot flashes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilkens et al. (2008)</td>
<td>R, DB, Plc</td>
<td>10 mg 25 mg placebo</td>
<td>12 11 10</td>
<td>3 m: -0.4% -25.8% 4.9% (NS)</td>
<td>NR</td>
<td>3 m: 33% 91% 0% (S for 25 mg)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Levens et al. (2008)</td>
<td>R, DB, Plc</td>
<td>10 mg 20 mg placebo</td>
<td>8 6 8</td>
<td>3 m: -36% -21% +6% (p = 0.01)</td>
<td>NR</td>
<td>3 m: 100% 100% 0%</td>
<td>NR</td>
<td>No</td>
<td>[61]</td>
</tr>
<tr>
<td>Nieman et al. (2011)</td>
<td>R, DB, Plc</td>
<td>10 mg 20 mg Placebo</td>
<td>14 14 14</td>
<td>3 m: -17% -24% +7% (p = 0.003) 6m (subgroup): -21% (10 mg) -11% (20 mg)</td>
<td>NR</td>
<td>3 m: 62% 92% 7%</td>
<td>3 m: one case of cystic glandular hyperplasia</td>
<td>NR</td>
<td>No</td>
</tr>
<tr>
<td>Donnez et al. (2012a)</td>
<td>R, DB, Plc</td>
<td>5 mg 10 mg placebo</td>
<td>48 95 98</td>
<td>3 m: -21.2% -12.3% +3% (p = 0.002, 0.006)</td>
<td>3 m: -12.1% -12.0% + 5.9% (p = 0.001, 0.003)</td>
<td>3 m: 73% 82% 6% (p &lt; 0.001)</td>
<td>3 m: 62% 57% 6%</td>
<td>&gt;16 mm/3 m: 11.2% 8.0% 2.1% reversible after end of treatment</td>
<td>No</td>
</tr>
<tr>
<td>Donnez et al. (2012b)</td>
<td>R, DB, c</td>
<td>5 mg 10 mg LA</td>
<td>97 103 101</td>
<td>3 m: -36% -42% -53%</td>
<td>3 m: -20% -22% -47%</td>
<td>3 m: 75% 89% 80%</td>
<td>3 m: 58% 59% 12%</td>
<td>&gt;16 mm/3 m: 11.8% 15.3% 1.1% reversible after end of treatment</td>
<td>[64]</td>
</tr>
</tbody>
</table>

Shaded rows indicate placebo or active controlled clinical trials.
C: Controlled; DB: Double-blind; LA: Leuprolide acetate; NR: Not reported; NS: Non significant; Plc: Placebo; OL: Open-label; R: Randomized; S: Significant.
bleeding, which seemed to be even superior to the effect of leuprolide acetate in the first 2 months and remained comparable to leuprolide acetate for the 3rd and 4th month of treatment. A dose-dependent decrease of fibroid volume which was comparable to the leuprolide acetate group and statistically significant for the 25 and 50 mg group when compared to the placebo group (-40.3% for 25 and 50 mg, -10.6% for placebo; \( p = 0.05 \)) could be demonstrated. There was an overall statistically significant difference between treatment groups when evaluating the mean change from baseline at different time points. However, despite the small size of the study arms (eight subjects per arm), two subjects in the 50 mg and 25 mg arm experienced an increase in transaminases, which nowadays is considered as a first alarming sign of the potential for drug induced liver toxicity.

**Asoprisnil**

Asoprisnil (J 867) which is a mixed progesterone antagonist/agonist was tested in uterine fibroids and endometriosis by Schering and TAP Pharmaceutical Products. In 2005, its clinical development was stopped in Phase III because of adverse endometrial effects. We could identify two small randomized, placebo controlled clinical trials which compared two (10 and 25 mg) [41] and three different doses of asoprisnil (5, 10 and 25 mg) to placebo [42]. Asoprisnil controlled uterine bleeding in a dose-dependent manner in 64 and 83% of subjects for the 10 and 25 mg dose, respectively. The dose of 5 mg was not as effective. Amenorrhea (no bleeding or spotting) was achieved in 36 and 70% of subjects in one trial, in 33 and 91% in the second clinical trial for the 10 and 25 mg dose, respectively. With regard to the volume of the largest fibroid by week 12, at the dose of 25 mg the median percentage decrease from baseline was -25.8% and -36% in the two clinical trials, respectively. The results for the total uterine volume reduction was only reported in one trial ranging from -9 to -17% and being statistically significant in the 5 and 25 mg asoprisnil groups.

**Ulipristal acetate**

Ulipristal acetate (CDB 2914, VA2914 or PGL4001), an SPRM with a mainly antagonistic activity at the PR, was initially developed in the indication of emergency contraception owing to its effect in delaying or inhibiting ovulation. In vitro,
Ulipristal acetate has a lower affinity to the glucocorticoid receptor than mifepristone and did not demonstrate an impact on the glucocorticoid receptor at clinically relevant doses [12]. In vivo, ulipristal acetate inhibits dose-dependently ovulation and induces amenorrhea without downregulating estradiol concentrations, combined with anti-proliferative effects on the endometrium demonstrated by absence of endometrial hyperplasia or thickening [43]. Four clinical trials investigated ulipristal acetate in uterine fibroid patients: two small randomized placebo controlled trials investigated the efficacy and safety of 10 and 20 mg/day [61,62] and two large randomized, double-blind Phase III trials compared ulipristal acetate 5 mg and 10 mg/day with placebo [63] or with leuprolide acetate [64]. In all four trials, ulipristal acetate demonstrated its very efficient bleeding control with amenorrhea achieved in 62–100% in the Phase II trials (Table 1). The two Phase III clinical trials included only subjects with uterine fibroids and strong menstrual bleeding. Uterine bleeding strength was measured by a Pictorial Blood Loss Assessment Chart (PBAC), and a PBAC Score above 100 which is the threshold for menorrhagia was necessary for inclusion [65]. The primary endpoint of the two trials was a PBAC <75 which is considered as eumenorrhea in clinical trials. This endpoint was achieved in 90 and 91% of subjects who received 5 mg and in 92 and 98% of subjects who received 10 mg of ulipristal acetate, as compared to only 19% of subjects who received placebo (p < 0.001). Controlled bleeding was achieved for about 85% of subjects directly after the end of menstruation at treatment start. In this population, amenorrhea was achieved in 73–89% (p < 0.001). More than 50% of patients treated with ulipristal acetate 5 mg and about 80% of women treated with ulipristal acetate 10 mg entered directly in amenorrhea after the end of the first menstruation lasting up to the end of therapy. This rapid control of the formerly heavy menstrual bleeding was significantly more rapid than the bleeding control obtained with the GnRH agonist. All placebo-controlled trials with ulipristal acetate could demonstrate a statistically significant percent reduction of fibroid volume ranging from 17 to 36% measured by MRI. In the large placebo-controlled Phase III trial, fibroid volume reduction was a co-primary endpoint. Median changes of total fibroid volume from baseline to end of treatment were -21%, -12% and +3% for the 5 mg, 10 mg and placebo groups, respectively, showing statistical significance. Uterine volume was reduced by 12% for the 5 mg and 10 mg groups compared to an increase of 6% for placebo (p = 0.001 [5 mg]; p = 0.003 [10 mg]). The fibroid volume and uterine volume in the leuprolide acetate-controlled trial were measured by ultrasound. Fibroid volume demonstrated a median percent reduction of 36% and 42% and a median uterine volume reduction of 20 and 22% for the 5 and 10 mg groups, respectively. The bleeding control and reduction in fibroid size was accompanied by an improvement in quality of life. Of note, all ulipristal acetate clinical trials were performed in a randomized, double-blind design and were either placebo- or active-controlled. They included 600 subjects and consequently provided substantial evidence of the efficacy of ulipristal acetate in the treatment of uterine fibroids. In 2012, ulipristal acetate 5 mg received the approval from the European Commission for the pre-operative treatment of uterine fibroids.

### Tolerability profile of SPRMs

In the group of SPRMs, some molecules were stopped during their clinical development because of emerging adverse effects. Onapristone which was under development for breast cancer was stopped owing to an observed liver toxicity in treated patients in Phase II [66]. Telapristone acetate Phase III clinical trials were stopped because of the occurrence of suspected drug-induced liver toxicity at higher oral doses, however, currently lower vaginal doses are under clinical evaluation. It has been suggested that a side group on the steroid ring shared by onapristone and telapristone acetate might be the cause for the observed liver toxicity of the two drugs and explain its absence with other SPRMs [67]. With other SPRMs like mifepristone or ulipristal acetate, only mild and transient transaminase elevations have been observed and are probably due to an adaptation process during the metabolism of the drug, like the ones reported for other drugs, such as isoniazid and tacrine. To date, only mifepristone and ulipristal acetate have reached the market, only few safety data on the tolerability of other SPRMs are available. The available data indicate that generally the SPRM class seems to be well tolerated. In case of ulipristal acetate, most of the data which could be retrieved are the most common adverse events across clinical trials of 6 months duration or less and these are headache, fatigue, nausea and hot flashes. The occurrence of hot flashes was inconsistently reported with ulipristal acetate and varied importantly between the clinical trials [63,64]. However, hot flashes under SPRM treatment occurred less frequently than under GnRH agonist therapy. Estrogen concentrations under SPRM therapy are maintained at follicular levels ensuring no impact on bone mineral density and less frequent occurrence of hot flashes which is a competitive advantage over GnRH agonists as proven with ulipristal acetate [64].

The administration of an SPRM with anti-glucocorticoid activity, such as mifepristone, may lead to a dose-dependent increase in adrenocorticotropic hormone (ACTH) and cortisol. This has been reported for mifepristone 50 mg [68]. In the clinical trials with ulipristal acetate, no influence on ACTH or cortisol was observed.

With several SPRMs, histological endometrial changes were reported with daily low-dose SPRM treatment. These histological changes are described under the name of PAEC [50]. This condition is still to be considered as a novelty in endometrial histology and consequently subject to future investigation, especially as only very limited data on PAEC occurrence after longer than 6 months exposure to SPRMs are available. Because of histological similarities with hyperplasia but especially owing to the absence of any other possible naming in available classifications, formerly these endometrial changes were reported as simple hyperplasia [24]. PAEC are currently considered to be a benign feature of the endometrium which appears under...
non-physiological conditions. Table 1 provides data on appearance of histological changes under therapy with different SPRMs. For ulipristal acetate, the only SPRM currently approved for the pre-surgical treatment of uterine fibroids, these changes occur in about 60% of endometrial biopsies at the end of the treatment. However, in follow-up biopsies taken 6 months after the end of the treatment, these changes were shown to be reversible and comparable to control groups and to baseline occurrence. For mifepristone, after 9 months exposure a comparable frequency of PAEC could be observed [69].

In addition to the histological changes observed under treatment with SPRMs, several clinical studies with mifepristone and ulipristal acetate have reported a higher prevalence of subjects with a thickened endometrium under therapy. After three months of therapy, an endometrial thickness of >16 mm was reported to be present in about 10–15% in subjects under ulipristal acetate without any dose-dependence. This was compared to 2.1% of subjects on placebo. However, the mean endometrial thickness was not statistically significantly different to placebo. In the follow-up period it could be demonstrated that the thickening of the endometrium was reversible after the end of the treatment [63,64]. For mifepristone, after 3 months of therapy, a thickening of the endometrium of >8 mm was observed for 21.2 and 48.6% of subjects in the 5 and 10 mg group, respectively. The frequency of occurrence did not increase with prolonged treatment exposure up to 9 months (Table 1) [69].

A potential adverse effect on breast tissue is often questioned, however, current knowledge from non-clinical and clinical studies rather suggest that SPRMs, as being predominantly PR antagonists, may have a protective effect on the breast tissue. Mifepristone was given to BRCA1/p53-deficient mice in a placebo-controlled trial over a 60-day period. All control and untreated animals developed palpable tumors with a mean tumor latency of 6.6 months, whereas, in the mifepristone-treated animals no tumors were palpable at 12 months of age [70]. A publication on telapristone acetate reports results from a cancer prevention study and a non-clinical carcinogenicity study in rats. Telapristone acetate significantly suppressed Ki-67-positive cells in a dose-dependent manner. Telapristone acetate showed to be an efficacious inhibitor of benign, hyperplastic, premalignant and spontaneous tumors when provided chronically through inhibition of cell proliferation and induction of apoptosis [71]. One study explored xenografted human normal breast tissue samples in athymic mice and analyzed PR and glucocorticoid receptor reporter gene transactivation and their respective endogenous target genes under ulipristal acetate administration. Ulipristal acetate had no impact on the mitotic index on xenografted human breast tissue suggesting that ulipristal acetate treatment would not be deleterious to normal breast tissue [72]. One clinical double-blind, placebo-controlled study on premenopausal women, assessed the effect of mifepristone on premenopausal women, assessed the effect of mifepristone on premenopausal women, assessed the effect of mifepristone on premenopausal women, assessed the effect of mifepristone on premenopausal women, assessed the effect of mifepristone on premenopausal women, assessed the effect of mifepristone on premenopausal women, assessed the effect of mifepristone on premenopausal women, assessed the effect of mifepristone on premenopausal women, assessed the effect of mifepristone on premenopausal women, assessed the effect of mifepristone on premenopausal women, assessed the effect of mifepristone on premenopausal women, assessed the effect of mifepristone on premenopausal women, assessed the effect of mifepristone on premenopausal women, assessed the effect of mifepristone on premenopausal women, assessed the effect of mifepristone on premenopausal women, assessed the effect of 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Key issues

- Selective progesterone receptor modulators are becoming an interesting target for the medical treatment of uterine fibroids.
- Selective progesterone receptor modulators inhibit fibroid cell proliferation and induce apoptosis in fibroid cells.
- In clinical trials, selective progesterone receptor modulators were shown to provide an efficient bleeding control with frequent occurrence of amenorrhea due to anovulation and a suggested direct effect on the endometrium.
- Clinical studies with ulipristal acetate demonstrated that, despite a high rate of anovulation, endogenous estradiol concentrations remain at physiological levels under selective progesterone receptor modulator treatment which has a protective effect on bone mineral density and reduces the risk of occurrence of hot flushes.
- Under selective progesterone receptor modulator therapy, non-physiological appearances of the endometrium are observed, and these are named as Progesterone receptor modulator Associated Endometrial Changes (PAEC). It is judged as benign condition and is shown to be reversible.
- Ulipristal acetate received approval from the European Commission for the treatment of uterine fibroids prior to surgery for 3 months. Studies to evaluate extended use are currently ongoing.
- Tolerability data of ulipristal acetate indicate low occurrence of headache, fatigue, nausea and hot flushes, with hot flushes occurring significantly less frequently compared to gonadotropin-releasing hormone agonist therapy.

References

The potential of selective progesterone receptor modulators for the treatment of uterine fibroids


50 Mutter GL, Bergeron C, Deligdisch L et al. The spectrum of endometrial pathology induced by progesterone receptor


