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(54) Title: SELECTIVE ESTROGEN RECEPTOR MODULATORS WITH SHORT HALF-LIVES AND USES THEREOF

(57) Abstract: The present invention relates to the long-term administration of a selective estrogen receptor modulator (SERM) with a short half-life for the treatment of a variety of estrogen receptor-mediated conditions. The SERM may be administered at a concentration at or below that of a SERM with a long half-life in order to achieve an equivalent therapeutic effect.

Figure 1

Subject	Enclomiphene Dose	Day 1 $AUC_{(0-24)}$	Day 14 $AUC_{(0-24)}$	Accumulation Index Day 14 / Day 1 AUC Ratio
1008	Enclomiphene 12.5 mg	12.2504	24.7157	2.0175
1043	Enclomiphene 12.5 mg	34.4866	69.7163	2.0215
1068	Enclomiphene 12.5 mg	10.0064	37.1102	3.7086
1071	Enclomiphene 12.5 mg	10.2108	36.9013	3.6139
1096	Enclomiphene 12.5 mg	1.4717	1.8622	1.2653
			Mean	2.5254
			SD	1.0822
			SE	0.4840
			Range	1.27 - 3.71

Subject	Enclomiphene Dose	Day 1 $AUC_{(0-24)}$	Day 14 $AUC_{(0-24)}$	Accumulation Index Day 14/Day 1 AUC Ratio
1010	Enclomiphene 25 mg	33.4381	67.8184	2.0282
1039	Enclomiphene 25 mg	9.4452	29.5313	3.1266
1078	Enclomiphene 25 mg	26.2345	125.6074	4.7879
1084	Enclomiphene 25 mg	40.4145	78.4035	1.9400
1090	Enclomiphene 25 mg	100.0801	231.2393	2.3105
			Mean	2.8386
			SD	1.1859
			SE	0.5304
			Range	1.94 - 4.79

Subject	Enclomiphene Dose	Day 1 $AUC_{(0-24)}$	Day 14 $AUC_{(0-24)}$	Accumulation Index Day 14/Day 1 AUC Ratio
1001	Enclomiphene 50 mg	37.2391	108.5459	2.9148
1037	Enclomiphene 50 mg	23.2863	36.3181	1.5596
1091	Enclomiphene 50 mg	48.851	131.3707	2.6892
1094	Enclomiphene 50 mg	43.6337	122.8372	2.8152
			Mean	2.4947
			SD	0.6302
			SE	0.3151
			Range	1.56 - 2.92

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SELECTIVE ESTROGEN RECEPTOR MODULATORS WITH SHORT HALF-LIVES AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 61/598,723, filed February 14, 2012, the contents of which are incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to the long-term (i.e. chronic) administration of a selective estrogen receptor modulator with a short half-life for the treatment of a variety of estrogen receptor-mediated conditions.

BACKGROUND

[0003] Selective estrogen receptor modulators (SERMs) are a class of compounds that bind to estrogen receptors (ERs) thereby inducing specific conformational changes in the receptors. SERMS can exert different effects in different tissues resulting from tissue-specific recruitment of coactivators (which enhance ER transcriptional activity) and corepressors (which repress ER transcriptional activity). SERMs are therefore distinguished from the so called "pure" estrogen receptor agonists/antagonists that uniformly activate or block estrogen effects independent of tissue type.

[0004] SERMS, by virtue of their effect on the estrogen receptor, are useful for treating a variety of disorders having an estrogen component. Many of these disorders are chronic disorders requiring long-term administration of the SERM. However, when administered over long periods of time, serious adverse effects have been observed, limiting the usefulness of these compounds. A significant advance in the art would occur if these SERMs could be administered to treat chronic estrogen receptor-mediated disorders.

SUMMARY OF THE INVENTION

[0005] The present invention provides methods for chronic administration of SERMs which reduce or eliminate the adverse effects resulting from long-term administration. According to the methods, a pharmaceutical composition comprising an effective amount of a SERM with a short half-life or a pharmaceutically acceptable salt thereof, is administered to a patient with

one or more estrogen receptor-mediated disorders in order to treat the disorder for a period of at least six months.

[0006] Examples of disorders that may be treated by chronic administration of an effective amount of a SERM with a short half-life (and which therefore may be treated according to the present invention) include, without limitation, secondary hypogonadism, type 2 diabetes, elevated cholesterol, elevated triglycerides, wasting, lipodystrophy, osteoporosis, female and male infertility, benign prostate hypertrophy, menopause, prostate cancer, breast cancer, uterine cancer and ovarian cancer.

BRIEF DESCRIPTION OF THE DRAWING

[0007] FIG. 1 Individual $AUC_{(0-24)}$ Values by Enclomiphene Dose on Days 1 and 14, Individual $AUC_{(0-24)}$ Ratios and Summary Statistics for $AUC_{(0-24)}$ Ratio. This figure depicts single dose and steady state pharmacokinetic data gathered during oral administration of trans-clomiphene at 12.5 mg, 25 mg, or 50 mg per day.

DETAILED DESCRIPTION

[0008] 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.

[0009] 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 from the data and numbers presented herein and all represent embodiments of the invention.

[0010] 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.

[0011] Definitions

[0012] 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.

[0013] The term "effective dosage" means an amount of the composition's active component sufficient to treat a particular condition.

[0014] The term "treat" or "treatment" as used herein refers to any treatment of any estrogen receptor-mediated 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.

[0015] The term "prevent" or "prevention," in relation to an estrogen receptor-mediated 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.

[0016] The term "pharmaceutically acceptable salt" refers to a salt prepared from a pharmaceutically acceptable non-toxic inorganic or organic acid. Inorganic acids include, but are not limited to, hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, and phosphoric. Organic acids include, but are not limited to, aliphatic, aromatic, carboxylic, and sulfonic organic acids including, but not limited to, formic, acetic, propionic, succinic, benzoic camphorsulfonic, citric, fumaric, gluconic, isethionic, lactic, malic, mucic, tartaric, para-toluenesulfonic, glycolic, glucuronic, maleic, furoic, glutamic, benzoic, anthranilic, salicylic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, pantothenic, benzenesulfonic, stearic, sulfanilic, alginic, and galacturonic acid.

[0017] The term "half-life" is understood to mean the time in which the concentration of the SERM in the blood plasma is halved.

[0018] The term "intermittent administration" means a period of administration of a therapeutically effective dose of a SERM, followed by a time period of discontinuance, which is then followed by another period of administration of a therapeutically effective dose, and so forth. The administration period of the therapeutically effective dose may comprise continuous dosing, as for example with a sustained-release formulation, or may comprise daily, every other day, weekly, or there between, dosing, as for example, with one, two or more tablets per day, so long as the dosing interval during the administration period is less than the discontinuance period.

[0019] Long term oral administration of tamoxifen is associated with a ~3-fold increase in vascular-related thrombotic events including stroke, deep vein thrombosis and pulmonary embolisms. Long term administration of tamoxifen is also associated with a ~2-fold increase in the risk of developing endometrial cancer and also significantly increases the risk of developing cataracts. Similar adverse events have also been reported in connection with long term oral administration of raloxifen, albeit to a lesser extent.

[0020] The present inventors have surprisingly discovered that adverse side effects of long term oral SERM administration can be reduced or even eliminated without loss of efficacy in treating disorders which are responsive to SERMs. This reduction or elimination occurs when the SERM has a short half-life, thereby achieving therapeutic effect and, within a short time, falling to sub-therapeutic concentrations. By employing a SERM with a short half-life, it is possible to treat estrogen receptor-mediated conditions that benefit from chronic SERM administration with a reduced or eliminated possibility of serious adverse side effects. During long-term administration of SERMs with a long half life such as tamoxifen (5-7 days), the drug may extensively accumulate over time. Accordingly, in several embodiments, the present invention provides a method for long-term administration of a SERM, wherein the half-life of the SERM is about 30 hours or less, in order to treat an estrogen receptor-mediated condition thereby minimizing or even eliminating these adverse effects. Preferably the SERM has a half-life of less than 27 hours, such as less than 26, less than 25, less than 24, less than 23, less than 22, less than 21, less than 20, less than 19, less than 18, less than 17, less than 16, less than 15, less than 14, less than 13, less than 12, less than 11, and less than 10.5 hours.

[0021] Surprisingly, therapeutic benefit may be seen at the same (or possibly even lower) dosage and administration frequency observed for SERMs with a longer half life, such as tamoxifen, despite more rapid clearance from the body. The present inventors have discovered that a "correction" of the hypothalamic-pituitary-gonadal axis can occur following a brief initial "loading phase" of the SERM, thereby compensating for the decreased half-life and possibly allowing for even lower dosage and/or administration frequency to achieve equivalent therapeutic effect. In this respect, tamoxifen, representative of SERMs with relatively long half-lives, is prescribed in an oral formulation containing 10 mg to 20 mg of tamoxifen to be administered once or twice per day. Thus, in one aspect, the present invention provides a method for treating an estrogen receptor-mediated condition comprising long-term administration of a SERM with a half-life of 30 hours or less, preferably less than 27 hours, at a dosage of 20-40 mg or less per day, such as between 1 and 19 mg per day, between 5 and 19 mg per day, between 5 and 10 mg per day, or between 1 and 9 mg per day. In a related embodiment, the SERM with a half-life of 30 hours or less may be administered intermittently such as every other day, weekly, every other week, monthly, or at any dosing interval there between at a dosage of 20-40 mg or less, e.g. at a dosage between 1 and 19 mg, between 5 and 10 mg or between 1 and 9 mg. Intermittent administration of the SERM may be preceded by an initial loading phase in which the SERM is administered at 10 - 20 mg or less for a period of at least 7 (e.g. at least 14) or more consecutive days.

[0022] A SERM with a half-life of 30 hours or less, preferably with a half-life less than 27 hours, may be administered for a period of at least 6 months, at least one year, at least 18 months, at least 2 years, at least 30 months, at least 3 years, at least 42 months, at least 4 years, at least 54 months, or at least (e.g. more than) 5 years in order to treat an estrogen receptor-mediated condition.

[0023] Any known SERM with a half-life of 30 hours or less, preferably less than 27 hours, may be administered for a period of at least 6 months according to the present invention. A list of SERMs along with their half-lives is provided at Table 1:

Table 1: Half-life of Several Selective Estrogen Receptor Modulators

SERM	Half-Life
Enclomiphene (trans-clomiphene)	10.5 hours
Droloxifene	24 hours
Levormeloxifene	24 hours
(Deaminohydroxy)toremifene	25-30 hours
Raloxifene	27 hours
Bazedoxifene	28 hours
Arzoxifene	30 hours
Toremifene	5 days
Tamoxifen	5-7 days
Clomid	5-7 days
Lasofoxifene	6 days
Ormeloxifene	7 days
Idoxifene	3 weeks

[0024] In a preferred embodiment, the SERM for use in the methods of the invention is selected from the group consisting of: droloxifene, trans-clomiphene, levormeloxifene, (Deaminohydroxy)toremifene, raloxifene, bazedoxifene and arzoxifene.

[0025] In another embodiment, a metabolite of trans-clomiphene with a relatively short half life is employed in the methods of the invention. The trans-clomiphene metabolite may be selected from 4-hydroxy-trans-clomiphene (4-OH-trans-clomiphene), 4'-hydroxy-trans-clomiphene (or 4'-OH-trans-clomiphene), 3-hydroxy-trans-clomiphene (or 3-OH-trans-clomiphene), 3,4-dihydroxy-trans-clomiphene, and N-desethyl-trans-clomiphene.

[0026] In another embodiment, the present invention relates to a method for identifying SERMs which have reduced or eliminated side effects when administered chronically by determining the half life of the SERM in the blood of a mammal, which is relevant for pharmacokinetic ratios in humans or in humans in phase I clinical trial development and comparing the half life of the SERM to that of tamoxifen. A SERM with reduced or eliminated side effects when administered chronically is identified if the SERM has a shorter half life than tamoxifen.

[0027] In various embodiments, the present invention also provides pharmaceutical compositions comprising one or more SERMs with a half-life of 30 hours or less or salts thereof as described and a pharmaceutically acceptable carrier, which can be used in the methods described herein.

[0028] In one embodiment, a method for elevating testosterone levels is provided comprising administering an effective amount of a SERM with a half-life of 30 hours or less or a salt thereof (or pharmaceutical composition comprising same) to a patient in need of such treatment for a period of at least 6 months. In a related embodiment, a method for treating a disorder related to testosterone deficiency including, without limitation, oligospermia, azoospermia, wasting and depression is provided. In a preferred embodiment the patient is a human male with secondary hypogonadism, in which case the SERM may be administered for a period of at least 6 months in order to treat the secondary hypogonadism.

[0029] In another embodiment, a method for decreasing cholesterol levels is provided, comprising administering an effective amount of a SERM with a half-life of 30 hours or less or a salt thereof (or pharmaceutical composition comprising same) to a patient in need of such treatment for a period of at least 6 months. In a preferred embodiment the patient is a human male with secondary hypogonadism

[0030] In another embodiment, a method for treating and/or preventing a condition selected from the group consisting of benign prostate hypertrophy, prostate cancer and elevated triglycerides is provided comprising administering an effective amount of a SERM with a half-life of 30 hours or less or a salt thereof (or pharmaceutical composition comprising same) to a patient in need of such treatment for a period of at least 6 months. In a preferred embodiment the patient is a human male with secondary hypogonadism.

[0031] In another embodiment, a method for treating infertility in a human male is provided comprising administering an effective amount of a SERM with a half-life of 30 hours or less or a salt thereof (or pharmaceutical composition comprising same) to a human male in need of such treatment for a period of at least 6 months. In a preferred embodiment the patient is a human male with secondary hypogonadism.

[0032] In another embodiment, a method for preventing the transition from metabolic syndrome to type 2 diabetes is provided comprising administering an effective amount of a SERM with a half-life of 30 hours or less or a salt thereof (or pharmaceutical composition comprising same) to a human male with secondary hypogonadism for a period of at least 6 months.

[0033] In yet another embodiment, a method for treating type 2 diabetes mellitus is provided comprising administering an effective amount of a SERM with a half-life of 30 hours or less

or a salt thereof (or pharmaceutical composition comprising same) to a human male in need of such treatment for a period of at least 6 months. Preferably, the human male is a human male with secondary hypogonadism.

[0034] In another embodiment, a method for the treatment of female infertility is provided comprising administering an effective amount of a SERM with a half-life of 30 hours or less or a salt thereof (or pharmaceutical composition comprising same) to a female in need of such treatment for at least six consecutive cycles. Preferably the SERM is administered as a daily dose in the early follicular phase of the menstrual cycle for five consecutive days. For example, an administration schedule could involve administration on days 5 to 9 or on days 3 to 7 of the menstrual cycle. Preferably the patient is an anovulatory female.

[0035] In another embodiment, a method for the treatment and/or prevention of breast cancer is provided comprising administering an effective amount of a SERM with a half-life of 30 hours or less or a salt thereof (or pharmaceutical composition comprising same) to a female in need of such treatment for a period of at least 6 months, preferably at least 5 years (e.g. more than 5 years). According to this embodiment, the SERM may be administered to a female at increased risk for developing breast cancer in order to prevent the development of breast cancer. Alternatively, the SERM may be administered to a female with breast cancer in order to treat the breast cancer. The SERM may also be administered as an adjuvant therapy following initial treatment with surgery in order to minimize the possibility of relapse. Preferably when administered as an adjuvant, the SERM is administered for a period of at least about 5 years.

[0036] In another embodiment, a method for the treatment of endometrial (or uterine) cancer is provided comprising administering an effective amount of a SERM with a half-life of 30 hours or less or a salt thereof (or pharmaceutical composition comprising same) to a female in need of such treatment for a period of at least 6 months.

[0037] In yet another embodiment, a method for the treatment of ovarian cancer is provided comprising administering an effective amount of a SERM with a half-life of 30 hours or less or a salt thereof (or pharmaceutical composition comprising same) to a female in need of such treatment for a period of at least 6 months.

[0038] In yet another embodiment, a method for treatment of osteoporosis is provided comprising administering an effective a SERM with a half-life of 30 hours or less or a salt

thereof (or a pharmaceutical composition comprising same) to a female in need of such treatment for period of at least 6 months.

[0039] The SERMs used in the compositions and methods described herein can be chemically synthesized according to known methods and include the salt form of each of the compounds. Raloxifene, 6-hydroxy-2(4-hydroxyphenyl)-3-[4-(2-piperdinoethoxy)benzoyl]benzo[b]thiophene, and its pharmacologically acceptable salts may be produced according to the methods described in U.S. Pat. Nos. 4,418,068 and 4,133,814, each of which is incorporated herein by reference. Droloxifene, E-1-[4'-(2-dimethylaminoethoxy)phenyl]-1-(3'-hydroxyphenyl)-2-phenyl-1-butene, and its pharmacologically acceptable salts may be produced according to the methods described in U.S. Pat. No. 5,047,431, which is incorporated herein by reference. Arzoxifene, 2-(4-Methoxyphenyl)-4-[4-[2-(1-piperidinyl)ethoxy]phenyoxy]benzo[b]thiophene-6-ol, and its pharmaceutically acceptable salts may be produced according to the methods described in U.S. Pat. No. 5,723,474, which is incorporated herein by reference. Bazedoxifene and its pharmaceutically acceptable salts may be produced according to the methods described in U.S. Pat. Nos. 5,998,402 and 6,479,535, each of which is incorporated herein by reference. Levormeloxifene, (-)-3R,4R-trans-7-methoxy-2,2-dimethyl-3-phenyl-4-{4-[2-(pyrrolidin-1-yl)e thoxy]phenyl}chromane, and its pharamaceutically acceptable salts may be produced according to the methods described in U.S. Pat. No. 4,447,622, which is incorporated herein by reference.

[0040] Pharmaceutical compositions according to the present invention may comprise or consist essentially of a SERM of the invention at a dosage between about one mg to about 200 mg (although the determination of optimal dosages is with the level of ordinary skill in the art). The composition may comprise a SERM of the invention at a dosage of about 1 mg, 2 mg, 3, mg, 4 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg or there between. In a preferred embodiment, the composition comprises a SERM of the invention at a dosage of about 1 mg to about 19 mg, more preferably at a dosage of about 1 mg to about 9 mg.

[0041] Pharmaceutical compositions may comprise 100% w/w of a SERM of the invention or may additionally comprise other active agents useful in achieving the desired therapeutic effect. Where the pharmaceutical composition comprises 100% w/w of a SERM of the

invention, one or more additional active agents may be separately co-administered sequentially or simultaneously to achieve a desired therapeutic effect. Thus, in several embodiments, the present invention provides a method for treating an estrogen receptor-mediated condition comprising co-administering a SERM of the invention with an additional therapeutic agent. The additional therapeutic agent may be any agent known to be effective in treating the estrogen receptor-mediated condition.

[0042] The terms "treat" or "treatment" as used in the instant application, refer to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological or psychological change or disorder, such as symptoms associated with secondary hypogonadism. For purposes of the present invention, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. Individuals in need of treatment include those already with the condition or disorder as well as those prone to develop the condition or disorder or those in whom the condition or disorder is to be prevented.

[0043] Suitable pharmaceutical compositions or unit dosage forms may be in the form of solids, such as tablets or filled capsules or liquids such as solutions, suspensions, emulsions, elixirs or capsules filled with the same, all for oral use. The compositions may also be in the form of sterile injectable solutions or emulsions for parenteral (including subcutaneous) use. The compositions may also be formulated for topical administration. For example, the composition may be formulated as a lotion, cream, ointment, gel, foam, or transdermal patch. In one preferred embodiment, the composition is formulated as a gel (e.g. an aqueous alcoholic gel) for transdermal administration (e.g. to the scrotum). Such pharmaceutical compositions and unit dosage forms thereof may comprise ingredients in conventional proportions.

[0044] Although oral administration is the preferred route, compositions according to the present invention may be administered by any route of administration including, but not limited to, intravenous, subcutaneous, buccal, transmucosal, intrathecal, intradermal,

intracisternal, intramuscular, transdermal, intraperitoneal, epidural, vaginal, rectal, intranasal, sublingual, intra-articular, intra-cerebrospinal and intrasynovial.

[0045] Compositions of the present invention may also be administered in fast-release formulations, slow-release formulations or mixtures of fast-release and slow-release formulations such as a multi-layer tablet comprising at least one fast-release layer and at least one slow-release layer.

[0046] All of the references discussed herein are incorporated by reference in their entirety.

[0047] The following Examples are meant to be illustrative of the invention and are not intended to limit the scope of the invention as set out is the appended claims.

EXAMPLE 1

Pharmacokinetic Profile of Trans-Clomiphene

[0048] A clinical study to estimate the pharmacokinetic (PK) profile of enclomiphene (trans-clomiphene) following single-dose and steady-state doses administered orally. 52 adult males between 18 and 75 years of age with total serum testosterone level <250 ng/dl or between 250 to 300 ng/dl and FSH/LH levels within the normal range, were randomly assigned to one of the following five treatment groups: (i) 12.5mg enclomiphene/day (ii) 25mg enclomiphene/day (iii) 50 mg enclomiphene/day (trans-clomiphene) (iv) Androgel® (1% topical testosterone applied daily) or (v) placebo. Enclomiphene citrate was provided as 12.5mg capsules and orally administered once (12.5mg arm) twice (25mg arm) or four times (50 mg arm) per day for 14 consecutive days. Single-dose and steady-state PK assessments were preformed in a subset of these males following the first (Day 1) and last (Day 14) dose. On Days 1 and 14, serial blood samples were obtained pre-dose (0 hours) and at 0.5, 1, 2, 3, 4, 6, 8, 12, 18 and 24 hours post-dose for plasma enclomiphene determination. Pre-dose plasma enclomiphene concentrations were also measured on Day 11 using a single blood sample. Pharmacokinetic (PK) endpoints were area under concentration time curve from zero to 24 hours (AUC_{0-24}), maximum concentration (C_{max}), time to C_{max} (T_{max}) and the elimination half-life ($t_{1/2}$) of plasma enclomiphene following single dose administration on Day 1 and steady-state dosing on Day 14. PK parameters were calculated using noncompartmental methods for subjects randomized to enclomiphene. The accumulation ratio, defined as the AUC_{0-24} on Day 14, divided by the AUC_{0-24} value on Day 1 was calculated.

[0049] On Day 1, mean (SD) C_{max} values for enclomiphene 12.5mg, 25mg and 50 mg were 1.98 (1.78), 4.79 (3.88) and 5.56 (1.09) ng/ml respectively. On Day 14, mean (SD) C_{max} values for enclomiphene 12.5mg, 25mg and 50 mg were 2.68 (1.68), 10.63 (9.58) and 12.09 (5.74) ng/ml respectively.

[0050] . On Day 1, median T_{max} values for enclomiphene 12.5mg, 25mg and 50 mg were 4.0, 2.0 and 2.0 hours, respectively, On Day 14, median T_{max} values for enclomiphene 12.5 mg, 25mg and 50 mg were 4.0, 3.0 and 2.0 hours respectively.

[0051] On Day 1, mean (SD) $T_{1/2}$ values for enclomiphene 12.5mg, 25mg, and 50 mg were 7.91 (4.91), 8.08 (2.01) and 6.53 (0.92) hours, respectively. On Day 14, mean (SD) $T_{1/2}$ values for enclomiphene 12.5mg, 25 mg and 50 mg were 9.31 (2.40), 10.73 (2.51) and 9.69 (0.92) hours, respectively.

[0052] The accumulation index for each enclomiphene dose group was calculated based on the arithmetic mean of the individual ratio of $AUC_{(0-24)}$ on Day 14 divided by $AUC_{(0-24)}$ on Day 1. Mean (SD) accumulation index values for enclomiphene 12.5mg, 25mg and 50 mg were 2.53 (1.08), 2.84 (1.19) and 2.49 (0.63), respectively.

[0053] The PK results are depicted in Figure 1. Based on the PK data obtained, the half life of enclomiphene was determined to be ~10.5 hours.

EXAMPLE 2

Long Term Administration of Tans-Clomiphene

[0054] 104 adult human males with secondary hypogonadism (serum testosterone < 300 ng/dl at the initial screening visit) who completed a six month study in which trans-clomiphene (citrate) was administered orally at dose of 12.5, 25 or 50 mg trans-clomiphene per day, were enrolled in a one year open label, multi-center extension study, with a total of 70 subjects completing the study. The overall mean age of subjects was 54.1 years of age with a body mass index (BMI) of 31.8 kg/m^2 and mean baseline total testosterone of 290.1 ng/dL. Subjects in the six month study had been randomly assigned to the following groups: (1) 12.5mg trans-clomiphene (2) 25mg trans-clomiphene (3) 50 mg trans-clomiphene (4) AndroGel® 1% topical testosterone or (5) placebo. All subjects in the extension study received a daily oral dose of 12.5 mg trans-clomiphene for up to one year. Adverse events as well as change from baseline in a variety of clinical parameters were assessed in patients

rolling over from each of the five treatment groups in the six month study during the course of the extension study. Assessments were made during laboratory visits which occurred at Day 0 [Visit 1], Month 1 [Visit 2] and at approximately 2-month intervals thereafter for 12 months (Month 1 [Visit 2] to Month 12 [Visit 7]). A follow up visit [Visit 8] occurred one month after cessation of treatment.

[0055] The primary efficacy endpoint of the study was the proportion of subjects at 1 year who showed morning total serum testosterone concentrations within the normal range (300 – 1040 ng/dl). A single morning's testosterone level has been shown to correlate highly to both maximum and average testosterone levels observed for a given subject. Overall, 62.5% of subjects had mean total serum testosterone levels within the normal reference range at 1 year. Overall mean increases in total serum testosterone from baseline to 1 year were statistically significant; during the study, overall mean increases in total testosterone concentration from baseline ranged from 9.8 to 251.3 ng/dl (Months 2 to follow-up visit inclusive).

[0056] Statistically significant improvements in libido were observed from baseline at months 4, 6 and 12 as assessed on the libido component of the International Index of Erectile Function (IIEF) questionnaire. However, no concomitantly significant changes were reflected in other questionnaires of sexual function such as the DeRogatis Interview for Sexual Function (DISF-SR II (M)) and Male Sexual Distress Scale IV-A (MSDS). During the study overall increases in testicular size mean values (measured using an orchidometer) ranged from 0.8 to 2.3 mL; a statistically significant increase was observed at Month 6 only.

[0057] Statistically significant increases in LH, FSH, sex hormone binding globulin (SHBG), estradiol, dihydrotestosterone (DHT) and DHT/testosterone ratio were observed at the majority or all of the timepoints; statistically significant decreases in prolactin were observed at the majority or all of the timepoints.

[0058] Statistically significant decreases in total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and triglycerides from baseline were observed at the majority or all of the timepoints.

[0059] Only five (5%) subjects experienced serious adverse effects (SAEs) – four of the five subjects had SAEs considered unrelated/unlikely related to the drug. Overall, 51.5% of subjects experienced at least one adverse event during the study; 18.8% of subjects (19/101) experienced at least one adverse event that was considered related to the study drug. The

majority of events were mild or moderate in severity; nine subjects experienced events that were considered severe. Nine subjects discontinued from the study due to AEs. Five of the 9 subjects who discontinued from the study experienced AEs that were considered possibly or probably related to study drug.

[0060] No subjects were discontinued due to a reduction in visual acuity.

[0061] Although clinically significant changes in some blood chemistry variables were observed in a small number of subjects, only one subject was discontinued from the study due to AEs of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increased. There were no clinically relevant changes in hematology, blood chemistry or urinalysis variables, or in vital signs, physical exam, prostate-specific antigen (PSA) values or electrocardiogram (ECG) readings.

[0062] These findings strongly support the efficacy of long term oral administration of SERMs with relatively long half lives at low concentrations for treating a variety of estrogen receptor mediated conditions while reducing or eliminating the serious adverse effects observed when SERMs with relatively long half lives (e.g. tamoxifen) are chronically administered. Over the course of 18 months of treatment with 12.5mg oral trans-clomiphene, the cardiovascular and ocular adverse effects observed during long term administration of tamoxifen (e.g. deep vein thrombosis, cataracts) were not observed. This data is consistent with animal safety pharmacology studies in rodent, baboon, rabbit and dog models which demonstrated no adverse effects in the central nervous, respiratory or cardiovascular systems in animals administered trans-clomiphene.

CLAIMS

1. A method for treating an estrogen receptor-mediated condition comprising administering a selective estrogen receptor modulator (SERM) or a pharmaceutically acceptable salt thereof having a half-life of 30 hours or less for a period of at least 6 months at a dosage of between 1 and 19 mg to a patient in need of such treatment, with the proviso that said SERM is other than *trans*-clomiphene.

2. The method of claim 1, wherein the SERM is administered at a dosage of between 1 and 10 mg.

3. The method of claim 1, wherein the SERM is selected from the group consisting of: droloxifene, levormeloxifene, (Deaminohydroxy)toremifene, raloxifene, bazedoxifene and arzoxifene.

4. The method of claim 1, wherein the SERM has a half-life of less than 27 hours.

5. The method of claim 4, wherein the SERM is administered at a dosage of between 1 and 10 mg.

6. The method of claim 4, wherein the SERM is selected from the group consisting of droloxifene, levormeloxifene, and (Deaminohydroxy)toremifene.

7. The method of claim 1, wherein the estrogen receptor-mediated condition is selected from the group consisting of: secondary hypogonadism, type 2 diabetes, elevated cholesterol, elevated triglycerides, wasting, lipodystrophy, osteoporosis, female infertility, male infertility, benign prostate hypertrophy, prostate cancer, breast cancer, uterine cancer and ovarian cancer.

8. The method according to any preceding claim, wherein the composition is administered daily.

9. The method of any preceding claim, wherein the composition is administered intermittently.

10. The method according to claim 9 wherein the composition is administered every other day, weekly, biweekly or monthly.

11. The method of claim 1, wherein the composition is administered to the patient for a period of more than 5 years.

12. The method of claim 1, wherein the patient is a human male with a serum testosterone level below 300 ng/DL.

13. The method of claim 1, wherein the composition is administered to an anovulatory female for at least 4 consecutive cycles, each cycle comprising an administration period of five consecutive days beginning on the second to fifth day after the onset of spontaneous or induced menstruation.

14. The method of claim 13 wherein the female is anovulatory.

15. The method according to claim 1, wherein the SERM is administered to treat type 2 diabetes in a human male.

16. The method according to claim 1, wherein the SERM is administered to treat and/or prevent breast cancer in a human female.

17. The SERM or pharmaceutically acceptable salt thereof according to claim 1, wherein the salt of the SERM is a citrate salt.

18. A method for treating an estrogen receptor-mediated condition comprising administering trans-clomiphene or a pharmaceutically acceptable salt thereof for a period of at least 6 months at a dosage of between 1 and 12 mg to a patient in need of such treatment.

19. The method according to claim 18 wherein trans-clomiphene is administered at a dosage of between 1 and 10 mg.

20. The method according to claim 18 or 19 wherein trans-clomiphene is administered daily.

21. The method according to claim 18 or 19 wherein the estrogen receptor-mediated condition is selected from the group consisting of: secondary hypogonadism, type 2 diabetes, elevated cholesterol, elevated triglycerides, wasting, lipodystrophy, osteoporosis, female infertility, male infertility, benign prostate hypertrophy, prostate cancer, breast cancer, uterine cancer and ovarian cancer.

22. The method according to any one of claims 1-21, wherein the SERM is administered orally.

23. The method according to any preceding claim wherein the SERM is administered daily for at least two weeks after which the SERM is administered intermittently.

24. The method according to claim 23 wherein intermittent administration comprises a 3 to 30 day interval between consecutive doses.

Figure 1

Subject	Enclomiphene Dose	Day 1 $AUC_{(0-24)}$	Day 14 $AUC_{(0-24)}$	Accumulation Index Day 14 / Day 1 AUC Ratio
1008	Enclomiphene 12.5 mg	12.2504	24.7157	2.0175
1043	Enclomiphene 12.5 mg	34.4866	69.7163	2.0215
1068	Enclomiphene 12.5 mg	10.0064	37.1102	3.7086
1071	Enclomiphene 12.5 mg	10.2108	36.9013	3.6139
1096	Enclomiphene 12.5 mg	1.4717	1.8622	1.2653
			Mean	2.5254
			SD	1.0822
			SE	0.4840
			Range	1.27 - 3.71

Subject	Enclomiphene Dose	Day 1 $AUC_{(0-24)}$	Day 14 $AUC_{(0-24)}$	Accumulation Index Day 14/Day 1 AUC Ratio
1010	Enclomiphene 25 mg	33.4381	67.8184	2.0282
1039	Enclomiphene 25 mg	9.4452	29.5313	3.1266
1078	Enclomiphene 25 mg	26.2345	125.6074	4.7879
1084	Enclomiphene 25 mg	40.4145	78.4035	1.9400
1090	Enclomiphene 25 mg	100.0801	231.2393	2.3105
			Mean	2.8386
			SD	1.1859
			SE	0.5304
			Range	1.94 - 4.79

Subject	Enclomiphene Dose	Day 1 $AUC_{(0-24)}$	Day 14 $AUC_{(0-24)}$	Accumulation Index Day 14/Day 1 AUC Ratio
1001	Enclomiphene 50 mg	37.2391	108.5459	2.9148
1037	Enclomiphene 50 mg	23.2863	36.3181	1.5596
1091	Enclomiphene 50 mg	48.851	131.3707	2.6892
1094	Enclomiphene 50 mg	43.6337	122.8372	2.8152
			Mean	2.4947
			SD	0.6302
			SE	0.3151
			Range	1.56 - 2.92

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/026178

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/00 A61K31/138 A61P5/50 A61P5/30 A61P5/32
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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, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/054248 A1 (REPROS THERAPEUTICS INC [US]; VAN AS ANDRE [US]) 14 May 2010 (2010-05-14) claims 1-5 paragraphs [0051], [0053], [0104] - [0106], [0107], [0133] paragraphs [0044], [0051], [0065], [0067], [0108] -----	1-17, 22-24

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

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

"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
21 March 2013	22/07/2013

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/026178

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-17, 22-24(all partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2013/026178

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010054248 A1	14-05-2010	AR 074302 A1	05-01-2011
		TW 201031400 A	01-09-2010
		WO 2010054248 A1	14-05-2010

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-17, 22-24(all partially)

   A method for treating an estrogen receptor-mediated condition comprising administering a selective estrogen receptor modulator (SERM) or a pharmaceutically acceptable salt thereof having a half-life of 30 hours or less for a period of at least 6 months at a dosage of between 1 and 19 mg to a patient in need of such treatment, wherein said SERM is droloxifene

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2. claims: 1-17, 22-24(all partially)

   A method for treating an estrogen receptor-mediated condition comprising administering a selective estrogen receptor modulator (SERM) or a pharmaceutically acceptable salt thereof having a half-life of 30 hours or less for a period of at least 6 months at a dosage of between 1 and 19 mg to a patient in need of such treatment, wherein said SERM is levormeloxifene

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3. claims: 1-17, 22-24(all partially)

   A method for treating an estrogen receptor-mediated condition comprising administering a selective estrogen receptor modulator (SERM) or a pharmaceutically acceptable salt thereof having a half-life of 30 hours or less for a period of at least 6 months at a dosage of between 1 and 19 mg to a patient in need of such treatment, wherein said SERM is (deaminohydroxy)toremifene

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4. claims: 1-5, 7-17, 22-24(all partially)

   A method for treating an estrogen receptor-mediated condition comprising administering a selective estrogen receptor modulator (SERM) or a pharmaceutically acceptable salt thereof having a half-life of 30 hours or less for a period of at least 6 months at a dosage of between 1 and 19 mg to a patient in need of such treatment, wherein said SERM is raloxifene

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5. claims: 1-5, 7-17, 22-24(all partially)

   A method for treating an estrogen receptor-mediated condition comprising administering a selective estrogen receptor modulator (SERM) or a pharmaceutically acceptable salt thereof having a half-life of 30 hours or less for a period of at least 6 months at a dosage of between 1 and 19 mg to a patient in need of such treatment, wherein said SERM

is bazedoxifene

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6. claims: 1-5, 7-17, 22-24(all partially)

A method for treating an estrogen receptor-mediated condition comprising administering a selective estrogen receptor modulator (SERM) or a pharmaceutically acceptable salt thereof having a half-life of 30 hours or less for a period of at least 6 months at a dosage of between 1 and 19 mg to a patient in need of such treatment, wherein said SERM is arzoxifene

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7. claims: 18-21(completely); 22-24(partially)

A method for treating an estrogen receptor-mediated condition comprising administering trans-clomiphene or a pharmaceutically acceptable salt thereof for a period of at least 6 months at a dosage of between 1 and 12 mg to a patient in need of such treatment

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A61P 19/10(2006.01)

权利要求书2页 说明书9页 附图1页

(54)发明名称

具有短半衰期的选择性雌激素受体调节剂及其用途

(57)摘要

本发明涉及用于治疗多种雌激素受体介导的病症的、具有短半衰期的选择性雌激素受体调节剂(SERM)的长期施用。可以在具有长半衰期的SERM的浓度或该浓度以下的浓度施用所述SERM，以便达到等效的治疗效果。

CN 104114162 A

1. 一种用于治疗雌激素受体介导的病症的方法，所述方法包括：以 1-19mg 的剂量给需要这种治疗的患者施用具有 30 小时或更小半衰期的选择性雌激素受体调节剂 (SERM) 或其药学上可接受的盐持续至少 6 个月的时段，前提条件是，所述 SERM 不是反式 - 氯米芬。

2. 根据权利要求 1 所述的方法，其中以 1-10mg 的剂量施用所述 SERM。

3. 根据权利要求 1 所述的方法，其中所述 SERM 选自屈洛昔芬、左美洛昔芬、（去氨基羟基）托瑞米芬、雷洛昔芬、巴多昔芬和阿佐昔芬。

4. 根据权利要求 1 所述的方法，其中所述 SERM 具有小于 27 小时的半衰期。

5. 根据权利要求 4 所述的方法，其中以 1-10mg 的剂量施用所述 SERM。

6. 根据权利要求 4 所述的方法，其中所述 SERM 选自屈洛昔芬、左美洛昔芬和（去氨基羟基）托瑞米芬。

7. 根据权利要求 1 所述的方法，其中所述雌激素受体介导的病症选自：继发性性腺功能减退症、II 型糖尿病、升高的胆固醇、升高的甘油三酯、消瘦、脂质营养不良、骨质疏松症、女性不育、男性不育、良性前列腺肥大、前列腺癌、乳腺癌、子宫癌和卵巢癌。

8. 根据任意前述权利要求所述的方法，其中每天施用所述组合物。

9. 根据任意前述权利要求所述的方法，其中间歇地施用所述组合物。

10. 根据权利要求 9 所述的方法，其中每隔一天、每周、每 2 周或每个月施用所述组合物。

11. 根据权利要求 1 所述的方法，其中将所述组合物施用给所述患者持续超过 5 年的时段。

12. 根据权利要求 1 所述的方法，其中所述患者是具有 300ng/DL 以下的血清睾酮水平的男人。

13. 根据权利要求 1 所述的方法，其中将所述组合物施用给停止排卵的女性持续至少 4 个连续循环，每个循环包括在自发的或诱导的月经起始之后第二天至第五天开始连续 5 天的施用时段。

14. 根据权利要求 13 所述的方法，其中所述女性是停止排卵的。

15. 根据权利要求 1 所述的方法，其中施用所述 SERM 以治疗男人中的 II 型糖尿病。

16. 根据权利要求 1 所述的方法，其中施用所述 SERM 以治疗和 / 或预防女人中的乳腺癌。

17. 根据权利要求 1 所述的 SERM 或其药学上可接受的盐，其中所述 SERM 的盐是柠檬酸盐。

18. 一种用于治疗雌激素受体介导的病症的方法，所述方法包括：以 1-12mg 的剂量给需要这种治疗的患者施用反式 - 氯米芬或其药学上可接受的盐持续至少 6 个月的时段。

19. 根据权利要求 18 所述的方法，其中以 1-10mg 的剂量施用反式 - 氯米芬。

20. 根据权利要求 18 或 19 所述的方法，其中每天施用反式 - 氯米芬。

21. 根据权利要求 18 或 19 所述的方法，其中所述雌激素受体介导的病症选自：继发性性腺功能减退症、II 型糖尿病、升高的胆固醇、升高的甘油三酯、消瘦、脂质营养不良、骨质疏松症、女性不育、男性不育、良性前列腺肥大、前列腺癌、乳腺癌、子宫癌和卵巢癌。

22. 根据权利要求 1-21 中的任一项所述的方法，其中口服施用所述 SERM。

23. 根据任意前述权利要求所述的方法，其中每天施用所述 SERM 持续至少 2 周，此后间

歇施用所述 SERM。

24. 根据权利要求 23 所述的方法，其中间歇施用包含在相邻给药之间的 3-30 天间隔。

具有短半衰期的选择性雌激素受体调节剂及其用途

[0001] 相关申请的交叉引用

[0002] 本申请要求2012年2月14日提交的美国临时申请号61/598,723的权益，其内容通过引用并入本文。

技术领域

[0003] 本发明涉及用于治疗多种雌激素受体介导的病症的、具有短半衰期的选择性雌激素受体调节剂的长期（即慢性）施用。

背景技术

[0004] 选择性雌激素受体调节剂(SERM)是一类结合雌激素受体(ER)并由此诱导所述受体中的特定构象变化的化合物。由于辅活化剂（其增强ER转录活性）和辅阻遏物（其抑制ER转录活性）的组织特异性募集，SERMS可以在不同组织中发挥不同作用。因此，SERM区别于所谓的“纯”雌激素受体激动剂/拮抗剂，所述“纯”雌激素受体激动剂/拮抗剂独立于组织类型而均匀地活化或阻断雌激素效应。

[0005] 由于它们对雌激素受体的作用，SERMS可用于治疗多种具有雌激素组分的障碍。这些障碍中的许多是需要长期施用SERM的慢性障碍。但是，当在长时间段内施用时，已经观察到严重的不良作用，从而限制了这些化合物的有用性。如果可以施用这些SERM来治疗慢性雌激素受体介导的障碍，将会实现本领域的一个重大进步。

发明内容

[0006] 本发明提供了慢性施用SERM的方法，其会减少或消除由长期施用引起不良作用。根据所述方法，将包含有效量的具有短半衰期的SERM或其药学上可接受的盐的药物组合物施用给具有一种或多种雌激素受体介导的障碍的患者，以便治疗所述障碍至少6个月的时段。

[0007] 通过慢性施用有效量的具有短半衰期的SERM可以治疗的障碍（且其因此可以根据本发明进行治疗）的例子包括、但不限于，继发性性腺功能减退症、II型糖尿病、升高的胆固醇、升高的甘油三酯、消瘦、脂质营养不良、骨质疏松症、女性和男性不育、良性前列腺肥大、绝经、前列腺癌、乳腺癌、子宫癌和卵巢癌。

附图说明

[0008] 图1在第1和14天恩氯米芬剂量的各个$AUC_{(0-24)}$值、各个$AUC_{(0-24)}$比率和$AUC_{(0-24)}$比率的总结统计。该图描绘了在以每天12.5mg、25mg或50mg口服施用反式-氯米芬过程中收集的单剂量和稳态药代动力学数据。

具体实施方式

[0009] 尽管本发明能够以不同的形式体现，但作出几个实施方案的以下描述，条件是本

公开内容应认为是本发明的例证，且无意将本发明限于所阐述的具体实施方案。标题仅为了方便而提供，且不应解释为以任何方式限制本发明。在任何标题下阐述的实施方案可与在任何其它标题下阐述的实施方案组合。

[0010] 应当理解，可由本文出示的数字或数据中的任一个形成的任何范围、比例和比例的范围代表本发明的其它实施方案。这包括含有或不含有有限上限和/或有限下限的可形成的范围。因此，技术人员应理解，许多这样的比例、范围和比例的范围可从本文出示的数据和数字明确导出，并且全部代表本发明的实施方案。

[0011] 在公开和描述本发明的化合物、组合物和方法之前，应当理解，本文中使用的术语仅用于描述特定实施方案的目的，而无意成为限制性的。必须指出，除非上下文另外清楚地指明，否则在本说明书和所附权利要求中使用的单数形式“一个”、“一种”和“所述”包括复数指示物。

[0012] 定义

[0013] 术语“口服”施用是指，活性剂是在被设计为摄取（即被设计为递送至胃肠系统用于吸收）的制剂中。

[0014] 术语“有效剂量”是指，足以治疗特定病症的组合物的活性组分的量。

[0015] 本文中使用的术语“治疗”表示，任意雌激素受体介导的障碍或病症的任意治疗，并且包括但不限于：抑制障碍或病症从而阻止障碍或病症的发展；缓解障碍或病症，例如造成障碍或病症的消退；或缓解由疾病或障碍引起的病症，从而缓解疾病或障碍的症状。

[0016] 与雌激素受体介导的障碍或病症有关的术语“预防”或“阻止”是指，如果障碍或病症尚未发生，则阻止障碍或病症发展的发作，或者如果障碍或病症已经存在，则阻止障碍或病症进一步发展。

[0017] 术语“药学上可接受的盐”表示，从药学上可接受的无毒的无机或有机酸制备的盐。无机酸包括、但不限于：盐酸、氢溴酸、氢碘酸、硝酸、硫酸和磷酸。有机酸包括、但不限于脂族酸、芳族酸、羧酸和磺酸有机酸，包括、但不限于，甲酸、乙酸、丙酸、琥珀酸、苯甲酸、樟脑磺酸、柠檬酸、富马酸、葡糖酸、羟乙磺酸、乳酸、苹果酸、粘酸、酒石酸、对-甲苯磺酸、羟乙酸、葡糖醛酸、马来酸、糠酸、谷氨酸、苯甲酸、邻氨基苯甲酸、水杨酸、苯乙酸、扁桃酸、双羟萘酸（扑酸）、甲磺酸、乙磺酸、泛酸、苯磺酸、硬脂酸、对氨基苯磺酸、海藻酸和半乳糖醛酸。

[0018] 术语“半衰期”被理解为是指，血浆中的 SERM 的浓度减半时的时间。

[0019] 术语“间歇施用”是指，施用治疗有效剂量的 SERM 一段时间，然后停药一段时间，然后施用治疗有效剂量另一段时间，诸如此类。治疗有效剂量的施用时段可以包含连续施用（例如作为持续释放制剂），或者可以包含每天、每隔一天、每周或之间的施用（例如，每天 1 片、2 片或更多片），只要在施用时段内的给药间隔小于停药阶段即可。

[0020] 他莫昔芬的长期口服施用与血管相关的血栓事件（包括中风、深静脉血栓形成和肺栓塞）的约 3 倍增加有关。他莫昔芬的长期施用也与发展子宫内膜癌的风险的约 2 倍增加有关，并且也会显著增加发展白内障的风险。还已经报道了与雷洛昔芬的长期口服施用有关的类似不利事件，尽管在程度上更低。

[0021] 本发明的发明人已经令人惊讶地发现，可以减少或甚至消除长期口服施用 SERM 的不利副作用，而不损失治疗对 SERM 有应答的障碍的效力。当 SERM 具有短半衰期时，发生

该减少或消除，由此实现治疗效果，并且在短时间内，下降至亚治疗浓度。通过采用具有短半衰期的 SERM，可能治疗从慢性 SERM 施用受益的雌激素受体介导的病症，并具有减少或消除的严重不利副作用的可能性。在长期施用具有长半衰期的 SERM 诸如他莫昔芬 (5-7 天）的过程中，所述药物可以随时间广泛地积累。因此，在几个实施方案中，本发明提供了一种长期施用 SERM 的方法，其中所述 SERM 的半衰期是约 30 小时或更小，以便治疗雌激素受体介导的病症，由此减少或甚至消除这些不良作用。优选地，所述 SERM 具有小于 27 小时（诸如小于 26 小时、小于 25 小时、小于 24 小时、小于 23 小时、小于 22 小时、小于 21 小时、小于 20 小时、小于 19 小时、小于 18 小时、小于 17 小时、小于 16 小时、小于 15 小时、小于 14 小时、小于 13 小时、小于 12 小时、小于 11 小时和小于 10.5 小时）的半衰期。

[0022] 令人惊奇地，在用具有较长半衰期的 SERM（诸如他莫昔芬）观察到的相同（或可能甚至更低）剂量和施用频率可以看到治疗益处，尽管更快速地从身体清除。本发明的发明人已经发现，在 SERM 的短暂初始“负载阶段”以后可以发生下丘脑 - 垂体 - 性腺轴的“校正”，由此补偿降低的半衰期，并可能允许用甚至更低的剂量和 / 或施用频率实现等效的治疗效果。在这方面，在每天施用 1 次或 2 次的含有 10mg 至 20mg 他莫昔芬的处方口服制剂中包含他莫昔芬，其为具有相对长半衰期的 SERM 的代表。因而，在一个方面，本发明提供了一种治疗雌激素受体介导的病症的方法，所述方法包括 :以每天 20-40mg 或更小（诸如 1-19mg/ 天、5-19mg/ 天、5-10mg/ 天或 1-9mg/ 天）的剂量，长期施用具有 30 小时或更小、优选小于 27 小时的半衰期的 SERM。在一个有关的实施方案中，可以以 20-40mg 或更小的剂量，例如以 1-19mg、5-10mg 或 1-9mg 的剂量，间歇地（诸如每隔一天、每周、每隔一周、每月或在之间的任意给药间隔）施用具有 30 小时或更小的半衰期的 SERM。在 SERM 的间歇施用之前可以存在初始负载阶段，其中在至少 7 天（例如至少 14 天）或更多连续天的时段内施用 10-20mg 或更小的 SERM。

[0023] 可以将具有 30 小时或更小的半衰期、优选地具有小于 27 小时的半衰期的 SERM 施用至少 6 个月、至少 1 年、至少 18 个月、至少 2 年、至少 30 个月、至少 3 年、至少 42 个月、至少 4 年、至少 54 个月或至少（例如超过）5 年的时段，以便治疗雌激素受体介导的病症。

[0024] 根据本发明，可以将具有 30 小时或更小、优选小于 27 小时的半衰期的任何已知 SERM 施用至少 6 个月的时段。在表 1 中提供了 SERM 的列表以及它们的半衰期 :

[0025] 表 1: 几种选择性雌激素受体调节剂的半衰期

[0026]

SERM	半衰期
恩氯米芬（反式 - 氯米芬）	10.5 小时
屈洛昔芬	24 小时
左美洛昔芬	24 小时
（去氨基羟基）托瑞米芬	25-30 小时
雷洛昔芬	27 小时

巴多昔芬	28 小时
阿佐昔芬	30 小时
托瑞米芬	5 天
他莫昔芬	5-7 天
枸橼酸氯芪酚胺	5-7 天
拉索昔芬	6 天
奥美昔芬	7 天
艾多昔芬	3 周

[0027] 在一个优选的实施方案中，用在本发明的方法中的 SERM 选自屈洛昔芬、反式 - 氯米芬、左美洛昔芬、（去氨基羟基）托瑞米芬、雷洛昔芬、巴多昔芬和阿佐昔芬。

[0028] 在另一个实施方案中，在本发明的方法中采用具有相对短半衰期的反式 - 氯米芬的代谢物。所述反式 - 氯米芬代谢物可以选自 4- 羟基 - 反式 - 氯米芬 (4-OH- 反式 - 氯米芬）、4'- 羟基 - 反式 - 氯米芬（或 4'-OH- 反式 - 氯米芬）、3- 羟基 - 反式 - 氯米芬（或 3-OH- 反式 - 氯米芬）、3,4- 二羟基 - 反式 - 氯米芬，和 N- 脱乙基 - 反式 - 氯米芬。

[0029] 在另一个实施方案中，本发明涉及一种鉴别当慢性施用时具有减少或消除的副作用的 SERM 的方法，所述方法包括：确定哺乳动物的血液中的 SERM 的半衰期，所述半衰期与人类中或处于 I 期临床试验开发的人类中的药代动力学比率有关，并将所述 SERM 的半衰期与他莫昔芬的半衰期进行对比。如果 SERM 具有比他莫昔芬更短的半衰期，那么鉴别出在慢性施用时具有减少或消除的副作用的 SERM。

[0030] 在不同的实施方案中，本发明也提供了可以用在本文所述的方法中的药物组合物，其包含一种或多种具有 30 小时或更小的半衰期的 SERM 或所述的它们的盐和药学上可接受的载体。

[0031] 在一个实施方案中，提供了一种用于升高睾酮水平的方法，所述方法包括：给需要这种治疗的患者施用有效量的具有 30 小时或更小的半衰期的 SERM 或其盐（或包含它们的药物组合物）持续至少 6 个月的时段。在一个有关的实施方案中，提供了一种用于治疗与睾酮缺乏有关的障碍的方法，所述障碍包括、但不限于，少精液症、无精子症、消瘦和抑郁症。在一个优选的实施方案中，所述患者是具有继发性性腺功能减退症的男人，在该情况下，可以施用 SERM 持续至少 6 个月的时段，以便治疗继发性性腺功能减退症。

[0032] 在另一个实施方案中，提供了一种用于降低胆固醇水平的方法，所述方法包括：给需要这种治疗的患者施用有效量的具有 30 小时或更小的半衰期的 SERM 或其盐（或包含它们的药物组合物）持续至少 6 个月的时段。在一个优选的实施方案中，所述患者是具有继发性性腺功能减退症的男人。

[0033] 在另一个实施方案中，提供了一种用于治疗和 / 或预防选自良性前列腺肥大、前列腺癌和升高的甘油三酯的病症的方法，所述方法包括：给需要这种治疗的患者施用有效

量的具有 30 小时或更小的半衰期的 SERM 或其盐（或包含它们的药物组合物）持续至少 6 个月的时段。在一个优选的实施方案中，所述患者是具有继发性性腺功能减退症的男人。

[0034] 在另一个实施方案中，提供了一种用于治疗男人不育的方法，所述方法包括：给需要这种治疗的男人施用有效量的具有 30 小时或更小的半衰期的 SERM 或其盐（或包含它们的药物组合物）持续至少 6 个月的时段。在一个优选的实施方案中，所述患者是具有继发性性腺功能减退症的男人。

[0035] 在另一个实施方案中，提供了一种用于预防从代谢综合征转变为 II 型糖尿病的方法，所述方法包括：给具有继发性性腺功能减退症的男人施用有效量的具有 30 小时或更小的半衰期的 SERM 或其盐（或包含它们的药物组合物）持续至少 6 个月的时段。

[0036] 在另一个实施方案中，提供了一种用于治疗 II 型糖尿病的方法，所述方法包括：给需要这种治疗的男人施用有效量的具有 30 小时或更小的半衰期的 SERM 或其盐（或包含它们的药物组合物）持续至少 6 个月的时段。优选地，所述男人是具有继发性性腺功能减退症的男人。

[0037] 在另一个实施方案中，提供了一种用于治疗女性不育的方法，所述方法包括：给需要这种治疗的女性施用有效量的具有 30 小时或更小的半衰期的 SERM 或其盐（或包含它们的药物组合物）持续至少 6 个连续循环。优选地，在月经周期的卵泡早期连续 5 天施用 SERM 作为每日剂量。例如，施用计划可以包括在月经周期的第 5-9 天或第 3-7 天施用。优选地，所述患者是停止排卵的女性。

[0038] 在另一个实施方案中，提供了一种用于治疗和 / 或预防乳腺癌的方法，所述方法包括：给需要这种治疗的女性施用有效量的具有 30 小时或更小的半衰期的 SERM 或其盐（或包含它们的药物组合物）持续至少 6 个月、优选至少 5 年（例如超过 5 年）的时段。根据该实施方案，可以将 SERM 施用给处于增加的发展乳腺癌风险中的女性，以便预防乳腺癌的发展。可替换地，可以将 SERM 施用给具有乳腺癌的女性，以便治疗乳腺癌。还可以施用 SERM 作为外科手术初次治疗以后的辅助疗法，以便使复发的可能性最小化。优选地，当作为佐剂施用时，施用 SERM 持续至少约 5 年的时段。

[0039] 在另一个实施方案中，提供了一种用于治疗子宫内膜（或子宫）癌症的方法，所述方法包括：给需要这种治疗的女性施用有效量的具有 30 小时或更小的半衰期的 SERM 或其盐（或包含它们的药物组合物）持续至少 6 个月的时段。

[0040] 在另一个实施方案中，提供了一种用于治疗卵巢癌的方法，所述方法包括：给需要这种治疗的女性施用有效量的具有 30 小时或更小的半衰期的 SERM 或其盐（或包含它们的药物组合物）持续至少 6 个月的时段。

[0041] 在另一个实施方案中，提供了一种用于治疗骨质疏松症的方法，所述方法包括：给需要这种治疗的女性施用有效量的具有 30 小时或更小的半衰期的 SERM 或其盐（或包含它们的药物组合物）持续至少 6 个月的时段。

[0042] 在本文描述的组合物和方法中使用的 SERM 可以根据已知方法化学合成，且包括每种化合物的盐形式。根据在美国专利号 4,418,068 和 4,133,814（它们中的每一篇通过引用并入本文）中描述的方法，可以生产雷洛昔芬 (6- 羟基 -2(4- 羟基苯基)-3-[4-(2- 哌啶基 (piperdino) 乙氧基）苯甲酰基] 苯并 [b] 噻吩）和它的药理学上可接受的盐。根据在美国专利号 5,047,431（其通过引用并入本文）中描述的方法，可以生产屈洛昔芬

(E-1-[4'-(2-二甲基氨基乙氧基)苯基]-1-(3'-羟基苯基)-2-苯基-1-丁烯)和它的药理学上可接受的盐。根据在美国专利号5,723,474(其通过引用并入本文)中描述的方法,可以生产阿佐昔芬(2-(4-甲氧基苯基)-4-[4-[2-(1-哌啶基)乙氧基]苯氧基]苯并[b]噻吩-6-醇)和它的药学上可接受的盐。根据在美国专利号5,998,402和6,479,535(它们中的每一篇通过引用并入本文)中描述的方法,可以生产巴多昔芬和它的药学上可接受的盐。根据在美国专利号4,447,622(其通过引用并入本文)中描述的方法,可以生产左美洛昔芬((-)-3R,4R-反式-7-甲氧基-2,2-二甲基-3-苯基-4-{4-[2-(吡咯烷-1-基)乙氧基]苯基}色满)和它的药学上可接受的盐。

[0043] 根据本发明的药物组合物可以包含在约1mg至约200mg之间的剂量的本发明的SERM或基本上由其组成(尽管最佳剂量的确定是在本领域的普通技术水平内)。所述组合物可以包含在约1mg、2mg、3、mg、4mg、5mg、10mg、15mg、20mg、25mg、30mg、35mg、40mg、45mg、50mg、55mg、60mg、65mg、70mg、75mg、80mg、85mg、90mg、95mg、100mg、110mg、120mg、130mg、140mg、150mg、160mg、170mg、180mg、190mg、200mg或之间的剂量的本发明的SERM。在一个优选的实施方案中,所述组合物包含在约1mg至约19mg的剂量、更优选地在约1mg至约9mg的剂量的本发明的SERM。

[0044] 药物组合物可以包含100%(w/w)的本发明的SERM,或者可以额外包含可用于实现期望的治疗效果的其它活性剂。在药物组合物包含100%(w/w)的本发明的SERM的情况下,可以依次或同时单独地共同施用一种或多种额外活性剂,以实现期望的治疗效果。因而,在几个实施方案中,本发明提供了一种治疗雌激素受体介导的病症的方法,所述方法包括:与额外治疗剂一起共同施用本发明的SERM。所述额外治疗剂可以是已知会有效地治疗雌激素受体介导的病症的任意药剂。

[0045] 如本申请中所用的术语"治疗"表示治疗性处理和预防性的或防止性的措施,其中目的是预防或减缓(减少)不希望的生理学或心理学变化或障碍,诸如与继发性性腺功能减退症有关的征状。就本发明的目的而言,有益的或期望的临床结果包括,但不限于:减轻征状、减轻疾病的程度、稳定(即,不恶化)疾病的状态、延缓或减慢疾病进展、改善或减缓疾病状态和缓解(无论部分还是全部)、无论可检测的或不可检测的。"治疗"还可以意味着,与如果不接受治疗的预期生存相比,延长生存。需要治疗的个体包括:已经患有所述病症或障碍的那些个体,以及易于发展所述病症或障碍的那些个体,或要预防所述病症或障碍的那些个体。

[0046] 合适的药物组合物或单位剂型可以呈固体(诸如片剂或填充的胶囊剂)或液体(诸如溶液、混悬液、乳剂、酏剂或装有它们的胶囊剂)的形式,都用于口服使用。所述组合物也可以呈无菌可注射溶液或用于胃肠外(包括皮下)使用的乳剂的形式。所述组合物也可以配制用于局部施用。例如,可以将所述组合物配制为洗剂、乳膏剂、软膏剂、凝胶、泡沫或透皮贴剂。在一个优选的实施方案中,将所述组合物配制为用于透皮施用(例如施用至阴囊)的凝胶(例如含水醇凝胶)。这样的药物组合物及其单位剂型可以包含常规比例的成分。

[0047] 尽管口服施用是优选的途径,根据本发明的组合物可以通过任意给药途径来施用,包括、但不限于,静脉内、皮下、含服、透粘膜、鞘内、真皮内、脑池内、肌肉内、透皮、腹膜内、硬膜外、阴道、直肠、鼻内、舌下、关节内、脑脊髓内和滑膜内。

[0048] 还可以以快速释放制剂、缓慢释放制剂或者快速释放制剂和缓慢释放制剂的混合物的形式施用本发明的组合物，诸如包含至少一个快速释放层和至少一个缓慢释放层的多层片剂。

[0049] 在本文中讨论的所有参考文献通过引用整体并入。

[0050] 下述实施例旨在作为本发明的示例，且无意限制在所附权利要求书中阐述的本发明的范围。

[0051] 实施例 1

[0052] 反式 - 氯米芬的药代动力学分布

[0053] 在口服施用单次剂量和稳态剂量以后估测恩氯米芬（反式 - 氯米芬）的药代动力学 (PK) 分布的临床研究。将 52 个 18-75 岁之间的成年男人随机分配至下述 5 个治疗组之一，所述成年男人具有 <250ng/dl 或在 250-300ng/dl 之间的总血清睾酮水平和在正常范围内的 FSH/LH 水平 :(i)12.5mg 恩氯米芬 / 天 (ii)25mg 恩氯米芬 / 天 (iii)50mg 恩氯米芬 / 天（反式 - 氯米芬）(iv) **Androgel®**（每天施用的 1％局部睾酮）或 (v) 安慰剂。将柠檬酸恩氯米芬提供为 12.5mg 胶囊剂，并每天口服施用 1 次 (12.5mg 组）、2 次 (25mg 组）或 4 次 (50mg 组），连续 14 天。在第一次（第 1 天）和最后一次（第 14 天）给药以后，在这些男人的子集中进行单次剂量和稳态 PK 评估。在第 1 和 14 天，在给药前 (0 小时）和在给药后 0.5、1、2、3、4、6、8、12、18 和 24 小时得到系列血液样品，用于血浆恩氯米芬测定。还使用单个血液样品，在第 11 天测量给药前血浆恩氯米芬浓度。药代动力学 (PK) 端点为从 0 至 24 小时在浓度 - 时间曲线下的面积 (AUC_{0-24})、在第 1 天单剂量施用和在第 14 天稳态给药以后的最大浓度 (C_{max})、达到 C_{max} 的时间 (T_{max}) 以及血浆恩氯米芬的消除半衰期 ($t_{1/2}$)。对于随机化至恩氯米芬的受试者，使用无房室方法计算 PK 参数。计算累积比率，其被定义为在第 14 天的 AUC_{0-24} 除以在第 1 天的 AUC_{0-24} 值。

[0054] 在第 1 天，12.5mg、25mg 和 50mg 恩氯米芬的平均 (SD) C_{max} 值分别为 1.98(1.78)、4.79(3.88) 和 5.56(1.09)ng/ml。在第 14 天，12.5mg、25mg 和 50mg 恩氯米芬的平均 (SD) C_{max} 值分别为 2.68(1.68)、10.63(9.58) 和 12.09(5.74)ng/ml。

[0055] 在第 1 天，12.5mg、25mg 和 50mg 恩氯米芬的中间 T_{max} 值分别为 4.0、2.0 和 2.0 小时。在第 14 天，12.5mg、25mg 和 50mg 恩氯米芬的中间 T_{max} 值分别为 4.0、3.0 和 2.0 小时。

[0056] 在第 1 天，12.5mg、25mg 和 50mg 恩氯米芬的平均 (SD) $T_{1/2}$ 值分别为 7.91(4.91)、8.08(2.01) 和 6.53(0.92) 小时。在第 14 天，12.5mg、25mg 和 50mg 恩氯米芬的平均 (SD) $T_{1/2}$ 值分别为 9.31(2.40)、10.73(2.51) 和 9.69(0.92) 小时。

[0057] 基于在第 14 天的 $AUC_{(0-24)}$ 除以在第 1 天的 $AUC_{(0-24)}$ 的各个比率的算术平均值，计算每个恩氯米芬剂量组的积累指数。12.5mg、25mg 和 50mg 恩氯米芬的平均 (SD) 积累指数值分别为 2.53(1.08)、2.84(1.19) 和 2.49(0.63)。

[0058] PK 结果描绘在图 1 中。基于得到的 PK 数据，确定恩氯米芬的半衰期为约 10.5 小时。

[0059] 实施例 2

[0060] 反式 - 氯米芬的长期施用

[0061] 在 1 年标签公开的多中心扩展研究中招收了 104 个具有继发性性腺功能减退症（在初次筛选就诊时血清睾酮 <300ng/dl) 的成年男人，他们完成了 6 个月研究，在该研究

中，以每天 12.5、25 或 50mg 反式 - 氯米芬的剂量口服施用反式 - 氯米芬（柠檬酸盐），共 70 位受试者完成了该扩展研究。受试者的总平均年龄是 54.1 岁，身体质量指数 (BMI) 为 31.8kg/m^2，平均基线总睾酮为 290.1ng/dL。已经将所述 6 个月研究中的受试者随机分配至下述组：(1)12.5mg 反式 - 氯米芬 (2)25mg 反式 - 氯米芬 (3)50mg 反式 - 氯米芬 (4) **AndroGel®** 1％局部睾酮或 (5) 安慰剂。在扩展研究中的所有受试者接受 12.5mg 反式 - 氯米芬的日口服剂量，持续多达 1 年。在扩展研究过程中，对 6 个月研究中的 5 个治疗组的每个组的患者评估不利事件以及多种临床参数相对于基线的变化。在实验室就诊过程中做出评估，所述就诊发生在第 0 天 [就诊 1]、第 1 个月 [就诊 2] 和此后以大约 2 个月间隔持续 12 个月（第 1 个月 [就诊 2] 至第 12 个月 [就诊 7])。随访就诊 [就诊 8] 发生在治疗停止以后 1 个月。

[0062] 该研究的主要效力端点是在 1 年时表现出在正常范围 (300-1040ng/dl) 内的早晨总血清睾酮浓度的受试者的比例。已经证实单个早晨睾酮水平与对给定受试者观察到的最大和平均睾酮水平高度相关。总体上，62.5％的受试者在 1 年时具有在正常参考范围内的平均总血清睾酮水平。从基线至 1 年的总血清睾酮的总平均增加是统计上显著的；在研究过程中，相对于基线的总睾酮浓度的总平均增加范围为 9.8-251.3ng/dl（第 2 个月至随访，包括短点）。

[0063] 如在国际勃起功能指数 (International Index of Erectile Function，IIEF) 问卷调查的性欲组分上所评估的，在第 4、6 和 12 个月时观察到性欲相对于基线的统计上显著的改善。但是，在性功能的其它问卷调查诸如关于性功能的 DeRogatis 面谈 (DeRogatis Interview for Sexual Function)(DISF-SR II(M)) 和男性性苦恼量表 (Male Sexual Distress Scale)IV-A(MSDS) 中，没有反映伴随地显著的变化。在研究过程中，睾丸尺寸平均值（使用睾丸测量计测量）的总增加范围为 0.8-2.3mL；仅在第 6 个月观察到统计上显著的增加。

[0064] 在大多数或所有时间点，观察到 LH、FSH、性激素结合球蛋白 (SHBG)、雌二醇、二氢睾酮 (DHT) 和 DHT/ 睾酮比率的统计上显著的增加；在大多数或所有时间点，观察到催乳素的统计上显著的减少。

[0065] 在大多数或所有时间点，观察到总胆固醇 (TC)、高密度脂蛋白胆固醇 (HDL-C) 和甘油三酯相对于基线的统计上显著的减少。

[0066] 仅五位 (5％）受试者经历严重的不良作用 (SAE) - 所述五位受试者中的四位具有被认为与药物无关 / 不可能相关的 SAE。总体上，51.5％的受试者在研究过程中经历了至少一个不利事件；18.8％的受试者 (19/101) 经历了至少一个被认为与研究药物有关的不利事件。大多数事件在严重程度上是轻度或中度；九位受试者经历了被认为严重的事件。九位受试者由于 AE 而中断研究。9 位中断研究的受试者中的 5 位经历了被认为可能或大概与研究药物有关的 AE。

[0067] 没有受试者由于视敏度的下降而中断。

[0068] 尽管在少数受试者中观察到某些血液化学变量的临床上显著的变化，仅一位受试者由于增加的丙氨酸氨基转移酶 (ALT) 和天冬氨酸氨基转移酶 (AST) 的 AE 而中断研究。在血液学、血液化学或尿分析变量中或在生命体征、体检、前列腺特异性的抗原 (PSA) 值或心电图 (ECG) 读出中不存在临床上有关的变化。

[0069] 这些发现有力地支持了低浓度的具有相对长半衰期的 SERM 的长期口服施用用于治疗多种雌激素受体介导的病症并同时减少或消除当慢性施用具有相对长半衰期的 SERM(例如他莫昔芬)时观察到的严重不良作用的效力。在使用 12.5mg 口服反式 - 氯米芬的 18 个月疗程中,没有观察到在长期施用他莫昔芬的过程中所观察到的心血管的和眼睛的不良作用(例如深静脉血栓形成、白内障)。该数据与在啮齿动物、狒狒、兔和狗模型中的动物安全性药理学研究一致,所述研究没有证实在施用反式 - 氯米芬的动物中对中枢神经系统、呼吸系统或心血管系统的不良作用。

受试者	恩氯米芬剂量	第1天 $AUC_{(0-24)}$	第14天 $AUC_{(0-24)}$	积累指数 第14天/第1天AUC比率
1008	恩氯米芬 12.5 mg	12.2504	24.7157	2.0175
1043	恩氯米芬 12.5 mg	34.4866	69.7163	2.0215
1068	恩氯米芬 12.5 mg	10.0064	37.1102	3.7086
1071	恩氯米芬 12.5 mg	10.2108	36.9013	3.6139
1096	恩氯米芬 12.5 mg	1.4717	1.8622	1.2653
			平均值	2.5254
			SD	1.0822
			SE	0.4840
			范围	1.27 - 3.71
受试者	恩氯米芬剂量	第1天 $AUC_{(0-24)}$	第14天 $AUC_{(0-24)}$	积累指数 第14天/第1天AUC比率
1010	恩氯米芬 25 mg	33.4381	67.8184	2.0282
1039	恩氯米芬 25 mg	9.4452	29.5313	3.1266
1078	恩氯米芬 25 mg	26.2345	125.6074	4.7879
1084	恩氯米芬 25 mg	40.4145	78.4035	1.9400
1090	恩氯米芬 25 mg	100.0801	231.2393	2.3105
			平均值	2.8386
			SD	1.1859
			SE	0.5304
			范围	1.94 - 4.79
受试者	恩氯米芬剂量	第1天 $AUC_{(0-24)}$	第14天 $AUC_{(0-24)}$	积累指数 第14天/第1天AUC比率
1001	恩氯米芬 50 mg	37.2391	108.5459	2.9148
1037	恩氯米芬 50 mg	23.2863	36.3181	1.5596
1091	恩氯米芬 50 mg	48.851	131.3707	2.6892
1094	恩氯米芬 50 mg	43.6337	122.8372	2.8152
			平均值	2.4947
			SD	0.6302
			SE	0.3151
			范围	1.56 - 2.92

图 1