Appeal decision

Appeal No. 2018-9319

Appellant ENDORECHERCHE, INC.

Patent Attorney MURAYAMA, Yasuhiko

Patent Attorney JITSUHIRO, Shinya

Patent Attorney ABE, Tatsuhiko

The case of appeal against the examiner's decision of refusal of Japanese Patent Application No. 2016-557002, entitled "TREATMENT OF MALE ANDROGEN DEFICIENCY SYMPTOMS OR DISEASES WITH SEX STEROID PRECURSOR COMBINED WITH SERM" (international publication dated September 17, 2015, International Publication No. WO2015/135061, national publication dated March 23, 2017, National Publication of International Patent Application No. 2017-507975) has resulted in the following appeal decision:

Conclusion

The appeal of the case was groundless.

Reason

[No. 1] History of the procedures

The present application was filed as an international patent application on March 9, 2015 (priority claim under the Paris Convention received by the foreign receiving office on March 10, 2014 in the US, one other). Then, an appeal against the examiner's decision of refusal was requested on July 5, 2018 and a written amendment was submitted at the same time. After that, a notice of reasons for refusal was issued by the body on September 18, 2019. In response to this, a written amendment was submitted on March 19, 2020 and a written opinion was submitted on the same date.

[No. 2] The Invention

The inventions recited in Claims 1 to 16 of the present application are specified by the matters stated in Claims 1 to 16 of the scope of claims in the written amendment submitted on March 19, 2020. Among them, the invention recited in Claim 1 is as follows (hereinafter, also may be referred to as "the Invention"):

"Use of a sex steroid precursor in combination with a selective estrogen receptor modulator in the manufacture of a medicament for reducing or eliminating the incidence of male androgen deficiency symptoms or diseases including male hypogonadism-associated symptoms and diseases in a male patient, wherein the selective estrogen receptor modulator stimulates LH secretion which increases the level of circulating testosterone, the sex steroid precursor is dehydroepiandrosterone, and the selective

estrogen receptor modulator is acolbifene or EM-800."

[No. 3] The reasons of refusal stated in the notice of reasons for refusal by the body

The brief summary of part of Refusal Reason 1 stated in the above notification for refusal dated September 18, 2019 (hereinafter, also simply referred to as "the notice of reasons for refusal") is that a person skilled in the art could have easily invented the Invention by taking into consideration matters in cited references distributed before the priority date of the application, specifically, by taking into consideration the invention disclosed in cited reference A1 in combination with the description of cited reference B or by taking into consideration the invention disclosed in cited reference A1 in combination with the description of any of cited references A2 to A6 and the description of cited reference B, and thus the Appellant should not be granted a patent under the provisions of Article 29(2) of the Patent Act.

[List of cited publications, etc.]
A1. National Publication of International Patent Application No. 2008-511615
A2. KATZ, DJ ET AL., BJU INT., (2012) 110(4) pp. 573-578
A3. TAYLOR, F. ET AL., J. SEX MED., (2010) 7(1 Pt1) pp. 269-276
A4. SHABSIGH, A. ET AL., J. SEX. MED., (2005) 2(5) pp. 716-721
A5. GUAY, AT ET AL., INT. J. IMPOT. RES., (2003) 15(3) pp. 156-165
A6. National Publication of International Patent Application No. 2003-50344
B. J. CLIN. ENDOCRINOL. METAB., (2013) 98 pp. 3615-3626

[No. 4] Judgment by the body
1. Described matters in Cited Publications

Among the publications cited in the notice of reasons for refusal, the following Publications A1, A6, and B respectively include the matters as stated below.
A1. National Publication of International Patent Application No. 2008-511615
A6. National Publication of International Patent Application No. 2003-503446
B. J. CLIN. ENDOCRINOL. METAB., (2013) 98 pp. 3615-3626
(Since the Cited Document is in English, the translation thereof by the body is indicated. Each underline is made by the body.)

(1) Publication A1

- (A1-1) Claims 1 to 9
"[Claim 1]

The use of a selective estrogen receptor modulator, or an isomer, isomer mixture, metabolite or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical preparation for use in a method for the treatment or prevention of androgen deficiency in a male individual.
[Claim 2]

The use according to claim 1, wherein the selective estrogen receptor modulator is a triphenyl alkane compound, a triphenyl alkene compound, where the alkene chain is halogen-substituted butene or propene, a benzo thiophene compound, EM652, EM800, EM776, EM651, EM312, ICI182780, ERA-923, zindoxifene, deacetylated zindoxifene, ZKl19010, TSE-4247, lasoxifene, a lasoxifene analogue, nafoxidine, basedoxifene,

GW5638, GW7604, ICI164384, RU58668, RU39411 or EM319, or an isomer, isomer mixture, metabolite, or pharmaceutically acceptable salt thereof.
...
[Claim 5]
The use according to any of claims 1 to 4, wherein the selective estrogen receptor modulator is a compound with tissue specific antiestrogenic or estrogenic effects suitable for men.
[Claim 6]
The use according to claim 5, wherein the selective estrogen receptor modulator is selected from the group consisting of ...,
(Z)-2-{2-[4-(4-Chloro-1,2-diphenylbut-1-enyl)phenoxy]ethoxy}ethanol (fispemifene), ..., or an isomer, isomer mixture, metabolite, or pharmaceutically acceptable salt thereof.
[Claim 7]
The use according to claim 6, wherein the selective estrogen receptor modulator is fispemifene or a metabolite or pharmaceutically acceptable salt thereof.
[Claim 8]
A use of a selective estrogen receptor modulator as defined in any of the claims 1-7, or an isomer, isomer mixture, metabolite, or pharmaceutically acceptable salt thereof in the manufacture of a pharmaceutical preparation useful for prevention or treatment of a disease or disorder in a male individual, said disease or disorder being caused by androgen deficiency in said individual.
[Claim 9]
The use according to claim 8, wherein said disease or disorder is selected from the group consisting of:
hypogonadism, particularly but not restricted to secondary hypogonadism resulting from disease or disorders such as Kallman's Syndrome, Prader-Labhart-Willi's Syndrome, Laurence-Moon-Biedl's Syndrome, pituitary insufficiency/adenomas, Pasqualini's Syndrome, hemochromatosis, hyperprolactinemia, pituitary- hypothalamic injury from tumors, trauma, irradiation, obesity, chronic illness, such as diabetes mellitus, hypotyroidism, or other disease or disorder that may affect central production of gonadotropin;
age-related testosterone deficiency and diseases or disorders resulting therefrom, such as impaired muscle strength, sexual dysfunction, decreased libido, loss of muscle mass, decreased bone density, depressed mood, and decreased cognitive function; and
any muscular atrophy/dystrophies; lipodistrophy; long-term critical illness; sarcopenia; frailty or age-related functional decline; reduced muscle strength and function; muscle wasting from HIV; chronic renal failure, reduced bone density or growth; catabolic side effects of glucocorticoids; chronic fatigue syndrome; reduced bone fracture repair; acute fatigue syndrome and muscle loss following elective surgery; cachesia; chronic catabolic state; eating disorders; side effects of chemotherapy; wasting; depression; nervousness irritability; stress; growth retardation; senescence outfall symptoms; reduced cognitive function; anaemia; male contraception; infertility; Syndrome X; diabetic complications, or obesity.
..."

- (A1-2) [0001] to [0008]
"[Technical Field]

[0001]

This invention relates to a method for treatment or prevention of androgen deficiency in a male individual, said method comprising administering to the individual an effective amount of a selective estrogen receptor modulator (SERM). The invention concerns further methods for treatment or prevention of diseases or disorders caused by said androgen deficiency.

[Background Art]

...

[0003]

Testosterone in men

Masculine sex hormones, the androgens, are responsible for the development of the masculine sex characteristics. Furthermore, they are required for reproduction. The main element of the androgens is testosterone, which is imperative for the development and function of the internal and external masculine sex organs, has a supportive influence regarding muscle growth, determines the distribution and the density of hair growth, and has a positive influence with respect to the production of erythrocytes and with respect to the distribution of erythropoietin and the cognitive functions. A deficiency of testosterone (hypogonadism) may be classified into two principle forms, which are designated primary and secondary hypogonadism. Diseases based on testosterone deficiency include, for instance, osteoporosis, muscle atrophy, senescence outfall symptoms, the decrease of libido and potency, depression, and anaemia.

[0004]

Primary hypogonadism

The lack of testosterone production or a decreased testosterone production within the body, originating from a malfunction of the testicles, which is the main synthesis location of testosterone, is designated primary hypogonadism. Primary hypogonadism includes testicular failure due to congenital or acquired anorchia, XYY Syndrome, XX males, Noonan's Syndrome, gonadal dysgenesis, Leydig cell tumors, maldescended testes, varicocele, Sertoli-Cell-Only Syndrome, cryptorchidism, bilateraltorsion, vanishing testis syndrome, orchiectomy, Klinefelter's Syndrome, chemotherapy, toxic damage from alcohol or heavy metals, and general disease (renal failure, liver cirrhosis, diabetes, myotonia dystrophica). Patients with primary hypogonadism show an intact feedback mechanism, in that the low serum testosterone concentrations are associated with high FSH (follicle- stimulating hormone) and LH (luteinizing hormone) concentrations. However, because of testicular or other organ failures, the high LH concentrations are not effective at stimulating testosterone production.

[0005]

Secondary hypogonadism

If the main reason for the diseases is a malfunction of the hypothalamus or the hypophysis, the disease is named secondary (or hypogonadotrophic) hypogonadism. This involves an idiopathic gonadotropin or LH-releasing hormone deficiency. This type of hypogonadism includes Kallman's Syndrome, Prader-Labhart-Willi's Syndrome, Laurence-Moon-Biedl's Syndrome, pituitary insufficiency/adenomas, Pasqualini's Syndrome, hemochromatosis, hyperprolactinemia, or pituitary- hypothalamic injury from tumors, trauma, radiation, or obesity. Because patients with secondary hypogonadism do not demonstrate an intact feedback pathway, the lower testosterone concentrations are not associated with increased LH or FSH levels. Thus, these patients have low

testosterone levels in serum but have gonadotropins in the normal to low range.
[0006]

Age-related testosterone deficiency

Men experience a slow but continuous decline in average serum testosterone after the age of approximately 20 to 30 years. Researchers estimate that the decline is about 1- 2% per year. Moreover, as men age, the circadian rhythm of testosterone concentration is often muted, dampened, or completely lost. The untreated testosterone deficiency in older men may lead to a variety of physical changes, including sexual dysfunction, decreased libido, loss of muscle mass, decreased bone density, depressed mood, and decreased cognitive function. The net result is male andropause, also known as late-onset hypogonadism or androgen decline in the aging male (ADAM).
[0007]

Diagnosis and treatment of testosterone deficiency

The normal ranges for testosterone concentration vary, as does the definition of the limit value to diagnose hypogonadism. The report of the Endocrine Society's Second Annual Andropause Consensus Meeting (Endocrine Society, 2002) delineated three categories for consideration in screening and diagnosing hypogonadism in men over 50 years of age: 1) if total testosterone is < 200 ng/dL (i.e., 7 nmol/L), diagnosis of androgen deficiency is confirmed; serious hypothalamic or pituitary disease in men with hypogonadotropic hypogonadism is to be ruled out; 2) if total testosterone levels are between 200 and 400 ng/dL (i.e., 7-14 nmol/L), additional measures of testosterone and further evaluation before considering testosterone therapy are recommended; and 3) if total testosterone levels are > 400 ng/dL (i.e., 14 nmol/L), there is no testosterone deficiency. Many studies have used the 300 to 350 ng/dL (i.e., 10-12 nmol/L) range of total testosterone as a cutoff for identifying hypogonadal patients (in Testosterone and Aging, Clinical Research Directions 2004, ed. Liverman CT and Blaxer DG). In addition to the low testosterone serum concentration, sign(s) and/or symptom(s) of testosterone deficiency should be present for the diagnosis.
[0008]

The treatment is usually a Substitution Therapy which effectively can be measured directly based on the testosterone concentration in serum. The aim of the testosterone substitution is to increase the testosterone concentration in serum to the normal value. Currently, testosterone/androgen compounds are used as treatments for hypogonadism."

- (A1-3) [0009] to [0022]
"[0009]

Selective estrogen receptor modulator

'SERM's (selective estrogen receptor modulators) have both estrogen-like and antiestrogenic properties (Kauffman & Bryant, Drug News Perspect 8:531 -539,1995). The effects may be tissue-specific as in the case of tamoxifen and toremifene which have estrogen-like effects in the bone, partial estrogen-like effect in the uterus and liver, and pure antiestrogenic effect in breast cancer. Raloxifene and droloxifene are similar to tamoxifen and toremifene, except that their antiestrogenic properties dominate. They are known to decrease total and LDL cholesterol, thus diminishing the risk of cardiovascular diseases, and they may prevent osteoporosis and inhibit breast cancer growth in postmenopausal women.
...

[Means for Solving the Problem]
[0011]

The inventors of the present invention have surprisingly found that compounds belonging to the group of selective estrogen receptor modulators are effective in raising the serum testosterone level in men.

...

[Best Mode for Carrying Out the Invention]
[0013]

Definitions

The term 'treatment' or 'treating' shall be understood to include complete curing of a disease or disorder, amelioration or alleviation and of said disease or disorder, and delaying the progress or onset of said disease or disorder.

[0014]

The term 'prevention' shall be understood to include complete prevention, prophylaxis, as well as lowering the risk of falling ill with said disease or disorder.

...

[0017]

The term 'androgen deficiency' shall mean a condition in the male individual where the serum level of masculine sex hormones, particularly testosterone and dihydrotestosterone, is decreased.

[0018]

The term 'testosterone deficiency' refers to a condition in the male individual where the serum level of testosterone is decreased, particularly decreased to a serum level below or at the lower range of the normal reference level. The reference level depends on the laboratory methods used.

[0019]

The wording 'selective estrogen receptor modulator' and any specific compound belonging to this group shall be understood to cover any geometric isomer, any stereoisomer, racemate, or other mixture of isomers of the compound. Furthermore, pharmaceutically acceptable salts and other derivatives such as esters as well as metabolites are also included.

[0020]

Diseases or disorders which can be prevented or treated by treating or preventing androgen deficiency using SERMs.

The inventors believe that SERMs are useful for prevention or treatment of any disease or disorder in a male individual, said disease or disorder being caused by androgen deficiency.

[0021]

Hypogonadism, particularly secondary hypogonadism, and age-related testosterone deficiency are examples of disorders which can treated or prevented by administrating SERMs according to this invention. Also specific diseases or disorders resulting from said hypogonadism or age-related testosterone deficiency can be treated or prevented. However, other diseases or disorders which are caused by androgen deficiency but which are unrelated to hypogonadism or age-related testosterone deficiency may be treated or prevented according to the method of this invention.

[0022]

Thus, as examples of specific diseases or disorder which can be treated or

prevented according to the present invention there can be mentioned:
1) hypogonadism, particularly but not restricted to secondary hypogonadism resulting from diseases or disorders such as Kallman's Syndrome, Prader-Labhart- Willi's Syndrome, Laurence-Moon-Biedl's Syndrome, pituitary insufficiency/adenomas, Pasqualini's Syndrome, hemochromatosis, hyperprolactinemia, pituitary-hypothalamic injury from tumors, trauma, radiation, obesity, chronic illness, such as diabetes mellitus, hypotyroidism, or other disease or disorder that may affect central production of gonadotropin;
2) age-related testosterone deficiency and diseases or disorders resulting therefrom, such as impaired muscle strength, sexual dysfunction, decreased libido, loss of muscle mass, decreased bone density, depressed mood, and decreased cognitive function; and
3) any muscular atrophy/dystrophies; lipodistrophy; long-term critical illness; sarcopenia; frailty or age-related functional decline; reduced muscle strength and function; muscle wasting from HIV; chronic renal failure, reduced bone density or growth; catabolic side effects of glucocorticoids; chronic fatigue syndrome; reduced bone fracture repair; acute fatigue syndrome and muscle loss following elective surgery; cachesia; chronic catabolic state; eating disorders; side effects of chemotherapy; wasting; depression; nervousness irritability; stress; growth retardation; senescence outfall symptoms; reduced cognitive function; anaemia; male contraception; infertility; Syndrome X; diabetic complications or obesity."

- (A1-4) [0024] to [0028]
"[0024]

Advantages of SERMs in the treatment of androgen deficiency

A SERM increasing testosterone sufficiently to treat testosterone deficiency may have several advantages in addition to direct testosterone substitution. The benefits of the increased testosterone can be achieved while a SERM compound having anti-estrogenic or estrogenic effects, simultaneously protects against the potential side-effects commonly associated with increased testosterone such as prostate stimulation, gynecomastia, or adverse effects on lipid metabolism.
[0025]

It is known that many estrogens/anti-estrogens/phytoestrogens/SERMs have antitumor effects mediated via estrogen receptor, and they can potentially prevent and treat prostate cancer (Ho S-M: Estrogens and Anti-Estrogens: Key Mediators of Prostate Carcinogenesis and New Therapeutic Candidates. 2004;91:491-503). The SERMs are antiestrogenic in breast and could therefore provide protection against gynecomastia, often associated with testosterone treatments.
[0026]

The SERMs provide beneficial effects on the lipid profile such as increased HDL, and decreased total cholesterol and LDL. Testosterone is known for instance to decrease HDL, and this adverse effect could thus be counteracted with the SERM. Both SERMs and testosterone have beneficial effects on bone metabolism by inhibiting bone turnover. Thus, the protective effect of a SERM on bone is likely to be enhanced if it has the ability to increase testosterone.
[0027]

To sum up, SERMs, particularly the SERMs according to formula (I) presented below, produce the positive response of androgen replacement therapy without the

undesired side effects of testosterone, such as adverse effects on the prostate or on lipid metabolism, or gynecomastia.
[0028]

These compounds increase testosterone and thus stimulate muscle growth and reduce subcutaneous and visceral abdominal fat in the treatment of obesity; increase energy and libido and minimize bone depletion; and have beneficial effects on lipid metabolism."

- (A1-5) [0029] to [0041]
"[0029]

Preferable SERMs

Suitable selective estrogen receptor modulators for use in this invention are, for example, the compounds disclosed in V Craig Jordan (2003).
[0030]

Thus, examples of suitable selective estrogen receptor modulators for use in the present invention include triphenylalkene or triphenylalkane compounds such as compounds disclosed in International Patent publication No. WO 01/36360, US Patent No. 4,996,225, US Patent No. 4,696,949, US Patent No. 5,750,576, and International Patent publication No. WO 99/42427, and the toremifene metabolites disclosed in L Kangas(Cancer Chemother Pharmacol (1990)27:8-12.) As examples of specific drugs disclosed in the aforementioned references there can be mentioned toreinifene, fispemifene, and ospemifene. ...
...
[0032]

As further examples of suitable SERMs there can be mentioned EM652, EM800, EM776, EM651, EM312, ICI182780, ERA-923, zindoxifene and deacetylated zindoxifene, ZK119010, TSE-4247, lasoxifene and its analogues, particularly those disclosed in European Patent Publication No.EP 802910, nafoxidine, basedoxifene, GW5638, GW7604, compound no. 32 disclosed in Jordan (2003), ICI 164384, RU 58668, RU 39411 and EM 319.
...
[0040]

For the purpose of this invention, the SERM or its isomer, isomer mixture, or their pharmaceutically acceptable salts can be administered by various routes. The suitable administration forms include, for example, oral formulations; parenteral injections including intravenous, intramuscular, intradermal, and subcutaneous injections; and transdermal or rectal formulations. Suitable oral formulations include, e.g., conventional or slow-release tablets and gelatin capsules.
[0041]

The required dosage of the SERM compounds will vary with the particular condition being treated, the severity of the condition, the duration of the treatment, the administration route, and the specific compound being employed. For example, fispemifene can be administered preferentially once daily. The daily dose may be 5 - 1500 mg, preferably 20-1500 mg. Fispemifene can be given as tablets or other formulations such as gelatin capsules alone or mixed in any clinically acceptable non-active ingredients which are used in the pharmaceutical industry."

- (A1-6) Examples ([0043] to [0046])
"[Examples]
[0043]

Methods and materials

Fispemifene has been studied in two phases I studies in humans - in a single dose study and a repeated dose study. Effect of fispemifene on hormone levels was one main focus of the repeated dose study. The phase I repeated dose study (number 101-50202) was a randomized, double-blind, placebo-controlled 28-day dose-escalation study performed in 32 healthy, elderly men, aged 50-68 years. The main objective of the study was to investigate the tolerability, safety, and pharmacokinetics of fispemifene after repeated oral doses, but the study focused also on the effects of fispemifene on serum testosterone, estradiol, and other relevant hormones. The fispemifene doses 10, 30, 100 and 300 mg were administered per day and placebo were administered once every morning as capsules containing 10 mg or 100 mg of fispemifene, or placebo. The dose was escalated to the next higher dose level, if the previous dose had been evaluated to be safe and well tolerated by the laboratory safety determinations and ultrasound of mammary glands.

[0044]

The variables for safety and tolerability were adverse events, vital signs, 12-lead ECG, clinical laboratory evaluations, physical examination, ultrasound examinations (mammary glands) and inhibin b. For pharmacokinetics, the concentrations of fispemifene and its metabolite(s) were to be evaluated. For pharmacodynamics, serum concentrations of FSH, LH, estradiol, testosterone, SHBG, prolactin, aldosterone, cortisol, and TSH before and during treatment were measured and compared with the concentrations in the placebo group.

[0045]

Summary of the effects of fispemifene on hormones

Surprisingly, fispemifene increased the serum concentrations of testosterone, FSH, LH, and SHBG (Table 1) during the 28 days of treatment. Testosterone was increased statistically significantly with 100 mg and 300 mg fispemifene as compared with placebo. With the 300 mg dose, the mean total increase of testosterone was about 75% compared to the baseline concentration. Two out of six men treated with the highest fispemifene dose had their serum testosterone level above the upper limit of normal range (i.e., 33 nmol/L) during treatment. The remaining two had a significant increase within the reference range. All the six men had normal testosterone value at baseline. With the 100 mg dose, the mean total increase of testosterone was about 32%, and all the six men in the group had their testosterone level increased within the reference range. The increase in total testosterone levels in serum is illustrated by group in Figure 1. There were no safety concerns raised with any dose, suggesting that even a higher dose could be utilized if deemed appropriate.

[Table 1]

Table 1. Serum total testosterone concentrations (mean and SD) and the other hormones at baseline and during treatment in the fispemifene study 101-50202 by dose.

	Placebo		Fispemifene 10 mg		Fispemifene 30 mg		Fispemifene 100 mg		Fispemifene 300 mg	
Testosterone (nmol/l)	**Mean**	***SD***	**Mean**	***SD***	**Mean**	***SD***	**Mean**	***SD***	**Mean**	***SD***
Baseline	17.25	*4.2*	19. 33	*4.7*	15.00	*3.5*	14.27	*4.0*	15.67	*3.6*
Day 8	18.50	*4.1*	19.83	*3.3*	14.40	*2.1*	18.67	*5.3*	23.17	*5.2*
Day 15	18.43	*4.4*	20.50	*4.9*	15.00	*2.7*	19.00	*6.0*	27.00	*6.5*
Day 22	17.50	*8.5*	22.00	*4.4*	15.80	*3.9*	17.83	*4.5*	27.83	*4.7*
Day 28	15.43	*3.2*	17.40	*7.2*	14.80	*5.3*	18.83	*4.8*	27.50	*10.3*
FSH (U/l)										
Baseline	5.60	*3.4*	5.42	*3.6*	9.14	*13.4*	6.30	*5.6*	6.80	*5.4*
Day 8	5.65	*2.9*	5.87	*4.2*	9.78	*14.2*	7.68	*7.8*	8.80	*7.6*
Day 15	4.67	*1.6*	5.20	*2.9*	10.14	*14.6*	8.10	*9.0*	8.73	*7.2*
Day 22	4.47	*1.6*	6.60	*4.1*	10.18	*15.1*	8.20	*9.0*	8.85	*8.1*
Day 28	4.29	*1.7*	5.66	*3.7*	8.42	*11.6*	7.73	*7.9*	7.57	*7.0*
LH (U/l)										
Baseline	3.11	*1.6*	3.47	*1.0*	3.58	*2.0*	4.12	*1.9*	4.58	*2.7*
Day 8	3.29	*0.8*	3.12	*1.5*	4.26	*2.2*	5.52	*4.2*	6.80	*3.5*
Day 15	3.31	*0.9*	2.87	*1.1*	5.02	*2.4*	6.82	*7.5*	6.75	*4.6*
Day 22	2.80	*0.8*	3.56	*1.2*	4.32	*2.3*	7.18	*8.3*	7.77	*6.6*
Day 28	2.71	*0.9*	3.02	*0.9*	4.42	*2.0*	7.60	*9.6*	6.70	*4.8*
Estradiol (pmol/l)										
Baseline	100.6	*31.2*	106.2	*20.9*	97.8	*17.9*	84.3	*22.6*	102.5	*30.0*
Day 8	93.8	*17.1*	94.7	*31.2*	105.6	*29.8*	108.3	*28.9*	104.0	*20.0*
Day 15	85.0	*31.6*	81.7	*25.4*	102.4	*22.2*	111.5	*48.2*	97.8	*26.9*
Day 22	75.0	*32.4*	116.6	*15.1*	99.6	*20.4*	106.3	*37.4*	95.5	*32.9*
Day 28	73.6	*32.6*	75.0	*20.1*	87.0	*22.2*	94.5	*48.4*	89.7	*30.9*
SHBG (nmol/l)										
Baseline	49.1	*18.6*	47.7	*19.9*	34.2	*12.8*	41.7	*29.4*	50.7	*15.1*
Day 8	44.5	*16.1*	46.3	*21.1*	34.2	*12.2*	47.7	*35.2*	64.2	*21.3*
Day 15	46.0	*19.1*	48.2	*22.8*	37.4	*20.8*	52.0	*39.5*	66.2	*21.1*
Day 22	44.9	*18.4*	50.2	*27.1*	37.2	*19.2*	55.7	*45.3*	65.2	*14.8*
Day 28	45.0	*18.5*	45.2	*24.3*	36.6	*19.1*	50.8	*42.8*	58.3	*12.3*

[0046]

Discussion and conclusions

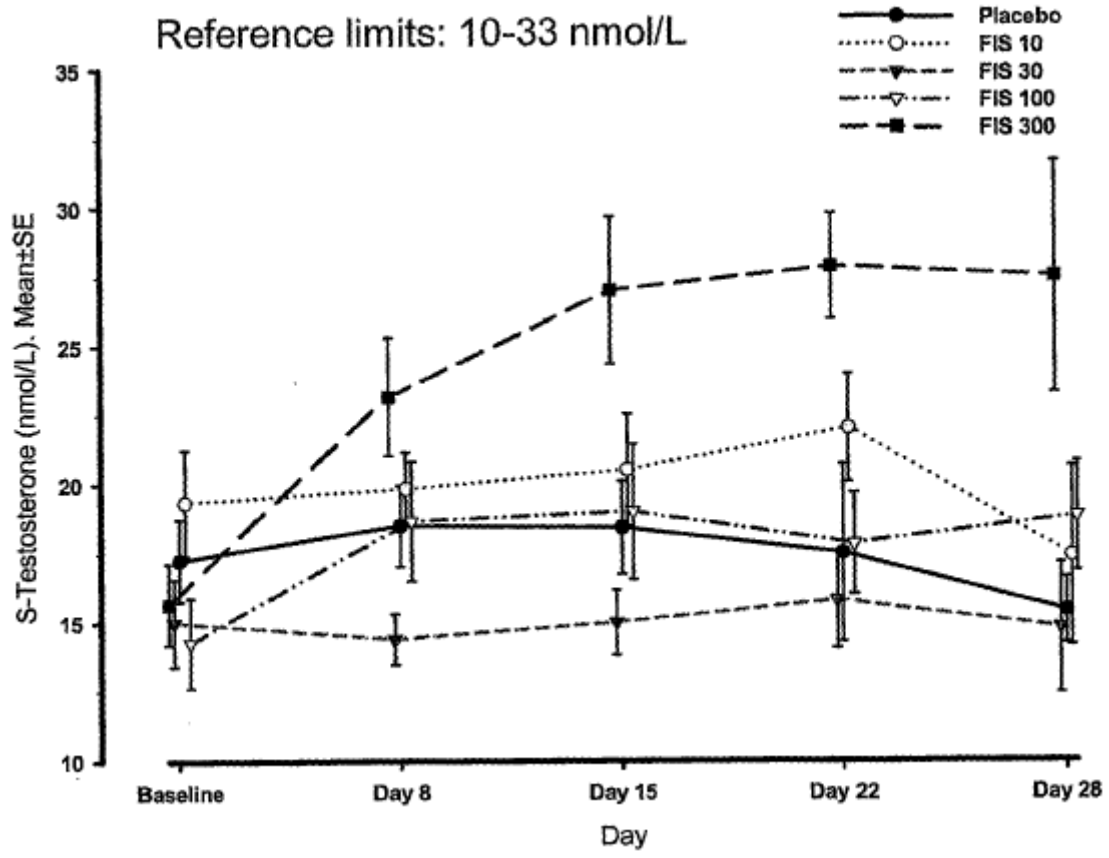
Fispemifene induced a clinically and statistically significant and dose dependent increase in the serum testosterone concentration within 28 days from the start of the treatment. Also, within the 28-day treatment, the increase in testosterone serum concentration was seen in all the patients treated with 100 mg or 300 mg fispemifene. An increase of 75% from baseline can be considered clinically highly significant, and thus clinical benefits in men with low testosterone can be expected. The increases also in LH and FSH suggest that fispemifene has an antiestrogenic effect on hypothalamus/hypophysis, and that the increase in testosterone occurs due to the increase in the hypophyseal hormones. The increase in testosterone is moderate and, therefore, no harmful effects often associated with external testosterone administration are expected. Furthermore, a SERM is likely to provide protection against possible safety problems of testosterone such as development of prostate cancer. Thus, a SERM increasing testosterone provides an optimal treatment for hypogonadism, balancing the efficacy and safety of the increased testosterone."

- (A1-7) [0048], FIG. 1

[Brief Description of Drawings]

[0048]

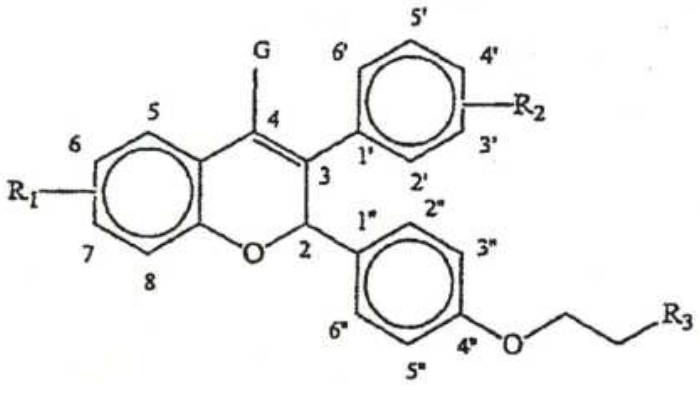
[FIG. 1] Figure 1 shows serum concentration of testosterone in men versus time during treatment with different doses of fispemifene.
FIG. 1



"

(2) Publication A6

- (A6-1) Claims 4 to 6
"A method of treating, or reducing the risk of development of insulin resistance, comprising administering to a subject in need of such treatment or reduction a therapeutically effective amount of a selective estrogen receptor modulator of the following general formula :



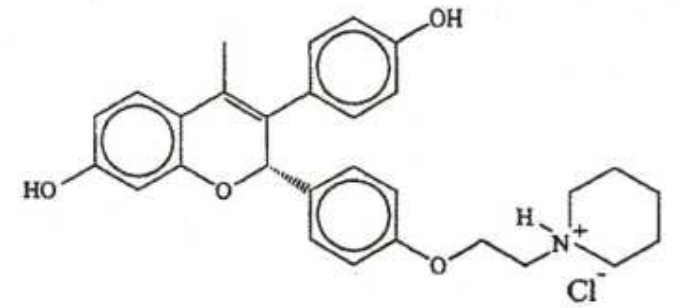
(wherein R_1 and R_2 are independently selected from the group consisting of hydrogen, hydroxyl, -OM (M being selected from the group consisting of straight or branched C_1-C_4 alkyl, straight or branched C_3-C_4 alkenyl, and straight or branched C_3-C_4 alkynyl) and a moiety convertible in vivo to hydroxyl;

wherein G is $-CH_3$; and

wherein R_3 is a species selected from the group consisting of pyrrolidinyl, piperidino, morpholino, and NRaRb (Ra and Rb being independently hydrogen, straight or branched C_1-C_6 alkyl, straight or branched C_3-C_6 alkenyl, and straight or branched C_3-C_6 alkynyl).

[Claim 5] The method of claim 4, further comprising administering a therapeutically effective acceptable amount of an estrogen selected from the group consisting of estradiol and premarin, or a sex steroid precursor (the sex steroid precursor is selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone sulfate, androst-5 -ene-3b, 17b-diol, and compounds converted *in vivo* to either).

[Claim 6] The method of claim 4, wherein the selective estrogen receptor is EM-652.HCl



."

- (A6-2) [0002]

"[0002]

[Field of the Invention]

The present invention relates to a method for treating and/or preventing obesity (especially abdominal obesity), and to treating or suppressing the acquisition of abnormal insulin resistance, in susceptible warm-blooded animals including humans. The methods involve administering compounds of the general formula I below, or their pharmaceutical compositions. In other embodiments, the methods involve administering a selective estrogen receptor modulator ('SERM') in combination with a sex steroid precursor."

- (A6-3) [0007] to [0009]

"[0007]

DHEA has also beneficial effects in the treatment and/or prevention of obesity. In aged Sprague-Dawley rats, Schwartz (..., 1982) has observed that body weight was reduced from 600 to 550 g by DHEA without affecting food intake. Schwartz (..., 1979) observed that C3H mice given DHEA (450 mg/kg, 3 times a week) gained significantly less weight and grew older than the control animals, had less body fat, and were more active. The reduction in body weight was achieved without loss of appetite or food restriction. Furthermore, DHEA could prevent weight gain in animals bred to become obese in adulthood.

[0008]

DHEA administration to lean Zucher rats decreased body weight gain despite increased food intake. Treated animals had smaller fat pads, thus overall suggesting that DHEA increases food metabolism, resulting in lower weight gain and fat accumulation (Svec et al., ..., 1997).

[0009]

Obesity was found to be improved in the A"7 mutant mouse (Yen et al., ..., 1983). DHEA-treated C_3H mice had a younger appearance than controls (Schwartz, ..., 1979)."

- (A6-4) [0015]-[0017]

"[0015]

... , sex steroid precursor (e.g., dehydroepiandrosterone, dehydroepiandrosterone sulfate, androst-5-ene-3b, 17b-diol) is administered in addition to a Selective Estrogen Receptor Modulator (SERM) for the treatment of obesity or for suppressing weight gain. Humans at or over fifty years of age are believed to respond well to the combination therapy, probably because precursor levels tend to undesirably decrease with age.

[0016]

Thus, in that aspect, the invention provides a method for the treatment of obesity or suppression of weight gain comprising administering to a subject in need of such suppression or treatment a therapeutically effective amount with or without a pharmaceutical diluent or carrier, of at least one SERM and an effective amount of at least one sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone sulfate, androst-5-ene-3b, 17b-diol, and compounds converted in vivo to any of the foregoing precursors.

[0017]

In another aspect, the invention provides a method for treating or reducing the risk of developing insulin resistance comprising administering, to a subject in need of such treatment or reduction, a therapeutically effective amount of at least one SERM. In some embodiments, an effective amount of at least one sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone sulfate, androst-5-ene-3b, 17b-diol, and compounds converted in vivo to either is administered also as part of a combination therapy."

- (A6-5) [0092] to [0093]

"[0092]

Examples 8A (male) and 8B (female) report data of the effectiveness of the invention in the prevention as well as in the treatment of obesity. To lean and obese Zucker male and female rats were administered 2.5 mg/kg/day of EM-652.HCl for 20 days. The model of prevention is represented by lean rats, while the model of treatment of obesity is represented by already obese rats. The data on body weight gain, lipoprotein lipase activity in white retroperitoneal adipose tissue and soleus muscle, as well as serumconcentrations of insulin, glucose, total cholesterol, and triglycerides are reported in Table 7 for male animals and Table 8 for female animals (see Example 3 for significance of these parameters).

[0093]

The antiestrogen EM-652.HCl significantly decreased body weight gain by 38% for lean male rats and 35% for obese male rats, while lipoprotein lipase activity in white

retroperitoneal adipose tissue and soleus muscle is not modified in either sex. Plasma insulin is reduced by 35%, 57%, and 48% in lean males, obese males, and lean females, respectively, while in obese females which show a much high level of insulin, EM-652.HCl has no significant effect. Plasma cholesterol, which is higher in the obese group, is also reduced by EM-652.HC1 administration. Serum glucose is not affected by EM-652.HC1 administration."

- (A6-6) [0098] to [0109]
"[0098]

Example 8A

Effect of EM-652.HCl on energy balance and lipid-lipoprotein metabolism in lean and obese Zucker male rats.

URMA-r-61-99

The objective of this study was to determine the effect of EM-652.HCl on energy balance and lipid-lipoprotein metabolism in lean and obese Zucker male rats. For this purpose, EM-652.HCl (2.5 mg/kg) was administered orally (gavage) once daily for 14 days to intact lean and obese Zucker male rats.

...

[0109]

...

Table 7

Male Zucker rats

GROUP		Weight gain	Lipoprotein lipase activity White retroperitoneal	Lipoprotein lipase activity soleus	Plasma insulin	Plasma glucose	Plasma total cholesterol	Plasma triglycerides
phenotype	treatment	g	μU/g protein	μU/g protein	nmol/L	mmol/L	mmol/L	mmol/L
Lean	control	73.0±4.2	2066±353	71.7±7.9	0.095±0.025	10.74±0.87	2.10±0.15	1.47±0.20
Lean	EM-652.HCl 2.5 mg/kg	44.9±3.5	1701±348	69.5±8.4	0.062±0.005	9.35±0.51	1.18±0.09	1.52±0.13
Obese	control	110.5±6.7	7233±511	51.9±8.8	1.092±0.369	11.06±0.84	5.07±0.28	4.21±0.78
Obese	EM-652.HCl 2.5 mg/kg	71.6±3.3	7046±1185	58.1±4.6	0.475±0.087	11.84±0.62	2.28±0.25	7.16±1.06

"

- (A6-7) [0170] to [0178]
(*Note by the body: Ruled lines are omitted for each table of [Table 17] to [Table 22])
"[0170]

PHARMACEUTICAL COMPOSITION EXAMPLES

Set forth below, by way of example and not of limitation, are several pharmaceutical compositions utilizing preferred active SERM EM-800 or EM-652.HCl alone or in combination with one of the preferred active sex steroid precursors DHEA, androst-5-ene-3b, 17b-diol 3-acetate or androst-5-ene-3b, and 17b-diol dihemisuccinate. Other compounds of the invention or a combination thereof may be used in place of (or in addition to) EM-800 or EM-652.HCl, DHEA, androst-5-ene-3b, 17b-diol 3-acetate or androst-5- ene-3b, 17b-diol dihemisuccinate. The concentration of active ingredient may be varied over a wide range as discussed herein. The amounts and types of other ingredients that may be included are well known in the art.

...

[0173]

Pharmaceutical composition for combination therapies

Example C

[Table 17]

Tablet

Ingredient	Weight % (by weight of total composition)
EM-652.HCl	5
DHEA	15
Gelatin	5
Lactose	58.5
Starch	16.5

[0174]

Example D

[Table 18]

Gelatin capsule

Ingredient	Weight % (by weight of total composition)
EM-652.HCl	5
DHEA	15
Lactose hydrous	65
Starch	4.8
Cellulose microcrystalline	9.8
Magnesium stearate	0.4

[0175]

KIT EXAMPLES

...

[0177]

Example A

The SERM is orally administered while the sex steroid precursor is percutaneously administered.

[Table 19]

SERM composition for oral administration (capsules)

Ingredient	Weight % (by weight of total composition)
EM-652.HCl	5
Lactose hydrous	80
Starch	4.8

Cellulose microcrystalline	9.8
Magnesium stearate	0.4

[Table 20]

Sex steroid precursor composition for topical administration (gel)

Ingredient	Weight% (by weight of total composition)
DHEA	10
Caprylic-capric triglyceride (Neobee M-5)	5
Hexylene Glycol	15
Transcutol (diethylene glycol monomethyl ether)	5
Benzyl alcohol	2
Cyclomethicone (Dow Corning 345)	5
Ethanol (absolute)	56
Hydroxypropyl Cellulose (1500cps) (KLUCEL)	2

[0178]

Example B

The SERM and the sex steroid precursor are orally administered.

Non-Steroidal Antiestrogen composition for oral administration (capsules)

[Table 21]

Ingredient	Weight% (by weight of total composition)
EM-652.HCl	5
Lactose hydrous	80
Starch	4.8
Cellulose microcrystalline	9.8
Magnesium stearate	0.4

Sex steroid precursor composition for oral administration (Gelatin capsule)

[Table 22]

Ingredient	Weight% (by weight of total composition)
DHEA	15
Cellulose microcrystalline	84.6
Magnesium stearate	0.4

"

(3) Publication B

- (B-1) Title

"Dehydroepiandrosterone Supplementation in Elderly Men: A Meta-Analysis Study of Placebo-Controlled Trials"

- (B-2) Abstract

"Context: Age-related dehydroepiandrosterone (DHEA) deficiency has been associated with a broad range of biological abnormalities in males.

Object: Our objective was to meta-analyze all double-blind, placebo-controlled randomized trials (RCTs) investigating the effect of oral DHEA (DHEA

supplementation) in comparison with placebo on sexual and metabolic outcomes in elderly men.

Data source: An extensive Medline Embase and Cochrane search was performed including the following words: DHEA, RCTs, and males.

Study selection: Only double-blind placebo-controlled trials performed in elderly men were included.

Data extraction: Data extraction was performed independently by 2 of the authors (A.S. and V.G.), and conflicts were resolved by the third investigator (G.C.). The quality of RCTs was assessed using the Cochrane criteria.

Results: Of 220 retrieved articles, 25 were included in the study. The available RCTs enrolled 1353 elderly men, with a mean follow-up of 36 weeks. DHEA supplementation was associated with a reduction of fat mass (standardized mean difference of -0.35 [-0.65 to -0.05]; P = .02). However, the association with fat mass disappeared in a multivariate regression model after adjusting for DHEA-related metabolite increases such as total testosterone and estradiol. In contrast to what was observed for fat mass, no effect of DHEA supplementation in comparison with placebo was observed for various clinical parameters, including lipid and glycemic metabolism, bone health, sexual function, and quality of life.

Conclusions: The present meta-analysis of intervention studies shows that DHEA supplementation in elderly men can induce a small but significant positive effect on body composition that is strictly dependent on DHEA conversion into its bioactive metabolites such as androgens or estrogens.

- (B-3) page 3615, left column, line 3 from the bottom to page 3616, right column, line 11

"Dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) are steroid hormones mainly secreted by the adrenal gland with daily production rates of approximately 5 to 8 mg and 6 to 20 mg, respectively. They were first isolated by Butenandt and Dannenbaum in 1934 (1) and Munson et al in 1944 (2), respectively. The serum concentration of DHEA is in the nanomolar range (3-30 nmol/L), whereas DHEAS levels are much higher (3-12 μmol/L), because the metabolic clearance rate of DHEAS is very low (3-5). DHEAS is generally considered a large plasma reservoir of DHEA, because the 2 hormones can be interconverted by extra-adrenal sulfotransferase and sulfatase enzymatic activities (3, 4).
...

DHEAS is secreted by the adrenal zona reticularis only, whereas DHEA can also be produced by the testes and ovaries and can be synthesized within the brain (3, 4). Although in women, adrenal production of DHEA and DHEAS contributes substantially to overall androgen production, in men, the adrenal contribution to the pool of biologically active androgens is very small (3-5). ... Similar to what has been observed in women, in males, an age-dependent reduction of circulating DHEAS has also been reported (3-5). In particular, by age 80, the concentrations are only about 20% of those at age 25 (6, 7).

Several experimental and uncontrolled studies have documented that DHEA and DHEAS might be implicated in a broad range of biological abnormalities, including obesity, diabetes, osteoporosis, sexual dysfunction, cancer, and mental disorders, leading to speculation that a relative DHEAS deficiency may contribute to the development of common age-related diseases or diminished longevity (3-7). Accordingly, there is a widespread, although nonsupervised, use of DHEA as a dietary supplement for elderly people, in the hope of finding the fountain of youth."

- (B-4) page 3617, right column, line 4 from the bottom to page 3618, left column, line 8, Table 1 (ruled lines omitted)
"Results

Of 236 retrieved articles, 25 were included in the study. .... The total flow is summarized in Figure 1 (12-35). The available RCTs enrolled 1353 elderly men overall, with a mean follow-up of 36 weeks. Although these trials enrolled, in the vast majority, healthy elderly subjects, they differed in basal DHEAS levels. In addition, DHEA was administered in different doses. The characteristics of the trials included in the meta-analysis are summarized in Table 1.

Table 1. Characteristics and Outcomes of the Randomized, Placebo-Controlled Clinical Studies Included in the Meta-Analysis

Study (Ref.)	No. of Patients (DHEA/Placebo)	Outcomes	Age, y[a]
Nestler et al., 1988(12)	5/5	BC, H,MP	24.1±1.0
Morales et al., 1994(13)	13/13	BC, H, MP, SF	53.7±2.5
Yen et al., 1995(14)	13/13	BC[b]	40-70
Morales et al., 1998(15)	9/9	BC, [b]H, MP, B	55.6±1.9
Flynn et al., 1999(16)	20/20	BC, H, MP	60-84
Reiter et al., 1999(17)	17/13	H, SF	56.5
Baulieu et al., 2000(18)	66/67	H, B	60-79
Arit et al., 2001(19)	22/22	H	59.3±5.6
van Niekerk et al., 2001(20)	46/46	SF, QOL	68.5±3.8
Khan et al., 2002(21)	43/43	H, B	66.0±6.4
Jedrzejuk et al., 2003(22)	12/12	BC, H, MP	59.0±4.8
Kawano et al., 2003(23)	12/12	H, MP	54.1±1.0
Villareal et al., 2004(24)	15/14	H	71.0±3.6
Jankowski et al., 2006(25)	35/35	BC, [b]B	68.8±6.5
Martina et al., 2006(26)	12/12	H, MP	65.4±3.4
Nair et al., 2006(27)	29/31	BC, [b]H, MP,	67.7±3.8
B, QOLVillareal et al., 2006(28)	29/27	H	71.5±4.0
Jankowski et al., 2008(29)	30/31	H	69.2±6.5
von Muhlen et al., 2008(30)	55/55	H,B	68.7±8.0
Kritz-Silverstein et al., 2008(31)	55/55	B, SF, QOL	68.7±8.0
Morales et al., 2009(32)	27/28	H, SF	60.5±10.7
Weiss et al., 2009(33)	28/27	B, H	
Srinivasan et al., 2010(34)	25/29	MP	66.9±3.7

Jankowski et al., 2011(35)	30/31	• • BC, MP	68.8±6.5 • •
Weiss et al., 2011(36)	28/27	• • BC[b]	• •

Abbreviations: ... ; B, bone parameters; BC, body composition; H, hormone parameters; MP, metabolic parameters; ... ; SF, sexual function.

[a] Mean ± SD or range

[b] Body composition evaluated with dual-energy x-ray absorptiometry.

"

- (B-5) page 3618, right column, line 1 to page 3620, left column, line 24

"Body composition and metabolic parameters

Data on the effect of DHEA supplementation on body composition or metabolic parameters were available in 10 studies, respectively. The Begg adjusted rank correlation test (Kendall τ coefficient-0.333; P = .179), calculated on the basis of DHEA supplementation group vs placebo group on fat mass, suggested no major publication bias. Combining the effect of DHEA supplementation among available RCTs, DHEA supplementation was associated with an overall reduction of fat mass and with a trend toward an increase of fat-free mass (Figure 2, A and B). The positive effect on fat mass was confirmed even when only studies using dual-energy x-ray absorptiometry (see also Table 1) or when only RCTs with parallel design were considered: ...

As expected, DHEA supplementation determined an overall increase in DHEAS levels (9.09 [8.00-10.19] μmol/L P < .0001), but also in TT (1.24 [0.0-2.49] nmol/L; P = .05) and E2 (24.76 [14.14 -35.39]; P < .0001) (Figure 3, A-C). The reduction of fat mass after DHEA supplementation was negatively related to the increase of TT and positively to the increase of E2 (r = -0.836 and 0.398; both P < .0001). In a multivariate regression model, considering the reduction of fat mass as a dependent variable and the increase of TT, E2, and DHEAS as covariates, the association of fat mass reduction with TT and E2 was confirmed (adjusted r = 0.415 and 0.478 both P < .0001 for TT and E2, respectively), whereas that with DHEAS was not confirmed (adjusted r = 0.057; P = .246). A sensitivity analysis was performed weighting further for the inverse of variance, confirming the lack of the association between DHEAS and reduction of fat mass (not shown).

In contrast to what was observed for fat mass, no effect of DHEA supplementation in comparison with placebo was observed for various metabolic parameters including glycemia, insulin, and total cholesterol (Figure 4, A-C), or for high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, and triglycerides (Supplemental Figure 1, A-C, ...)."

- (B-6) Fig. 2 (* Each graphical image part ("• • •") in A and B is omitted)

"A

Source	FAT mass standardized mean differences	Diff. in mean	LL, 95%CI	UL, 95%CI	p
Nestler et al., 1988(12)	• • •	-1,46	-2,86	-0,07	0,04
Morales et al., 1994(13)	• • •	-0,04	-0,81	0,72	0,91
Yen et al., 1995(14)	• • •	-1,07	-2,12	-0,02	0,04
Morales et al., 1998(15)	• • •	-1,22	-2,22	-0,21	0,02
Flynn et al., 1999(16)	• • •	-0,10	-0,72	0,52	0,74
Flynn et al., 1999*(16)	• • •	0,08	-0,56	0,72	0,81
Jedrzejuk et al., 2003(22)	• • •	-0,08	-0,51	0,34	0,70
Jankowski et al., 2006(25)	• • •	0,03	-0,47	0,53	0,91
Nair et al., 2006(27)	• • •	-0,21	-0,71	0,30	0,43
Weiss et al., 2011(36)	• • •	-1,00	-1,60	-0,41	0,00
Overall	• • •	-0,35	-0,65	-0,05	0,02

B

Source	FAT free mass standardized mean differences	Diff. in mean	LL, 95%CI	UL, 95%CI	p
Yen et al., 1995(14)	• • •	1,00	0,09	1,91	0,03
Morales et al., 1998(15)	• • •	0,70	-7,62	9,02	0,87
Flynn et al., 1999(16)	• • •	0,20	-6,00	6,40	0,95
Flynn et al., 1999(16)*	• • •	0,00	-8,27	8,27	1,00
Jankowski et al., 2006(25)	• • •	-0,20	-1,21	0,81	0,70
Nair et al., 2006(27)	• • •	0,87	-0,02	1,76	0,06
Jankowski et al., 2011(35)	• • •	-0,10	-0,91	0,71	0,81
Overall	• • •	0,39	-0,05	0,84	0,08

Figure 2. Weighted standardized differences (with 95% confidence interval) of mean fat (A) and fat-free mass (B) at endpoint across RCTs evaluating the effect of DHEA vs placebo therapy. ... . *, Placebo was administered first.
"

- (B-7) Fig. 3 (* Each graphical image part ("• • •") in Tables A to C is omitted)
"A

Source	DHEAS mean differences (ng/ml)	Diff. in mean	LL, 95%CI	UL, 95%CI	p
Nestler et al., 1988(12)	• • •	30,10	7,90	52,30	0,01
Flynn et al., 1999(16)	• • •	12,06	7,50	16,62	0,00
Flynn et al., 1999*(16)	• • •	17,62	11,85	23,38	0,00
Baulieu et al., 2000(18)	• • •	8,01	6,45	9,56	0,00
Arit et al., 2001(19)	• • •	7,70	5,83	9,57	0,00
Jedrzejuk et al., 2003(22)	• • •	21,20	18,59	23,82	0,00

Villareal et al., 2004(24)	• • •	8,44	7,85	9,02	0.00
Nair et al., 2006(27)	• • •	9,00	4,78	13,22	0.00
Villareal et al., 2006(28)	• • •	7,40	6,85	7,95	0,00
Jankowski et al., 2008(29)	• • •	5,90	4,16	7,64	0,00
von Muhlen et al., 2008(30)	• • •	6,50	5,91	7,09	0,00
Weiss et al., 2011(36)	• • •	8,13	7,88	8,38	0,00
Overall	• • •	9,09	8,00	10,19	0,00

B

Source	TT mean differences (nmol/L)	Diff. in mean	LL, 95%CI	UL, 95%CI	p
Nestler et al., 1988(26)	• • •	-0,40	-10,40	9,60	0,94
Morales et al., 1994(13)	• • •	1,00	-4,32	6,32	0,71
Morales et al., 1998(15)	• • •	0,00	2,77	2,77	1,00
Reiter et al., 1999(17)	• • •	3,43	1,54	5,32	0,00
Flynn et al., 1999(16)	• • •	1,32	-1,53	4,17	0,36
Flynn et al., 1999*(16)	• • •	-2,64	-5,17	-0,10	0,04
Baulieu et al., 2000(18)	• • •	5,49	2,05	8,93	0,00
Arit et al., 2001(19)	• • •	-0,50	-3,18	2,18	0,71
Khan et al., 2002(21)	• • •	1,37	-0,95	3,69	0,25
Jedrzejuk et al., 2003(22)	• • •	1,03	-3,51	5,56	0,66
Kawano et al., 2003(23)	• • •	-0,12	-4,58	4,34	0,96
Villareal et al., 2004(24)	• • •	-0,34	-3,21	2,53	0,81
Martina et al., 2006(26)	• • •	6,30	3,91	8,69	0,00
Villareal et al., 2006(28)	• • •	0,70	-2,86	4,26	0,70
Jankowski et al., 2008(29)	• • •	-1,70	-3,72	0,32	0,10
von Muhlen et al., 2008(30)	• • •	1,50	-1,57	4,57	0,34
Morales et al., 2009(32)	• • •	3,00	0,19	5,81	0,04
Weiss et al., 2009(33)	• • •	1,47	-2,97	5,92	0,52
Overall	• • •	1,24	0,00	2,49	0,05

(* Note by the body: Considering the consistency with the reference number of "Nestler et al., 1988" in other tables, "Nestler et al., 1988 (26)" in Table B above is presumed to be a typographical error of "Nestler et al., 1988 (12).")

C

Source	E2 mean differences (pmol/L)	Diff. in mean	LL, 95%CI	UL, 95%CI	p
Nestler et al., 1988(12)	• • •	9,40	-6,60	25,40	0,25
Morales et al., 1994(13)	• • •	26,00	-20,46	72,46	0,273
Flynn et al., 1999(16)	• • •	85,81	50,32	121,30	0,000
Flynn et al., 1999*(16)	• • •	77,94	34,86	121,02	0,000
Baulieu et al., 2000(18)	• • •	1,67	-8,09	11,42	0,738
Arit et al., 2001(19)	• • •	1,00	-6,71	8,71	0,799

Jedrzejuk et al., 2003(22)	• • •	2,57	-27,60	32,75	0,867
Villareal et al., 2004(24)	• • •	41,18	23,65	58,70	0,000
Martina et al., 2006(26)	• • •	16,00	3,45	28,55	0,012
Nair et al., 2006(27)	• • •	20,00	10,62	29,38	0,000
Villareal et al., 2006(28)	• • •	50,40	34,30	66,50	0,000
Jankowski et al., 2008(29)	• • •	59,50	27,75	91,25	0,000
von Muhlen et al., 2008(30)	• • •	3,00	-7,58	13,58	0,578
Weiss et al., 2009(33)	• • •	23,16	8,81	37,52	0,002
Overall	• • •	24,76	14,14	35,39	0,000

Figure 3. Weighted standardized differences (with 95% confidence interval) of DHEAS (A), TT (B), and E2 (C) at endpoint across RCTs evaluating the effect of DHEA vs placebo therapy. ... *, Placebo was administered first."

(B-8) page 3621, right column, line 1 to page 3622, right column, line 20
"Discussion

This is the first systematic and comprehensive meta-analysis of clinical outcomes from the available RCTs that administered DHEA to elderly men. Our results show that DHEA supplementation was associated with a reduction of fat mass and with a trend toward an increase in lean mass; however, these effects were small and can be accounted for by adjustment for DHEA-derived metabolites. No additional effect of DHEA supplementation on several other outcomes, including metabolic profile, bone health, sexual function, and QOL, was observed.

Sex steroids play a pivotal role in regulating body composition in both men and women. Data derived from the present meta-analysis show that DHEA supplementation exerts some positive effects on body composition, in particular, reducing fat mass. However, multivariate analysis of the data suggests that this effect could be related more to a variation in circulating levels of TT and E2 (increase) than to DHEA itself. The data should be interpreted with caution, because they could be the effect of ecological fallacy. In fact, they were derived from synthesis of the results of available studies without direct access to individual patient data. Hence, DHEA supplementation in elderly men could induce sex-steroid modifications, which in turn regulate fat mass distribution. It is well known that in men the relationship between fat mass and testosterone levels is bidirectional; testosterone administration can reduce adiposity, and adiposity can induce a reduction of testosterone and gonadotropins (37-40). In fact, much evidence indicates that obesity, type 2 diabetes, and metabolic syndrome in men are all characterized by a hypogonadotropic hypogonadism, strictly related to body fat mass (37-40). The estrogen excess, due to a fat-related increase in aromatase activity and its associated negative feedback at the pituitary level, has been advocated as the most plausible explanation (37-40). In line with this view, in a meta-analysis of the available trials investigating the effect of weight loss, obtained either by lifestyle or bariatric intervention, we observed that the weight loss-induced fall in estrogen levels was associated with a rise in gonadotropins and testosterone (41). Furthermore, testosterone replacement therapy (TRT) in hypogonadal men can ameliorate fat mass distribution. A meta-analysis of RCTs investigating the effect of TRT in hypogonadal men with type 2 diabetes and metabolic syndrome demonstrated a positive effect of TRT in reducing both fat mass and waist circumference (42, 43). Similar results have been reported in patients

with Klinefelter's syndrome (44, 45), in those with hypogonadotropic hypogonadism (46), or in healthy nonobese aging men (47). The TT-dependent reduction of fat mass observed after DHEA supplementation is in line with this evidence."

(B-9) page 3624, left column, lines 20 to 30
"Limitations of the present meta-analysis are essentially associated with the overall weakness of the studies reviewed, including the small size of the studies, the low statistical power, often unreliable analytical methods for steroid detection, confounding factors, or other differences in the clinical endpoints or populations analyzed. However, meta-analysis is particularly useful in addressing questions for which multiple data sources are conflicting or when there are a variety of reports with low statistical power; thus, pooling data can improve power and provide a convincing result."

(B-10) page 3624, left column, lines 31 to 51
"In conclusion, although DHEAS levels may be correlated with many age-related phenomena such as diabetes, insulin resistance, hypertension, atherosclerosis, coronary artery disease, decreased BMD, cancer, dementia, depressed mood, and eating disorders (3), the present meta-analysis of intervention studies shows that DHEA supple- mentation in elderly men can induce only a small, but statistically significant, positive effect on body composition that is strictly dependent on DHEA conversion into its bioactive metabolites such as androgens or estrogens. Although a specific binding site for DHEA has been previously described in endothelial cells (65), our data confirm the view that DHEA and DHEAS should be considered as prohormones, which are converted peripherally into other sex steroids (especially testosterone and estradiol) mediating the biological effect via their cognate receptors. In addition, because local production of active steroid metabolites from DHEA depends on the particular predominant enzymatic portfolio in that particular tissue, final biological effects of DHEA dosing are therefore unpredictable."

2. Comparison / Judgment

(1) Invention disclosed in Publication A1

According to the above summarized matters (A1-1) to (A1-7), Publication A1 discloses the following matters:
- "The use of a selective estrogen receptor modulator, or an isomer, isomer mixture, metabolite, or pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical preparation for use in a method for the treatment or prevention of androgen deficiency in a male individual." ((A1-1) Claim 1) (hereinafter, "a selective estrogen receptor modulator, ... or a pharmaceutically acceptable salt thereof" may be collectively referred to "SERM"); Examples of SERM used herein include triphenyl-alkene compounds, such as toremifene and fispemifene, as well as compounds of various chemical structures known as SERMs including EM652, EM800, and the like or isomers, isomer mixtures, metabolites, or pharmaceutically acceptable salts thereof ((A1-1) Claims 2 to 7 and (A1-5));
- Examples of "androgen deficiency in a male individual" include "age-related testosterone deficiency" ((A1-2) [0006]) in addition to primary hypogonadism and secondary hypogonadism in men ((A1-2) [0004] to [0005]), and various symptoms that

may occur due to the androgen deficiency may be covered by the pharmaceutical preparation of claim 1 ((A1-1) Claim 9 and (A1-3) [0021] to [0022]);
- SERMs are effective in raising testosterone (TT) levels in male serum ((A1-3) [0011], etc.) and, in comparison to direct testosterone substitution, SERMs "produce the positive response of androgen replacement therapy without the undesired side effects of testosterone, such as adverse effects on prostate or on lipid metabolism, or gynecomastia" ((A1-4) [0027]), thereby causing an increase in TT levels in male patients with the above androgen deficiency or various symptoms associated therewith and exerting a beneficial effect on fat metabolism, such as reduction of subcutaneous and visceral abdominal fat ((A1-4) [0028]).
- As a pharmacological test example related to the application of SERM, fispemifene was orally administered at 10, 30, 100, or 300 mg per day to healthy elderly men aged 50 to 68 years ((A1-6) [0043]), and fispemifene caused increased TT, FSH, LH, and SHBG serum concentrations, and the administration of 100 mg or 300 mg of fispemifene particularly caused a significant increase in TT concentrations as compared with the placebo-administered group ((A1-6 [0045], Table 1 and (A1-70 Figure 1)). From these test results, administration of SERM exemplified by fispemifene can be expected to have a clinical effect in men with low TT concentration. Increased levels of LH and FSH suggest that fispemifene has an anti-estrogen effect on the hypothalamus/pituitary gland, and that an increase in TT is caused by an increase in pituitary hormone. Since the increase in TT is moderate, no harmful effects often associated with the external TT administration are expected (A1-6) [0046]).

According to the recitation of Claim 1 of (A1-1) based on the description of Publication A1 including these matters (A1-1) to (A1-7), it is recognized that Publication A1 discloses the invention as follows:
"A pharmaceutical preparation for increasing serum LH concentration in AD-deficient human males, or for treating or preventing a disease by the increase thereof, comprising: a selective estrogen receptor modulator (SERM) as an active ingredient, which increases serum LH concentration;
and
A method of using SERM as an active ingredient in the production of the pharmaceutical preparation," which are hereinafter also collectively and merely referred to as "Cited Invention A1."

(2) Comparison / Judgment

(i) Comparison

The Invention and the aspects of the method of use of Cited Invention A1 are compared below.

Since fispemifene, EM652, and EM800, which are mentioned as examples of SERM in Publication A1 ((A1-1) and (A1-5)) correspond to those mentioned as examples of the "selective estrogen receptor modulator" of the Invention in [0054] and [0197] to [0198] of the specification, it is recognized that the selective estrogen receptor modulator (SERM) of Cited Invention A1 corresponds to the "selective estrogen receptor modulator" (SERM) of the Invention. Based on this fact, the two are common in the point that
"use of a selective estrogen receptor modulator in the manufacture of a medicament for

male androgen deficiency symptoms including male hypogonadism-associated symptoms and diseases." However, they are different from each other in the following points (1) to (3):
1) In the present invention, "acolbifene or EM-800" is used as a "selective estrogen receptor modulator," (SERM) and the "acolbifene or EM-800" "stimulates LH secretion, which increases the level of circulating testosterone." In Cited Invention A1, on the other hand, there is no such limitation on the SERM.
2) In the present invention, "dehydroepiandrosterone" (DHEA), which is a "sex steroid precursor," is used in combination with the above "selective estrogen receptor modulator." In Cited Invention A1, on the other hand, there is no limitation on using DHEA or other "sex steroid precursor" equivalent component in combination with "selective estrogen receptor modulator."
3) Regarding the use of the "medicament" to be manufactured, the "medicament" in the present invention is "for reducing or eliminating the incidence of male androgen deficiency symptoms or diseases including male hypogonadism-associated symptoms and diseases in a male patient," whereas the "medicament" in Cited Invention A1 is "for increasing serum LH concentration in AD-deficient human males, or for treating or preventing a disease by the increase."
(Hereinafter, they may be referred to as "Different Feature 1" to "Different Feature 3" in order).

(ii) Judgment
Above-mentioned Different Features 1 to 3 are examined below.

(ii-1) Regarding Different Feature 1
(a) Publication A1 includes no specific description for actual pharmacological test results or the like for SERMs other than fispemifene of Examples ((A1-6) to (A1-7)), but includes recitations for possible use of EM800, EM652, or salts thereof as SERMs in addition to the fispemifene ((A1-1) Claim 2, and (A1-5)). Based on these recitations, as necessary, a person skilled in the art could adopt EM800 and EM652 or the SERM compound (EM-652HCl, i.e., the "acolbifene" of the Invention) recited in, for example, Claim 6 of Publication A6 ((A6-1)), which is the HCl salt of the EM652, as the SERM of Cited Invention A1 to cause an increase in testosterone (TT) concentration in serum in a similar manner or to anticipate treatment or prevent androgen deficiency in a male individual by increasing the serum TT concentration.
(b) At that time, a person skilled in the art would have expected that LH secretion is stimulated by the action of those EM800 and EM652, which are anti-estrogen SERMs (e.g., (A6-5) [0093]) or EM-652.HCl (acolbifene) to cause an increase in circulating TT levels in light of the following (1) and (2):
1) At the time of the priority date of the application of the patent, a person skilled in the art would have known well the technical matters that SERM with anti-estrogen activity can block the usual negative feedback mechanism through the binding of estradiol (estrogen) to the hypothalamic estrogen receptor by competitively inhibiting the binding (of estradiol to the estrogen receptor) and has an action that can increase the secretion of LH and FSH from the pituitary gland by the blocking, as is evident from the fact that, for example, the description showing the results of an administration test of fispemifene in the example of Publication A1 ((A1-6)), the descriptions in Publication A3: TAYLOR,

F. ET AL., J. SEX MED., (2010) 7 (1 Pt 1) pp.269-276 (page 270, left column, lines 22 to 31 and Publication A4: SHABSIGH, A. ET AL., J. SEX. MED., (2005) 2 (5) pp.716-721 (page 717, left column, lines 20-31) cited in the notice of reasons for refusal about clomiphene citrate, which is also a type of the above SERM.
2) At the time of the priority date of the application of the patent, a person skilled in the art would have known well that the LH acts on stromal cells (Leydig cells) of the masculine (male) testis to promote the biosynthesis and secretion of androgens (testosterone, etc.) (regarding this point, if necessary, see the section "Luteinizing Hormone" in "Encyclopedia of Biochemistry (Seikagaku Jiten)" supervised by K Imahori and T Yamakawa (4th edition) (1st print issued on December 10, 2007), Tokyo Kagaku Dojin Co., Ltd., pages 234 to 235).

(ii-2) Regarding Different Feature 2
(a) It is as described in Publication B that substitution therapy with DHEA well known as androgen together with testosterone and the like (i.e., androgen substitution therapy using DHEA) may have an effect of treating and/or preventing an increase in blood TT concentration in an elderly man and the accompanying male androgen deficiency (e.g., an effect of reducing body fat mass).

More specifically, furthermore, it is understood that the main targets as elderly males ((B-1), etc.) in Publication B referred to herein are mainly human males (B-3) who are elderly males after the age of 25. The amounts of their circulating (blood) DHEA/DHEAS levels are relatively decreased depending on the age as compared with those at the young age of 25. They are at risk of developing androgen deficiency conditions such as obesity and sexual dysfunction. It is thus desired to reduce or suppress the onset of the symptom (by DHEA supplementation). In fact, almost all patients in the patient population (except patients in reference (12)) of references (12) to (36) in Table 1 (B-4), which were included in the meta-analysis in Publication B, are at least over 40 years old (mostly in their 60s or over).

(b) 1) Publication A1 describes that SERMs can elicit a beneficial response to androgen substitution therapy while protecting against the side effects that can be caused by increased blood TT ((A1-4) [0027]). Thus, based on the description of publication A1, a person skilled in the art could easily consider and carry out anticipation of an additive or synergistic improvement in the pharmacological effects of treatment and/or prevention of increased blood TT concentration or associated male androgen deficiency in elderly men using the substitution therapy with DHEA described in the publication B (corresponding to the substitution therapy with androgen in the above (A1-4) [0027]) in combination with Cited Invention A1.

2) In general, in the field of medicine, using two or more medicinal components in combination optimizing the dosage and administration in order to solve a problem well known to a person skilled in the art, such as to increase a drug effect or to reduce a side effect, is an exercise of ordinary creativity of a person skilled in the art (Examination Handbook for Patent and Utility Model in Japan, Annex B, Chapter 3, Medical Inventions, "2.3 Inventive Step (Article 29(2))" 2. 3. 2(3)).

In fact, as an example of such combination use, for example, use of EM-652.HCl (SERM) and DHEA (androgen) in combination, which are two types of medicament

components that have weight gain/obesity reduction effects, is also found in publication A6, along with description of such a formulation example.

Then, considering these matters together, the two have common pharmacological effects (anti-obesity effects, etc.) related to the treatment and/or prevention of increased blood TT concentration and accompanying male androgen deficiency to solve the well-known problem stated above, even if it does not depend on the description or suggestion of (A1-4) of publication A1 stated in the above (1). It can be therefore said that a person skilled in the art could easily conceive of using the SERM component in Cited Invention A1 in combination with the DHEA of the publication B.

(ii-3) Regarding Different Feature 3
(a) (Regarding age-related male androgen deficiency symptoms or diseases)
1) In the Invention, there are no specific restriction on the causes of "hypogonadism-associated symptoms and diseases," the degree of androgen deficiency, objective diagnostic criteria, etc. in "male androgen deficiency symptoms or diseases including male hypogonadism-associated symptoms and diseases" of "a male patient."

It should be noted that this point is only described in the specification of the application of the patent as follows, for example.
"[0003]
The precise threshold testosterone level below which symptoms of androgen deficiency and adverse health outcomes occur is not known and may be age-dependent (Kelleher, Conway et al. 2004; Zitzmann, Faber et al. 2006; Hall. Esche et al. 2008).
[0004]
At a threshold of 3.0 ng testosterone/mL, symptoms occur more below this value (Kelleher, Conway et al. 2004; Zitzmann, Faber et al. 2006; Bhasin, Cunningham et al. 2010). The guidelines from the US Endocrine Society have defined LOH as a serum testosterone less than 2.0 ng/mL in conjunction with one or more signs and symptoms of classical hypogonadism (Bhasin, Cunningham et al. 2006). The American Society of Andrology recommends less than 3.0 ng/mL in symptomatic men (American Society of Andrology 2006). On the other hand, according to the International Society for the Study of the Aging Male (ISSAM), symptomatic aged men should be considered hypogonadal at less than 3.50 ng/mL testosterone/mL (Wang, Nieschlag et ai. 2009a).
[0005]
In parallel, the testosterone concentration below which testosterone administration improves outcomes is unclear and may vary among individuals and among target organs. Therefore, the available evidence does not support use of an arbitrary threshold for testosterone level below which clinical androgen deficiency occurs and that confirms the diagnosis of hypogonadism in all patients (Bhasin, Cunningham et al. 2006)."
"[0020]
Aging itself is often associated with a decline in sexual functioning in men (Vermeulen 2003; Ebert, Jockenhovel et al., 2005).
"[0156]
A patient in need of treatment or of reducing the risk of onset of a given disease is one who has either been diagnosed with such disease or one who is susceptible of acquiring such disease."
(Each underline is made by the body)

In other words, some prior findings for the recommended threshold testosterone level for diagnosing hypogonadism in men have been found as illustrated in the above [0004]. However, in view of the descriptions in [0003] and [0005] before and after that, it is not recognized that the concentration of androgen such as testosterone in blood and the objective diagnostic criteria in "male androgen deficiency symptoms or diseases including male hypogonadism-associated symptoms and diseases" of "a male patient" in the Invention is clearly defined in the specification of the application of the patent.

Furthermore, it is understood that the specification of the application of the patent only suggests that, although it depends on an individual (an individual person), the age (aging or old age) itself causes a relative decrease in sexual function compared to the younger age (such a relative decline in sexual function is also indistinguishable from the "male androgen deficiency symptoms or diseases including male hypogonadism-related symptoms and diseases" of the Invention) ([0003] and [0020]), and older males can be said to be male patients having " the risk of onset" of "male androgen deficiency symptoms or diseases including male hypogonadism-associated symptoms and diseases" ([0156]) or males patients who are "susceptible of acquiring" such "symptoms or diseases" ([0156]).

2) On the other hand, according to (A1-2) of Publication A1, causes of androgen deficiency in human males include primary hypogonadism and secondary hypogonadism, as well as "aging" itself ((A1-2)). The cause is as follows: "Men experience a slow but continuous decline in average serum testosterone after approximately age 20 to 30 years. Researchers estimate that the decline is about 1- 2% per year. Moreover, as men age, the circadian rhythm of testosterone concentration is often muted, dampened, or completely lost." ((A1-2) [0006]).

Then, from such a description, regarding "androgen deficiency" in Cited Invention A1, human males older than 20 to 30 years have blood testosterone concentrations relatively lower than those at their ages of 20 to 30. In response to this decline, it can be inferred that relative decline occurs in hypogonadism and/or other age-related testosterone (androgen) relative deficiency (symptoms) as described in (A1-3) [0021]-[0022]. (Even if the symptoms of any specific disease as exemplified in (A1-3) [0022] are not apparently noticeable in such an elderly human male, such elderly human male is none other than one having "risk of developing" such a disease as compared to at the age of 20 to 30 and is "one who is susceptible of acquiring" such disease (the specification, [0156]).

Furthermore, human males actually adopted as subjects in the example of (A1-6) of Publication A1, which is provided as a pharmacological test example of Cited Invention A1, are "elderly men, aged 50-68 years"(human males older than those at "age 20 to 30 years" in (A1-2) [0006]). Thus, the blood testosterone concentration of each of the elderly men is relatively lower due to aging than at the age of 20 to 30 years. It can be thus recognized that the patients are those who have a relative decline in hypogonadism and/or other age-related testosterone (androgen) relative deficiency or are at risk of developing symptoms of such disease (susceptible of acquiring such disease) in response to the relative decline (A1-3) [0021] to [0022].).

3) Based on the considerations in the above 1) and 2), among the human males to whom the pharmaceutical preparation of Cited Invention A1 is applied, the human elderly

men with a relative decrease in age-related hypogonadism can be substantially indistinguishable from male patients who want to reduce or eliminate the occurrence of male androgen deficiency symptoms or diseases including male hypogonadism-related symptoms and diseases.

Therefore, Different Feature 3 is not a substantial difference.

In addition, when elderly men with age-related androgen deficiency listed in (A1-2) [0006] are men who present with particularly remarkable hypogonadism or related symptoms (e.g., an elderly male patient to whom "diagnosis of androgen deficiency is confirmed" as the "total testosterone is ≤200 ng/dL (i.e., 7 nmol/L)" that meets the diagnostic criteria of (A1-2) [0007] and an elderly male patient who is prominently presenting with any specific disease symptoms as exemplified in (A1-3) [0022]), these elderly male patients are clearly indistinguishable from male patients whose development of male androgen deficiency symptoms or diseases including male hypogonadism-related symptoms and diseases is desired to be reduced or eliminated.

Thus, even in this case, Different Feature 3 cannot be said to be a substantial difference. In addition, based on the description of Publication A1, a person skilled in the art could easily select among elderly men an elderly male patient who exhibits remarkable hypogonadism or related symptoms as stated above as a human male to which the pharmacological preparation of Cited Invention A1 is applied.

(b) (Regarding male androgen deficiency symptoms or diseases caused by causes other than aging)

In addition to elderly men with age-related testosterone deficiency, Publication A1 also describes men with primary hypogonadism or secondary hypogonadism as human males to which the pharmacological preparation of Cited Invention A1 is applied ((A1-2) [0004] to [0005], etc.). The men with primary hypogonadism or secondary hypogonadism can be substantially indistinguishable from male patients who want to reduce or eliminate the occurrence of male androgen deficiency symptoms or diseases including male hypogonadism-related symptoms and diseases.

Therefore, even if the androgen deficiency in Cited Invention A1 is due to a cause other than aging, Different Feature 3 is not a substantial difference. As an application target of the pharmaceutical preparation of Cited Invention A1, based on the description of Publication A1, a person skilled in the art could easily select a male patient with such primary hypogonadism or secondary hypogonadism or a male patient whose occurrence of primary hypogonadism or secondary hypogonadism is desired to be reduced or eliminated.

(ii-4) Effects of the Invention

(a) 1) In the specification of the application of the patent, female animals were adopted as all of the subjects in Examples 3, 4, and the like as in vivo pharmacological tests for administration of acolbifene (EM-652.HCl) or a combination medicament of EM-800 and DHEA according to the Invention.

The above subjects are decisively different from the human males (males) to which the above combination medicament of the Invention is applied, in that the subjects do not have the testes, which is the main synthetic organ of androgens, such as TT and DHEA, and also do not have the masculine (dominant) reproductive organ other than the testes.

Thus, it is clear that the female animals do not exhibit any of the diseases corresponding to the "male hypogonadism-related symptoms and diseases" of the Invention. Therefore, the results of pharmacological tests of Examples 3 and 4 using the above female animals as subjects cannot be reasonably taken into consideration in the evaluation of the pharmacological action of the combination medicament for human male (male) subjects involved in the Invention.

2) Pharmacological test results for masculine (male) subjects specifically described in the specification are only those obtained in the test described in [0148] (hereinafter, referred to as the "[0148] test") describing that "male cynomolgus monkeys" were dosed with the SERM of the present invention, acolbifene or EM-800, alone (i.e., without DHEA) under the specific dosage and administration conditions described in the descriptions in FIGS. 13 and 14 in [0088] and caused changes in serum TT concentration observed as shown in FIGS. 13 and 14.

Then, because of the following points (2-1) and (2-2), it cannot be recognized that the [0148] test can concretely or rationally support the pharmacological action of the combination medicament of the Invention "for reducing or eliminating the incidence of male androgen deficiency symptoms or diseases including male hypogonadism-associated symptoms and diseases in a male patient."

- 2-1) The subjects covered by the [0148] test are simply described as "male cynomolgus monkeys." The subjects are not human males and cannot be immediately recognized as models exhibiting symptoms or diseases corresponding to "male androgen deficiency symptoms or diseases including male hypogonadism-associated symptoms and diseases" in the "male patients" involved in the Invention. Therefore, it cannot be said that the subjects in the test are suitable for use in a test showing the pharmacological action of the combination medicament of the Invention.

- 2-2) Even if the "male cynomolgus monkeys" used in the test are models that exhibit symptoms or diseases corresponding to "male androgen deficiency symptoms or diseases including male hypogonadism-associated symptoms and diseases" in the "male patients" involved in the Invention, the [0148] test employs the administration of acolbifene or EM-800 alone and thus does not show any test result of administration of the combination medicament with DHEA of the Invention.

(b) As a result, it cannot be said that it has been clarified that use of a combination of acolbifene or EM-800 and DHEA involved in the Invention, which also meets the requirements of Different Features 1 to 3 in the above (i), exerts an excellent effect on the pharmacological action "for reducing or eliminating the incidence of male androgen deficiency symptoms or diseases including male hypogonadism-associated symptoms and diseases in a male patient" beyond the scope of the matters described or suggested in Publications A1 and A6 and/or Publication B.

(ii-5) Summary

As considered and aforementioned in the above (ii-1) to (ii-4), therefore, the Invention could be easily made by a person ordinarily skilled in the art based on the invention disclosed in Publication A1 in combination of the descriptions in Publication A1 and the descriptions in Publication B, or based on the invention disclosed in Publication A1 in combination with the descriptions in Publications A1 and A6, and the

descriptions in Publication B.

(iii) Appellant's allegation

The Appellant states the test results shown in [0148] to [0149] and FIGS. 13 and 14 of the specification in the written opinion dated March 19, 2020. However, as stated in (ii) (ii-4), the statements about the test results do not explain the following points in any concrete and rational manner:

- Whether the use of a combination of acolbifene or EM-800 and DHEA involved in the Invention, which also meets the requirements of Different Features 1 to 3 in the above (i) exerts an excellent effect on the pharmacological action "for reducing or eliminating the incidence of male androgen deficiency symptoms or diseases including male hypogonadism-associated symptoms and diseases in a male patient" beyond the scope of the matters described or suggested in Publications A1 and A6 and/or Publication B; and

- Which part of the specification can be said to support the excellent effect.

In addition, even in the same written opinion, no concrete and rational explanation is given on these points.

Therefore, such an allegation cannot be adopted as a reason for canceling the judgment regarding the denial of inventive step stated in (ii).

In addition, other allegations in the written opinion and the described matters in References 1 to 18 attached to the written supplemental amendment dated March 19, 2020 cited in the written opinion do not reasonably hinder the above judgment by the body regarding the denial of inventive step of the Invention.

3. Closing

As stated above, a patent shall not be granted for the invention recited in Claim 1 of the present application under the provision of Article 29(2) of the Patent Act. The patent application should be rejected without discussing other claims. Therefore, the appeal decision shall be made as described in the conclusion.

October 16, 2020

Chief administrative judge: OKAZAKI, Miho

Administrative judge: OKUBO, Motohiro

Administrative judge: TOMINAGA, Midori