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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 May 2014 (08.05.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/070517 A1

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

(21) **International Application Number**:
PCT/US2013/066095

(22) **International Filing Date**:
22 October 2013 (22.10.2013)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
61/722,095 2 November 2012 (02.11.2012) US

(71) **Applicant**: **REPROS THERAPEUTICS INC.** [US/US]; 2408 Timberloch Place, Suite B-7, The Woodlands, TX 77380 (US).

(72) **Inventors**: **PODOLSKI, Joseph, S.**; 3 Pebble Hollow Court, The Woodlands, TX 77381 (US). **WIEHLE, Ronald, D.**; 13903 Viewfield Court, Houston, TX 77059 (US).

(74) **Agents**: **CLOUGH, David, W.** et al.; Morgan, Lewis & Bockius LLP, Attention: Docketing Department, 1111 Pennsylvania Avenue, N.W., Washington, DC 20004 (US).

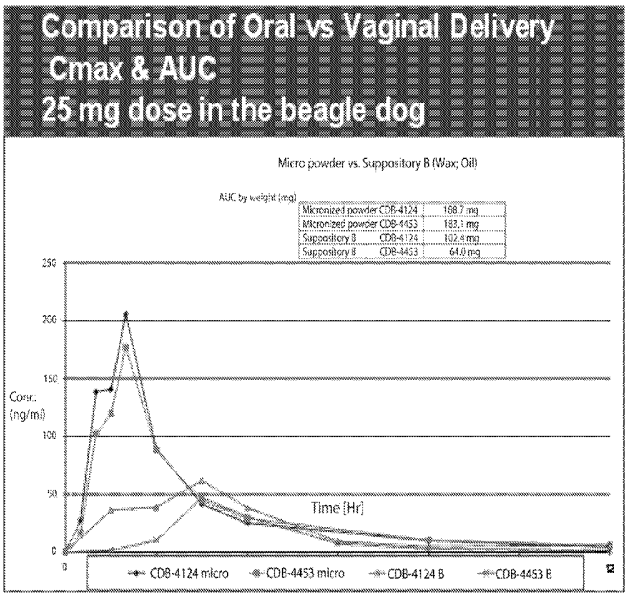
(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS,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

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

[Continued on next page]

(54) **Title**: METHODS AND COMPOSITIONS FOR TREATING PROGESTERONE-DEPENDENT CONDITIONS

Figure 1



(57) **Abstract**: The subject matter of the instant invention is pertinent to the field of treatment of hormone-dependent conditions. Methods for treating these conditions are provided comprising systemically administering an antiprogestin and contemporaneously locally administering an antiprogestin. Embodiments of the instant invention disclose methods for treating endometriosis, dysmenorrhea, breast cancer, uterine fibroids and endometrial hyperproliferation.

WO 2014/070517 A1

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *of inventorship (Rule 4.17(iv))*

Published:

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

METHODS AND COMPOSITIONS FOR TREATING PROGESTERONE-DEPENDENT CONDITIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[00001] This application claims the benefit of U.S. Provisional Application No. 61/722,095, filed November 2, 2012, the contents of which are incorporated herein by reference.

FIELD OF THE INVENTION

[00002] In several embodiments, the present invention relates to improved antiprogestin administration regimens for treating progesterone-dependent conditions comprising contemporaneous local and systemic administration of the antiprogestin.

BACKGROUND OF THE INVENTION

[00003] The effect of the steroid hormone progesterone on the reproductive system has been well-documented. For example, progesterone is vital to establishing and maintaining pregnancy and exerts actions on various tissues of the reproductive system. The action of progesterone on tissues outside the reproductive system has been reported but is less well characterized.

[00004] Antiprogestins, compounds which inhibit the action of progesterone, have considerable potential for use in the pharmacological regulation of fertility and a variety of conditions and diseases such as breast cancer and endometriosis. The first reported antiprogestin, mifepristone (RU 486), is one of a number of 19-nortestsosterone derivatives with strong affinity for both the progesterone and glucocorticoid receptors and with antiprogestational and antiglucocorticoid activity. A variety of antiprogestins based on the 19-norprogesterone backbone have also been synthesized.

[00005] Several drawbacks are associated with current antiprogestin administration regimes. If these and other limitations associated with antiprogestin treatment could be improved, a significant advance in the treatment of hormone-dependent disorders would result.

SUMMARY OF THE INVENTION

[00006] In several embodiments, the present invention provides methods for preventing or treating a hormone (i.e. estrogen and/or progesterone) dependent condition comprising systemically administering an antiprogestin to a patient in need of such treatment and contemporaneously administering an antiprogestin locally to the patient. In related embodiments, systemic administration occurs daily or every other day and local administration of the antiprogestin occurs by daily, periodic or intermittent dosing scheme. A preferred antiprogestin for use in the methods is CDB-4124 (21-methoxy-17α-acetoxy-11β-(4 N, N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione; telapristone). A preferred salt of CDB-4124 for use in the methods is the acetate salt (telapristone acetate).

[00007] In some embodiments, the antiprogestin is administered systemically by oral administration. In preferred embodiments, the present invention provides methods for treating or preventing a hormone dependent disorder comprising orally administering an antiprogestin and contemporaneously administering an antiprogestin locally to the patient wherein: the antiprogestin is orally administered for a period beginning during the luteal phase of the subject's menstrual cycle and ending at least one week after the menstrual phase of the subsequent cycle and the antiprogestin is locally administered for a period beginning less than one week after the menstrual phase of the subsequent cycle and continuing until the end of the treatment period. Oral administration of the antiprogestin preferably occurs by daily administration of a dose of from about 1 mg to about 25 mg, preferably from about 3 mg to about 12.5 mg.

[00008] In other embodiments, the antiprogestin is administered locally by administration to the vaginal mucosa or breast tissue. In preferred embodiments, the present invention provides methods for treating or preventing a hormone dependent disorder comprising orally administering an antiprogestin and contemporaneously administering an antiprogestin to the vaginal mucosa or breast tissue of the patient. Local administration preferably occurs by daily administration of a dose of from about 1 mg to about 25 mg, preferably from about 3 to about 20 mg, more preferably from about 3 mg to about 15 mg, more preferably at about 3, 6, or 12 mg. In some embodiments, the locally administered antiprogestin is in the form of a suppository, a gel, a cream, a transdermal patch or a bioadhesive carrier.

[00009] In a particularly preferred embodiment, the present invention provides a method for treating or preventing a hormone dependent disorder comprising orally administering an antiprogestin and contemporaneously administering an antiprogestin vaginally to the patient wherein: the antiprogestin is orally administered for a period beginning during the luteal phase of the subject's menstrual cycle and ending about 1-3 weeks after the menstrual phase of the subsequent cycle at a dose of from about 3 mg to about 25 mg per day and the antiprogestin is vaginally administered for a period beginning less than one week after the menstrual phase of the subsequent cycle and continuing until the end of the treatment period at a dosage of from about 3 mg to about 25 mg per day.

[00010] In several embodiments, the treatment period is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months, 2, 3, 4, or 5 years or any range there between.

[00011] Hormone-dependent conditions that may be treated by compositions of the invention include, without limitation, endometriosis and pain associated therewith, adenomyosis, endometriomas of the ovary, dysmenorrhea, endocrine hormone-dependent tumors, uterine fibroids, endometrial hyperproliferation, ovarian cancer, cervical cancer and breast cancer. Compositions of the instant invention may also be used to induce menses, to induce labor and for contraception.

BRIEF DESCRIPTION OF THE DRAWINGS.

[00012] Fig. 1 illustrates a comparison of the Cmax (peak serum concentration) and area under the curve (AUC) following oral and vaginal administration of CDB-4124 or CDB-4453 at a 25 mg dose in beagles.

[00013] Fig. 2 illustrates the actual Cmax observed for Proellex (CDB-4124) and its monodemethylated metabolite CDB-4453, following oral administration of CDB-4124 at 12.5 mg, 25 mg and 50 mg doses as well as the projected Cmax for 3 mg, 6 mg and 9 mg doses. Fig. 2 also illustrates the actual Cmax observed for Proellex (CDB-4124) and its monodemethylated metabolite CDB-4453, following vaginal administration of CDB-4124 at 12.5 mg, 25 mg and 50 mg doses.

[00014] Fig. 3 illustrates a comparison of the inhibition of progesterone-induced endometrial proliferation in estradiol-primed immature rabbits following subcutaneous injection and oral administration of CDB-4124.

[00015] Fig. 4 compares the antiprogestational effects of three doses of CDB-4124 when delivered orally versus when delivered to the vaginal mucosa of estradiol-primed immature rabbits in the presence of progesterone, as measured by a decrease in the McPhail index. Treatment with progesterone alone (vehicle control) provided a baseline measurement of progestational activity.

DETAILED DESCRIPTION OF THE INVENTION

[00016] While the present invention is capable of being embodied in various forms, the description below of several embodiments is made with the understanding that the present disclosure is to be considered as an exemplification of the invention, and is not intended to limit the invention to the specific embodiments illustrated. Headings are provided for convenience only and are not to be construed to limit the invention in any way. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

[00017] It is to be understood that any ranges, ratios and ranges of ratios that can be formed by any of the numbers or data present herein represent further embodiments of the present invention. This includes ranges that can be formed that do or do not include a finite upper and/or lower boundary. Accordingly, the skilled person will appreciate that many such ratios, ranges and ranges of ratios can be unambiguously derived form the data and numbers presented herein and all represent embodiments of the invention.

[00018] Before the present compounds, compositions and methods are disclosed and described, it is to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting. It must be noted that, as used in the present specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise.

[00019] Definitions

[00020] The term "oral" administration means that the active agent is in a formulation designed to be ingested, i.e. designed to be delivered to the gastrointestinal system for absorption.

[00021] The term "effective dosage" means an amount of the composition's active component sufficient to treat a particular condition.

[00022] The term "selective progesterone receptor modulators" means compounds that affect functions of progesterone receptor in a tissue-specific manner. The compounds act as progesterone receptor antagonists in some tissues (for example, in breast tissue) and as progesterone receptor agonists in other tissues (for example, in the uterus).

[00023] The term "treat" or "treatment" as used herein refers to any treatment of any hormone-dependent disorder or disease, and includes, but is not limited to, inhibiting the disorder or disease arresting the development of the disorder or disease; relieving the disorder or disease, for example, causing regression of the disorder or disease; or relieving the condition caused by the disease or disorder, relieving the symptoms of the disease or disorder.

[00024] The term "prevent" or "prevention," in relation to a hormone-dependent disorder or disease, means preventing the onset of disorder or disease development if none had occurred, or preventing further disorder or disease development if the disorder or disease was already present. For example, compositions of the present invention may be used to prevent the recurrence of tumors. Recurrence of tumors may occur because of residual microscopic groups or nests of tumor cells which subsequently expand into clinically detectable tumors.

[00025] The present invention provides methods for treating or preventing hormone-dependent conditions including without limitation, endometriosis and pain associated therewith, dysfunctional uterine bleeding, adenomyosis, endometriomas of the ovary, dysmenorrhea, endocrine hormone-dependent tumors, uterine fibroids, endometrial hyperproliferation, ovarian cancer, cervical cancer and breast cancer. The methods are particularly useful for treating endometriosis (and pain associated therewith), dysfunctional uterine bleeding and uterine fibroids.

[00026] In several embodiments, the present methods utilize one or more progesterone antagonists, defined herein as compounds that bind to a progesterone receptor and inhibit the effect of progesterone. Progesterone antagonists include so-called "pure" antiprogestins such as mifepristone, as well as selective progesterone receptor modulators (SPRMs) such as asoprisnil and CDB-4124 which may act as progesterone receptor agonists in certain tissues and progesterone receptor antagonists in others. The methods are particularly useful for long-term (chronic) administration of selective progesterone receptors.

[00027] Non-limiting examples of progesterone antagonists include the steroid compounds disclosed in U.S. Patent Nos. 6,861,415 and 6,900,193, the contents of which are incorporated herein by reference. In a preferred embodiment, the steroid compound is CDB-4124 (21-methoxy-17α-acetoxy-11β-(4 N, N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione; telapristone) or CDB-4453 (21-methoxy-17α-acetoxy-11β-(4-N-methylaminophenyl)-19-norpregna-4,9-diene-3,20-dione).

[00028] Other preferred progesterone antagonists for practicing the methods of the invention include, without limitation, Mifepristone (RU-486; 11β-[4 N,N-dimethylaminophenyl]-17β-hydroxy-17-(1-propynyl)-estra-4,9-dien-3-one), Lilopristone (11β-(4 N,N-dimethylaminophenyl)-17β-hydroxy-17-((Z)-3-hydroxypropenyl)estra-4,9-dien-3-one), Onapristone (11β-(4 N,N-dimethylaminophenyl)-17α-hydroxy-17-(3-hydroxypropyl)-13α-estra-4,9-dien-3-one), asoprisnil (benzaldehyde, 4-[(11β,17β)-17-methoxy-17-(methoxymethyl)-3-oxoestra-4,9-dien-11-yl]-1-(E)-oxim; J867), its metabolite J912 (4-[17β-Hydroxy-17α-(methoxymethyl)-3-oxoestra-4,9-dien-11β-yl]benzaldehyd-(1E)-oxim) and CDB-2914 (17α-acetoxy-11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-dien-3,20-dione).

[00029] Other antiprogestins include compounds described in U.S. Patent Nos.: 4,386,085, 4,447,424, 4,536,401, 4,519,946, 4,609,651, 4,634,695, 4,780,461, 4,814,327, 4,829,060, 4,871,724, 4,921,845, 4,921,845, 5,095,129, 5,446,178, 5,478,956, 5,232,915 5,089,488, 5,093,507, 5,244,886, 5,292,878, 5,439,913, 5,446,036, 5,576,310; 5,684,151, 5,688,808, 5,693,646, 5,693,647, 5,696,127, 5,696,130, 5,696,133 5,739,125, 5,407,928, 5,273,971, 5,728,689, 5,753,655, 5,843,933, 5,843,931, 6,509,334, 6,566,358, 6,713,478, 6,391,907, 6,417,214, 6,380,235, 6,339,098, 6,306,851, 6,441,019, 6,369,056, and 6,358,948, the contents of each of which are incorporated herein by reference.

[00030] Yet other antiprogestins useful in practicing the methods of the invention, include without limitation JNJ-1250132, (6α,11β,17β)-11-(4-dimethylaminophenyl)-6-methyl-4',5'-dihydrospiro[estra-4,9-diene-17,2'(3'H)-furan]-3-one (ORG-31710); (11β,17α)-11-(4-acetylphenyl)-17,23-epoxy-19,24-dinorchola-4,9,20-trien-3-one (ORG-33628); (7β,11β,17β)-11-(4-dimethylaminophenyl-7-methyl]-4',5'-dihydrospiro[estra-4,9-diene-17,2'(3'H)-furan]-3-one (ORG-31806); ZK-112993; ORG-31376; ORG-33245; ORG-31167; ORG-31343; RU-2992; RU-1479; RU-25056;

RU-49295; RU-46556; RU-26819; LG1127; LG120753; LG120830; LG1447; LG121046; CGP-19984A; RTI-3021-012; RTI-3021-022; RTI-3021-020; RWJ-25333; ZK-136796; ZK-114043; ZK-230211; ZK-136798; ZK-98229; ZK-98734; ZK-137316; 4-[17β-Methoxy-17α-(methoxymethyl)-3-oxoestra-4,9-dien-11β-yl]benzaldehyde-1-(E)-oxime; 4-[17β-Methoxy-17α-(methoxymethyl)-3-oxoestra-4,9-dien-11β-yl]benzaldehyde-1-(E)-[O-(ethylamino)carbonyl]oxime; 4-[17β-Methoxy-17α-(methoxymethyl)-3-oxoestra-4,9-dien-11β-yl]benzaldehyde-1-(E)-[O-(ethylthio)carbonyl]oxime; (Z)-6'-(4-cyanophenyl)-9,11α-dihydro-17β-hydroxy-17α-[4-(1-oxo-3-methylbutoxy)-1-butenyl]4'H-naphtho[3',2',1';10,9,11]estr-4-en-3-one; 11β-(4-acetylphenyl)-17β-hydroxy-17α-(1,1,2,2,2-pentafluoroethyl)estra-4,9-dien-3-one; 11beta-(4-Acetylphenyl)-19,24-dinor-17,23-epoxy-17alpha-chola-4,9,20-trien-3-one; (Z)-11beta,19-[4-(3-Pyridinyl)-o-phenylene]-17beta-hydroxy-17α-[3-hydroxy-1-propenyl]-4-androsten-3-one; 11beta-[4-(1-methylethenyl)phenyl]-17α-hydroxy-17beta-(3-hydroxypropyl)-13α-estra-4,9-dien-3-one; 4',5'-Dihydro-11beta-[4-(dimethylamino)phenyl]-6beta-methylspiro[estra-4,9-dien-17beta,2'(3'H)-furan]-3-one.

[00031] In some embodiments a single progesterone antagonist is administered systemically and the identical progesterone antagonist is locally administered. In a preferred embodiment, CDB-4124 is administered systemically, preferably by the oral route, and CDB-4124 is contemporaneously administered locally, preferably vaginally or transdermally to the breast. In other embodiments, a single progesterone antagonist is administered systemically and a different progesterone antagonist is locally administered.

[00032] Also useful with the methods of the invention are salts of progesterone antagonists. Depending on the process conditions the salt compound obtained may be either in neutral or salt form. Salt forms include hydrates and other solvates and also crystalline polymorphs. Both the free base and the salts of these end products may be used in accordance with the invention.

[00033] Acid addition salts may in a manner known per se be transformed into the free base using basic agents such as alkali or by ion exchange. The free base obtained may also form salts with organic or inorganic acids.

[00034] In the preparation of acid addition salts, preferably such acids are used which form suitably pharmaceutically acceptable salts. Examples of such acids are

hydrochloric acid, sulfuric acid, phosphoric acid, nitric acid, aliphatic acid, alicyclic carboxylic or sulfonic acids, such as formic acid, acetic acid, propionic acid, succinic acid, glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, glucuronic acid, fumaric acid, maleic acid, hydroxymaleic acid, pyruvic acid, aspartic acid, glutamic acid, p-hydroxybenzoic acid, embonic acid, ethanesulfonic acid, hydroxyethanesulfonic acid, phenylacetic acid, mandelic acid, alogenbensenesulfonic acid, toluenesulfonic acid, galactaric acid, galacturonic acid or naphthalenesulfonic acid. All crystalline form polymorphs may be used in accordance with the invention. A preferred salt is the acetate salt.

[00035] Base addition salts may also be used in accordance with the invention and may be prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in the conventional manner. Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkali earth metals or organic amines. Examples of metals used as cations are sodium, potassium, calcium, magnesium and the like. Examples of suitable amines are amino acids such as lysine, choline, diethanolamine, ethylenediamine, N-methylglucamine and the like.

[00036] Systemic and local administration of the progesterone antagonist may be independently accomplished by daily administration, periodic administration (i.e., administration at uniform intervals less frequent than daily such as every other day, weekly, bi-weekly or monthly) or intermittent administration by which it is meant that the progesterone antagonist is administered daily or periodically for an administration period then administration of the progesterone antagonist is discontinued for a period of time greater than the dosing interval during the previous administration period but less than the administration period, then the progesterone antagonist is administered daily or periodically for an administration period, then administration is discontinued and so on. For the treatment of endometriosis and pain associated therewith, adenomyosis, endometriomas of the ovary, dysmenorrhea, uterine fibroids, endometrial hyperproliferation, ovarian cancer, and cervical cancer, systemic administration is preferably accomplished by administering the progesterone antagonist daily or every other day, preferably orally.

[00037] For the treatment of endometriosis and pain associated therewith, adenomyosis, endometriomas of the ovary, dysmenorrhea, uterine fibroids,

endometrial hyperproliferation, ovarian cancer, and cervical cancer, a progesterone antagonist is administered orally for a period beginning during the luteal phase of the female's menstrual cycle and ending during the follicular, ovulatory or luteal phase of the subsequent cycle, preferably between 1 to 3 weeks after the menstrual phase of the subsequent cycle. In other embodiments, the progesterone antagonist is administered orally for a period beginning during the luteal phase of the female's menstrual cycle and continuing for about 3-5 weeks, preferably about 4 weeks, after which oral administration is discontinued. In related embodiments, a progesterone antagonist is contemporaneously administered vaginally for a period beginning during the menstrual phase or follicular phase of the subsequent cycle, preferably within one week after the menstrual phase of the subsequent cycle and ending when the desired therapeutic effect is achieved. In certain embodiments, the progesterone antagonist is administered vaginally for an administration period of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or more months and even for a period of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more years. In related embodiments, oral and vaginal administration each occurs by daily administration of a progesterone antagonist at dose of from 3 to 25 mg.

[00038] In a particularly preferred embodiment, CDB-4124 is administered daily at a dose of 3 mg to 25 mg to a female patient by the oral route for a period beginning on day 16 to 28 of a female's menstrual cycle and ending on day 11-25 of the subsequent cycle and CDB-4124 is contemporaneously administered vaginally beginning on day 1-10, preferably day 2-10, more preferably day 3-7 of the subsequent cycle and continuing until a desired therapeutic effect is achieved in order to treat endometriosis and pain associated therewith, adenomyosis, endometriomas of the ovary, dysmenorrhea, uterine fibroids, endometrial hyperproliferation, ovarian cancer, or cervical cancer. Preferably, no further oral administration of CDB-4124 occurs after day 11-25 of the subsequent cycle.

[00039] In another preferred embodiment, a method for treating breast cancer is provided comprising oral and contemporaneous transdermal administration of CDB-4124 to a breast tumor wherein oral and transdermal administration independently occur by daily administration, periodic administration or intermittent administration. In some embodiments, oral and transdermal administration occur by daily administration.

[00040] The contemporaneous systemic and local administration of antiprogestins provides several important advantages. Systemic administration of antiprogestins,

particularly by the oral route, subjects the drug to metabolism by gastrointestinal and hepatic enzymes which results in a significant reduction in the effective concentration of unmetabolized drug. This "first pass" effect results in a need to administer a correspondingly higher dose of the drug to achieve therapeutic effect – these higher doses can result in liver damage when the antiprogestin is administered chronically. Local administration, particularly vaginal administration, avoids first pass effects and consequently a lower dose can be administered directly to the site where the drug's effect is desired. However, the present inventors have discovered that, when progesterone antagonists are administered locally, e.g. vaginally, the onset of therapeutic benefit is delayed, apparently because an effective concentration of the drug is not immediately achieved. The methods of the present invention provide a solution to this problem by combining a relatively brief period of systemic (e.g. oral) administration of the progesterone antagonist (e.g. orally) beginning during the luteal phase of the female's menstrual cycle and contemporaneously initiating long term local (e.g.; vaginal) administration of the progesterone antagonist. Thus, following an initial menses at the beginning of the subsequent menstrual cycle which acts to refresh the endometrium and prevent subsequent adverse endometrial events, the therapeutic effect of the antiprogestin is expedited relative to when the antiprogestin is only administered locally.

[00041] Contemporaneous systemic and local administration of antiprogestins to treat hormally responsive breast cancer (i.e. the breast tumor contains estrogen and/or progesterone receptor) has advantages as well. The present inventors have discovered that oral administration of a relatively low dose (about 3-25 mg) of an SPRM, CDB-4124, is able to partially but not completely suppress ovulation through central effects on the hypothalamic pituitary axis (HPA) without the toxic liver effects that accompany chronic oral administration at higher doses; ovarian estrogens are lowered but not suppressed to the low levels typical of menopausal women. The present inventors have also discovered that CDB-4124 is surprisingly active when delivered locally (non-orally) despite achieving systemic levels only a very small fraction of an equivalent oral dose. Contemporaneous local and systemic administration therefore provides a surprisingly effective means of treating breast cancer that avoids toxic liver side effects and side effects that occur when serum estrogen levels are drastically reduced.

[00042] In some embodiments, local administration of the progesterone is intermittent such that the subject undergoes menses during at least two discontinuance periods. At least two, and preferably every discontinuance period is of sufficient length for the subject to experience menstruation. More preferably, the subject experiences menstruation during every discontinuance period. In a particularly preferred embodiment, local administration of the progesterone antagonist comprises daily administration to the vagina for an administration period of four months, followed by a discontinuance period during which the subject experiences menstruation, followed by another administration period of four months and so on.

[00043] Therapeutically effective doses of the antiprogestin when administered locally may be less than 50 mg/day, less than 40 mg/day, less than 30 mg/day less than 20 mg/day, less than 10 mg/day, less than 5mg/day, between 5mg/day and 50mg/day, between 5mg/day and 40mg/day, between 5mg/day and 30mg/day, between 5mg/day and 20mg/day, or between 5mg/day and 10mg/day. In another related embodiment, the effective amount of the compound when administered locally is less than the effective amount when administered systemically, for example, the effective amount when administered locally to the vaginal mucosa may be 2-fold, 3-fold, 4-fold 5-fold, 6-fold, 7-fold, 8-fold, 9-fold and even 10-fold less than the effective amount when administered systemically to treat endometriosis, uterine fibroids and other diseases located in that region.

[00044] In one embodiment of the invention, a progesterone receptor antagonist is administered to a female patient in need thereof according to the present methods in order to suppress endometrial proliferation. In a preferred embodiment, the progesterone receptor antagonist is a selective progesterone receptor modulator (SPRM), more preferably CDB-4124, at a systemic and local dose of from about 5 to about 25 mg.

[00045] In a related embodiment of the invention, a progesterone receptor antagonist is administered to a female patient in need thereof according to the present methods in order to treat endometriosis. In a preferred embodiment, the progesterone receptor antagonist is an SPRM, more preferably CDB-4124 at a systemic and local dose of from about 3 to about 25 mg.

[00046] In a related embodiment of the invention, a progesterone receptor antagonist is administered to a female patient in need thereof according to the present methods in order to treat dysmenorrhea. In a preferred embodiment, the progesterone

receptor antagonist is an SPRM, more preferably CDB-4124 at a systemic and local dose of from about 3 to about 25 mg.

[00047] In yet another embodiment of the invention, a progesterone receptor antagonist is administered to a female patient in need thereof according to the present methods in order to treat uterine fibroids. In a preferred embodiment, the progesterone receptor antagonist is an SPRM, more preferably CDB-4124 at a systemic and local dose of from about 3 to about 25 mg.

[00048] In yet another embodiment of the invention, a progesterone receptor antagonist is administered to a female patient in need thereof according to the present methods in order to treat dysfunctional uterine bleeding. In a preferred embodiment, the progesterone receptor antagonist is an SPRM, more preferably CDB-4124 at a systemic and local dose of from about 3 to about 25 mg

[00049] For local administration, the progesterone antagonist may be prepared in any formulation suitable for local administration. For example, the compound may be formulated, without limitation, as an intravaginal preparation such as a doughnut-shaped hormone-releasing vaginal ring; a vaginal suppository; a vaginal pill; an intra-uterine preparation such as an intrauterine device (IUD) or matrix preparation; an implantable drug delivery device; a topical gel; a cream, an ointment, a trans-dermal patch or in a bioadhesive carrier such as those described in U.S. Patent No. 4,615,697, which is incorporated herein by reference. The bioadhesive carrier may be in gel, cream, tablet, pill, capsule (e.g. pullulan capsule), suppository, or film form or any other pharmaceutically acceptable form that will adhere to the vaginal mucosa. Preferably the formulation comprises a unit dose of the progesterone antagonist of between 3 mg and 25 mg, or any range there between, such as 3 mg, 5 mg, 8 mg, 12 mg, 15 mg, 20 mg or 25 mg and one or more pharmaceutically acceptable carriers.

[00050] For systemic administration, the progesterone antagonist may be prepared in the form of a dose unit or dose units suitable for systemic administration. For example, the compound may be formulated in a solid dosage unit suitable for oral administration such as a tablet (*e.g.* standard hard tablets, suspension tablets, rapid dispersion tablets, chewable tablets, effervescent tablets, bilayer tablets, *etc.*), caplet, capsule (*e.g.*, a soft or a hard gelatin capsule), powder (*e.g.* a packaged powder, a dispensable powder or an effervescent powder), lozenge, sachet, cachet, troche, pellet granules, microgranules, encapsulated microgranules, or any other solid dosage form. Alternatively, the compound may be formulated in suitable liquid dosage forms such

as solutions, aqueous suspensions, elixirs, syrups, *etc.* Preferably the formulation comprises a unit dose of the progesterone antagonist of between 3 mg and 25 mg, or any range there between, such as 3 mg, 5 mg, 8 mg, 12 mg, 15 mg, 20 mg or 25 mg and one or more pharmaceutically acceptable carriers. The systemic administration dose should in any event be lower than the effective dose when administered systemically in the absence of contemporaneous local administration.

[00051] Compositions of the invention can, if desired, include one or more pharmaceutically acceptable excipients. The term "excipient" herein means any substance, not itself a therapeutic agent, used as a carrier or vehicle for delivery of a therapeutic agent to a subject or added to a pharmaceutical composition to improve its handling or storage properties or to permit or facilitate formation of a unit dose of the composition. Excipients include, by way of illustration and not limitation, diluents, disintegrants, binding agents, adhesives (e.g. bioadhesives), wetting agents, lubricants, glidants, surface modifying agents or surfactants, fragrances, suspending agents, emulsifying agents, nonaqueous vehicles, preservatives, antioxidants, adhesives, agents to adjust pH and osmolarity (*e.g.* buffering agents), preservatives, thickening agents, sweetening agents, flavoring agents, taste masking agents, colorants or dyes, penetration enhancers and substances added to improve appearance of the composition.

[00052] A therapeutically effective amount of the composition required for use in therapy varies with the length of time that activity is desired, and the age and the condition of the patient to be treated, among other factors, and is ultimately determined by the attendant physician. In general, however, doses employed for human treatment typically are in the range of about 0.001 mg/kg to about 500 mg/kg per day, for example about 1 μg/kg to about 1 mg/kg per day or about 1 μg/kg to about 100 μg/kg per day. For most large mammals, the total daily dosage is from about 1 to 100 mg, preferably from about 2 to 80 mg, more preferably from about 3 to about 25 mg. The dosage regimen may be adjusted to provide the optimal therapeutic response. The desired dose may be conveniently administered in a single dose, or as multiple doses administered at appropriate intervals, for example as two, three, four or more subdoses per day.

[00053] Patients undergoing treatments with the compositions of the instant invention should be monitored routinely for their serum estrogen and glucocorticoid levels.

[00054] The following non-limiting examples are provided to aid in understanding the teachings of the instant invention.

Example 1. Measuring *in vitro* binding affinities of Antiprogestins

[00055] Competitive binding assays are performed using cytosolic preparations.

[00056] For measuring binding to rabbit progesterone receptor (PR) and glucocorticoid receptor (GR), cytosol is prepared from uterus or thymus, respectively, of estradiol-primed immature rabbits. For binding to rabbit uterine PR, cytosol containing rabbit uterine PR is prepared in TEGMD buffer (10 mM Tris, pH 7.2, 1.5 mM EDTA, 0.2 mM sodium molybdate, 10% glycerol, 1 mM DTT) and incubated with 6 nM 1,2-[^{3}H]progesterone (NEN Life Science Products; 52 Ci/mmol); test compounds are added at concentrations from 2 to 100 nM. For binding to rabbit thymic GR, cytosol is prepared in TEGMD buffer and incubated with 6 nM 6,7-[^{3}H]dex (NEN; 35 or 40 Ci/mmol); test compounds are added at concentrations from 2 to 100 nM.

[00057] For measuring binding to human progesterone receptor-A (rhPR-A) or progesterone receptor-B (rhPR-B), cytosolic extracts from Sf9 insect cells infected with recombinant baculovirus expressing either hPR-A or hPR-B is prepared. Sf9 cytosol (prepared in TEGMD buffer containing the following protease inhibitors: bacitracin at 100 μg/ml, aprotinin at 2 μg/ml, leupeptin at 94 μg/ml, pepstatin A at 200 μg/ml) is incubated with 6.8 nM 1,2,6,7,16,17-[^{3}H]progesterone (NEN; 143 Ci/mmol); test compounds are added at concentrations from 1 to 100 nM.

[00058] After overnight incubation at 4 C, bound and unbound [^{3}H]-steroids are separated by addition of dextran-coated charcoal and centrifugation at 2100 x *g* for 15 minutes at 4 C. Supernatants from GR assays are decanted and counted in a Beckman LS-1800 liquid scintillation counter. Supernatants containing PR are pipetted into 24-well microplates and counted in a Packard TopCount liquid scintillation counter. Counts per minute (cpm) are entered into Packard's RIASmart™ for calculation of EC_{50}'s. Relative binding affinity for each test compound is calculated as follows:

(EC_{50} of standard)/(EC_{50} of competitor) x 100. The standard for the PR binding assays is P4 and the standard for the GR binding assays is dex.

Example 2. Measuring antiglucocorticoid activity and progesterone antagonist activity *in vivo*.

[00059] For measuring *in vivo* progesterone antagonist activity of test compounds, T47D-CO human breast cancer cells, grown in monolayer culture in phenol red-free DMEM supplemented with 10% fetal bovine serum (FBS), 10 U/ml penicillin G and 10 μg/ml streptomycin sulfate, are transfected with a suitable hormone sensitive reporter gene plasmid, for example PRE_2-tk-LUC, which contains two copies of a progestin/glucocorticoid/androgen response element upstream of the thymidine kinase (tk) promoter and the firefly luciferase (LUC) reporter gene. Transfected T47D-CO cells are incubated with a (predetermined) maximum stimulatory concentration of a progestogen, for example P_4, in the absence or presence of various concentrations of test compound for 20 hours. LUC activity is determined using Promega's Luciferase Assay System and the IC_{50} of the test compound is determined.

[00060] For measuring *in vivo* glucocorticoid antagonist activity, HepG2 human hepatoblastoma cells, grown in monolayer culture in phenol red-free MEMα supplemented with 10% FBS and pen/strep, are cotransfected with a suitable hormone sensitive reporter gene plasmid such as PRE_2-tk-LUC and a GR expression plasmid. Transfected HepG2 cells are incubated with a (predetermined) maximum stimulatory concentration of dexamethasone in the absence or presence of various concentrations of test compound for 20 hours. IC_{50} of the test compound is determined by measuring LUC activity.

Example 3. Chronic Daily Administration of CDB-4124 is Associated with Toxic Liver Effects.

[00061] Initial studies conducted with Proellex (aka CDB-4124) demonstrated efficacy of the drug at every dose tested. Development of Proellex has focused on the two highest doses tested, 25 mg and 50 mg based on data suggesting that higher doses suppressed endometrial thickening and the potential for breakthrough uterine bleeding. Neither animal preclinical studies nor small trials in women in Europe at the higher doses for periods of up to six months of exposure predicted the liver toxicity exhibited in the Phase III clinical studies conducted in a diverse population in the United States.

Proellex, delivered orally at a dose of 50 mg/day, exhibited severe liver toxicity in roughly 3-4% of the women receiving this dose. At 12.5 mg there were no adverse liver toxicity signals different from placebo. The maximum concentrations of CDB-4124 and its mono-demethylated metabolite (CDB-4453) for the 12.5 mg dose were 25% of the 50 mg dose. All liver toxicities resolved in those women that returned for safety follow-ups, including those subjects that developed liver-associated serious adverse effects (SAEs). The effects observed when Proellex was administered orally at 50 mg/day were significantly lower in frequency and intensity when Proellex was delivered at 25 mg/day. This observation was further amplified by the fact that longer durations of exposure have been safely achieved at a 25 mg/day dose than at a 50 mg/day dose suggesting that duration of exposure at lower doses does not necessarily result in the same liver toxicity than that observed at the 50 mg/day dose.

[00062] To date, over 600 patients, including women with confirmed cases of endometriosis or uterine fibroids, have participated in double blind and open label clinical trials in which patients were administered daily oral capsules containing doses of 12.5mg, 25mg or 50mg CDB-4124 (Proellex) for over one month. Of these patients, about 500 received Proellex and about 130 received a placebo. Of the patients receiving Proellex, about 190 received a dose of 50mg CDB-4124 per day, about 260 received a dose of 25mg CDB-4124 per day and about 55 received a dose of 12.5mg per day.

[00063] Liver enzymes were frequently monitored in participating subjects. The liver enzyme level at which the clinical trials would be discontinued was set at an increase in liver aminotransferases greater than, or equal to three times the Upper Limit of Normal ($\geq$ 3 x ULN).

[00064] During clinical trials, thirteen subjects were found to exhibit an increase in liver enzymes $\geq$ 3 x ULN, but this was confirmed by a repeat test in 48 hours in only nine subjects. Of the nine subjects with a confirmed increase in liver enzymes $\geq$ 3 x ULN, seven were severe enough elevations to be reported to the FDA as SAEs. One of these seven subjects had been receiving a dose of 25mg CDB-4124 per day; the remaining six subjects had been receiving a dose of 50mg CDB-4124 per day. Liver enzymes $\geq$ 3 x ULN persisted in five of the nine subjects with a confirmed increase in liver enzymes $\geq$ 3 x ULN. These five subjects had previously been dosed with the 50mg dose. One of these subjects is receiving oral medication for treatment of her liver condition. Clinical trials involving CDB-4124 at all doses were voluntarily

suspended as a result of these SAEs and were subsequently placed on clinical hold by the United States Food and Drug Administration for safety reasons.

[00065] Pharmacokinetic studies performed on participating subjects detected a high C_{max} and a T_{max} at 1-2 hours following administration. Large quantities of the monodemethylated metabolite of CDB-4124 were also detected, clearly indicating first pass metabolism of the antiprogestin. Providing further evidence of first pass metabolism, primary cultures of human and animal hepatocytes rapidly produce the mono-demethylated metabolite of CDB-4124. Metabolism of CDB-4124 by the liver provides the opportunity for liver damage and greatly reduces the concentration of the antiprogestin before it reaches the systemic circulation. Thus, alternative routes of administration of antiprogestins that avoid first pass metabolism such as, without limitation, intravenous, intramuscular, and sublingual, should allow antiprogestins to be absorbed directly into the systemic circulation and thereby provide a method for treating progestone-dependent conditions while avoiding liver toxicity. Administration routes which avoid first pass metabolism may also require less drug per dose to achieve the same therapeutic benefit relative to oral administration.

[00066] Pre-clinical studies were performed on rodents with breast tumors induced by 7,12-Dimethylbenz(a)anthracene (DMBA). These studies demonstrated efficacy of non-oral delivery methods of CDB-4124. In particular, CDB-4124 delivered by subcutaneous injection was effective in reducing the quantity and size of DMBA-induced breast tumors providing proof of concept.

Example 4. Vaginal Delivery of CDB-4124 and CDB-4453 Reduces Systemic Concentrations Compared to Oral Administration and Avoids First Pass Metabolism

[00067] Beagles were administered 25 mg of CDB-4124 or CDB-4453 (the monodemethylated metabolite of CDB-4124) formulated as either a micronized powder or a vaginal suppository. As illustrated at Figure 1, CDB-4124 and CDB-4453, when administered orally as a micronized powder, are rapidly metabolized after a peak plasma concentration (Cmax) is achieved. In contrast, when the same compounds are administered locally via vaginal suppository, the drugs are metabolized slowly and peak plasma concentrations (Cmax) are relatively low. Moreover, systemic exposure of the drug is much lower when administered locally (compare AUC for CDB-4124 and CDB-4453 when administered vaginally vs. orally).

[00068] The maximum circulating concentrations (Cmax) of CDB-4124 obtained following vaginal administration to beagles were extrapolated to humans for the 12.5mg, 25mg and 50 mg doses actually administered during the Phase III clinical studies. As can be seen from Fig. 2, the predicted Cmax for vaginal administration of the 12.5 mg dose of CDB-4124 in humans is approximately 6.5% of the same dose when administered orally and the predicted Cmax for vaginal administration of the 50 mg dose of CDB-4124 in humans is approximately 2% of the same dose when administered orally.

Example 5. Bioavailability of CDB-4124 at the Uterus is Surprisingly Low When Administered Orally

[00069] To determine whether the low circulating levels of CDB-4124 when administered locally could have any impact predictive of efficacy, an anti-Clauberg study was run in which immature estradiol-primed rabbits were coadministered progesterone and various doses of CDB-4124 by either subcutaneous or oral administration. At least 3 different highly trained individuals evaluated the rabbit uterus for glandular growth, for complexity and overall progesterone-induced "development". The inhibition (by percentage) of progesterone-induced endometrial proliferation at each dose was assayed. As illustrated at Figure 3, maximal inhibition was observed at a dose of less than 1 mg/kg when CDB-4124 was administered subcutaneously. However, maximal inhibition required a ~8-fold increase in dosage when administered orally (i.e. 8 mg/kg). Importantly 8 mg/kg corresponds closely to the 50mg/day dose of CDB-4124 administered to the female subjects described in Example 3. This demonstrates that the effective local concentration of CDB-4124 at the endometrium is greatly decreased when the drug is administered orally, most likely due to first-pass metabolism of the drug. Accordingly, in order to achieve therapeutic effect, e.g. for indications localized to the pelvic and reproductive tract, a relatively high dosage of CDB-4124 is required when administered orally, corresponding closely to the dosage of CDB-4124 at which toxic liver effects were observed in Example 3.

[00070] Another anti-Clauberg study was run in which immature estradiol-primed rabbits were administered progesterone alone (vehicle control) or were co-administered progesterone and three doses of CDB-4124 by either vaginal or oral administration. The inhibition of progesterone-induced endometrial proliferation at each dose was assayed. Fig. 3 illustrates the decrease in the McPhail index following

increasing doses of CDB-4124 administered by either route. Maximal inhibition (i.e. a decrease in the McPhail index to 1.5) occurred at 0.2 mg/kg CDB-4124 when administered vaginally, compared to 0.8 mg/kg when administered orally. The data from this study show that vaginal delivery of CDB-4124 exhibits four times the antiprogestational activity of the same oral dose.

[00071] Cumulatively, the data indicate that a four-fold lower dose of antiprogestin can be administered vaginally compared to the effective dose when orally administered, while attaining only a small fraction of the maximal circulating concentrations compared to oral administration, thereby avoiding liver toxicity. For example, equivalent antiprogestational activity at the uterus is observed for a 50 mg oral dose of CDB-4124 and a 12.5 mg vaginal dose; however, the Cmax observed with a 12.5 mg vaginal dose is only 2% that observed with a 50mg oral dose. The relatively high local concentration of the drug achieved by local administration allows a relatively low dose of the drug (compared with oral administration) to achieve therapeutic effect for indications localized to the pelvic and reproductive tract (e.g. endometriosis, uterine fibroids and ovarian cancer). Because a high concentration of the drug in the systemic circulation (and associated first pass metabolism of the drug) is not reached by local administration, avoidance of the severe liver toxicity observed in a small percentage of subjects following oral administration of CDB-4124 in previous Phase III clinical studies at doses of 25 and 50 mg is a surprising advantage of administering the drug locally. Similar advantages should inure to local administration of other antiprogestins.

Example 6. Vaginal Administration of CDB-4124 for the Treatment of Uterine Fibroids

[00072] Seven human females with uterine fibroids have completed 4 months of treatment as part of a single blind study. These females were vaginally administered a daily dose of 12 mg CDB-4124 for a period of four months, with dosing initiated during the luteal phase of the females' menstrual cycles. At the end of the four month treatment period, all seven females stopped menstruating and all reported a Pictural Blood Loss Assessment Chart (PBAC) score of 0 ($p=0.002$). A statistically significant and highly clinically meaningful reduction in Uterine Fibroid Symptom Quality of Life Survey (UFSQOL) scores was also observed. The mean UFSQOL score at baseline was 43.8 and at the end of the four month treatment period the mean score was 1.33

(p=0.001). Both bleeding and bulk related symptoms assessed by the UFSQOL were dramatically reduced with six of the seven females responding that they no longer experienced any fibroid related symptoms. As a reference, women with fibroids typically score 40 or higher, whereas women without fibroids report scores of approximately 20.

[00073] Change in fibroid volume at the end of the four month treatment period determined by magnetic resonance imagining (MRI) was assessed and a statistically significant (chi square analysis) median reduction of total fibroid volume of 36% was observed.

[00074] In an oral study, doses of 1, 3, 6, 9 and 12 mg of CDB-4124 were administered for a period of 10 weeks. In the oral study, all doses were well tolerated and reliable cessation of menses was induced at doses as low as 3 mg. Cessation of menses directly correlated to efficacy of an oral dose in both uterine fibroids and endometriosis. Pharmacokinetic analysis revealed that vaginal administration of 12 mg of CDB-4124 resulted in about 1/6th the systemic exposure of an equivalent oral dose based on area under the curve (AUC) and a maximum exposure (C_{max}) about 1/100th of a 50mg oral dose.

[00075] The concentration of CDB-4124 was observed to build slowly when the drug is vaginally administered relative to oral administration. Thus, the onset of amenorrhea is delayed when the drug is administered vaginally, necessitating that the drug be vaginally administered during subsequent menstruations, which tends to reduce absorption of the drug and is unpleasant and technically challenging for the patient. The methods of the present invention provide a solution to this problem by providing a brief period of oral administration, preceding and overlapping vaginal administration, which expedites the onset of amenorrhea while retaining the benefits of vaginal administration.

What is claimed is:

1. A method for treating a progesterone-dependent condition selected from the group consisting of endometriosis and pain associated therewith, adenomyosis, endometriomas of the ovary, dysmenorrhea, uterine fibroids, endometrial hyperproliferation, ovarian cancer, and cervical cancer in a female in need of such treatment comprising:

(a) orally administering a composition comprising a selective progesterone receptor modulator (SPRM) to the female for a period beginning on day 16 to 28 of a first menstrual cycle and ending on day 11-25 of a subsequent second menstrual cycle; and

(b) contemporaneously vaginally administering a composition comprising an SPRM to the female for period beginning on day 1-10 of the second menstrual cycle and continuing until a desired therapeutic effect is achieved.

2. The method of claim 1, wherein the orally administered and vaginally administered SPRMs are the same.

3. The method of claim 2 wherein the SPRM is CDB-4124.

4. The method of any of claims 1-3 wherein the SPRM is orally administered at a dose of from 3 mg to 30 mg.

5. The method of any of claims 1-4 wherein the SPRM is vaginally administered at a dose of from 3 mg to 30 mg.

6. The method of any of claims 1-5 wherein the orally administered composition is administered daily or every other day.

7. The method of any of claims 1-6 wherein the vaginally administered composition is administered daily or every other day.

8. The method of any of claims 1-7 wherein the orally administered composition is a tablet or capsule.

9. The method of any of claims 1-8 wherein the vaginally administered composition comprises a bioadhesive carrier.

10. The method of any of claims 1-9 wherein the SPRM is vaginally administered at a dose of 3, 6, 12 or 24 mg.

11. The method of claim 10 wherein the SPRM is vaginally administered at a dose of 12 mg.

12. The method of any of claims 1-11 wherein the SPRM is orally administered at a dose of 3, 6, 12, or 24 mg.

13. The method of any of claims 1-12 wherein the progesterone-dependent condition is uterine fibroids or endometriosis.

14. The method of any of claims 1-13 wherein the vaginal administration is intermittent.

15. The method of claim 14 wherein the composition is administered vaginally on a daily basis consecutively over a period of about four months followed by a discontinuation period of sufficient length to allow the female to menstruate by means of a continual lack of treatment, after which the composition is administered on a daily basis for period of about four months, followed by a discontinuation period of sufficient length to allow the female to menstruate, after which the composition is administered on a daily basis and repeating this pattern of administration and discontinuance of administration for as long as necessary to achieve treatment of the progesterone-related condition.

16. A method for preventing or treating breast cancer in a female in need of such treatment comprising:

(a) orally administering a composition comprising a selective progesterone receptor modulator (SPRM) to the female; and

(b) contemporaneously transdermally administering a composition comprising an SPRM to the female until a desired therapeutic effect is achieved.

17. The method of claim 16, wherein the orally administered and transdermally administered SPRMs are the same.

18. The method of claim 17 wherein the SPRM is CDB-4124.

19. The method of any of claims 16-18 wherein the SPRM is orally administered at a dose of from 3 mg to 30 mg such as 3, 6, 12 or 24 mg.

20. The method of any of claims 16-19 wherein the SPRM is transdermally administered at a dose of 3 mg to 30 mg.

21. The method of any of claims 16-20 wherein the transdermally administered composition is a transdermal patch.

22. The method of any of claims 16-21 wherein oral administration is co-extensive with transdermal administration.

23. The method of any of claims 16-22 wherein oral administration comprises daily administration.

24. The method of any of claims 16-23 wherein transdermal administration comprises daily administration.

Figure 1

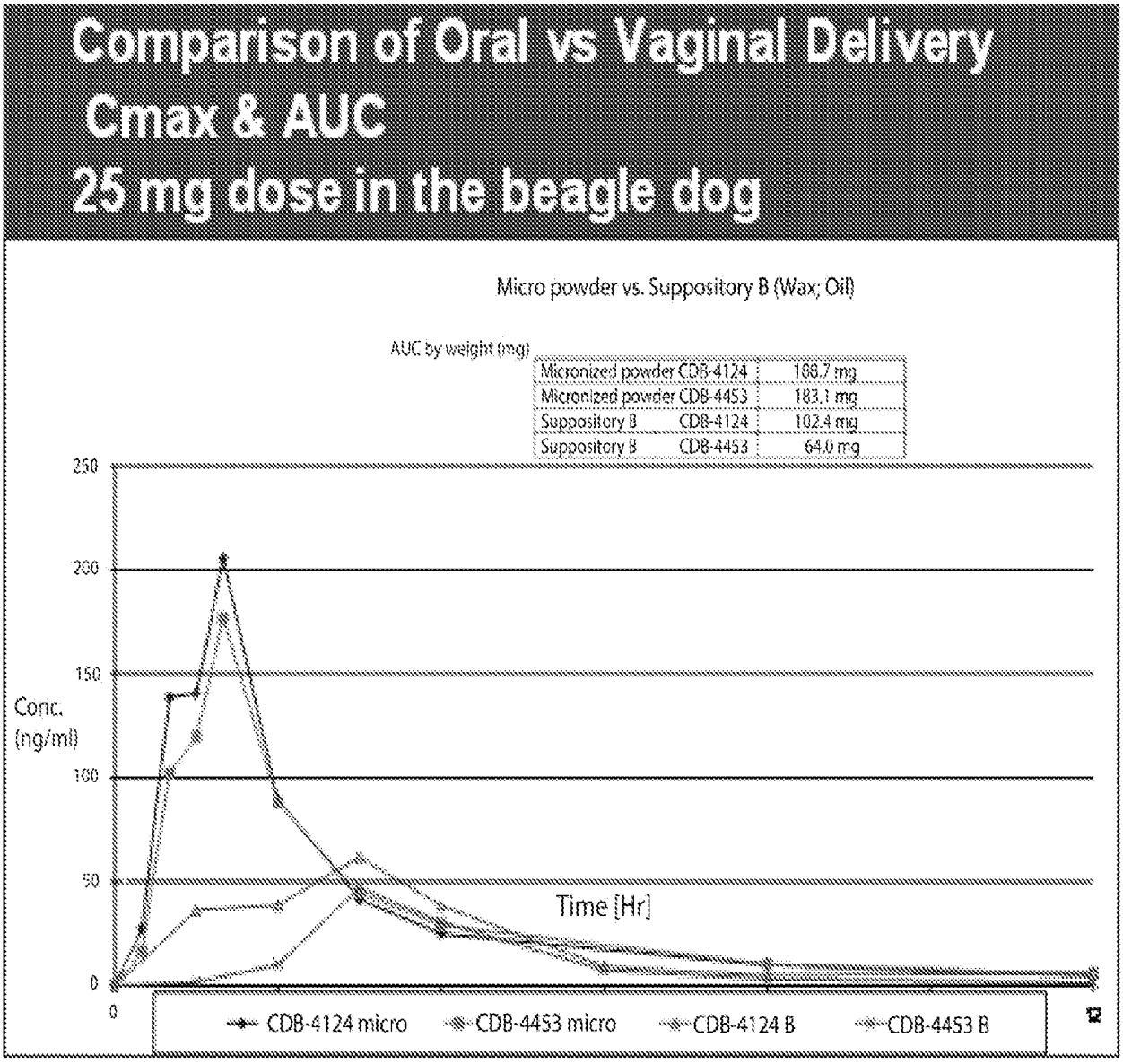

Comparison of Oral vs Vaginal Delivery
Cmax & AUC
25 mg dose in the beagle dog
Micro powder vs. Suppository B (Wax; Oil)
AUC by weight (mg)
Micronized powder CDB-4124 188.7 mg
Micronized powder CDB-4453 183.1 mg
Suppository B CDB-4124 102.4 mg
Suppository B CDB-4453 64.0 mg
250
200
150
100
50
0
Conc. (ng/ml)
Time [Hr]
0
CDB-4124 micro
CDB-4453 micro
CDB-4124 B
CDB-4453 B

Figure 2

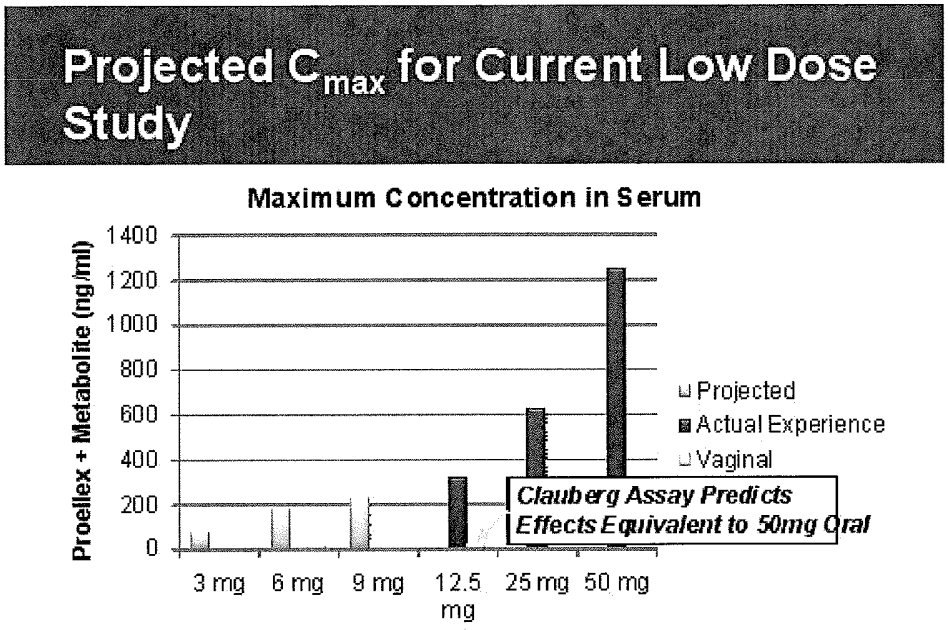

Projected C_{max} for Current Low Dose Study
Maximum Concentration in Serum
Proellex + Metabolite (ng/ml)
1400
1200
1000
800
600
400
200
0
3 mg
6 mg
9 mg
12.5 mg
25 mg
50 mg
Projected
Actual Experience
Vaginal
Clauberg Assay Predicts Effects Equivalent to 50mg Oral

Figure 3

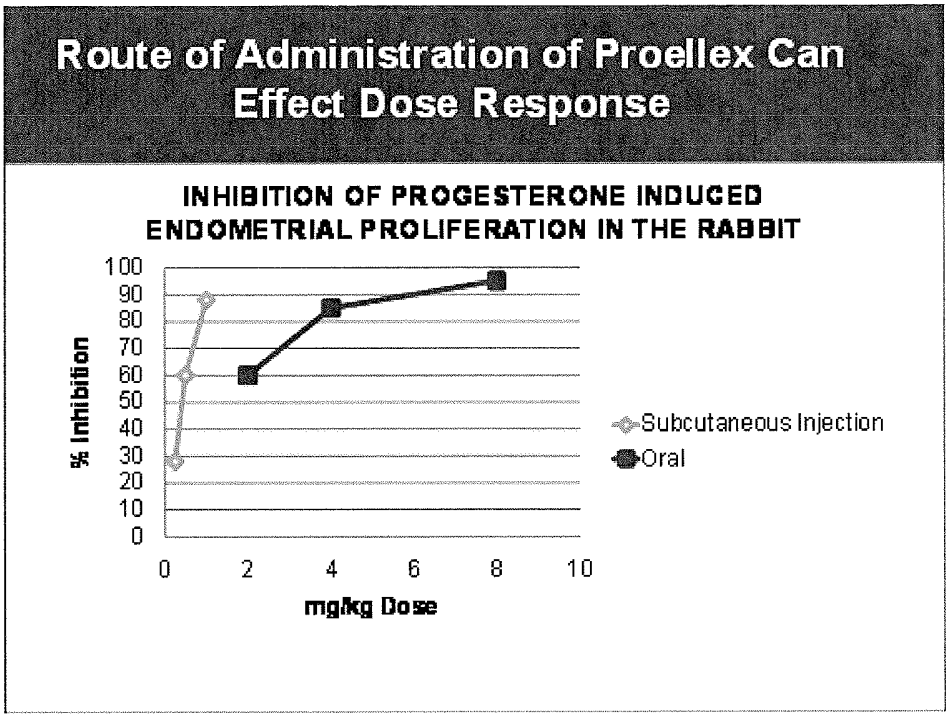
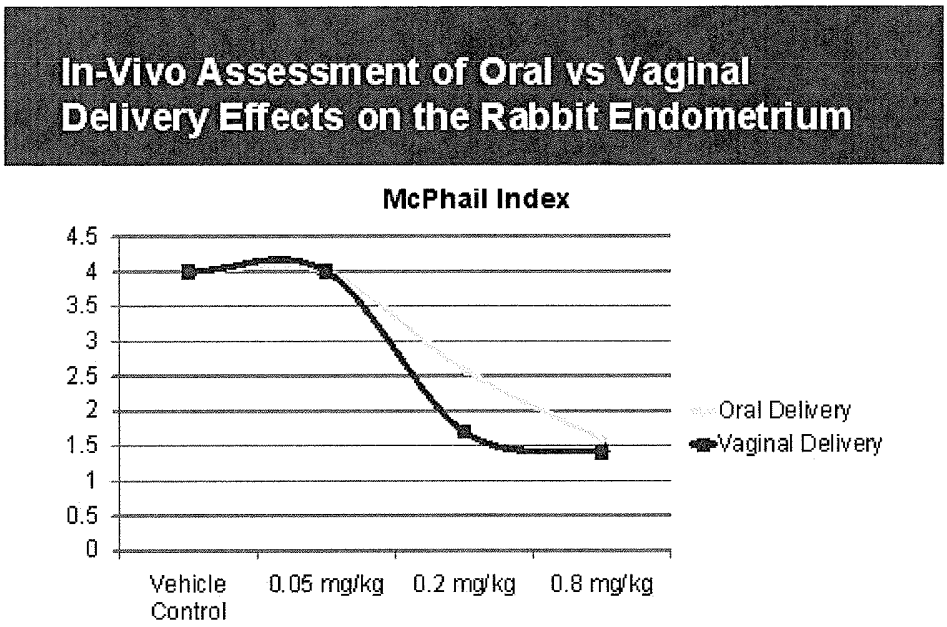

Route of Administration of Proellex Can Effect Dose Response
INHIBITION OF PROGESTERONE INDUCED ENDOMETRIAL PROLIFERATION IN THE RABBIT
% Inhibition
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
mg/kg Dose
Subcutaneous Injection
Oral

Figure 4


In-Vivo Assessment of Oral vs Vaginal Delivery Effects on the Rabbit Endometrium
McPhail Index
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Vehicle Control
0.05 mg/kg
0.2 mg/kg
0.8 mg/kg
Oral Delivery
Vaginal Delivery

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/066095

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/57 A61K45/06 A61P15/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS, FSTA, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2012/121767 A1 (ARSTAT INC [US]; RUBIN ARKADY [US]) 13 September 2012 (2012-09-13) claims 1,13, 20-22, 27	1-24
Y	US 2007/213306 A1 (HAUSKNECHT RICHARD [US]) 13 September 2007 (2007-09-13) claims 1,6	1-24
Y	US 2011/046098 A1 (PODOLSKI JOSEPH S [US]) 24 February 2011 (2011-02-24) claims 1,7 paragraphs [0031] - [0037] examples 10-12	1-24

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 November 2013	26/11/2013

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

1

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

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SPITZ IRVING M: "Clinical utility of progesterone receptor modulators and their effect on the endometrium", CURRENT OPINION IN OBSTETRICS AND GYNECOLOGY, RAPID SCIENCE PUBLISHERS, US, vol. 21, no. 4, August 2009 (2009-08), pages 318-324, XP009148241, ISSN: 1040-872X abstract page 319, column 2, paragraph 2 - page 321, column 1, paragraph 1 table 1	1-24
Y	R. WIEHLE ET AL: "CDB-4124, a Progesterone Receptor Modulator, Inhibits Mammary Carcinogenesis by Suppressing Cell Proliferation and Inducing Apoptosis", CANCER PREVENTION RESEARCH, vol. 4, no. 3, March 2011 (2011-03), pages 414-424, XP055088581, ISSN: 1940-6207, DOI: 10.1158/1940-6207.CAPR-10-0244 abstract	1-24
Y	WO 2012/087389 A1 (REPROS THERAPEUTICS INC [US]; PODOLSKI JOSEPH S [US]; WIEHLE RONALD D) 28 June 2012 (2012-06-28) paragraphs [0052] - [0071] examples 3-5	1-24
Y	SPITZ IRVING M: "Progesterone receptor antagonists", CURRENT OPINION IN INVESTIGATIONAL DRUGS, PHARMAPRESS, US, vol. 7, no. 10, October 2006 (2006-10), pages 882-890, XP009110067, ISSN: 1472-4472 abstract page 884, column 1, paragraph 5 - column 2, paragraph 1 figures 1,4	1-24
Y	PHILIPPE BOUCHARD ET AL: "Selective progesterone receptor modulators in reproductive medicine: pharmacology, clinical efficacy and safety", FERTILITY AND STERILITY, vol. 96, no. 5, November 2011 (2011-11), pages 1175-1189, XP055088587, ISSN: 0015-0282, DOI: 10.1016/j.fertnstert.2011.08.021 page 1176, column 2, paragraph 2 tables 1, 2 figure 2	1-24

-/--

1

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/066095

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BENAGIANO GIUSEPPE ET AL: "Selective progesterone receptor modulators 3: use in oncology, endocrinology and psychiatry", EXPERT OPINION ON PHARMACOTHERAPY, ASHLEY PUBLICATIONS LTD, LONDON, UK, vol. 9, no. 14, October 2008 (2008-10), pages 2487-2496, XP009110411, ISSN: 1465-6566, DOI: 10.1517/14656566.9.14.2487 abstract page 488, column 1, paragraph 4-5 -----	1-24
Y	C. LANARI ET AL: "Antiprogestins in breast cancer treatment: are we ready?", ENDOCRINE RELATED CANCER, vol. 19, no. 3, 20 February 2012 (2012-02-20), pages R35-R50, XP055088591, ISSN: 1351-0088, DOI: 10.1530/ERC-11-0378 page R37, column 2, paragraph 3 -----	1-24
Y	US 5 468 741 A (YEN SAMUEL S C [US]) 21 November 1995 (1995-11-21) claims 1, 5-10 -----	1-24

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2013/066095

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2012121767 A1	13-09-2012	NONE	
US 2007213306 A1	13-09-2007	US 2007213306 A1	13-09-2007
		US 2012115831 A1	10-05-2012
		WO 2007103510 A2	13-09-2007
US 2011046098 A1	24-02-2011	AR 071516 A1	23-06-2010
		AU 2009241355 A1	05-11-2009
		CA 2722753 A1	05-11-2009
		CN 102014923 A	13-04-2011
		EA 201071249 A1	30-08-2011
		EP 2293797 A1	16-03-2011
		JP 2011518845 A	30-06-2011
		KR 20110014162 A	10-02-2011
		KR 20130059442 A	05-06-2013
		NZ 589533 A	29-06-2012
		TW 200950786 A	16-12-2009
		US 2011046098 A1	24-02-2011
		US 2013289008 A1	31-10-2013
		WO 2009134718 A1	05-11-2009
WO 2012087389 A1	28-06-2012	AU 2011345341 A1	04-07-2013
		CA 2820877 A1	28-06-2012
		EP 2655394 A1	30-10-2013
		SG 191207 A1	31-07-2013
		WO 2012087389 A1	28-06-2012
US 5468741 A	21-11-1995	NONE	

(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 104755087 A
(43)申请公布日 2015.07.01

(21)申请号 201380057256.X
(22)申请日 2013.10.22
(30)优先权数据
61/722095 2012.11.02 US
(85)PCT国际申请进入国家阶段日
2015.04.30
(86)PCT国际申请的申请数据
PCT/US2013/066095 2013.10.22
(87)PCT国际申请的公布数据
WO2014/070517 EN 2014.05.08
(71)申请人 利普生物药剂公司
地址 美国德克萨斯州
(72)发明人 J.S. 波多尔斯基 R.D. 维勒
(74)专利代理机构 中国专利代理(香港)有限公司 72001
代理人 李慧惠 黄希贵
(51)Int.Cl.
A61K 31/57(2006.01)
A61K 45/06(2006.01)
A61P 15/00(2006.01)

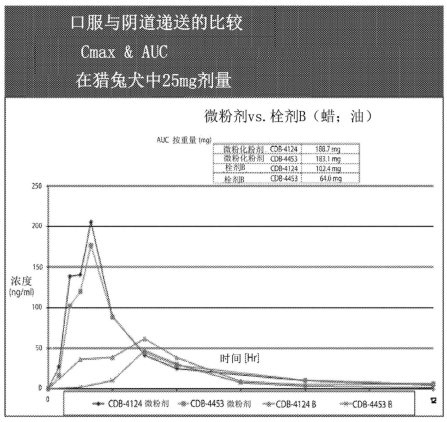
权利要求书2页 说明书11页 附图3页

(54)发明名称

治疗孕酮依赖性病况的方法和组合物

(57)摘要

本发明的主题涉及治疗激素依赖性病况的领域。提供了治疗这种病况的方法,包括全身施用抗孕素并且同时局部施用抗孕素。本发明的实施方式公开了治疗子宫内膜异位、痛经、乳腺癌、子宫肌瘤和子宫内膜增生的方法。



CN 104755087 A

1. 一种治疗在需要这种治疗的雌性中的孕酮依赖性病况的方法，所述病况选自子宫内膜异位和与之相关的疼痛、子宫腺肌病、卵巢的子宫内膜异位、痛经、子宫肌瘤、子宫内膜、过度增生、卵巢癌和宫颈癌，包括：

(a) 口服施用包括选择性孕酮受体调节剂 (SPRM) 的组合物至所述雌性，持续期间开始于第一月经周期的第 16-28 天并且终止于后面第二月经周期的第 11-25 天；和

(b) 同时阴道施用包括 SPRM 的组合物至所述雌性，持续期间开始于所述第二月经周期的第 1-10 天并且持续直到获得期望的治疗效果。

2. 根据权利要求 1 所述的方法，其中所述口服施用和阴道施用的 SPRM 相同。

3. 根据权利要求 2 所述的方法，其中所述 SPRM 是 CDB-4124。

4. 根据权利要求 1-3 任一项所述的方法，其中所述 SPRM 以 3mg 至 30mg 的剂量口服施用。

5. 根据权利要求 1-4 任一项所述的方法，其中所述 SPRM 以 3mg 至 30mg 的剂量阴道施用。

6. 根据权利要求 1-5 任一项所述的方法，其中所述口服施用的组合物是每天或每隔天施用。

7. 根据权利要求 1-6 任一项所述的方法，其中所述阴道施用的组合物是每天或每隔天施用。

8. 根据权利要求 1-7 任一项所述的方法，其中所述口服施用的组合物是片剂或胶囊。

9. 根据权利要求 1-8 任一项所述的方法，其中所述阴道施用的组合物包括生物粘性载体。

10. 根据权利要求 1-9 任一项所述的方法，其中所述 SPRM 以 3、6、12 或 24mg 的剂量阴道施用。

11. 根据权利要求 10 所述的方法，其中所述 SPRM 以 12mg 的剂量阴道施用。

12. 根据权利要求 1-11 任一项所述的方法，其中所述 SPRM 以 3、6、12 或 24mg 的剂量口服施用。

13. 根据权利要求 1-12 任一项所述的方法，其中所述孕酮依赖性病况是子宫肌瘤或子宫内膜异位。

14. 根据权利要求 1-13 任一项所述的方法，其中所述阴道施用是间歇性的。

15. 根据权利要求 14 所述的方法，其中所述组合物基于每天持续地阴道施用大约四个月的期间，然后是通过连续缺乏治疗中断足够长的期间以允许所述雌性月经，之后基于每天将所述组合物施用大约 4 个月的期间，然后中断足够长的期间以允许所述雌性月经，在之后基于每天施用所述组合物，并且重复这种模式的施用和中断施用，持续获得治疗所述孕酮相关病况所需的长时间。

16. 一种预防或治疗需要这种治疗的雌性中乳腺癌的方法，包括：

(a) 口服施用包括选择性孕酮受体调节剂 (SPRM) 的组合物至所述雌性；和

(b) 同时透皮施用包括 SPRM 的组合物至所述雌性，直到获得期望的治疗效果。

17. 根据权利要求 16 所述的方法，其中所述口服施用和透皮施用的 SPRM 相同。

18. 根据权利要求 17 所述的方法，其中所述 SPRM 是 CDB-4124。

19. 根据权利要求 16-18 任一项所述的方法，其中所述 SPRM 以 3mg 至 30mg 例如 3、6、

12 或 24mg 的剂量口服施用。

20. 根据权利要求 16-19 任一项所述的方法，其中所述 SPRM 以 3mg 至 30mg 的剂量透皮施用。

21. 根据权利要求 16-20 任一项所述的方法，其中所述透皮施用的组合物是透皮贴剂。

22. 根据权利要求 16-21 任一项所述的方法，其中所述口服施用与透皮施用是共同延长的。

23. 根据权利要求 16-22 任一项所述的方法，其中所述口服施用包括每天施用。

24. 根据权利要求 16-23 任一项所述的方法，其中透皮施用包括每天施用。

治疗孕酮依赖性病况的方法和组合物

[0001] 相关申请的交叉引用

[0002] 本申请要求2012年11月2日提交的美国临时申请61/722,095的权益，通过引用将其内容并入本文。

发明领域

[0003] 在几个实施方式中，本发明涉及用于治疗孕酮依赖性病况的改进的抗孕素施用方案，包括同时局部和全身施用抗孕素。

[0004] 发明背景

[0005] 类固醇激素孕酮对生殖系统的影响已经被很好地证明。例如，孕酮对于建立和维持怀孕至关重要，并且对生殖系统的各种组织发挥作用。孕酮对生殖系统外面组织的作用已经有报道，但是没有得到很好表征。

[0006] 抗孕素——抑制孕酮作用的化合物——用于药理学调节生育力以及各种病况和疾病例如乳腺癌和子宫内膜异位具有可观的潜力。第一个报道的抗孕素米非司酮(RU 486)是许多19-去甲睾酮衍生物中的一种，对孕酮和糖皮质激素受体都具有强亲合力，并且具有抗孕酮和抗糖皮质激素活性。也已经合成了多种基于19-去甲孕酮骨架的抗孕素。

[0007] 当前的抗孕素施用方案具有几个缺点。如果能够改善与抗孕素治疗相关的这些和其他局限，则会产生激素依赖性病症治疗的显著进步。

[0008] 发明概述

[0009] 在几个实施方式中，本发明提供预防或治疗激素（例如雌激素和/或孕酮）依赖性病况的方法，包括全身施用抗孕素到需要这种治疗的患者以及同时局部施用抗孕素到该患者。在相关实施方式中，全身施用每天或每隔天进行，并且局部施用抗孕素按每天周期性或间歇给药方案进行。在所述方法中使用的优选的抗孕素是CDB-4124(21-甲氧基-17α-乙酰氧基-11β-(4N,N-二甲基氨基苯基)-19-去甲孕-4,9-二烯-3,20-二酮；特拉司酮(telapristone))。用于所述方法的CDB-4124的优选的盐是醋酸盐（醋酸特拉司酮）。

[0010] 在一些实施方式中，通过口服施用，全身施用抗孕素。在优选的实施方式中，本发明提供治疗或预防激素依赖性病症的方法，包括口服施用抗孕素以及同时局部施用抗孕素到患者，其中：口服施用抗孕素的期间开始于对象的月经周期的黄体期并且终止于后一周期的月经期之后至少一周，以及局部施用抗孕素的期间开始于后一周期的月经期之后少于一周并且继续直到治疗期间结束。口服施用抗孕素优选地按每天施用大约1mg至大约25mg的剂量进行，优选地大约3mg至大约12.5mg。

[0011] 在其他实施方式中，通过施用至阴道粘膜或乳房组织，局部施用抗孕素。在优选的实施方式中，本发明提供治疗或预防激素依赖性病症的方法，包括口服施用抗孕素和同时施用抗孕素至患者的阴道粘膜或乳房组织。优选地，通过每天施用大约1mg至大约25mg的剂量进行局部施用，优选地大约3至大约20mg，更优选地大约3mg至大约15mg，更优选地大约3、6或12mg。在一些实施方式中，局部施用的抗孕素为栓剂、凝胶、乳霜、透皮贴剂或生物

粘合剂载体的形式。

[0012] 在特别优选的实施方式中，本发明提供用于治疗或预防激素依赖性病症的方法，包括口服施用抗孕素和同时阴道内施用抗孕素至患者，其中：口服施用抗孕素的期间开始于对象的月经周期的黄体期并且终止于后一周期的月经期之后大约 1-3 周，剂量为每天大约 3mg 至大约 25mg，以及阴道内施用抗孕素的期间开始于后一周期的月经期之后少于一周并且继续直到治疗期间结束，剂量为每天大约 3mg 至大约 25mg。

[0013] 在几个实施方式中，治疗期间是 1、2、3、4、5、6、7、8、9、10、11 或 12 个月，2、3、4 或 5 年，或者之间的任何范围。

[0014] 可以通过本发明组合物治疗的激素依赖性病况包括但不限于子宫内膜异位和与之相关的疼痛、子宫腺肌病、卵巢的子宫内膜异位、痛经、内分泌激素依赖性肿瘤、子宫肌瘤、子宫内膜增生、卵巢癌、宫颈癌和乳腺癌。本发明的组合物也可用于诱导月经、诱导分娩和用于避孕。

[0015] 附图简述

[0016] 图 1 图解了在小猎犬中以 25mg 剂量口服和阴道施用 CDB-4124 或 CDB-4453 之后 Cmax（血清浓度峰值）和曲线下方面积 (AUC) 的比较。

[0017] 图 2 图解了在以 12.5mg、25mg 和 50mg 剂量口服施用 CDB-4124 之后观察到的 Proellex(CDB-4124) 及其单去甲基化代谢物 CDB-4453 的实际 Cmax，以及对于 3mg、6mg 和 9mg 剂量设计的 (projected)Cmax。图 2 也图解了在以 12.5mg、25mg 和 50mg 剂量阴道施用 CDB-4124 之后观察到的 Proellex(CDB-4124) 及其单去甲基化代谢物 CDB-4453 的实际 Cmax。

[0018] 图 3 图解了在皮下注射和口服施用 CDB-4124 之后在喂足雌二醇的未成年兔中抑制孕酮诱导的子宫内膜增生的比较。

[0019] 图 4 比较了在孕酮存在下当口服递送时较之当递送至喂足雌二醇的未成年兔阴道内膜时的三种剂量 CDB-4124 的抗孕酮作用，通过 McPhail 指数的下降测量。只用孕酮治疗（载体对照）提供孕酮活性的基线测量。

[0020] 发明详述

[0021] 虽然本发明能够具体化为各种形式，但是下面几个实施方式的描述是基于下述理解做出：本公开应当视为本发明的示范而不旨在限制本发明为阐明的具体实施方式。提供标题仅仅是为了方便而绝不应当被解释为限制本发明。在任何标题下方阐明的实施方式可以与在任何其他标题下方阐明的实施方式结合。

[0022] 应当理解，可以由本文呈现的任何数字或数据形成的任何范围、比例以及比例范围代表本发明的进一步的实施方式。这包括可以形成的包括或不包括有限上边界和 / 或下边界的范围。因此，本领域技术人员将理解，许多这样的比例、范围和比例范围可以毫无疑义地从本文提供的数据和数字推出，并且都代表本发明的实施方式。

[0023] 在公开和描述本化合物、组合物和方法之前，应当理解，本文使用的术语仅用于描述具体实施方式的目的，并且不意欲是限制性的。必须注意，如本说明书和所附权利要求中使用的，单数形式“一个 (a)”、“一个 (an)”和“该 (the)”包括复数指代物，除非文中清楚地另外指明。

[0024] 定义

[0025] 术语“口服”施用是指活性剂为这样的制剂，其被设计用于咽下，即被设计用于递送至肠胃系统进行吸收。

[0026] 术语“有效剂量”指足以治疗具体病况的组合物活性组分的量。

[0027] 术语“选择性孕酮受体调节剂”指以组织特异性方式影响孕酮受体的功能的化合物。所述化合物在一些组织（例如乳房组织）中作为孕酮受体拮抗剂起作用，在其他组织（例如子宫）中作为孕酮受体激动剂。

[0028] 术语“治疗”如本文所用指的是任何激素依赖性病症或病况的任何治疗，包括但不限于抑制病症或疾病，阻止病症或疾病的发展；缓解病症或疾病，例如，引起病症或疾病的衰退；或者缓解疾病或病症造成的病况，缓解疾病或病症的症状。

[0029] 与激素依赖性病症或疾病相关，术语“预防”指如果什么都没有发生则预防病症或疾病发展的开始，或者如果病症或疾病已经存在，则预防进一步的病症或疾病发展。例如，本发明的组合物可用于预防肿瘤的复发。肿瘤的复发可以是因为残留的肿瘤细胞微小组或群后来扩散成为临床可检测肿瘤而复发。

[0030] 本发明提供治疗或预防激素依赖性病况的方法，包括但不限于，子宫内膜异位和与之相关的疼痛，功能失调性子宫出血，子宫腺肌病，卵巢的子宫内膜异位，痛经，内分泌激素依赖性肿瘤，子宫肌瘤，子宫内膜增生，卵巢癌，宫颈癌以及乳腺癌。所述方法尤其可用于治疗子宫内膜异位（和与之相关的疼痛）、功能失调性子宫出血和子宫肌瘤。

[0031] 在几个实施方式中，本方法利用一种或多种孕酮拮抗剂，其在本文中限定为与孕酮受体结合并抑制孕酮作用的化合物。孕酮拮抗剂包括所谓“纯”抗孕素，例如米非司酮，以及选择性孕酮受体调节剂(SPRM)，例如asoprisnil和CDB-4124，其在某些组织中作为孕酮受体激动剂起作用，在其他组织中作为孕酮受体拮抗剂起作用。所述方法尤其可用于长期（慢性）施用选择性孕酮受体。

[0032] 孕酮拮抗剂的非限制性实例包括在美国专利6,861,415和6,900,193中公开的类固醇化合物，通过引用将其内容并入本文。在优选的实施方式中，类固醇化合物是CDB-4124(21-甲氧基-17α-乙酰氧基-11β-(4N,N-二甲基氨基苯基)-19-去甲孕-4,9-二烯-3,20-二酮；特拉司酮）或CDB-4453(21-甲氧基-17α-乙酰氧基-11β-(4-N-甲基氨基苯基)-19-去甲孕-4,9-二烯-3,20-二酮）。

[0033] 用于实践本发明方法的其他优选的孕酮拮抗剂包括但不限于米非司酮(RU-486；11β-[4N,N-二甲基氨基苯基]-17β-羟基-17-(1-丙炔基)-雌-4,9-二烯-3-酮），利洛司酮(Lilopristone)(11β-(4N,N-二甲基氨基苯基)-17β-羟基-17-((Z)-3-羟基丙烯基）雌-4,9-二烯-3-酮），奥那司酮(Onapristone)(11β-(4N,N-二甲基氨基苯基)-17α-羟基-17-(3-羟基丙基)-13α-雌-4,9-二烯-3-酮），asoprisnil(苯甲醛，4-[(11β,17β)-17-甲氧基-17-(甲氧基甲基)-3-氧代雌-4,9-二烯-11-基-1-(E)-肟；J867)，其代谢物J912(4-[17β-羟基-17α-(甲氧基甲基)-3-氧代雌-4,9-二烯-11-基]苯甲醛-(1E)-肟）以及CDB-2914(17α-乙酰氧基-11β-(4-N,N-二甲基氨基苯基)-19-去甲孕-4,9-二烯-3,20-二酮）。

[0034] 其他抗孕素包括在下述中描述的化合物：美国专利：4,386,085、4,447,424、4,536,401、4,519,946、4,609,651、4,634,695、4,780,461、4,814,327、4,829,060、4,871,724、4,921,845、4,921,845、5,095,129、5,446,178、5,478,956、5,232,915、

5,089,488、5,093,507、5,244,886、5,292,878、5,439,913、5,446,036、5,576,310、5,684,151、5,688,808、5,693,646、5,693,647、5,696,127、5,696,130、5,696,133、5,739,125、5,407,928、5,273,971、5,728,689、5,753,655、5,843,933、5,843,931、6,509,334、6,566,358、6,713,478、6,391,907、6,417,214、6,380,235、6,339,098、6,306,851、6,441,019、6,369,056、和 6,358,948，通过引用将它们每一篇的内容并入本文。

[0035] 可用于实践本发明方法的还有其他抗孕素包括但不限于 JNJ-1250132，(6α，11β，17β)-11-(4- 二甲基氨基苯基)-6- 甲基 -4′，5′ - 二氢螺 [雌 -4,9- 二烯 -17，2′ (3′ H)- 呋喃]-3- 酮 (ORG-31710)；(11β，17α)-11-(4- 乙酰苯基)-17,23- 环氧 -19，24- 二降胆 -4,9,20- 三烯 -3- 酮 (ORG-33628)；(7β，11β，17β)-11-(4- 二甲基氨基苯基 -7- 甲基]-4′，5′ - 二氢螺 [雌 -4,9- 二烯 -17,2′ (3′ H)- 呋喃]-3- 酮 (ORG-31806)；Z-112993；ORG-31376；ORG-33245；ORG-31167；ORG-31343；RU-2992；RU-1479；RU-25056；RU-49295；RU-46556；RU-26819；LG1127；LG120753；LG120830；LG1447；LG121046；CGP-19984A；RTI-3021-012；RTI-3021-022；RTI-3021-020；RWJ-25333；Z-136796；ZK-114043；ZK-230211；ZK-136798；ZK-98229；ZK-98734；ZK-137316；4-[17β- 甲 氧基 -17α-(甲氧基甲基)-3- 氧代雌 -4,9- 二烯 -11- 基] 苯甲醛 -1-(E)- 肟；4-[17β- 甲氧基 -17α-(甲氧基甲基)-3- 氧代雌 -4,9- 二烯 -11β- 基] 苯甲醛 -1-(E)-[O-(乙基氨基) 羰基] 肟；4-[17β- 甲氧基 -17α-(甲氧基甲基)-3- 氧代雌 -4,9- 二烯 -11β- 基] 苯甲醛 -1-(E)-[O-(乙基硫代) 羰基] 肟；(Z)-6′ -(4- 氰基苯基)-9,11α- 二氢 -17β- 羟基 -17α-[4-(1- 氧代 -3- 甲基丁氧基)-1- 丁烯基]4′ H- 萘并 [3′，2′，1′ ;10,9,11] 雌 -4- 烯 -3- 酮；11β-(4- 乙酰苯基)-17β- 羟基 -17α-(1,1,2,2,2- 五氟乙基) 雌 -4,9- 二烯 -3- 酮；11β-(4- 乙酰苯基)-19,24- 二降 -17,23- 环氧 -17α- 胆 -4,9,20- 三烯 -3- 酮；(Z)-11β，19-[4-(3- 吡啶基)-o- 亚苯基]-17β- 羟基 -17α-[3- 羟基 -1- 丙烯基]-4- 雄烯 -3- 酮；11β-[4-(1- 甲基乙烯基) 苯基]-17α- 羟基 -17β-(3- 羟基丙基)-13- 雌 -4,9- 二烯 -3- 酮；4′，5′ - 二氢 -11β-[4-(二甲基氨基) 苯基]-6β- 甲基螺 [雌 -4,9- 二烯 -17β，2′ (3′ H)- 呋喃]-3- 酮。

[0036] 在一些实施方式中，全身施用单一孕酮拮抗剂，并且局部施用相同的孕酮拮抗剂。在优选的实施方式中，全身施用 CDB-4124，优选地通过口服途径，并且同时局部施用 CDB-4124，优选地通过阴道施用或者通过透皮地施用至乳房。在其他实施方式中，全身施用单一孕酮拮抗剂并且局部施用不同的孕酮拮抗剂。

[0037] 也可用于本发明方法的是孕酮拮抗剂的盐。取决于工艺条件，获得的盐化合物可以是中性形式或盐形式。盐形式包括水合物以及其他溶剂合物，也包括多晶形。游离碱以及这些最终产品的盐可以用于本发明。

[0038] 使用碱性试剂例如碱或通过离子交换，可以以本身已知的方式将酸加成盐转化为游离碱。获得的游离碱也可以用有机或无机酸形成盐。

[0039] 在制备酸加成盐中，优选地使用这样的酸，其合适地形成药学可接受的盐。这样的酸的实例是盐酸、硫酸、磷酸、硝酸、脂族酸、脂环羧酸或磺酸，例如甲酸、乙酸、丙酸、琥珀酸、乙醇酸、乳酸、苹果酸、酒石酸、柠檬酸、抗坏血酸、葡萄糖醛酸、富马酸、马来酸、羟基马来酸、丙酮酸、天冬氨酸、谷氨酸、对羟基苯甲酸、帕莫酸 (embonic acid)、乙磺酸、羟基乙磺酸、苯基乙酸、扁桃酸、卤代苯磺酸 (alogenbensenesulfonic acid)、甲苯磺酸、粘酸

(galactaric acid)、半乳糖醛酸或萘磺酸。所有的多晶形可用于本发明。优选的盐是乙酸盐。

[0040] 碱加成盐也可用于本发明，以及可通过以常规方式将游离酸形式与足够量的期望碱接触以产生盐进行制备。游离酸形式可通过以常规方式将盐形式与酸接触并且分离游离酸进行再生。药学可接受的碱加成盐用金属或胺形成，例如碱金属和碱土金属或有机胺。

[0041] 用作阳离子的金属的实例为钠、钾、钙、镁等。合适胺的实例是氨基酸如赖氨酸、胆碱、二乙醇胺、乙二胺、N- 甲基葡萄糖胺等。

[0042] 孕酮拮抗剂的全身和局部施用可以独立地通过每天施用、周期性施用（即以均匀的间隔施用，该间隔频率少于每天，例如每隔一天、每周、每两周或每月）或间歇施用完成，间歇施用是指孕酮拮抗剂每天或周期性施用，持续一定施用期间，然后孕酮拮抗剂的施用被中断一段时间，该段时间大于前一施用期间的给药间隔但是小于施用期间，然后孕酮拮抗剂每天或周期性施用一定施用期间，然后中断施用，等等。对于治疗子宫内膜异位和与之相关的疼痛、子宫腺肌病、卵巢的子宫内膜异位、痛经、子宫肌瘤、子宫内膜增生、卵巢癌和宫颈癌，全身施用优选地通过每天或每隔一天施用孕酮拮抗剂完成，优选口服。

[0043] 对于治疗子宫内膜异位和与之相关的疼痛、子宫腺肌病、卵巢的子宫内膜异位、痛经、子宫肌瘤、子宫内膜增生、卵巢癌和宫颈癌，孕酮拮抗剂口服施用的期间开始于雌性月经周期的黄体期期间，终止于后一周期的卵泡期、排卵期或黄体期期间，优选在后一周期的月经期之后 1-3 周。在其他实施方式中，孕酮拮抗剂口服施用的期间开始于雌性月经周期的黄体期，并且持续大约 3-5 周，优选大约 4 周，之后中断口服施用。在相关实施方式中，孕酮拮抗剂同时阴道施用的期间开始于后一周期的月经期或卵泡期期间，优选在后一周期的月经期之后一周，并且终止于获得期望的治疗效果时。在某些实施方式中，孕酮拮抗剂阴道施用的施用期间为至少 1、2、3、4、5、6、7、8、9、10、11、12 或更多个月，甚至该期间为至少 1、2、3、4、5、6、7、8、9、10 或更多年。在相关实施方式中，口服和阴道施用每一种通过每天以 3-25mg 剂量施用孕酮拮抗剂进行。

[0044] 在特别优选的实施方式中，CDB-4124 通过口服途径每天以 3mg-25mg 的剂量施用至雌性患者，期间开始于雌性月经周期的第 16-28 天，终止于后一周期的 11-25 天，并且同时阴道施用 CDB-4124 开始于后一周期的第 1-10 天，优选第 2-10 天，更优选第 3-7 天，并且持续直到获得期望的治疗效果，以治疗子宫内膜异位和与之相关的疼痛、子宫腺肌病、卵巢的子宫内膜异位、痛经、子宫肌瘤、子宫内膜增生、卵巢癌或宫颈癌。优选地，在后一周期的第 11-25 天之后不再进行 CDB-4124 的进一步口服施用。

[0045] 在另一优选实施方式中，提供治疗乳腺癌的方法，包括口服以及同时透皮施用 CDB-4124 至乳房肿瘤，其中口服和透皮施用独立地通过每天施用、周期性施用或间歇施用进行。在一些实施方式中，口服和透皮施用通过每天施用进行。

[0046] 同时全身和局部施用抗孕素提供了数个重要的优点。全身施用抗孕素，特别是通过口服途径，使得药物被肠胃和肝的酶代谢，导致未代谢药物有效浓度显著减小。这种“首过 (first pass)”效应导致需要施用相应地较高剂量的药物以获得治疗效果，当长期施用抗孕素时这些较高剂量可能导致肝脏损害。局部施用，特别是阴道施用，避免了首过效应，并且因此可以将较低剂量直接施用至期望药物作用的部位。然而，本发明人已经发现，当局部施用孕酮拮抗剂时，例如通过阴道，延迟了治疗益处的开始，这显然是因为没有立即获得

有效浓度的药物。本发明方法提供了这个问题的解决方案，其是通过结合相对短期间的全身（例如口服）施用孕酮拮抗剂（例如口服）——其开始于雌性月经周期的黄体期期间和同时启动长期的局部（例如阴道）施用孕酮拮抗剂。因此，在后一月经周期开始时的初始月经期——其作用是恢复子宫内膜和阻止后面的不利子宫内膜事件——之后，相对于仅局部施用抗孕素时，抗孕素的治疗作用得到加速。

[0047] 同时全身和局部施用抗孕素以治疗正常应答性乳腺癌（即包含雌激素和/或孕酮受体的乳房肿瘤）也具有优势。本发明人已经发现，口服施用相对低剂量（大约 3-25mg）的 SPRM CDB-4124 能够部分但不是完全抑制排卵，其是通过对下丘脑垂体轴 (HPA) 的中枢作用，而没有伴随较高剂量长期口服施用的肝脏毒性作用；卵巢雌激素降低但没有被抑制到绝经期妇女典型的低水平。本发明人也已经发现，当局部递送（非口服）时 CDB-4124 出乎意料地有活性，尽管获得全身水平仅非常少部分的同等口服剂量。因此，同时局部和全身施用提供了出乎意料的治疗乳腺癌的有效方法，其避免了对肝脏的毒性副作用以及在血清雌激素水平急剧降低时发生的副作用。

[0048] 在一些实施方式中，局部施用孕酮是间歇性的，以便对象在至少两个中断期间经历月经期。至少两个并且优选地每个中断期间具有足够长度以便对象经历月经。更优选地，对象在每个中断期间经历月经。在特别优选的实施方式中，局部施用孕酮拮抗剂包括每天施用至阴道，持续四个月的施用期间，然后是中断期间，在此期间对象经历月经，然后是另一个四个月的施用期间，等等。

[0049] 在局部施用时抗孕素的治疗有效剂量可以是小于 50mg/ 天、小于 40mg/ 天、小于 30mg/ 天、小于 20mg/ 天、小于 10mg/ 天、小于 5mg/ 天、5mg/ 天 -50mg/ 天、5mg/ 天 -40mg/ 天、5mg/ 天 -30mg/ 天、5mg/ 天 -20mg/ 天、或 5mg/ 天 -10mg/ 天。在另一相关实施方式中，当局部施用时化合物的有效量小于全身施用时的有效量，例如，局部施用至阴道粘膜时的有效量可以是小于全身施用时有效量的 2 倍、3 倍、4 倍、5 倍、6 倍、7 倍、8 倍、9 倍和甚至 10 倍，以治疗子宫内膜异位、子宫肌瘤以及其他位于该区域的疾病。

[0050] 在本发明的一个实施方式中，孕酮受体拮抗剂被根据本方法施用至有需要的雌性患者，以抑制子宫内膜增生。在优选的实施方式中，孕酮受体拮抗剂是选择性孕酮受体调节剂 (SPRM)，更优选 CDB-4124，其全身和局部剂量为大约 5 至大约 25mg。

[0051] 在本发明的相关实施方式中，孕酮受体拮抗剂被根据本发明施用至有需要的雌性患者，以治疗子宫内膜异位。在优选的实施方式中，孕酮受体拮抗剂是 SPRM，更优选地 CDB-4124，其全身和局部剂量是大约 3 至大约 25mg。

[0052] 在本发明的相关实施方式中，孕酮受体拮抗剂被根据本发明施用至有需要的雌性患者，以治疗痛经。在优选的实施方式中，孕酮受体拮抗剂是 SPRM，更优选地 CDB-4124，其全身和局部剂量是大约 3 至大约 25mg。

[0053] 在本发明的又一实施方式中，孕酮受体拮抗剂被根据本发明施用至有需要的雌性患者，以治疗子宫肌瘤。在优选的实施方式中，孕酮受体拮抗剂是 SPRM，更优选地 CDB-4124，其全身和局部剂量是大约 3 至大约 25mg。

[0054] 在本发明的又一实施方式中，孕酮受体拮抗剂被根据本发明施用至有需要的雌性患者，以治疗功能失调性子宫出血。在优选的实施方式中，孕酮受体拮抗剂是 SPRM，更优选地 CDB-4124，其全身和局部剂量是大约 3 至大约 25mg。

[0055] 对于局部施用，孕酮拮抗剂可以被制备为适于局部施用的任何制剂。例如，非限制地，可以将化合物配制为阴道内制剂，例如圆环形激素释放阴道环；阴道栓剂；阴道药丸；子宫内制剂，例如子宫内器械（IUD），或基质制剂；可植入药物递送器械；局部凝胶；乳霜，药膏，透皮贴剂，或者在生物粘性载体中，例如美国专利 4,615,697 中公开的那些，通过引用将其并入本文。生物粘性载体可以是凝胶、乳霜、片剂、丸剂、胶囊（例如普鲁兰胶囊）、栓剂或膜形式或者任何其他药学可接受的将粘附于阴道粘膜的形式。优选地，制剂包括 3mg-25mg 的单位剂量的孕酮拮抗剂，或之间的任何其他范围，例如 3mg、5mg、8mg、12mg、15mg、20mg 或 25mg，以及一种或多种药学上可接受的载体。

[0056] 对于全身施用，孕酮拮抗剂可以制备为适于全身施用的剂量单位或多个剂量单位的形式。例如，化合物可以被配制为适于口服施用的固体剂量单位，例如片剂（例如标准硬片、悬浮片（suspension tablet）、快速分散片、可咀嚼片、泡腾片、双层片等）、囊片、胶囊（例如软或硬凝胶胶囊）、粉剂（例如封装的粉剂、可分散的粉剂或泡腾粉剂）、锭剂、小袋、扁胶剂、药片、丸粒、微胶囊、封装的微胶囊或其他任何固体剂型。可选地，化合物可被配制为合适的液体剂型，例如溶液、水性悬液、酏剂、糖浆等。优选地，制剂包括 3mg-25mg 的单位剂量的孕酮拮抗剂，或之间的任何其他范围，例如 3mg、5mg、8mg、12mg、15mg、20mg 或 25mg，以及一种或多种药学上可接受的载体。在任何情况下，全身施用剂量应当低于在不存在同时局部施用的情况下全身施用时的有效剂量。

[0057] 如果期望，本发明组合物可以包括一种或多种药学上可接受的赋形剂。术语“赋形剂”在此指任何这样的物质，其本身不是治疗剂，被用作递送治疗剂至对象的载体或运载体，或者被添加至药物组合物以改善其处理或储存性能或者以允许或促进组合物单位剂量的形成。说明性并且非限制性地，赋形剂包括稀释剂、崩解剂、粘结剂、粘合剂（例如生物粘合剂）、润湿剂、润滑剂、增滑剂、表面改性剂或表面活性剂、香料、悬浮剂、乳化剂、非水性运载体、防腐剂、抗氧化剂、粘合剂、pH 和渗透压调节剂（例如缓冲剂）、防腐剂、增稠剂、增甜剂、增香剂、味道掩蔽剂、着色剂或染料、渗透增强剂以及加入来改进组合物外观的物质。

[0058] 用于治疗所需的组合物的治疗有效量随着期望活性的时间长度和要治疗患者的年龄和病况等因素变化，并且最终由主治医生确定。然而，一般地，用于人治疗的剂量通常在下述范围：每天大约 0.001mg/kg 至大约 500mg/kg，例如每天大约 1μg/kg 至大约 1mg/kg 或每天大约 1μg/kg 至大约 100μg/kg。对于最大型哺乳动物，总每天剂量是大约 1 至 100mg，优选地大约 2 至 80mg，更优选地大约 3 至大约 25mg。可以调整剂量方案以提供最佳治疗反应。可以方便地以单剂量施用期望的剂量，或者作为多剂量以合适的间隔施用，例如作为每天施用两个、三个、四个或更多个子剂量。

[0059] 应当常规地监测用本发明组合物进行治疗的患者的血清雌激素和糖皮质激素水平。

[0060] 提供下面的非限制性实施例以帮助理解本发明的教导。

[0061] 实施例 1 测量抗孕素的体内结合亲和性

[0062] 使用胞质制剂进行竞争性结合试验

[0063] 为了测量与兔孕酮受体（PR）和糖皮质激素受体（GR）的结合，分别地从喂足雌二醇的未成年兔的子宫或胸腺制备胞质溶胶（cytosol）。为了结合兔子宫 PR，在 TEGMD 缓冲液（10mM Tris，pH 7.2，1.5mM EDTA，0.2mM 钼酸钠，10％甘油，1mM DTT）中制备含有兔子宫

PR 的胞质溶胶并且用 6nM 1,2-[^{3}H] 孕酮 (NEN Life Science Products ;52Ci/mmol) 温育 ;以 2-100nM 的浓度加入测试化合物。为了结合兔胸腺 GR,在 TEGMD 缓冲液中制备胞质溶胶并且用 6nM 6,7-[^{3}H]dex(NEN ;35 或 40Ci/mmol) 温育 ;以 2-100nM 的浓度加入测试化合物。

[0064] 为了测量与人孕酮受体 -A(rhPR-A) 或孕酮受体 -B(rhPR-B) 的结合,制备 Sf9 昆虫细胞的胞质提取物,其用表达 hPR-A 或 hPR-B 的重组杆状病毒感染。Sf9 胞质溶胶 (在含有下面的蛋白酶抑制剂的 TEGMD 缓冲液中制备 :100 μ g/ml 杆菌肽,2 μ g/ml 抑肽酶,94 μ g/ml 亮抑酶肽,200 μ g/ml 抑肽素 A) 用 6.8nM 1,2,6,7,16,17-[^{3}H] 孕酮 (NEN ;143Ci/mmol) 温育 ;以 1-100nM 的浓度加入测试化合物。

[0065] 在 4℃过夜温育后,通过在 4℃加入葡聚糖包衣的炭并且以 2100x g 离心 15 分钟,分离结合的和未结合的 [^{3}H]- 类固醇。倾倒出 GR 试验的上清液,并且在 Beckman LS-1800 液体闪烁计数器中计数。将含有 PR 的上清液移液到 24 孔微量板中,并且在 Packard TopCount 液体闪烁计数器中计数。将每分钟计数 (cpm) 输入 Packard′ s RIASmart™,以计算 EC_{50}。如下计算每种测试化合物的相对结合亲和性 :(标样的 EC_{50})/(竞争样的 EC_{50})x 100。PR 结合试验的标样是 P4,GR 结合试验的标样是 dex。

[0066] 实施例 2 测量体内抗糖皮质激素活性和孕酮拮抗剂活性

[0067] 为测量测试化合物的体内孕酮拮抗剂活性,用合适的激素敏感报道基因质粒例如 PRE_2-tk-LUC 转染 T47D-CO 人乳腺癌细胞,该细胞生长在补充有 10％胎牛血清 (FBS)、10U/ml 青霉素 G 和 10 μ g/ml 硫酸链霉素的无苯酚红 DMEM 中的单层培养基中,所述合适的激素敏感报道基因质粒在胸苷激酶 (tk) 启动子和荧火虫荧光素酶 (LUC) 报道基因的上游包含两个拷贝的孕激素 / 糖皮质激素 / 雄激素应答元件。在存在或不存在各种浓度测试化合物的情况下,转染的 T47D-CO 细胞用 (预先确定的) 最大刺激浓度的孕激素例如 P4 温育 20 小时。使用 Promega′ s Luciferase Assay System 测定 LUC 活性,并且测定测试化合物的 IC_{50}。

[0068] 为测量体内糖皮质激素拮抗剂活性,用合适的激素敏感报道基因质粒例如 PRE_2-tk-LUC 和 GR 表达质粒共转染 HepG2 人肝母细胞瘤细胞,该细胞生长在补充有 10％ FBS 和 pen/strep 的无苯酚红 MEM α 中的单层培养基中。在存在或不存在各种浓度测试化合物的情况下,转染的 HepG2 细胞用 (预先确定的) 最大刺激浓度的地塞米松温育 20 小时。通过测量 LUC 活性,确定测试化合物的 IC_{50}。

[0069] 实施例 3 长期每天施 CDB-4124 与肝毒性作用相关联

[0070] 用 Proellex(aka CDB-4124) 进行的初始研究说明每种测试剂量的药物效应。Proellex 的研发集中在两种最高的测试剂量,25mg 和 50mg,这是基于表明较高剂量抑制子宫内膜增厚和突波子宫出血的可能性的数据。动物临床前研究以及欧洲妇女以较高剂量暴露至多六个月期间的小型试验预测肝毒性在美国不同人群中进行的 III 期临床研究中显示。以 50mg/ 天剂量口服递送的 Proellex 在接受该剂量的妇女的大约 3-4％中显示严重肝毒性。在 12.5mg,没有不同于安慰剂的不利肝毒性信号。对于 12.5mg 剂量,CDB-4124 及其单去甲基化代谢物 (CDB-4453) 的最大浓度是 50mg 剂量的 25％。在返回进行安全跟踪的那些妇女中分析所有肝毒性,包括发展了肝相关严重副作用 (SAE) 的那些对象。在 50mg/ 天口服施用 Proellex 时观察到的作用在频率和强度上明显低于 25mg/ 天递送 Proellex 时。这种观察结果进一步由下述事实放大 :25mg/ 天剂量与 50mg/ 天剂量相比,安全地获得了更

长的暴露时间，表明在较低剂量下的暴露时间不一定产生与在 50mg/ 天剂量观察到的相同的肝毒性。

[0071] 至今，超过 600 位患者，包括确认了子宫内膜异位或子宫肌瘤情况的妇女在内，已经参与了双盲和开放标记临床试验，其中患者每天口服施用胶囊超过一个月，胶囊包含 12.5mg、25mg 或 50mg CDB-4124(Proellex) 的剂量。在这些患者中，大约 500 位接受了 Proellex，大约 130 位接受了安慰剂。在接受 Proellex 的患者中，大约 190 位每天接受了 50mg CDB-4124 的剂量，大约 260 位每天接受了 25mg CDB-4124 的剂量，大约 55 位每天接受了 12.5mg 的剂量。

[0072] 在参与的对象中频繁监测肝酶。临床试验中断的肝酶水平设定为肝转氨酶的增加大于或等于正常的上限的三倍 (≥ 3x ULN)。

[0073] 在临床试验中，发现十三位对象显示肝酶的增加≥ 3x ULN，但这通过 48 小时中的重复试验仅在九位对象中得到确认。在确认肝酶的增加≥ 3x ULN 的九位对象中，七位上升足够严重，要作为 SAE 报告给 FDA。这七位对象的一位已经接受每天 25mg CDB-4124 的剂量 ；其余六位对象已经接受每天 50mg CDB-4124 的剂量。在九位确认肝酶的增加≥ 3x ULN 的对象中的五位中一直是肝酶≥ 3x ULN。这五位对象在之前给了 50mg 剂量。这些对象中一位正接受口服药物以治疗她的肝脏病况。作为这些 SAE 的结果，涉及所有剂量 CDB-4124 的临床试验主动停止，并且为了安全原因，随后置于美国食品和药品管理局主持的临床中。

[0074] 对参与对象进行的药物代谢动力学在施用后 1-2 小时检测到高 Cmax 和 T max。也检测到 CDB-4124 的大量单去甲基代谢物，这清楚表明了抗孕素的首过代谢。提供首过代谢的进一步证据，人和动物肝细胞的初级培养物快速产生 CDB-4124 的单去甲基代谢物。肝脏代谢 CDB-4124 为肝脏损伤提供了机会，并且在它到达全身循环之前大大减小了抗孕素的浓度。避免首过代谢的抗孕素施用可选途径例如但不限于静脉内、肌肉内和舌下应当允许抗孕素直接被吸收到全身循环中，并且因此提供了治疗孕酮依赖性病况同时避免肝毒的方法。避免首过代谢的施用途径相对于口服施用也可以每剂量需要更少的药物来获得相同的治疗益处。

[0075] 在具有由 7,12- 二甲基苯并蒽 (DMBA) 诱导的乳房肿瘤的啮齿目动物上进行临床前研究。这些研究显示了 CDB-4124 非口服递送方法的功效。具体地，通过皮下注射递送的 CDB-4124 在减小 DMBA 诱导的乳房肿瘤的数量和体积上是有效的，这提供了概念证明。

[0076] 实施例 4 阴道递送 CDB-4124 和 CDB-4453 与口服施用相比减小了全身浓度，并且避免了首过代谢

[0077] 给猎兔犬施用 25mg CDB-4124 或 CDB-4453(CDB-4124 的单去甲基代谢物)，其被配制为微粉化粉剂或阴道栓剂。如图 1 所示，当作为微粉化粉剂口服施用时 CDB-4124 和 CDB-4453 在获得峰值血浆浓度 (Cmax) 后被快速代谢。比较而言，当通过阴道栓剂局部施用相同化合物时药物缓慢代谢，峰值血浆浓度 (Cmax) 相对较低。而且，当局部施用时药物的全身暴露量低得多 (阴道施用与口服施用对比，比较 CDB-4124 和 CDB-4453 的 AUC)。

[0078] 对于在 III 期临床研究期间实际施用的 12.5mg、25mg 和 50mg 剂量，将在阴道施用给猎兔犬后获得的 CDB-4124 最大循环浓度 (Cmax) 外推至人。从图 2 可见，在人中阴道施用 12.5mg 剂量 CDB-4124 的预期 Cmax 大约是口服施用时同样剂量的 6.5％，在人中阴道施用 50mg 剂量 CDB-4124 的预期 Cmax 大约是口服施用时同样剂量的 2％。

[0079] 实施例 5 当口服施用时 CDB-4124 在子宫的生物利用率出乎意料的低

[0080] 为了确定局部施用时 CDB-4124 的低循环水平是否可具有预期的任何功效作用，进行了抗 Clauberg 研究，其中通过皮下或口服施用，将孕酮和各种剂量的 CDB-4124 共同施用给未成年的喂足雌二醇的兔。至少 3 个不同的高度培训的个体评估兔子宫的腺生长、复杂性和总体孕酮诱导的“发育”。分析每种剂量的孕酮诱导子宫内膜增生的抑制（百分比）。如在图 2 中说明，当皮下施用 CDB-4124 时在小于 1mg/kg 的剂量，观察到最大抑制。然而，当口服施用时最大抑制需要剂量增加～ 8 倍（即 8mg/kg）。重要地，8mg/kg 非常对应于施用给实施例 3 所述雌性对象的 50mg/ 天剂量的 CDB-4124。这表明，当口服施用时 CDB-4124 在子宫内膜的有效局部浓度大大降低，这最有可能是由于药物的首过代谢。因此，为了获得治疗作用，例如对于骨盆和生殖道的局部征兆，在口服施用时需要相对高剂量的 CDB-4124，这非常对应于在实施例 3 观察到肝毒作用的 CDB-4124 剂量。

[0081] 进行另一抗 Clauberg 研究，其中给未成年的喂足雌二醇的兔仅施用孕酮（载体对照），或者共同施用孕酮和三剂量的 CDB-4124，通过阴道或口服施用。分析每种剂量的孕酮诱导子宫内膜增生的抑制。图 3 说明在通过任一途径施用增加剂量的 CDB-4124 之后 McPhail 指数的增加。与口服施用时的 0.8mg/kg 相比，阴道施用时在 0.2mg/kg CDB-4124 出现了最大抑制（即 McPhail 指数减小至 1.5）。该研究的数据表明，CDB-4124 的阴道递送显示了四倍于相同口服剂量的抗孕酮活性。

[0082] 累积起来，数据表明，与口服施用时的有效剂量相比，可以阴道施用四倍更低剂量的抗孕素，同时与口服施用相比，仅获得最大循环浓度的一小部分，从而避免了肝毒性。例如，对于 50mg 口服剂量的 CDB-4124 和 12.5mg 的阴道剂量，观察到在子宫的相同抗孕酮活性；然而，对于 12.5mg 的阴道剂量观察到的 Cmax 仅是对于 50mg 口服剂量观察到的 2％。局部施用获得的相对高的局部药物浓度允许相对低剂量的药物（与口服施用相比）获得骨盆和生殖道局部征兆（例如子宫内膜异位、子宫肌瘤和卵巢癌）的治疗效果。由于药物（以及相关的药物首过代谢物）在全身循环中的高浓度通过局部施用达不到，因此在之前 III 期临床研究中以 25 和 50mg 剂量口服施用 CDB-4124 之后在小百分比的对象中观察到的严重肝毒的避免是局部施用药物的出乎意料的优势。其他抗孕素的局部施用应当有相似的优势。

[0083] 实施例 6 阴道施用 CDB-4124 以治疗子宫肌瘤

[0084] 具有子宫肌瘤的七位女性完成了 4 个月的治疗，作为单盲研究的一部分。这些女性阴道施用了 12mg CDB-4124 每日剂量，持续四个月期间，在女性月经周期的黄体期开始给药。在四个月治疗期间结束时，所有七位女性停止月经，并且都报告月经失血图 (Pictural Blood Loss Assessment Chart)(PBAC) 评分为 0($p = 0.002$)。也观察到子宫肌瘤症状及健康相关生活质量问卷 (Uterine Fibroid Symptom Quality of Life Survey)(UFSQOL) 评分在统计学上显著的以及高度临床有意义的减小。基线处平均 UFSQOL 分数是 43.8，在四个月治疗期间结束时平均分数是 1.33($p = 0.001$)。对于七位女性中的六位，UFSQOL 评估的出血和体积相关症状都急剧减少，这反映她们不再经受任何纤维瘤相关症状。作为参考，具有纤维瘤的妇女通常评分为 40 或更高，而没有纤维瘤的妇女报告评分为大约 20。

[0085] 评估了在四个月治疗结束时通过磁共振成像 (MRI) 测定的纤维瘤体积的改变，并且观察到统计学显著的（卡方分析）总体纤维瘤体积的中位减小为 36％。

[0086] 在口服研究中，将1、3、6、9和12mg剂量CDB-4124施用10周期间。在口服研究中，所有的剂量都是很好耐受的，并且可靠的月经停止在低至3mg的剂量诱导。月经停止在子宫肌瘤和子宫内膜异位二者中与口服剂量的功效直接相关。药代动力学揭示阴道施用12mg CDB-4124产生相同口服剂量全身暴露的大约1/6，这是基于曲线(AUC)下方的面积，以及大约是50mg口服剂量的1/100的最大暴露量(Cmax)。

[0087] 观察到相对于口服施用在阴道施用药物时CDB-4124的浓度缓慢形成。因此，阴道施用药物时延迟了停经的开始，这使得在后面月经期间阴道施用药物成为必要，其往往减少了药物的吸收并且是不令人愉快的和对于患者是技术挑战。本发明方法通过提供短期的口服施用、提前和重叠的阴道施用提供了这种问题的解决方案，其加快了停经的开始，同时保持阴道施用的益处。

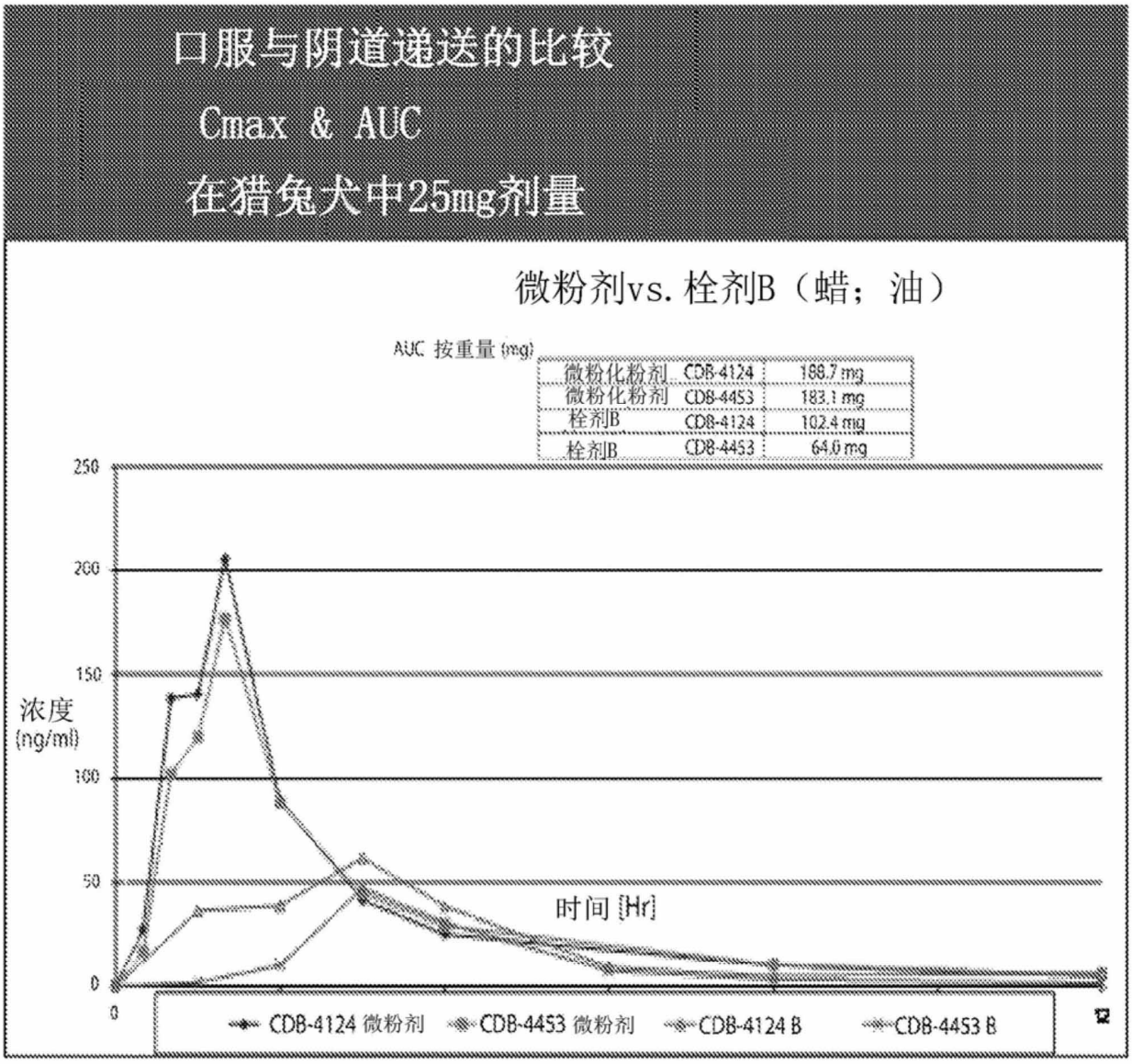

口服与阴道递送的比较
Cmax & AUC
在猎兔犬中25mg剂量
微粉剂vs.栓剂B（蜡；油）
AUC 按重量 (mg)
微粉化粉剂 CDB-4124 188.7 mg
微粉化粉剂 CDB-4453 183.1 mg
栓剂B CDB-4124 102.4 mg
栓剂B CDB-4453 64.0 mg
250
200
150
100
50
0
浓度 (ng/ml)
时间 [Hr]
0
CDB-4124 微粉剂
CDB-4453 微粉剂
CDB-4124 B
CDB-4453 B

图 1

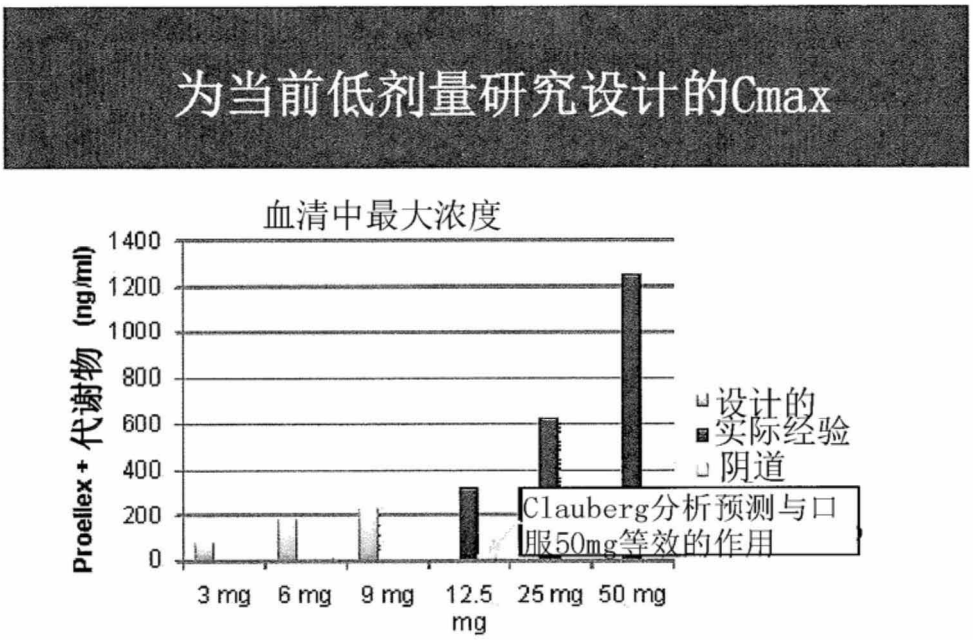

为当前低剂量研究设计的Cmax
血清中最大浓度
Proellex + 代谢物 (ng/ml)
1400
1200
1000
800
600
400
200
0
3 mg
6 mg
9 mg
12.5 mg
25 mg
50 mg
设计的
实际经验
阴道
Clauberg分析预测与口服50mg等效的作用

图 2

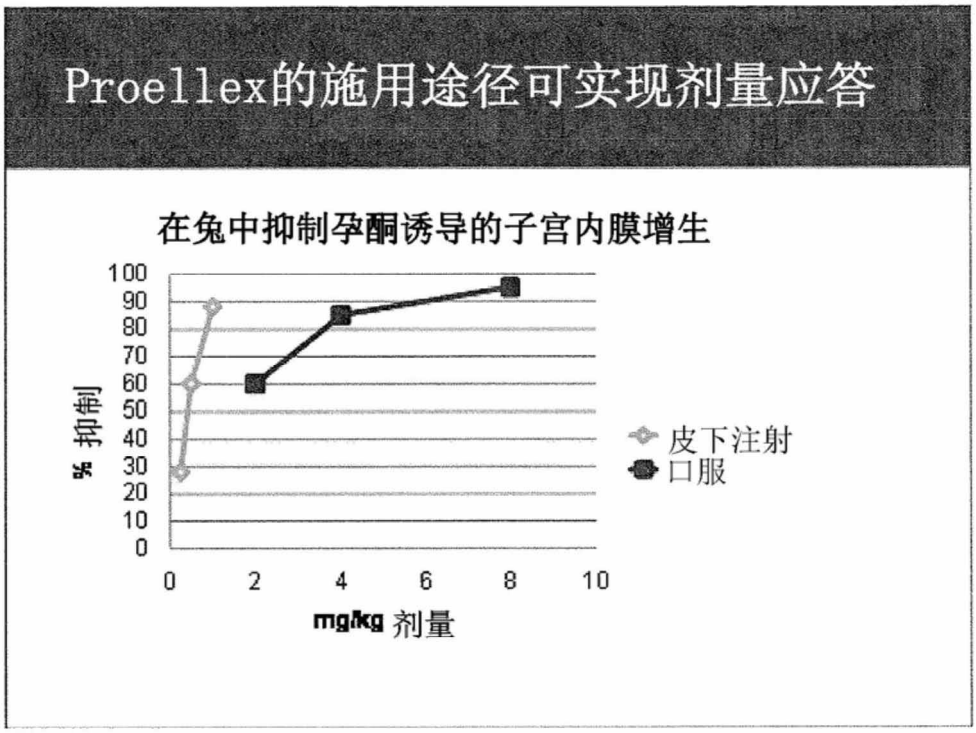

Proellex的施用途径可实现剂量应答
在兔中抑制孕酮诱导的子宫内膜增生
% 抑制
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
mg/kg 剂量
皮下注射
口服

图 3

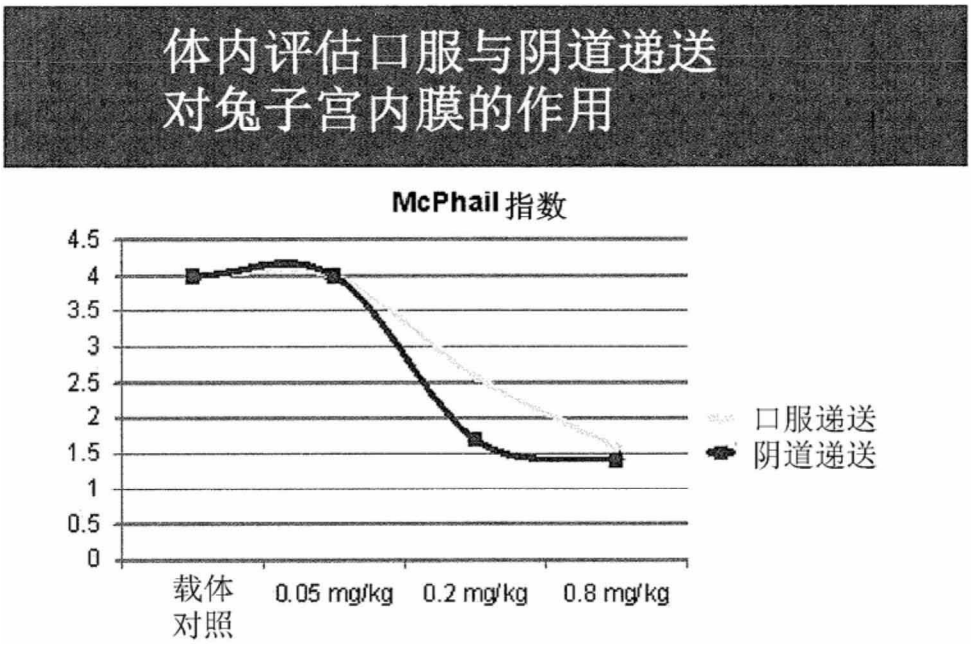

体内评估口服与阴道递送
对兔子宫内膜的作用
McPhail 指数
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
载体
对照
0.05 mg/kg
0.2 mg/kg
0.8 mg/kg
口服递送
阴道递送

图 4