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(54) Title: COMPOSITIONS AND METHODS FOR INDUCING HAIR GROWTH

(57) Abstract: Novel therapeutic methods and pharmaceutical compositions utilizing tellurium-containing compounds for inducing hair growth for the treatment of various types of alopecia and other conditions associated with hair loss.



WO 2006/030439 A2

COMPOSITIONS AND METHODS FOR INDUCING HAIR GROWTH

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to novel therapeutic methods and pharmaceutical
5 compositions for inducing hair growth and, more particularly, to compositions
comprising and methods utilizing tellurium-containing compounds for inducing hair
growth and thus for the treatment of various types of alopecia and other conditions
associated with hair loss.

Alopecia is the most common hair growth disorder in humans. Hair loss most
10 commonly occurs from the scalp. However, any hair-bearing area can be affected,
including eyebrows, eyelashes, beard and body areas.

Hair is composed of keratin, a strong structural protein. Each strand of hair
consists of three layers:

- (i) An innermost layer or medulla, which is only present in large thick
15 hairs;
- (ii) The middle layer known as the cortex, which provides strength and
both the color and the texture of hair; and
- (iii) The outermost layer, known as the cuticle, which is thin and colorless
and serves as a protector of the cortex.

20 Below the surface of the skin is the hair root, which is enclosed within a hair
follicle. The hair follicle is a dynamic structure that generates hair through complex
and exquisitely regulated cycles of growth and remodeling. It represents an
ectodermal-mesenchymal interaction unit that displays unique life-long, cyclic
transformations between stages of rapid growth and production of a pigmented hair
25 shaft (anagen), apoptosis-driven regression (catagen), and relative resting (telogen).

Every phase in the hair cycle is characterized by defined, tightly coordinated
programs of tissue proliferation, differentiation, and apoptosis, that are controlled by
the local balance of numerous growth-stimulatory and growth-inhibitory signals [1, 2].
Growth and development of hair follicles is influenced by a variety of growth factors
30 and cytokines, such as epidermal growth factor [3], transforming growth factor [4],
hepatocyte growth factor [5], interleukin-1 [6], Glial cell line-derived neurotrophic
factor [7], parathyroid hormone-related protein [8], bone morphogenetic protein-4, and
several members of the fibroblast growth factor family (FGF) [3]. It has been

previously proposed that one member of this family, FGF-7, known as the keratinocyte growth factor (KGF), is an important endogenous mediator of normal hair growth and development [9].

At the base of the hair follicle is the dermal papilla, which is fed by the
5 bloodstream, which carries nourishment to produce new hair. The dermal papilla contains receptors for male hormones and androgens. Androgens regulate hair growth and may cause the hair follicle to get progressively smaller and the hairs to become finer in individuals who are genetically predisposed to this type of hair loss.

Alopecia can be divided into disorders in which the hair follicle is normal but
10 the cycling of hair growth is abnormal, and disorders in which the hair follicle is damaged. Six major types of alopecia are known: androgenetic alopecia, alopecia areata, anagen effluvium, self-induced hair loss, telogen effluvium and scarring alopecia.

Androgenetic alopecia includes male pattern baldness and female pattern
15 baldness. Androgenetic alopecia accounts for 95 % of all hair loss. This genetically determined disorder is progressive through the gradual conversion of large, thick, pigmented, terminal hairs into thinner, shorter, indeterminate hairs and finally to short, wispy, non-pigmented, vellus hairs. Patients have a reduction in the terminal-to-vellus hair ratio, normally at least 2:1. Following miniaturization of the follicles,
20 fibrous tracts remain. Patients with this disorder usually have a typical distribution of hair loss.

A recent study [10] has discussed the fact that female pattern baldness is clearly an entirely different disease from male pattern baldness for a number of reasons:

25 (i) Male pattern alopecia begins with the recession of the hairline and results in complete hair loss, while female pattern alopecia causes diffuse thinning of the hair at and behind the hairline and there is no recession of the hairline;

(ii) Male pattern alopecia begins in the late teens and early 20's when the testosterone levels are high, while female pattern alopecia begins in the late 30's and
30 reaches its peak after 50 when testosterone levels are falling;

(iii) Male pattern alopecia affects up to 70% of all males, whereas female pattern alopecia affects up to 30% of women. If they were the same disease, the incidence would be the same;

(iv) Females with predisposition for male pattern alopecia rapidly develop
5 typical male pattern baldness if given high doses of testosterone

(v) A study described young women with hypopituitarism who presented with clinical and histological features of female androgenetic alopecia in the absence of detectable levels of circulation androgens or other signs of post-pubertal androgenation showing this pattern of hair loss is not androgen dependent; and

10 (vi) Treatment with 5 α alpha-reductase inhibitors certainly helps male pattern alopecia and has no effect on female pattern alopecia.

The male hormone dihydrotestosterone (DHT), which is converted from the enzyme testosterone by the enzyme 5-alpha-reductase, is responsible for androgenetic alopecia in those who are genetically predisposed. DHT causes a gradual reduction of
15 scalp hair follicle size and reduced time in the anagen stage of the growth cycle, leading to more hair follicles in the telogen stage.

Proven treatments for androgenetic alopecia include topical application of minoxidil and oral administration of finestidine.

Minoxidil (marketed under the name RogaineTM), as described in U.S. Patent
20 no. 4,139,619, appears to work by stimulating the conversion of vellus hair to terminal hair, as well as increasing the rate of growth of terminal hair. This has the effect of gradually enlarging and lengthening hair follicles which have been gradually shrinking due to androgenetic alopecia, and extending the growth phase, giving the hairs an opportunity to reach a longer length before they fall out. The two main
25 disadvantages associated with minoxidil are its high cost, and the need for its continuous application in order to maintain the results achieved. In addition, its application is associated with side effects such as itching of the scalp, skin irritations such as eczema, irritant dermatitis, allergic and contact dermatitis, nonspecific allergic reactions, such as hives, allergic rhinitis, facial swelling, and sensitivity, headache,
30 dizziness, diarrhea, nausea, vomiting and visual disturbances. Cardiovascular side effects and excessive hair growth have also occurred as a result of topical application of minoxidil. Edema, salt and water retention, pericardial effusion, pericarditis,

tamponade, tachycardia, and angina as a result of oral administration of minoxidil have also been reported. Patients with underlying heart disease may be at increased risk for these or other cardiovascular adverse effects.

Finasteride (PropeciaTM), as described in EP 155096B1 to Merck, is a 4-aza-steroid compound that is a specific inhibitor of type 2 5-alpha-reductase. Reported side effects include breast enlargement and tenderness, skin rashes, and swelling of the lips, abdominal pain, back pain, decreased libido, diarrhea, dizziness, headache, impotence, and decreased volume of ejaculate.

Further suggested treatments for androgenetic alopecia include retin-A; ketoconazole; azelaic acid; zinc; Saw Palmetto extract; gamma linoleic acid; vitamin B6; and polysorbate 80.

Treatments for female pattern baldness include use of cimetidine, cyproterone acetate, or spironolactone, all of which block the binding of DHT dihydrotestosterone to its receptors; and ketoconazole, which can cause a reduction in the production of testosterone and other androgens by the adrenal gland and by the male and female reproductive organs; or of a combined treatment of cyproterone acetate with ethinyloestradiol, which blocks the peripheral action of male hormones commonly present in the female body. Propecia has been found to be ineffective in treating women suffering from androgenetic alopecia.

Alopecia areata is thought to be an autoimmune disease in which T-lymphocytes attack the hair follicles, causing the hair to stop growing and enter into the telogen phase. At the end of the telogen phase, the hair falls out. Alopecia areata affects both men and women equally and is often experienced first in childhood. There are three subtypes of alopecia areata which are named according to their severity: (i) Alopecia areata, which involves mild patchy hair loss on the scalp; (ii) Alopecia totalis which involves loss of all scalp hair; and (iii) Alopecia universalis which involves loss of scalp and all body hair.

At present, no cure for alopecia areata is known and current treatments must be continued for as long as symptoms are present.

Current treatments for patients with less than 50 % hair loss include direct application of a corticosteroid cream or lotion to the bald areas; injection of corticosteroid directly onto and around the bald area; application of dithranol ointment to the scalp; topical application of minoxidil; and application of retin-A,

optionally in combination with minoxidil, to the area of hair loss, all of which are associated with adverse side effects as follows: side effects of corticosteroid application include adrenal gland suppression, Cushing's Syndrome, skin thinning, easy bruising and tearing of the skin, perioral dermatitis, enlarged blood vessels, and susceptibility to skin infections; application of dithranol commonly results in irritation and staining of the skin; and side effects of retin-A include blistering, altered pigmentation and increased sensitivity to light.

Oral zinc has been shown to be of occasional benefit in alopecia areata and appears to possess an immunomodulatory effect as well as an anti-androgenetic effect. However very high doses are needed for it to be effective and this may result in side effects, which can include vomiting and diarrhea.

Current treatments for patients with greater than 50 % hair loss include use of oral cortisone; PUVA treatment, which involves use of a psoralen, which is a light sensitive drug, followed by a short period of exposure to long-wave ultraviolet light; application of irritants or allergens to the scalp, which cause an allergic reaction, drawing the T-lymphocytes away from the hair follicle, thus allowing the hair a chance to start regrowing; and use of immunosuppressive drugs.

Possible side effects of oral cortisone include fluid retention and weight increase, osteoporosis, hypertension, sugar diabetes, indigestion or worsening of a peptic ulcer, mood changes, impaired healing of cuts, increased growth of facial hair, increased risk of infection, muscle weakness, joint pain and cataract of the eye. Side-effects of immuno-suppressive drugs include lowered resistance to infection.

Anagen effluvium is the sudden hair loss, which occurs as a result of exposure to chemicals or radiation, such as the hair loss that results during certain types of chemotherapy or radiation treatment, or as a result of exposure to toxic chemicals such as thallium and arsenic.

In anagen effluvium the hair does not enter a resting stage. The hair loss is usually sudden occurring 1 to 3 weeks after exposure to the chemicals or radiation has occurred. In most cases hair growth will return to normal once treatment is finished.

The drugs which are most likely to cause hair loss include amsacrine; cisplatin; cytosine arabinoside; cyclophosphamide; doxorubicin; epirubicin; etoposide ifosfamide; and vincristine. It has been found that agents which protect against alopecia induced by a particular drug may be ineffective in protecting against a

different drug. For example, a composition obtained from the bacteria *Serratia marcescens* has been used to protect against the alopecia which is associated with the use of cytosine araginoside and doxorubicin. This composition had no effect on alopecia which was induced by cyclophosphamide.

5 Self-induced hair loss may be inflicted consciously or unconsciously. The two main types of self-induced hair loss are trichotillomania and traction alopecia.

Trichotillomania is self-induced hair loss which results from the continuous pulling or plucking of the hair. It occurs most commonly among young children, adolescents and women and affects twice as many females as males. The hair is often
10 pulled out in distinct patches on the scalp. However some individuals also pull out eyebrows and eyelashes. The treatment for trichotillomania often involves counseling or psychiatric help, whereby in some cases an antidepressant is prescribed.

Traction alopecia is usually caused by continuous and excessive pulling on the hair due to various types of hairstyling, which gradually results in hair loss that may
15 become permanent. Generally, however, a change in hairstyle that reduces the traction on the hair and hair follicle is sufficient to reverse the hair loss in this case.

Telogen effluvium is sudden or severe stress related hair loss, which appears as thinning throughout the whole scalp.

A sudden or stressful event can cause the hair follicles to prematurely stop
20 growing and enter into a resting phase. The hair will then stay in the resting phase for about 3 months after which time a large amount of hair will be shed. In most cases the hair loss is temporary and the hair soon recovers. However in some cases the hair loss continues until the underlying cause is removed.

Events which may lead to telogen effluvium include childbirth; termination of
25 pregnancy; starting or stopping birth control pills; use of various medications; and severe emotional stress.

Increased levels of hormones estrogen and progesterone during pregnancy cause more hairs than normal to remain in the growth phase. Following childbirth or termination of pregnancy, many of the hair follicles that had delayed entering the
30 resting phase suddenly enter the resting phase due to the rapid drop in hormone levels.

Birth control pills affect the hormone levels within the body and these hormone levels can affect hair growth. In some cases hair thinning may occur due to the male hormones present in some types of contraceptive pills, resulting in hair loss

similar to that of androgenetic alopecia. Discontinuation of the pill can result in hair loss similar to that which occurs after childbirth, due to the drop in hormone levels.

Drugs which may cause hair loss as a side effect include anti-gout agents such as allopurinol; blood thinners such as heparin and coumarin; and cholesterol
5 lowering drugs such as clofibrate and gemfibrozil.

Telogen effluvium may also occur after a traumatic event such as the death of a loved one, an accident, abuse or any other severely traumatic event. These events may trigger hair follicles to enter the resting phase prematurely in which case an increase in the amount of hair shed will be noticed about 3 months after the event.

10 Other causes of telogen effluvium include thyroid gland malfunction (hypothyroidism or hyperthyroidism, which occurs when the thyroid gland produces too little or too much, respectively, of the thyroid hormone, thyroxin); diabetes; anaemia; and the autoimmune disease, systemic lupus erythematosus.

Scarring alopecia occurs as a result of inflammation of the hair follicles due to
15 infection.

Scarring alopecia may be caused by discoid lupus erythematosus, a diffuse connective tissue disease; lichenplanus, which is an inflammatory disease that strikes primarily the skin and mucous membranes; Pseudopelade of Brocq, a rare scarring alopecia which has no potential for regrowth; aplasia cutis congenita, a rare disorder
20 that often results as a small blistered atrophied area usually in the midline of the scalp and present from birth; or congenital trichia.

Other types of hair loss include syphilitic alopecia, a secondary manifestation of syphilis; scleroderma; and tinea capitis (ringworm).

Hence, while the prior art teaches the use of various medications for treating
25 the different types of alopecia, these treatments are oftentimes limited by high cost, prolonged treatment periods, insufficient efficacy and/or adverse side effects.

There is thus a widely recognized need for, and it would be highly advantageous to have, novel compositions and methods for treating one or more of the above-cited alopecia types, devoid of the above limitations.

30 U.S. Patent No. 5,262,149 teaches a method for treatment or prevention of alopecia which is induced by an antineoplastic agent, by administration of a tellurium-containing compound prior to the administration of the antineoplastic agent. U.S. Patent No. 6,552,089 teaches a method for treatment or prevention of male pattern

baldness by administration of a tellurium-containing compound. The preferred tellurium-containing compounds utilized in the methods taught by these patents are widely described in, for example, U.S. Patents Nos. 4,752,614; 4,761,490; 4,764,461 and 4,929,739, which are all incorporated by reference as if fully set forth herein. One
5 of the most promising compounds described in these patents is ammonium trichloro(dioxyethylene-O,O')tellurate, which is also referred to herein and in the art as AS101. AS101, as a representative example of the family of tellurium-containing compound discussed hereinabove, has been found to have act as an immunomodulator which stimulates the innate and acquired arms of the immune system, and is a potent
10 inducer of interferon (IFN) in mice and in humans.

U.S. Patents Nos. 5,262,149 and 6,522,089, however, fail to demonstrate the efficacy of these tellurium-containing compounds in treating types of alopecia other than male pattern baldness and alopecia induced by an antineoplastic agent. Although U.S. Patent No. 5 6,522,089 refers to non-scarring alopecia as including toxic
15 alopecia, alopecia areata and trichotillomania, and teaches that non-scarring alopecia may be avoided or reduced by administration of an effective amount of an effective tellurium compound, this patent fails to provide enabling examples with regard to forms of alopecia other than alopecia induced by chemotherapeutic agents. This document therefore merely provides an invitation to try to find forms of alopecia
20 which are treatable by tellurium compounds, without any disclosure as to which particular forms, other than alopecia induced by an antineoplastic agent, are suitable for such treatment.

In human clinical studies (*FASEB J* 18: 400-402, 2004), AS101 exhibited the ability to protect cancer patients from both bone marrow toxicity and alopecia induced
25 by chemotherapy. AS101 has been found to induce hair growth in nude mice, normal mice, and in humans. In nude mice, AS101 exerts this effect when applied systemically, orally or topically. AS101 possesses the dual ability to both induce anagen and retard spontaneous catagen in the C57BL/6 mouse model. Anagen induced by AS101 is mediated by keratinocyte growth factor (KGF) since it is
30 abrogated both in nude mice co-treated with AS101 and neutralizing anti-KGF antibodies, and in AS101-treated transgenic mice expressing a dominant negative KGF receptor transgene in basal keratinocytes. AS101 upregulates KGF expression by interacting with the Cys118 residue in p21^{ras} and activating the ras signalling

pathway in cultured fibroblasts. AS101-induced delayed catagen is associated with inhibition of terminal differentiation marker expression in epidermal follicular keratinocytes and in cultures of primary mouse follicular keratinocytes induced to differentiate both in nude and C57BL/6 mice. This activity is associated with relatively sustained elevation of p21^{waf}, found crucial for activity of AS101, since delayed expression of terminal differentiation markers was not induced by AS101 from 21^{waf} knockout mice. While these studies demonstrate the effect of AS101 in the treatment of anagen effluvium,, the efficacy of AS101 in treating other types of alopecia have not been demonstrated.

In a recently filed U.S. Provisional Patent Application No. 60/610,660, which is also incorporated by reference as if fully set forth herein, a novel family of tellurium-containing compounds has been disclosed. However, the effect of these recently disclosed tellurium-containing compounds on hair growth in general and in treating alopecia in particular has not been suggested nor practiced.

SUMMARY OF THE INVENTION

According to one aspect of the present invention there is provided a method of treating or preventing alopecia, excluding male pattern baldness and alopecia induced by antineoplastic agents, the method comprising administration to a subject in need thereof a therapeutically effective amount of a compound having at least one tellurium dioxide moiety.

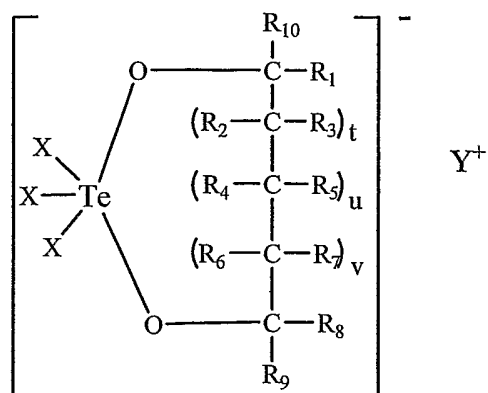
According to another aspect of the present invention there is provided use of at least one tellurium-containing compound having at least one tellurium dioxide moiety, in treating or preventing alopecia, excluding male pattern baldness and alopecia induced by antineoplastic agents.

According to yet another aspect of the present invention there is provided a pharmaceutical composition, identified for use in the treatment or prevention of alopecia, excluding male pattern baldness and alopecia induced by antineoplastic agents, the composition comprising at least one tellurium-containing compound having at least one tellurium dioxide moiety.

According to further features in any of the above aspects of the present invention, the tellurium dioxide moiety is optionally and preferably at least one of

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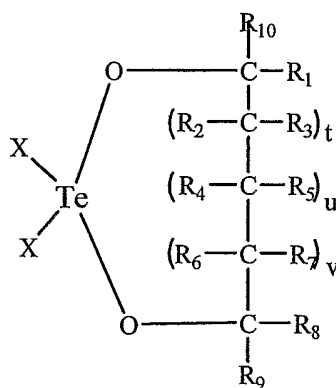
tellurium dioxide (TeO_2) *per se*, an organic complex of TeO_2 (as detailed hereinbelow), a compound having general Formula I:



Formula I

5

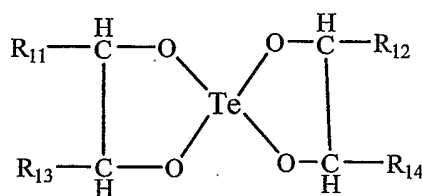
a compound having general Formula II:



Formula II

10 and

a compound having general Formula III:



15

Formula III

wherein:

each of t, u and v is independently 0 or 1;

each of m and n is independently an integer from 0 to 3;

Y is selected from the group consisting of ammonium, phosphonium, potassium, sodium and lithium;

5 X is a halogen atom; and

each of R₁-R₁₄ is independently selected from the group consisting of hydrogen, hydroxyalkyl, hydroxy, thiohydroxy, alkyl, alkenyl, alkynyl, alkoxy, thioalkoxy, halogen, haloalkyl, carboxy, carbonyl, alkylcarbonylalkyl, carboxyalkyl, acyl, amido, cyano, N-monoalkylamidoalkyl, N,N-dialkylamidoalkyl, cyanoalkyl, 10 alkoxyalkyl, carbamyl, cycloalkyl, heteroalicyclic, sulfonyl, sulfinyl, sulfate, amine, aryl, heteroaryl, phosphate, phosphonate and sulfonamido.

According to an embodiment in which the tellurium-containing compound has general Formula I, preferably t, u and v are each 0. More preferably, each of R₁, R₈, R₉ and R₁₀ is hydrogen; more preferably X is a halogen atom, most preferably the 15 halogen atom is chloro. More preferably, Y is ammonium. The preferred compound according to this embodiment is referred to hereinafter as AS101.

According to further features in this aspect of the present invention, the method may optionally further comprise administering a therapeutically effective amount of an additional active agent for treating alopecia.

20 According to still further features of the method of the present invention, administration of the tellurium-containing compound may be effected by the intraperitoneal, parenteral, oral, topical, rectal, transmucosal, intestinal, intrathecal, direct intraventricular, intravenous, intranasal, or intraocular route.

According to still further features of the method of the present invention, a 25 therapeutically effective amount administered intraperitoneally preferably ranges from about 0.025 to about 0.8 mg/kg of body weight.

Alternatively, a therapeutically effective amount for parenteral administration preferably ranges from about 0.025 to about 2.5 mg/kg of body weight.

Also alternatively, a therapeutically effective amount for oral administration 30 preferably ranges from about 0.025 to about 7.5 mg/kg of body weight.

Further alternatively, administering is effected topically, preferably by applying a therapeutically effective amount of a tellurium-containing compound onto a treated skin area.

According to further features in this aspect of the present invention, administering is preferably effected according to a regime that ranges from twice daily to once weekly. In one preferred embodiment, administering is effected on a daily basis.

5 According to further features in this aspect of the present invention administering is effected for a time period that ranges from 1 day to 90 days and more preferably from 7 days to 90 days.

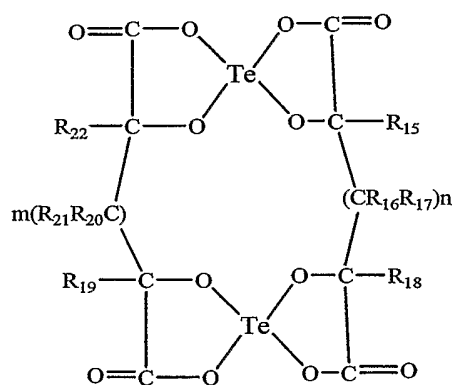
According to yet further features in the described preferred embodiments, the tellurium-containing compound of the method or use of the present invention forms a
10 part of a pharmaceutical composition, further comprising a pharmaceutically acceptable carrier. More preferably, the pharmaceutical composition is formulated as a gel, a cream, an ointment, a paste, a lotion, a milk, a suspension, an aerosol, a spray, a foam, a serum, a swab, a pledglet, a pad or a patch. Preferably, a concentration of tellurium-containing compound of formula I, II or III in the carrier ranges from about
15 0.01 weight percent to about 50 weight percents, more preferably from about 0.01 weight percent to about 20 weight percents of the total weight of the composition.

According to further features in this aspect of the present invention, the composition of the present invention may optionally further comprise at least one additional active agent for treating alopecia. According to yet further features in the
20 described preferred embodiments the additional active agent of the method, use or composition of the present invention may be, for example, minoxidil, finasteride, retin-A; ketoconazole; azelaic acid; zinc; Saw Palmetto extract; gamma linoic acid; vitamin B6; polysorbate 80; cyproterone acetate; ethinyloestradiol; cimetidine; spironolactone; ketoconazole, a corticosteroid; dithranol; an immunosuppressive drug
25 or an irritant. Preferably, the additional active agent is minoxidil, finasteride or a combination thereof.

According to further features in the described preferred embodiments, the alopecia treated or prevented by the method, use or pharmaceutical composition of the present invention may optionally comprise alopecia induced by an autoimmune
30 disease (such as alopecia areata); female pattern baldness; self-induced alopecia; traction alopecia; telogen effluvium; and scarring alopecia (such as that caused by discoid lupus erythmatosus, lichen planus, aplasia cutis congenital or congenital atrichia).

According to yet further features in the described preferred embodiments, tellogen effluvium treated or prevented by the method, use or pharmaceutical composition of the present invention may be, for example, that associated with administration of a drug, such as a contraceptive pill, an anti-gout agent, a blood thinner, or a cholesterol lowering agent, including, but not limited to allopurinol, heparin, coumarin, clofibrate and gemfibrozil. Alternatively the tellogen effluvium may be due to a condition such as, for example, thyroid gland malfunction, diabetes, anemia or systemic lupus erythematosus.

According to another aspect of the present invention there is provided a method of inducing hair growth and/or reducing or preventing hair loss, the method comprising administering to a subject in need thereof a therapeutically effective amount of at least one tellurium-containing compound having general Formula IV:



Formula IV

wherein:

each of m and n is independently an integer from 0 to 3; and

each of R₁₅-R₂₂ is independently selected from the group consisting of hydrogen, hydroxyalkyl, hydroxy, thiohydroxy, alkyl, alkenyl, alkynyl, alkoxy, thioalkoxy, halogen, haloalkyl, carboxy, carbonyl, alkylcarbonylalkyl, carboxyalkyl, acyl, amido, cyano, N-monoalkylamidoalkyl, N,N-dialkylamidoalkyl, cyanoalkyl, alkoxyalkyl, carbamyl, cycloalkyl, heteroalicyclic, sulfonyl, sulfinyl, sulfate, amine, aryl, heteroaryl, phosphate, phosphonate and sulfoneamido.

According to yet another aspect of the present invention there is provided use of a therapeutically effective amount of at least one tellurium-containing compound

having general Formula IV, as defined above, in inducing hair growth and/or reducing or preventing hair loss in a subject in need thereof.

According to yet another aspect of the present invention there is provided a pharmaceutical composition, identified for use in inducing hair growth and/or reducing or preventing hair loss in a subject in need thereof, the composition comprising a therapeutically effective amount of at least one tellurium-containing compound having general Formula IV, as defined above.

Preferably, n and m of the compound of general Formula IV are each 0. More preferably, each of R_{15} , R_{18} , R_{19} and R_{22} is hydrogen. The preferred compound according to this embodiment is referred to hereinafter as SAS.

According to further features in the described preferred embodiments comprising the compound of general Formula IV, the method of the present invention further comprises administering a therapeutically effective amount of an additional active agent for inducing hair growth and/or reducing or preventing hair loss.

According to further features in the use of the present invention, the tellurium-containing compound is used in combination with at least one additional active agent for inducing hair growth and/or reducing or preventing hair loss.

According to yet further features in the described preferred embodiments the additional active agent of the method, use or composition of the present invention may be, for example, minoxidil, finasteride, retin-A; ketoconazole; azelaic acid; zinc; Saw Palmetto extract; gamma linoic acid; vitamin B6; polysorbate 80; cyproterone acetate; ethinyloestradiol; cimetidine; spironolactone; ketaconazole, a corticosteroid; dithranol; an immunosuppressive drug or an irritant. Preferably, the additional active agent is minoxidil, finasteride, or combinations thereof.

According to still further features of the method of the present invention, administration of the tellurium-containing compound may be effected by the intraperitoneal, parenteral, oral, topical, rectal, transmucosal, intestinal, intrathecal, direct intraventricular, intravenous, intranasal, or intraocular route.

According to still further features of the method of the present invention, a therapeutically effective amount of the compound of formula IV administered intraperitoneally preferably ranges from about 0.04 to about 1.3 mg/kg of body weight.

Alternatively, a therapeutically effective amount of the compound of formula IV for parenteral administration preferably ranges from about 0.04 to about 4.2 mg/kg of body weight.

Also alternatively, a therapeutically effective amount of the compound of formula IV for oral administration preferably ranges from about 0.04 to about 12.7 mg/kg of body weight.

Preferably, administration is effected topically by applying onto a treated skin or mucosal membrane area a therapeutically effective amount of the at least one tellurium-containing compound described above.

According to further features in this aspect of the present invention, administering is preferably effected according to a regime that ranges from twice daily to once weekly, more preferably for a time period that ranges from 1 day to 90 days and more preferably from 7 days to 90.

According to further features in the described preferred embodiments, the method, use or pharmaceutical composition of the present invention may preferably be used for treating a condition in which inducing hair growth and/or preventing hair loss is beneficial, such as, for example, androgenetic alopecia, alopecia areata, anagen effluvium (such as induced by an antineoplastic agent), self-induced hair loss, telogen effluvium and scarring alopecia (such as caused by discoid lupus erythematosus, lichen planus, aplasia cutis congenital and congenital atrichia). The telogen effluvium treated or prevented by the method, use or pharmaceutical composition of this aspect of the present invention may be due to a drug such as a contraceptive pill, an anti-gout agent, a blood thinner, or a cholesterol lowering agent, such as, for example, allopurinol, heparin, coumarin, clofibrate and gemfibrozil, which may optionally be co-administered together with the tellurium-containing compound. The telogen effluvium may optionally be due thyroid gland malfunction, diabetes, anemia or systemic lupus erythematosus.

According to further features in the described preferred embodiments, tellurium-containing compound of the method or use or pharmaceutical composition of the present invention may optionally form a part of a pharmaceutical composition comprising a pharmaceutically acceptable carrier, more preferably the composition is formulated as a gel, a cream, an ointment, a paste, a lotion, a milk, a suspension, an aerosol, a spray, a foam, a serum, a swab, a pledget, a pad or a patch.

Preferably, a concentration of tellurium-containing compound of formula IV in the carrier ranges from about 0.1 weight percent to about 85 weight percents, more preferably from about 0.1 weight percents to about 40 weight percents of the total weight of the composition.

5 The present invention successfully addresses the shortcomings of the presently known configurations by providing methods, uses and compositions for treatment or prevention of alopecia other than male pattern baldness and alopecia caused by antineoplastic agents, and further provides methods, uses and compositions for inducing hair growth and/or reducing or preventing hair loss. Unless otherwise
10 defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

As used herein, the term "treating" includes abrogating, substantially inhibiting, slowing or reversing the progression of a condition, substantially
15 ameliorating clinical or aesthetical symptoms of a condition or substantially preventing the appearance of clinical or aesthetical symptoms of a condition.

The term "comprising" means that other steps and ingredients that do not affect the final result can be added. This term encompasses the terms "consisting of" and "consisting essentially of".

20 The phrase "consisting essentially of" means that the composition or method may include additional ingredients and/or steps, but only if the additional ingredients and/or steps do not materially alter the basic and novel characteristics of the claimed composition or method.

The term "method" refers to manners, means, techniques and procedures for
25 accomplishing a given task including, but not limited to, those manners, means, techniques and procedures either known to, or readily developed from known manners, means, techniques and procedures by practitioners of the chemical, pharmacological, biological, biochemical and medical arts.

The term "therapeutically effective amount" or "pharmaceutically effective
30 amount" denotes that dose of an active ingredient or a composition comprising the active ingredient that will provide the therapeutic effect for which the active ingredient is indicated.

As used herein, the singular form "a," "an," and "the" include plural references unless the context clearly dictates otherwise. For example, the term "a compound" or "at least one compound" may include a plurality of compounds, including mixtures thereof.

5 Throughout this disclosure, various aspects of this invention can be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well
10 as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

15 Whenever a numerical range is indicated herein, it is meant to include any cited numeral (fractional or integral) within the indicated range. The phrases "ranging/ranges between" a first indicate number and a second indicate number and "ranging/ranges from" a first indicate number "to" a second indicate number are used herein interchangeably and are meant to include the first and second indicated
20 numbers and all the fractional and integral numerals therebetween.

Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are
25 illustrative only and not intended to be limiting.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it
30 is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of the preferred embodiments of the present invention only, and are presented in the cause of providing what is believed to be the most useful and readily understood description of the principles and conceptual aspects of the

invention. In this regard, no attempt is made to show structural details of the invention in more detail than is necessary for a fundamental understanding of the invention, the description taken with the drawings making apparent to those skilled in the art how the several forms of the invention may be embodied in practice.

5 In the drawings:

FIG. 1 is an example of the analysis of results obtained in the present study using the TrichoScan system;

FIGs. 2a and 2b present graphical representation of results obtained in the study described in Example 1 for a representative female subject aged 39 (Figure 2a) and a representative male subject aged 29 (Figure 2b); and

FIG. 3 shows results obtained by a specific patient with twice daily administration of AS101.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

15 The present invention is of the use of tellurium-containing compounds for treating and/or preventing alopecia. Specifically, the present invention provides methods utilizing tellurium-containing compound having at least one tellurium dioxide moiety, to treat or prevent alopecia, excluding male pattern baldness and alopecia induced by antineoplastic agents. The present invention further provides other tellurium-containing compounds, which can be used for inducing hair growth and/or reducing or preventing hair loss.

The principles and operation of the compounds, compositions and methods according to the present invention may be better understood with reference to the accompanying descriptions.

25 Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not limited in its application to the details set forth in the following description or exemplified by the Examples. The invention is capable of other embodiments or of being practiced or carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein is for the purpose of description and should not be regarded as limiting.

30 As used herein, the phrase "tellurium-containing compound" encompasses any compound that includes one or more tellurium atoms and exhibits immunomodulating properties.

Preferably, the tellurium-containing compounds include one or more tellurium dioxide moiety.

As used herein the term "about" refers to $\pm 10\%$.

As is described hereinabove, the various types of alopecia differ in their
5 underlying causes, which take effect according to various mechanisms of actions. Furthermore, as further described hereinabove, a composition obtained from the bacteria *Serratia marcescens* which was found to protect against the alopecia which is associated with the use of cytosine arabinoside and doxorubicin had no effect on alopecia which was induced by cyclophosphamide. Hence, it is apparent that the
10 various types of alopecia may respond differently to a particular compound for treatment of alopecia.

Hence, for example, alopecia areata, which is an autoimmune disease, would not be expected to be responsive to compounds which treat or prevent androgenetic alopecia, caused by dihydrotestosterone production, or those which treat or prevent
15 scarring alopecia, which is caused by inflammation.

As is further described hereinabove, U.S. Patent No. 5,262,149 teaches use of a tellurium containing compound of general formula I, II or III, preferably AS101, for treatment or prevention of alopecia which is induced by an antineoplastic agent, and U.S. Patent No. 6,552,089 teaches use of these compounds for treatment or prevention
20 of male pattern baldness.

The background art does not teach or suggest the efficacy of these tellurium-containing compounds in treating types of alopecia other than male pattern baldness and alopecia induced by an antineoplastic agent.

U.S. Provisional Patent Application No. 60/610,660 discloses a novel family
25 of tellurium-containing compounds, (which are collectively represented by general formula IV herein), use of which has not been suggested nor practiced for inducing hair growth and/or reducing or preventing hair loss.

It has been suggested that AS101, as well as other tellurium-containing immunomodulators, stimulate the innate and acquired arm of the immune response.
30 For example, it has been shown that AS101 is a potent activator of interferon (IFN) (IFN) in mice (*J. Natl. Cancer Inst.* 88(18):1276-84, 1996) and humans (*Nat. Immun. Cell Growth Regul.* 9(3):182-90, 1990; *Immunology* 70(4):473-7, 1990; *J. Natl. Cancer Inst.* 88(18):1276-84, 1996.)

It has also been demonstrated that AS101, as well as other tellurium-containing immunomodulators, induce the secretion of a spectrum of cytokines, such as IL-1, IL-6 and TNF- α , and that macrophages are one main target for AS101 (*Exp. Hematol.* 23(13):1358-66, 1995) and it was found to inhibit IL-10 at the m-RNA
5 level, and this inhibition may cause an increase in IL-12 (*Cell Immunol.* 176(2):180-5, 1997); *J. Natl. Cancer Inst.* 88(18):1276-84, 1996).

The process of hair follicle development consists of a series of dermal-epidermal signaling events that culminate with the mesenchymal cells of the dermal papilla inducing epithelial cells of the hair plug to grow and differentiate into a
10 follicle. It follows from this that substances that mediate intercellular signaling events, that in turn affect intracellular control mechanisms inside follicular keratinocytes, would enhance the maintenance of normal hair growth.

As further discussed hereinabove, growth and development of hair follicles is known to be influenced by growth factors and cytokines, such as epidermal growth
15 factor [3], transforming growth factor [4], hepatocyte growth factor [5], interleukin-1 [6], Glial cell line-derived neurotrophic factor [7], parathyroid hormone-related protein [8], bone morphogenetic protein-4, and several members of the fibroblast growth factor family (FGF) [3].

Therefore, while conceiving the present invention, the present inventors have
20 postulated that the immunomodulatory effect of the tellurium containing compound AS101 can be harnessed to treat alopecia other than male pattern baldness and alopecia caused by antineoplastic agents, and also to induce hair growth and/or reduce or prevent hair loss.

The different types of alopecia, as discussed in detail hereinabove, are known
25 to be associated with entirely different mechanisms. Hence, androgenetic alopecia, which includes male pattern baldness and female pattern baldness, is known to be caused by the hormone dihydrotestosterone; alopecia areata is believed to be an autoimmune disease in which T-lymphocytes attack the hair follicles; anagen effluvium occurs during certain types of chemotherapy or radiation treatment, or as a result of
30 exposure to toxic chemicals, such that the hair is prevented from entering the resting stage; self-induced hair loss is related to an underlying psychological factor; traction alopecia is caused by physical strain exerted on the hair, such as pulling due to a specific hairstyle; telogen effluvium is caused by sudden or stressful event, which

may be an emotional trauma, or a hormone-induced stress, such as that following childbirth; and scarring alopecia occurs as a result of inflammation of the hair follicles due to infection.

Due to the different underlying mechanisms causing the different types of alopecia, tellurium-containing compounds which are known to be effective in treating
5 alopecia due to antineoplastic agents and male pattern baldness, could not be anticipated to be effective in treating other types of alopecia.

While reducing the present invention to practice, it was surprisingly found that AS101 and related tellurium-containing compounds are effective in treatment or
10 prevention of many types of alopecia, in addition to those described in the background art.

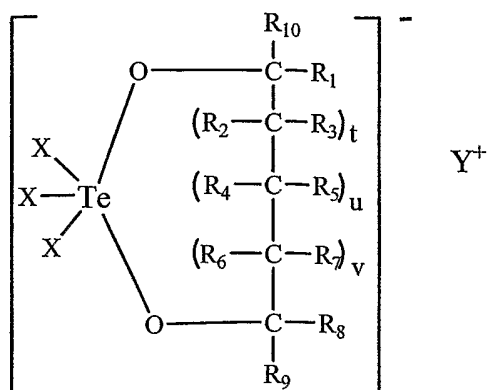
It was further surprisingly found that as a result of the influence on the hair growth cycle as a result of the immunomodulatory effect described above, compounds of the general formula IV can be effective in generally inducing hair growth and/or
15 reducing or preventing hair loss.

As shown in the Examples section below, patients treated by a weekly administration of AS101 show a significant increase in hair density, terminal hair density, and vellus hair density after about 1 month of treatment. These patients had not been treated with antineoplastic agents, and the treatment was surprisingly found
20 to be effective for both male and female subjects.

In a female patient, treated daily with AS101, a significant increase in the three categories of hair density studied was seen, which continued for the 6 month period of the trial. Since this patient is a female, and therefore cannot be considered to be suffering from male pattern baldness, and had not received antineoplastic treatment,
25 these results clearly demonstrate that AS101 is effective in treating alopecia other than male pattern baldness or alopecia due to antineoplastic agents.

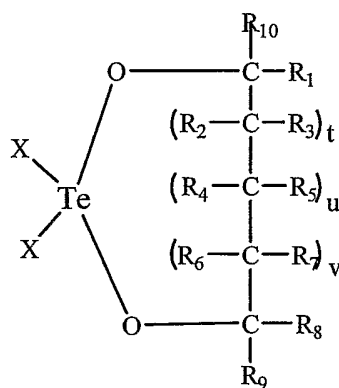
The present invention therefore provides a method of treating or preventing alopecia, excluding male pattern baldness and alopecia induced by antineoplastic agents, by administration of a therapeutically effective amount of at least one tellurium-containing compound having at least one tellurium dioxide moiety, and optionally and preferably selected from the group consisting of tellurium dioxide (TeO_2) *per se*, an organic complex of TeO_2 (as detailed hereinbelow), a compound having general Formula I:

22



Formula I

5 a compound having general Formula II:

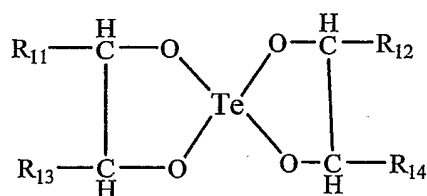


Formula II

and

10

a compound having general Formula III:



Formula III

wherein:

each of t, u and v is independently 0 or 1;

15

23

each of m and n is independently an integer from 0 to 3;

Y is selected from the group consisting of ammonium, phosphonium, potassium, sodium and lithium;

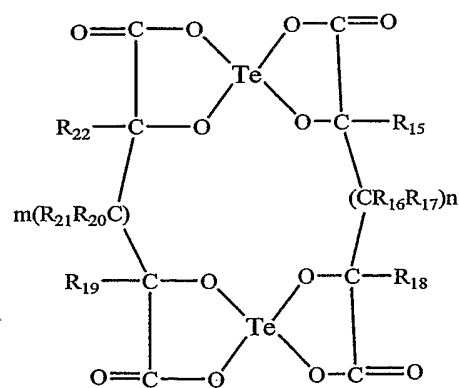
X is a halogen atom; and

5 each of R_1 - R_{14} is independently selected from the group consisting of hydrogen, hydroxyalkyl, hydroxy, thiohydroxy, alkyl, alkenyl, alkynyl, alkoxy, thioalkoxy, halogen, haloalkyl, carboxy, carbonyl, alkylcarbonylalkyl, carboxyalkyl, acyl, amido, cyano, N-monoalkylamidoalkyl, N,N-dialkylamidoalkyl, cyanoalkyl, alkoxyalkyl, carbamyl, cycloalkyl, heteroalicyclic, sulfonyl, sulfinyl, sulfate, amine, 10 aryl, heteroaryl, phosphate, phosphonate and sulfonamido.

According to an embodiment in which the tellurium-containing compound has general Formula I, preferably t, u and v are each 0. More preferably, each of R_1 , R_8 , R_9 and R_{10} is hydrogen; more preferably X is a halogen atom, most preferably the halogen atom is chloro. More preferably, Y is ammonium. The preferred compound 15 according to this embodiment is referred to hereinafter as AS101.

The present invention further provides a method of inducing hair growth and/or reducing or preventing hair loss, the method comprising administering to a subject in need thereof a therapeutically effective amount of at least one tellurium-containing compound having general Formula IV:

20



Formula IV

25 wherein:

each of m and n is independently an integer from 0 to 3; and

each of R₁₅-R₂₂ is independently selected from the group consisting of hydrogen, hydroxyalkyl, hydroxy, thiohydroxy, alkyl, alkenyl, alkynyl, alkoxy, thioalkoxy, halogen, haloalkyl, carboxy, carbonyl, alkylcarbonylalkyl, carboxyalkyl, acyl, amido, cyano, N-monoalkylamidoalkyl, N,N-dialkylamidoalkyl, cyanoalkyl, alkoxyalkyl, carbamyl, cycloalkyl, heteroalicyclic, sulfonyl, sulfinyl, sulfate, amine, aryl, heteroaryl, phosphate, phosphonate and sulfoneamido. Preferably, according to this embodiment, n and m are each 0. More preferably, each of R₁₅, R₁₈, R₁₉ and R₂₂ is hydrogen. The preferred compound according to this embodiment is referred to hereinafter as SAS.

10 The hair loss treated or prevented may be alopecia. .

As used herein, the term "alkyl" refers to a saturated aliphatic hydrocarbon including straight chain and branched chain groups. Preferably, the alkyl group has 1 to 20 carbon atoms. Whenever a numerical range; *e.g.*, "1-20", is stated herein, it implies that the group, in this case the alkyl group, may contain 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc., up to and including 20 carbon atoms. More preferably, the alkyl is a medium size alkyl having 1 to 10 carbon atoms. Most preferably, unless otherwise indicated, the alkyl is a lower alkyl having 1 to 5 carbon atoms. The alkyl group may be substituted or unsubstituted. When substituted, the substituent group can be, for example, hydroxyalkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, halo, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, sulfate, cyano, nitro, sulfonamide, phosphonyl, phosphinyl, carbonyl, thiocarbonyl, carboxy, thiocarboxy, carbamate, thiocarbamate, amido, sulfonamido, and amino, as these terms are defined herein.

As used herein, the term "hydroxyalkyl" refers to an alkyl, as this term is defined herein, substituted by a hydroxy group, as defined herein, and includes, for example, hydroxymethyl, hydroxyethyl, hydroxypropyl and hydroxy-n-butyl.

The term "haloalkyl" refers to an alkyl, as this term is defined herein, substituted by a halogen, as defined herein, and includes, for example, chloromethyl, 2-iodoethyl, 4-bromo-n-butyl, iodoethyl, 4-bromo-n-pentyl and the like.

30 The term "alkanoyloxy" refers to a carbonyl group, as define herein and includes, for example, acetyl, propionyl, butanoyl and the like.

The term "carboxyalkyl" refers to an alkyl, as this term is defined herein, substituted by a carboxy group, as defined herein, and includes, for example, carboxymethyl, carboxyethyl, ethylenecarboxy and the like.

The term "alkylcarbonylalkyl" refers to an alkyl, as this term is defined herein, substituted by a carbonyl group, as defined herein, and includes, for example, methanoylmethyl, ethanoylethyl and the like.

The term "amidoalkyl" refers to an alkyl, as this term is defined herein, substituted by an amide group, as defined herein, and includes, for example, -CH₂CONH₂; -CH₂CH₂CONH₂; -CH₂CH₂CH₂CONH₂ and the like.

The term "cyanoalkyl" refers to an alkyl, as this term is defined herein, substituted by a cyano group, as defined herein, and includes, for example, -CH₂CN; -CH₂CH₂CN; -CH₂CH₂CH₂CN and the like.

The term "N-monoalkylamidoalkyl" refers to an alkyl, as this term is defined herein, substituted by an amide group, as defined herein, in which one of R' and R" is an alkyl, and includes, for example, -CH₂CH₂CONHCH₃, and -CH₂CONHCH₂CH₃.

The term N,N-dialkylamidoalkyl refers to an alkyl, as this term is defined herein, substituted by an amide group, as defined herein, in which both R' and R" are alkyl, and includes, for example, -CH₂CON(CH₃)₂; CH₂CH₂CON(CH₂-CH₃)₂ and the like.

A "cycloalkyl" group refers to an all-carbon monocyclic or fused ring (*i.e.*, rings which share an adjacent pair of carbon atoms) group wherein one of more of the rings does not have a completely conjugated pi-electron system. Examples, without limitation, of cycloalkyl groups are cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, cyclohexadiene, cycloheptane, cycloheptatriene, and adamantane. A cycloalkyl group may be substituted or unsubstituted. When substituted, the substituent group can be, for example, alkyl, hydroxyalkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, halo, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, cyano, nitro, phosphonyl, phosphinyl, carbonyl, thiocarbonyl, carboxy, thiocarboxy, carbamate, thiocarbamate, amido, sulfonamido, and amino, as these terms are defined herein.

An "alkenyl" group refers to an alkyl group which consists of at least two carbon atoms and at least one carbon-carbon double bond.

An "alkynyl" group refers to an alkyl group which consists of at least two carbon atoms and at least one carbon-carbon triple bond.

An "aryl" group refers to an all-carbon monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of carbon atoms) groups having a completely
5 conjugated pi-electron system. Examples, without limitation, of aryl groups are phenyl, naphthalenyl and anthracenyl. The aryl group may be substituted or unsubstituted. When substituted, the substituent group can be, for example, alkyl, hydroxyalkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, halo, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy,
10 sulfinyl, sulfonyl, sulfate, cyano, nitro, phosphonyl, phosphinyl, phosphonium, carbonyl, thiocarbonyl, carboxy, thiocarboxy, carbamate, thiocarbamate, amido, sulfonamido, and amino, as these terms are defined herein.

A "heteroaryl" group refers to a monocyclic or fused ring (*i.e.*, rings which share an adjacent pair of atoms) group having in the ring(s) one or more atoms, such
15 as, for example, nitrogen, oxygen and sulfur and, in addition, having a completely conjugated pi-electron system. Examples, without limitation, of heteroaryl groups include pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrimidine, quinoline, isoquinoline and purine. The heteroaryl group may be substituted or unsubstituted. When substituted, the substituent group can be, for
20 example, alkyl, hydroxyalkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, halo, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, sulfate, cyano, nitro, phosphonyl, phosphinyl, phosphonium, carbonyl, thiocarbonyl, carboxy, thiocarboxy, carbamate, thiocarbamate, amido, sulfonamido, and amino, as these terms are defined herein.

25 A "heteroalicyclic" group refers to a monocyclic or fused ring group having in the ring(s) one or more atoms such as nitrogen, oxygen and sulfur. The rings may also have one or more double bonds. However, the rings do not have a completely conjugated pi-electron system. The heteroalicyclic may be substituted or unsubstituted. When substituted, the substituted group can be, for example, lone pair
30 electrons, alkyl, hydroxyalkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, halo, hydroxy, alkoxy, aryloxy, thiohydroxy, thioalkoxy, thioaryloxy, sulfinyl, sulfonyl, sulfate, cyano, nitro, phosphonyl, phosphinyl, phosphonium, carbonyl, thiocarbonyl, carboxy, thiocarboxy, carbamate,

thiocarbamate, amido, sulfonamido, and amino, as these terms are defined herein. Representative examples are piperidine, piperazine, tetrahydro furane, tetrahydropyrane, morpholino and the like.

A "hydroxy" group refers to an -OH group.

5 An "alkoxy" group refers to both an -O-alkyl and an -O-cycloalkyl group, as defined herein.

An "aryloxy" group refers to both an -O-aryl and an -O-heteroaryl group, as defined herein.

A "thiohydroxy" group refers to a -SH group.

10 A "thioalkoxy" group refers to both an -S-alkyl group, and an -S-cycloalkyl group, as defined herein.

A "thioaryloxy" group refers to both an -S-aryl and an -S-heteroaryl group, as defined herein.

A "carbonyl" group refers to a -C(=O)-R' group, where R' is hydrogen, alkyl, 15 alkenyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) or heteroalicyclic (bonded through a ring carbon) as defined herein.

A "thiocarbonyl" group refers to a -C(=S)-R' group, where R' is as defined herein for R'.

20 A "carboxy" group refers to a -C(=O)-O-R' or a -O-C(=O)-R' group, where R' is as defined herein.

A "sulfinyl" group refers to an -S(=O)-R' group, where R' is as defined herein.

A "sulfonyl" group refers to an -S(=O)₂-R' group, where R' is as defined herein.

25 A "sulfate" group refers to a -O-S(=O)₂-OR' group, where R' is as defined herein.

A "sulfonamido" group refers to a -S(=O)₂-NR'R'' group or a R'S(=O)₂-NR'', with R' is as defined herein and R'' is as defined for R'.

A "carbamyl" or "carbamate" group refers to an -OC(=O)-NR'R'' group or a R''OC(=O)-NR'- group, where R' and R'' are as defined herein.

30 A "thiocarbamyl" or "thiocarbamate" group refers to an -OC(=S)-NR'R'' group or an R''OC(=S)NR'- group, where R' and R'' are as defined herein.

An "amino" group refers to an -NR'R'' group where R' and R'' are as defined herein.

An "amido" group refers to a $-C(=O)-NR'R''$ group or a $R'C(=O)-NR''$ group, where R' and R'' are as defined herein.

A "nitro" group refers to an $-NO_2$ group.

A "cyano" group refers to a $-C\equiv N$ group.

5 The term "phosphonyl" describes a $-O-P(=O)(OR')(OR'')$ group, with R' and R'' as defined hereinabove.

The term "phosphinyl" describes a $-PR'R''$ group, with R' and R'' as defined hereinabove.

10 As cited hereinabove, the compounds in this category are salts of organic tellurium-containing compounds. The salts can be, for example, ammonium salts, phosphonium salts and alkaline salts such as potassium salts, sodium salts, lithium salts and the like.

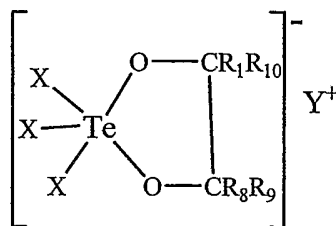
Hence, Y in Formula I above can be a phosphonium group, as defined herein, an ammonium group, as defined herein, potassium (K^+), sodium (Na^+) or lithium (Li^+).

As used herein, the term "phosphonium" describes a $-P^+R'R''R'''$ group, with R' and R'' as defined herein and R''' is as defined for R' . The term "phosphonium", as used herein, further refers to a $-P^+R_6$ group, wherein each of the six R substituents is independently as defined herein for R , R'' and R''' .

20 The term "ammonium" describes a $-N^+R'R''R'''$ group, with R' , R'' and R''' as defined herein.

More preferred compounds in this category include compounds having the general Formula I described above, in which Y is ammonium or phosphonium, t, u and v are each 0, and each of R_1 , R_8 , R_9 and R_{10} is independently hydrogen or alkyl.

25 These compounds can be represented by the following structure:

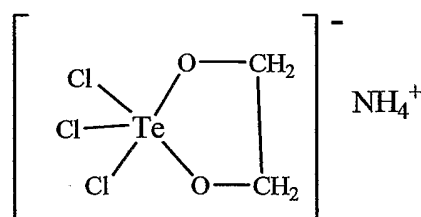


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wherein each of R_1 , R_8 , R_9 and R_{10} is independently hydrogen or alkyl, preferably methyl, and X is halogen, preferably chloro.

The presently most preferred compound for use in the context of the present invention has the following structure:

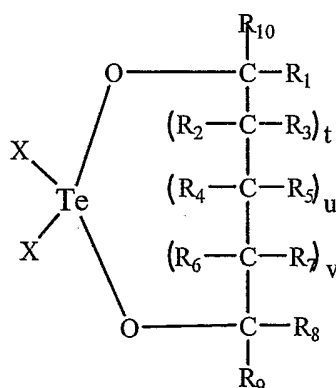
5



This compound is ammonium trichloro(dioxyethylene-O,O')tellurate, which is also referred to herein and in the art as AS101.

10 Additional representative examples of organic tellurium-containing compound that are suitable for use in the context of the present invention include halogenated tellurium having a bidentate cyclic moiety attached to the tellurium atom. The bidentate cyclic moiety is preferably a di-oxo ligand having two oxygen atoms attached to the tellurium atom. Alternatively, the bidentate cyclic moiety can be a di-
15 thio ligand, in which two sulfur atoms are attached to the tellurium atom.

Preferred compounds in this category can be represented by the general Formula II:

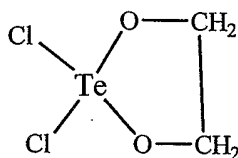


20

Formula II

wherein t, u, v, X and R_1 - R_{10} are as defined hereinabove.

More preferred compounds are those in which t, u, and v are each 0, and X is chloro, such as, but not limited to, the compound having the following structure:



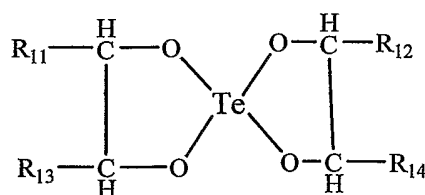
5

The above compound is also known and referred to herein as AS103.

The organic tellurium-containing compounds having Formulae I and II can be readily prepared by reacting tetrahalotelluride such as TeCl_4 with a dihydroxy compound, as is described in detail in U.S. Patents Nos. 4,752,614, 4,761,490, 10 4,764,461 and 4,929,739, which are incorporated by reference as if fully set forth herein.

Additional representative examples of organic tellurium-containing compounds that are suitable for use in the context of the present invention include compounds in which two bidentate cyclic moieties are attached to the tellurium atom. 15 Preferably, each of the cyclic moieties is a di-oxo moiety. Alternatively, one or more of the cyclic moieties is a di-thio moiety.

Preferred compounds in this category are collectively represented by the general Formula III:



20

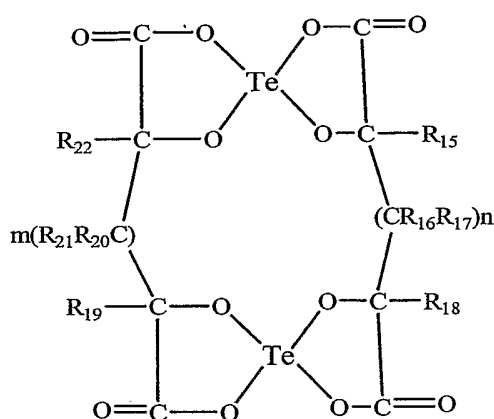
Formula III

wherein each of R_{11} - R_{14} is independently selected from the group consisting of 25 hydrogen, hydroxyalkyl, hydroxy, thiohydroxy, alkyl, alkenyl, alkynyl, alkoxy, thioalkoxy, halogen, haloalkyl, carboxy, carbonyl, alkylcarbonylalkyl, alkoxy, carboxyalkyl, acyl, amido, cyano, N-monoalkylamidoalkyl, N,N-dialkylamidoalkyl, cyanoalkyl, alkoxyalkyl, carbamyl, cycloalkyl, heteroalicyclic, sulfonyl, sulfinyl,

sulfate, amine, aryl, heteroaryl, phosphate, phosphonate and sulfoneamido, as these terms are defined herein.

The most preferred compound in this category is a compound in which each of R_{11} - R_{14} is hydrogen. This compound is also known as AS102.

5 Additional representative examples of organic tellurium-containing compounds that are suitable for use in the context of the present invention include the recently disclosed bis-tellurium compounds having general Formula IV:



Formula IV

10

wherein each of R_{15} - R_{22} is independently selected from the group consisting of hydrogen, hydroxyalkyl, hydroxy, thiohydroxy, alkyl, alkenyl, alkynyl, alkoxy, thioalkoxy, halogen, haloalkyl, carboxy, carbonyl, alkylcarbonylalkyl, alkoxy, carboxyalkyl, acyl, amido, cyano, N-monoalkylamidoalkyl, N,N-dialkylamidoalkyl, cyanoalkyl, alkoxyalkyl, carbamyl, cycloalkyl, heteroalicyclic, sulfonyl, sulfinyl, sulfate, amine, aryl, heteroaryl, phosphate, phosphonate and sulfoneamido, as these terms are defined herein; and

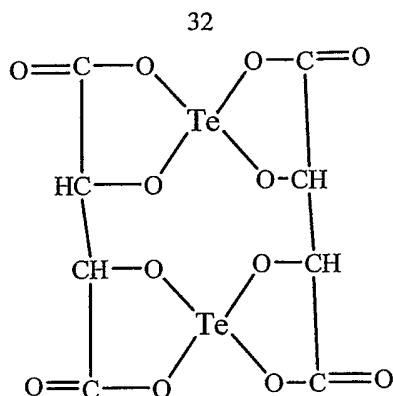
15

m and n are each an integer from 0 to 3.

20

Preferred compounds in this category are those in which m and n are each 0.

The presently most preferred compound in this family is a compound in which R_{15} , R_{18} , R_{19} and R_{22} are all hydrogen, referred to hereinafter as SAS, and which has the following structure:



Compounds having the general Formula IV can be readily prepared by reacting substantially equimolar amounts of a tellurium tetralkoxide and a polycarboxylic acid.

- 5 These materials are combined in the presence of a water free organic solvent such as dried ethanol, dimethyl sulfoxide, i-propanol and the like. Generally the reaction may take place at ambient conditions but if desired higher or lower temperatures and higher or lower pressures may be utilized.

Exemplary tellurium tetraalkoxide compounds that are usable in the preparation of the compounds having general Formula IV above include, without limitation, tetramethoxide, tetraethoxide, tetrapropoxide, tetraisopropoxide, tetrabutoxide, and tetrapentoxide tellurium compounds.

Useful polycarboxylic acids include also polyhydroxy polycarboxylic and hydroxy polycarboxylic acids. Exemplary polycarboxylic acids that are usable in the preparation of the compounds having general Formula IV above include, without limitation, tartaric acid, glutaric acid, succinic acid, malonic acid, gluconic acid and the like.

Any of the tellurium-containing compounds of the present invention may be provided as a pharmaceutical composition, further comprising a pharmaceutically acceptable carrier.

As used herein a "pharmaceutical composition" refers to a preparation of one or more of the active with other chemical components such as physiologically suitable carriers and excipients. The purpose of a pharmaceutical composition is to facilitate administration of a compound or a mixture of compounds to the subject treated.

25 Hereinafter, the phrases "physiologically acceptable carrier" and "pharmaceutically acceptable carrier" which may be interchangeably used refer to a

carrier or a diluent that does not cause significant irritation to the subject and does not abrogate the biological activity and properties of the administered compound.

Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin. Such compositions will contain a therapeutically effective amount of the compound, preferably in purified form,
5 together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should be suitable for the mode of administration.

Such pharmaceutical carriers can be sterile liquids, such as water and oils,
10 including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions.

Herein the term "excipient" refers to an inert substance added to a pharmaceutical composition to further facilitate administration of an active ingredient. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable
15 oils and polyethylene glycols.

Suitable pharmaceutical excipients include without limitation, calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils, polyethylene glycols, sodium stearate, glycerol monostearate, talc, sodium chloride, glycerol, propyleneglycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or
20 emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like.

The pharmaceutical compositions herein described may also comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients
30 include, but are not limited to, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin and polymers such as polyethylene

Pharmaceutical compositions of the present invention may be manufactured by processes well known in the art, e.g., by means of conventional mixing, dissolving,

granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes, utilizing a tellurium-containing compound as described herein..

Further techniques for formulation and administration of active ingredients
5 may be found in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, latest edition, which is incorporated herein by reference as if fully set forth herein.

Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in conventional manner using one or more pharmaceutically
10 acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the active ingredients into preparations which, can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

More preferably, the pharmaceutical composition is formulated as a gel, a cream, an ointment, a paste, a lotion, a milk, a suspension, an aerosol, a spray, a foam,
15 a serum, a swab, a pledget, a pad or a patch.

Preferably, a concentration of tellurium-containing compound of formula I, II or III in the carrier ranges from about 0.01 weight percent to about 50 weight percents, more preferably from about 0.01 weight percent to about 20 weight percents, of the total weight of the composition. Also preferably, a concentration of tellurium-
20 containing compound of formula IV in the carrier ranges from about 0.02 weight percent to about 85 weight percents, more preferably from about 0.02 weight percents to about 40 weight percents of the total weight of the composition.

Thus, depending on the condition being treated and the composition form, the concentration of the tellurium-containing compound of formula I, II or II can be, for
25 example, 0.01 weight percent, 0.05 weight percent, 0.1 weight percent, 0.5 weight percent, 1 weight percent, 2 weight percents, 3 weight percents, 4 weight percents, 5 weight percents, 10 weight percents, 15 weight percents, 20 weight percents, 30 weight percents, 40 weight percents and up to 50 weight percents of the total weight of the composition. The concentration of the tellurium-containing compound of formula IV
30 can be for example, 0.02 weight percent, 0.05 weight percent, 0.1 weight percent, 0.5 weight percent, 1 weight percent, 2 weight percents, 5 weight percents, 10 weight percents, 20 weight percents, 30 weight percents, 40 weight percents, 50 weight

percents, 60 weight percents, 70 weight percents, 80 weight percents, and up to 85 weight percents of the total weight of the composition.

The pharmaceutical composition is preferably identified for use in the treatment or prevention of alopecia, excluding male pattern baldness and alopecia induced by antineoplastic agents. The composition of the present invention may optionally further comprise at least one additional active agent for treating alopecia, such as minoxidil, finasteride, retin-A; ketoconazole; azelaic acid; zinc; Saw Palmetto extract; gamma linoic acid; vitamin B6; polysorbate 80; cyproterone acetate; ethinyloestradiol; cimetidine; spironolactone; ketoconazole, a corticosteroid; dithranol; an immunosuppressive drug or an irritant. Preferably, the additional active agent is minoxidil, finasteride, or a combination thereof.

The alopecia treated may include that induced by an autoimmune disease (such as alopecia areata); female pattern baldness; self-induced alopecia; traction alopecia; tellogen effluvium; and scarring alopecia (such as that caused by discoid lupus erythematosus, lichen planus, aplasia cutis congenital or congenital atrichia). Tellogen may be, for example, that associated with administration of a drug, such as a contraceptive pill, an anti-gout agent, a blood thinner, or a cholesterol lowering agent, including, but not limited to allopurinol, heparin, coumarin, clofibrate and gemfibrozil. Alternatively the tellogen effluvium may be due to a condition such as, for example, thyroid gland malfunction, diabetes, anemia or systemic lupus erythematosus.

Administration of the tellurium-containing compounds may be effected by the intraperitoneal, parenteral, oral, topical, rectal, transmucosal, intestinal, intrathecal, direct intraventricular, intravenous, intranasal, or intraocular route.

For intraperitoneal administration, an effective therapeutic amount of any of the compounds of formulae I-III preferably ranges from about 0.025 to about 0.8 mg/kg of body weight. Also preferably, an effective therapeutic amount of the compound of formulae IV for parenteral administration preferably ranges from about 0.4 to about 1.3 mg/kg of body weight.

The active ingredients described herein may be formulated for parenteral administration, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multidose containers with optionally, an added preservative. The compositions may be suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain

formulatory agents such as suspending, stabilizing and/or dispersing agents. Pharmaceutical compositions for parenteral administration include aqueous solutions of the active preparation in water-soluble form. Additionally, suspensions of the active ingredients may be prepared as appropriate oily injection suspensions.

5 Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acids esters such as ethyl oleate, triglycerides or liposomes. Aqueous injection suspensions may contain substances, which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the
10 solubility of the active ingredients to allow for the preparation of highly concentrated solutions.

 An effective therapeutic amount of any of the compounds of formulae I-III for parenteral administration preferably ranges from about 0.025 to about 2.5 mg/kg of body weight. An effective therapeutic amount of the compound of formula IV for
15 parenteral administration preferably ranges from about 0.04 to about 4.2 mg/kg of body weight.

 Formulations for oral delivery can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Such carriers enable the active
20 ingredients of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for oral ingestion by a patient. Pharmacological preparations for oral use can be made using a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries if desired, to obtain tablets or dragee cores. Suitable
25 excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carbomethylcellulose; and/or physiologically acceptable polymers such as polyvinylpyrrolidone (PVP). If desired, disintegrating
30 agents may be added, such as cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

 Pharmaceutical compositions, which can be used orally, include push-fit capsules made of gelatin as well as soft, sealed capsules made of gelatin and a

plasticizer, such as glycerol or sorbitol. The push-fit capsules may contain the active ingredients in admixture with filler such as lactose, binders such as starches, lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active ingredients may be dissolved or suspended in suitable liquids,
5 such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for the chosen route of administration.

An effective therapeutic amount of any of the compounds of formulae I-III for oral administration preferably ranges from about 0.025 to about 7.5 mg/kg of body
10 weight. An effective therapeutic amount of the compound of formula IV for oral administration preferably ranges from about 0.04 to about 12.7 mg/kg of body weight. For topical administration, the ingredients for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from a pressurized pack with the use of a suitable propellant, e.g., dichlorodifluoromethane,
15 trichlorofluoromethane, dichloro-tetrafluoroethane or carbon dioxide. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Topical administration is preferably effected by applying a therapeutically effective amount of a tellurium-containing compound onto a treated skin area.

20 When administered topically, preferably, a pharmaceutical composition as described herein, formulated for topical application, is applied onto the treated area. The amount applied and the concentration of the compound in the composition depend on the composition form, and the area and condition being treated.

25 Administering is preferably effected according to a regime that ranges from twice daily to once weekly. In a preferred embodiment, administering is effected on a daily basis.

Further preferably, administering is effected from 1 day to 90 days and more preferably from 7 days to 90 days.

30 The dosage may vary depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen individually.

Compositions of the present invention may, if desired, be presented in a pack or dispenser device, such as an FDA (the U.S. Food and Drug Administration) approved kit, which may contain one or more unit dosage forms containing the active ingredient. The pack may, for example, comprise glass, plastic foil, such as, but not limited to a blister pack or a pressurized container. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied by a notice associated with the container in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the compositions for human or veterinary administration. Such notice, for example, may be of labeling approved by the U.S. Food and Drug Administration for prescription drugs or of an approved product insert. Compositions according to the present invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for use in immunization.

In any of the aspects described herein, the phrase "tellurium-containing compound" encompasses any compound that includes one or more tellurium atoms and exhibits immunomodulating properties.

Additional objects, advantages, and novel features of the present invention will become apparent to one ordinarily skilled in the art upon examination of the following examples, which are not intended to be limiting. Additionally, each of the various embodiments and aspects of the present invention as delineated hereinabove and as claimed in the claims section below finds experimental support in the following examples.

EXAMPLES

Reference is now made to the following examples, which together with the above descriptions, illustrate the invention in a non limiting fashion.

EXAMPLE 1

Two small-scale human clinical studies were each conducted over a 6 month period to evaluate the potential use of an 0.01 % AS101 spray formulation for the

prevention of hair shedding and/or enhancing hair growth. Patients received no other alopecia treatment for at least 3 months prior to commencement of the study.

The sample group consisted of 36 patients, of which 6 withdrew due to non-compliance. Data from a further 14 patients was considered to be unsuitable for analysis with the TrichoScan system, for example, due to untraceable tattoos. 16 patients were therefore available for evaluation.

During an initial visit, a designated area of the scalp (about 0.7 cm²) was shaved. Three days later, the area was tattooed using red ink, and photographed (Nikon digital camera). Patients were provided with a topical spray composition comprising 0.01 % AS101 in 20 % propylene glycol, 20 % water and 60 % ethyl alcohol, and were instructed to apply about 2 ml of the composition on the designated area on a daily basis for the first week, and once a day, twice a week thereafter. .

Patients were examined upon enrollment, and then after about 2 months, after about 3 months, and after about 6 months. Hair density, terminal hair density, and vellus hair density were analyzed, using the DatInf^R Image DB image archiving system, and TichoScan software.

Analysis of the subject group showed that 37.5 % of the patients who completed the study responded to treatment with a consistent increase in hair density, and a further 18.75 % responded partially, i.e. an increase was observed during part of the treatment period. No side-effects were observed.

Figure 1 shows micrographs obtained in this study from an individual patient using the above-described archiving TrichoScan system.

Results were calculated in terms of hair density, terminal hair density, and vellus hair density.

Figures 2a and 2b present the data obtained for the hair density, terminal hair density and vellus hair density, each per cm², with two representative individuals of the study. The above parameters were measured at commencement of the study, after about 1 month, after about 3 months, and after about 6 months. All results were obtained using the DatInf^R Image DB image archiving system, and TichoScan software.

As shown in Figures 2a and 2b, a significant increase in the three categories of hair density analyzed was seen after about 1 month.

EXAMPLE 2

An individual patient, a woman over the age of 60 applied a spray containing 0.01 % AS101 in 20 % propylene glycol, 20 % water and 60 % ethyl alcohol twice daily. The results obtained, as presented in Figure 3, show a significant increase in the three categories of hair density studied, which continued for the 6 month period of the trial. It is therefore demonstrated that a dosage regime of twice daily administration of AS101 results in increased hair density in a subject suffering from female pattern baldness.

EXAMPLE 3

A patient suffering from alopecia induced by an autoimmune disease applies a spray containing 0.01 % AS101 in 20 % propylene glycol, 20 % water and 60 % ethyl alcohol twice daily. The results are monitored at commencement of the study, after about 1 month, after about 3 months, and after about 6 months. Hair density, terminal hair density, and vellus hair density are analyzed, using the DatInf^R Image DB image archiving system, and TichoScan software.

EXAMPLE 4

A patient suffering from self-induced alopecia applies a spray containing 0.01 % AS101 in 20 % propylene glycol, 20 % water and 60 % ethyl alcohol twice daily. The results are monitored at commencement of the study, after about 1 month, after about 3 months, and after about 6 months. Hair density, terminal hair density, and vellus hair density are analyzed, using the DatInf^R Image DB image archiving system, and TichoScan software.

EXAMPLE 5

A patient suffering from traction alopecia applies a spray containing 0.01 % AS101 in 20 % propylene glycol, 20 % water and 60 % ethyl alcohol twice daily. The results are monitored at commencement of the study, after about 1 month, after about 3 months, and after about 6 months. Hair density, terminal hair density, and vellus hair density are analyzed, using the DatInf^R Image DB image archiving system, and TichoScan software.

EXAMPLE 6

A patient suffering from telogen effluvium applies a spray containing 0.01 % AS101 in 20 % propylene glycol, 20 % water and 60 % ethyl alcohol twice daily. The results are monitored at commencement of the study, after about 1 month, after about 3 months, and after about 6 months. Hair density, terminal hair density, and vellus hair density are analyzed, using the DatInf[®] Image DB image archiving system, and TichoScan software.

EXAMPLE 7

A patient suffering from scarring alopecia applies a spray containing 0.01 % AS101 in 20 % propylene glycol, 20 % water and 60 % ethyl alcohol twice daily. The results are monitored at commencement of the study, after about 1 month, after about 3 months, and after about 6 months. Hair density, terminal hair density, and vellus hair density are analyzed, using the DatInf[®] Image DB image archiving system, and TichoScan software.

EXAMPLE 8

A patient suffering from hair loss applies a spray containing 0.017 % SAS in 20 % propylene glycol, 20 % water and 60 % ethyl alcohol twice daily. The results are monitored at commencement of the study, after about 1 month, after about 3 months, and after about 6 months. Hair density, terminal hair density, and vellus hair density are analyzed, using the DatInf[®] Image DB image archiving system, and TichoScan software.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad

scope of the appended claims. All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein
5 by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention.

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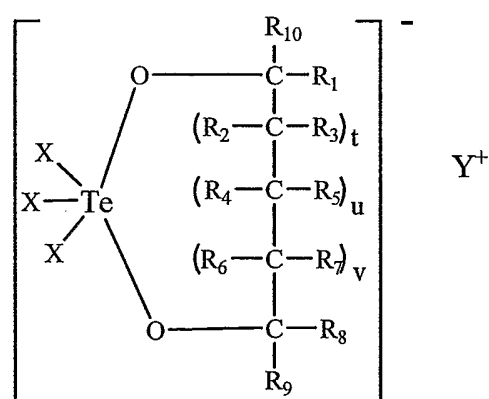
WHAT IS CLAIMED IS:

1. A method of treating or preventing alopecia, excluding male pattern baldness and alopecia induced by antineoplastic agents, the method comprising administration to a subject in need thereof a therapeutically effective amount of at least one tellurium-containing compound having at least one tellurium dioxide moiety.

2. Use of at least one tellurium-containing compound having at least one tellurium dioxide moiety in treating or preventing alopecia, excluding male pattern baldness and alopecia induced by antineoplastic agents.

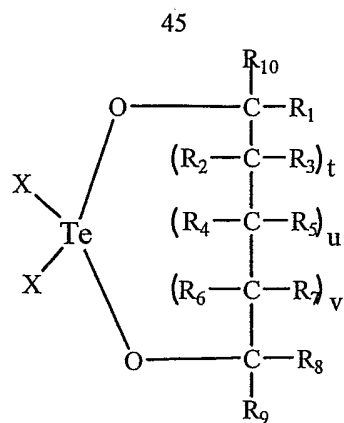
3. A pharmaceutical composition, identified for use in the treatment or prevention of alopecia, excluding male pattern baldness and alopecia induced by antineoplastic agents, the composition comprising at least one tellurium-containing compound having at least one tellurium dioxide

4. The method, use or composition of any of claims 1 to 3, wherein said at least one tellurium-containing moiety is selected from the group consisting of tellurium dioxide (TeO_2), a complex of TeO_2 , a compound having general Formula I:



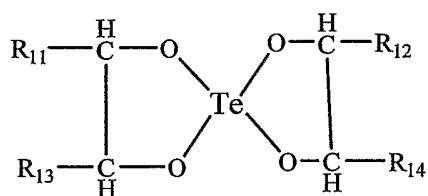
Formula I

a compound having general Formula II:



Formula II

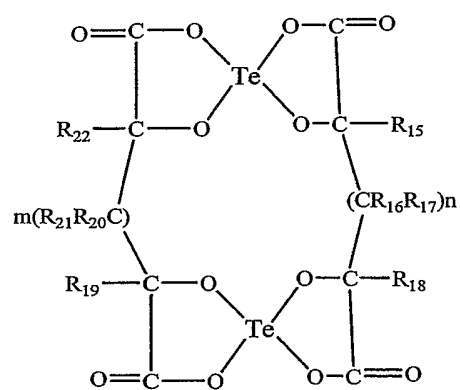
a compound having general Formula III:



Formula III

and

a compound having general Formula IV:



Formula IV

wherein:

each of t, u and v is independently 0 or 1;

each of m and n is independently an integer from 0 to 3;

Y is selected from the group consisting of ammonium, phosphonium, potassium, sodium and lithium;

X is a halogen atom; and

each of R₁-R₂₂ is independently selected from the group consisting of hydrogen, hydroxyalkyl, hydroxy, thiohydroxy, alkyl, alkenyl, alkynyl, alkoxy, thioalkoxy, halogen, haloalkyl, carboxy, carbonyl, alkylcarbonylalkyl, carboxyalkyl, acyl, amido, cyano, N-monoalkylamidoalkyl, N,N-dialkylamidoalkyl, cyanoalkyl, alkoxyalkyl, carbamyl, cycloalkyl, heteroalicyclic, sulfonyl, sulfinyl, sulfate, amine, aryl, heteroaryl, phosphate, phosphonate and sulfoneamido.

5. The method, use or pharmaceutical composition of any of claims 1-3, wherein said alopecia is selected from the group consisting of alopecia induced by an autoimmune disease, female pattern baldness, self-induced alopecia, traction alopecia, telogen effluvium and scarring alopecia.

6. The method, use or pharmaceutical composition of claim 5, wherein said alopecia induced by an autoimmune disease is alopecia areata.

7. The method, use or pharmaceutical composition of claim 5, wherein said telogen effluvium is associated with administration of a drug selected from the group consisting of a contraceptive pill, an anti-gout agent, a blood thinner, and a cholesterol lowering agent.

8. The method, use or pharmaceutical composition of claim 7, wherein said drug is selected from the group consisting of allopurinol, heparin, coumarin, clofibrate and gemfibrozil.

9. The method, use or pharmaceutical composition of claim 7, wherein said telogen effluvium is due to a condition selected from the group consisting of thyroid gland malfunction, diabetes, anemia and systemic lupus erythematosus.

10. The method, use or pharmaceutical composition of claim 5, wherein said scarring alopecia is caused by a condition selected from the group consisting of discoid lupus erythematosus, lichen planus, aplasia cutis congenital and congenital atrichia.

11. The method, use or pharmaceutical composition of any of claims 4-10, wherein said tellurium-containing compound is a compound having said general Formula I.

12. The method, use or pharmaceutical composition of claim 11, wherein t, u and v are each 0.

13. The method, use or pharmaceutical composition of claim 12, wherein each of R₁, R₈, R₉ and R₁₀ is hydrogen.

14. The method, use or pharmaceutical composition of claim 13, wherein X is a halogen atom.

15. The method, use or pharmaceutical composition of claim 14, wherein X is chloro.

16. The method, use or pharmaceutical composition of claim 15, wherein Y is ammonium.

17. The method or use of any of claims 1 and 2, wherein said at least one tellurium-containing compound forms a part of a pharmaceutical composition, said pharmaceutical composition further comprising a pharmaceutically acceptable carrier.

18. The method, use or pharmaceutical composition of any of claims 3 and 17, wherein said pharmaceutical composition is formulated in a form selected from the group consisting of a gel, a cream, an ointment, a paste, a lotion, a milk, a suspension, an aerosol, a spray, a foam, a serum, a swab, a pledget, a pad and a patch.

19. The method, use or pharmaceutical composition of any of claims 3 and 17, wherein a concentration of said at least one tellurium-containing compound ranges from about 0.1 weight percent to about 50 weight percents of the total weight of said composition.

20. The method of claim 1, further comprising administering to said subject a therapeutically effective amount of an additional active agent for treating alopecia.

21. The use of claim 2, wherein said at least one tellurium-containing compound is used in combination with at least one additional active agent for treating alopecia.

22. The pharmaceutical composition of claim 3, further comprising at least one additional active agent for treating alopecia.

23. The method, use or pharmaceutical composition of any of claims 20-22, wherein said additional active agent is selected from the group consisting of minoxidil, finasteride, retin-A; ketoconazole; azelaic acid; zinc; Saw Palmetto extract; gamma linoic acid; vitamin B6; polysorbate 80; cyproterone acetate; ethinyloestradiol; cimetidine; spironolactone; ketaconazole, cortocosteroids; dithranol; immunosuppressive drugs and irritants.

24. The method, use or pharmaceutical composition of claim 23, wherein said additional active agent is selected from the group consisting of minoxidil, finasteride, or a combination thereof.

25. The method of claim 1, wherein said administering is effected by a route selected from the group consisting of intraperitoneal, parenteral, oral, topical, rectal, transmucosal, intestinal, intrathecal, direct intraventricular, intravenous, intranasal, and intraocular administration.

26. The method of claim 25, wherein said administering is effected intraperitoneally and said therapeutically effective amount ranges from about 0.025 to about 0.8 mg/kg of body weight.

27. The method of claim 25, wherein said administering is effected parenterally and said therapeutically effective amount ranges from about 0.025 to about 2.5 mg/kg of body weight.

28. The method of claim 25, wherein said administering is effected orally and said therapeutically effective amount ranges from about 0.025 to about 7.5 mg/kg of body weight.

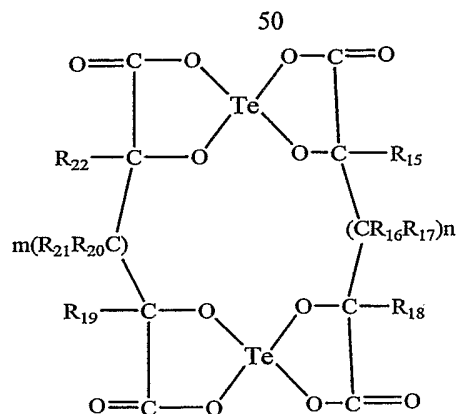
29. The method of claim 25, wherein said administering is effected topically.

30. The method of claim 1, wherein said administering is effected according to a regime that ranges from twice daily to once weekly.

31. The method of claim 30, wherein said administering is effected daily.

32. The method of claim 30, wherein said administering is effected for a time period that ranges from 1 day to 90 days.

33. A method of inducing hair growth and/or reducing or preventing hair loss, the method comprising administering to a subject in need thereof a therapeutically effective amount of at least one tellurium-containing compound having general Formula IV:



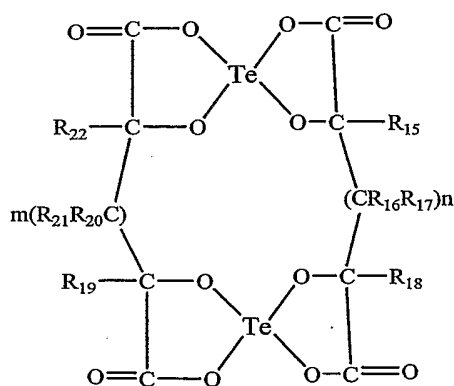
Formula IV

wherein:

each of m and n is independently an integer from 0 to 3; and

each of R₁₅-R₂₂ is independently selected from the group consisting of hydrogen, hydroxyalkyl, hydroxy, thiohydroxy, alkyl, alkenyl, alkynyl, alkoxy, thioalkoxy, halogen, haloalkyl, carboxy, carbonyl, alkylcarbonylalkyl, carboxyalkyl, acyl, amido, cyano, N-monoalkylamidoalkyl, N,N-dialkylamidoalkyl, cyanoalkyl, alkoxyalkyl, carbamyl, cycloalkyl, heteroalicyclic, sulfonyl, sulfinyl, sulfate, amine, aryl, heteroaryl, phosphate, phosphonate and sulfoneamido.

34. Use of a therapeutically effective amount of at least one tellurium-containing compound having general Formula IV:



Formula IV

wherein:

each of t, u and v is independently 0 or 1;

each of m and n is independently an integer from 0 to 3;

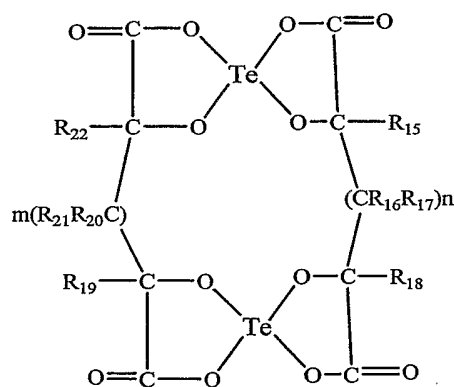
Y is selected from the group consisting of ammonium, phosphonium, potassium, sodium and lithium;

X is a halogen atom; and

each of R₁-R₂₂ is independently selected from the group consisting of hydrogen, hydroxyalkyl, hydroxy, thiohydroxy, alkyl, alkenyl, alkynyl, alkoxy, thioalkoxy, halogen, haloalkyl, carboxy, carbonyl, alkylcarbonylalkyl, carboxyalkyl, acyl, amido, cyano, N-monoalkylamidoalkyl, N,N-dialkylamidoalkyl, cyanoalkyl, alkoxyalkyl, carbamyl, cycloalkyl, heteroalicyclic, sulfonyl, sulfinyl, sulfate, amine, aryl, heteroaryl, phosphate, phosphonate and sulfoneamido,

in inducing hair growth and/or reducing or preventing hair loss in a subject in need thereof.

35. A pharmaceutical composition, identified for use in inducing hair growth and/or reducing or preventing hair loss in a subject in need thereof, the composition comprising a therapeutically effective amount of at least one tellurium-containing compound having general Formula IV:



Formula IV

wherein:

each of t, u and v is independently 0 or 1;

each of m and n is independently an integer from 0 to 3;

Y is selected from the group consisting of ammonium, phosphonium, potassium, sodium and lithium;

X is a halogen atom; and

each of R₁-R₂₂ is independently selected from the group consisting of hydrogen, hydroxyalkyl, hydroxy, thiohydroxy, alkyl, alkenyl, alkynyl, alkoxy, thioalkoxy, halogen, haloalkyl, carboxy, carbonyl, alkylcarbonylalkyl, carboxyalkyl, acyl, amido, cyano, N-monoalkylamidoalkyl, N,N-dialkylamidoalkyl, cyanoalkyl, alkoxyalkyl, carbamyl, cycloalkyl, heteroalicyclic, sulfonyl, sulfinyl, sulfate, amine, aryl, heteroaryl, phosphate, phosphonate and sulfoneamido.

36. The method, use or pharmaceutical composition of any of claims 33-35, wherein n and m are each 0.

37. The method, use or pharmaceutical composition of claim 36, wherein each of R₁₅, R₁₈, R₁₉ and R₂₂ is hydrogen.

38. The method, use or pharmaceutical composition of claim 33, being used for treating a condition in which inducing hair growth and/or preventing hair loss is beneficial.

39. The method, use or pharmaceutical composition of claim 38, wherein said condition is selected from the group consisting of androgenetic alopecia, alopecia areata, anagen effluvium, self-induced hair loss, telogen effluvium and scarring alopecia.

40. The method, use or pharmaceutical composition of claim 39, wherein said anagen effluvium is induced by an antineoplastic agent.

41. The method, use or pharmaceutical composition of claim 33, wherein said telogen effluvium is due to a drug selected from the group consisting of a contraceptive pill, an anti-gout agent, a blood thinner, and a cholesterol lowering agent.

42. The method, use or pharmaceutical composition of claim 41, wherein said tellurium-compound is co-administered together with said drug.

43. The method, use or pharmaceutical composition of claim 41, wherein said drug is selected from the group consisting of allopurinol, heparin, coumarin, clofibrate and gemfibrozil.

44. The method, use or pharmaceutical composition of claim 33, wherein said tellogen effluvium is due to a condition selected from the group consisting of thyroid gland malfunction, diabetes, anemia and systemic lupus erythematosus.

45. The method, use or pharmaceutical composition of claim 33, wherein said scarring alopecia is caused by a condition selected from the group consisting of discoid lupus erythmatosus, lichen planus, aplasia cutis congenital and congenital atrichia.

46. The method, use or pharmaceutical composition of any of claims 33 and 34, wherein said at least one tellurium-containing compound forms a part of a pharmaceutical composition, said pharmaceutical composition further comprising a pharmaceutically acceptable carrier.

47. The method, use or pharmaceutical composition of any of claims 35 and 46, wherein said pharmaceutical composition is formulated in a form selected from the group consisting of a gel, a cream, an ointment, a paste, a lotion, a milk, a suspension, an aerosol, a spray, a foam, a serum, a swab, a pledglet, a pad and a patch.

48. The method, use or pharmaceutical composition of any of claims 35 and 46, wherein a concentration of said at least one tellurium-containing compound ranges from about 0.1 weight percent to about 85 weight percents of the total weight of said composition.

49. The method of claim 33, further comprising administering to said subject a therapeutically effective amount of an additional active agent for inducing hair growth and/or reducing or preventing hair loss.

50. The use of claim 34, wherein said at least one tellurium-containing compound is used in combination with at least one additional active agent for inducing hair growth and/or reducing or preventing hair loss.

51. The pharmaceutical composition of claim 35, further comprising at least one additional agent for inducing hair growth and/or reducing or preventing hair loss.

52. The method, use or pharmaceutical composition of any of claims 49-51, wherein said additional active agent is selected from the group consisting of minoxidil, finasteride, retin-A; ketoconazole; azelaic acid; zinc; Saw Palmetto extract; gamma linoic acid; vitamin B6; polysorbate 80; cyproterone acetate; ethinyloestradiol; cimetidine; spironolactone; ketaconazole, cortocosteroids; dithranol; immunosuppressive drugs and irritants.

53. The method, use or pharmaceutical composition of claim 52, wherein said additional active agent is selected from the group consisting of minoxidil, finasteride, or a combination thereof.

54. The method of claim 33, wherein said administering is effected by a route selected from the group consisting of intraperitoneal, parenteral, oral, topical, rectal, transmucosal, intestinal, intrathecal, direct intraventricular, intravenous, intranasal, and intraocular administration.

55. The method of claim 54, wherein said administering is effected intraperitoneally and said therapeutically effective amount ranges from about 0.04 to about 1.3 mg/kg of body weight.

55

56. The method of claim 54, wherein said administering is effected parenterally and said therapeutically effective amount ranges from about 0.04 to about 4.2 mg/kg of body weight.

57. The method of claim 54, wherein said administering is effected orally and said therapeutically effective amount ranges from about 0.04 to about 12.7 mg/kg of body weight.

58. The method of claim 57, wherein said administering is effected topically by applying said therapeutically effective amount onto a treated skin area.

59. The method, use or pharmaceutical composition of any of claims 33-58, wherein said administering is effected according to a regime that ranges from twice daily to once weekly.

60. The method of claim 59, wherein said administering is effected for a time period that ranges from 1 day to 90 days.

1/4

Figure 1

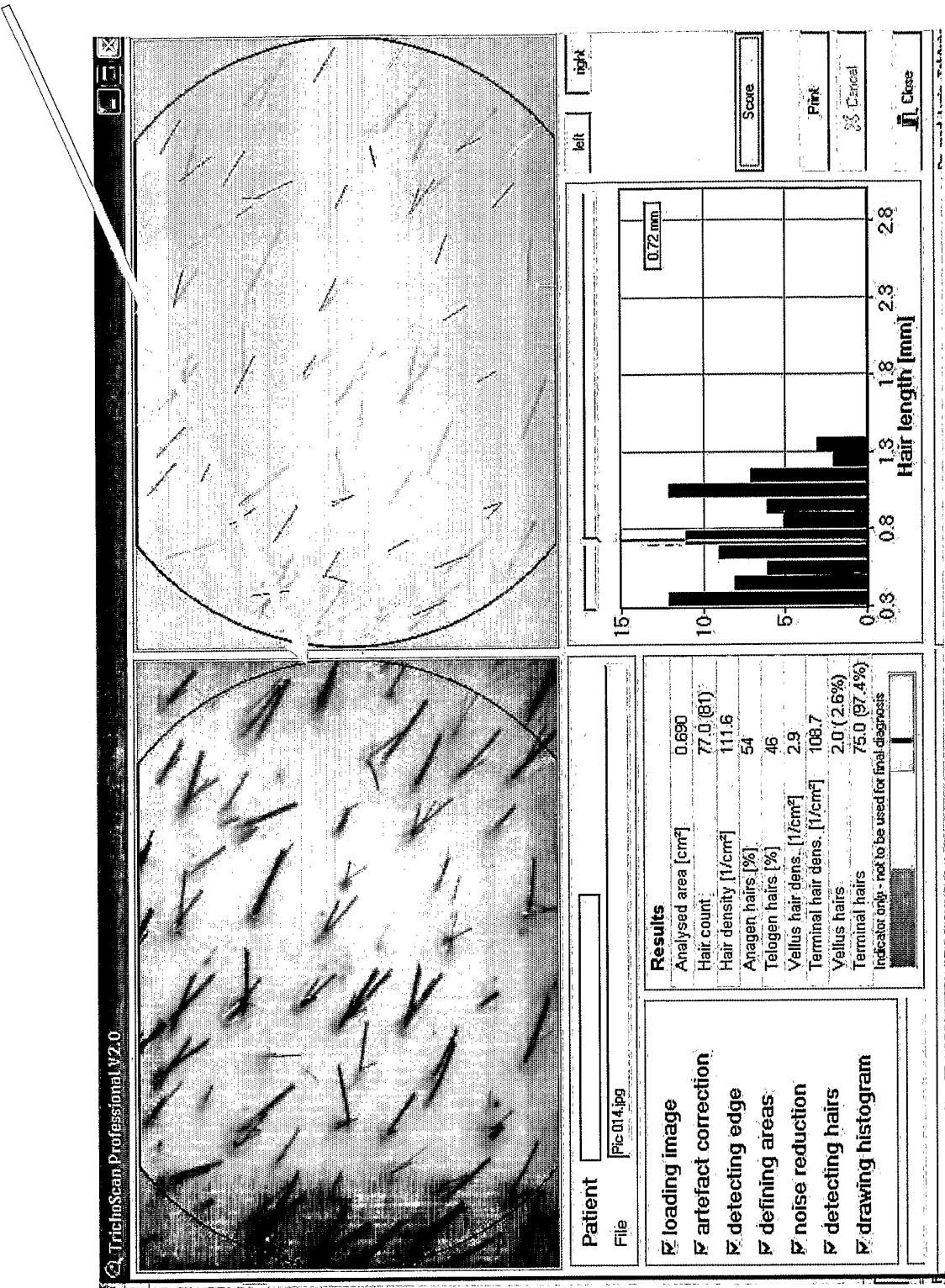


Figure 2a

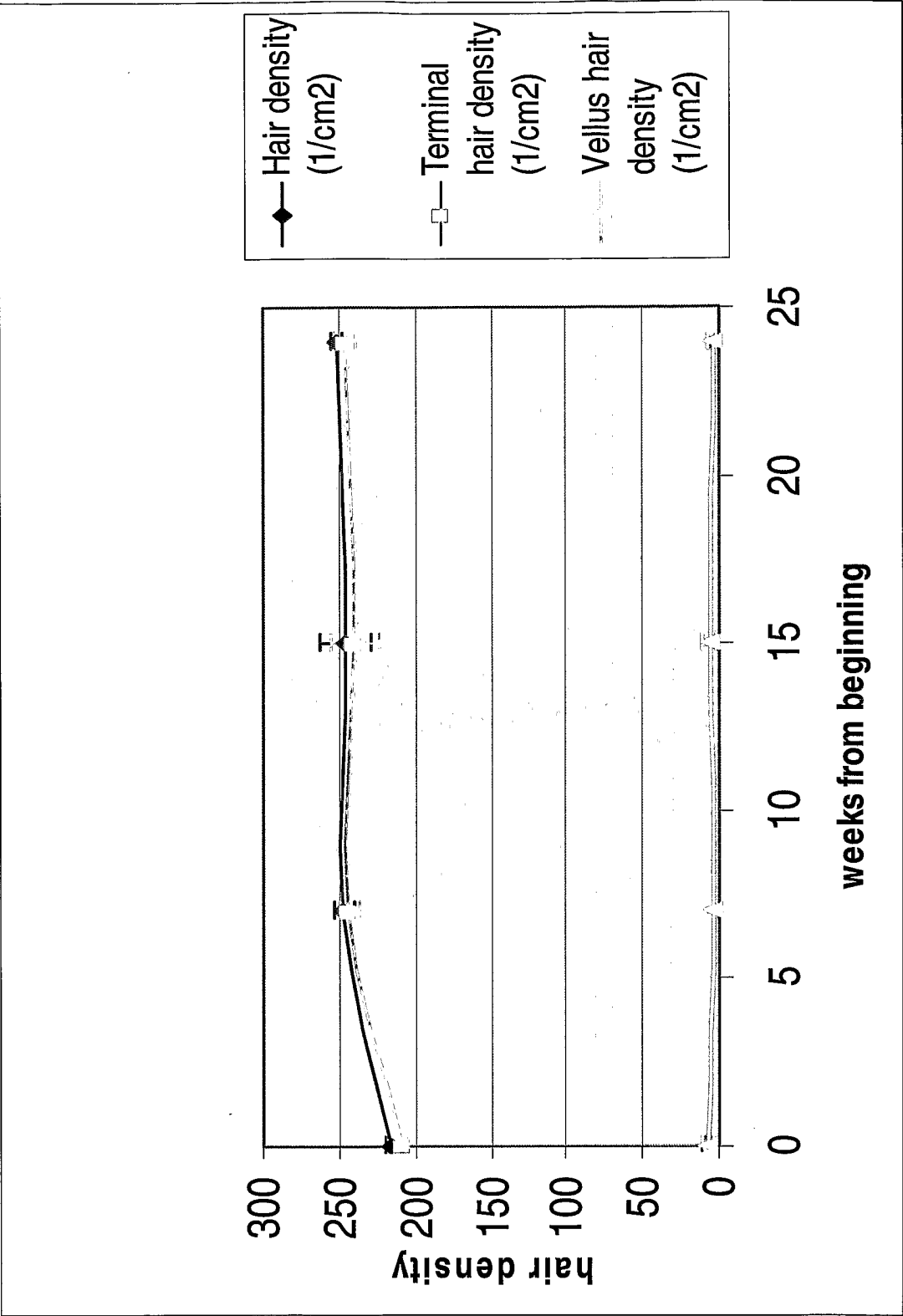


Figure 2b

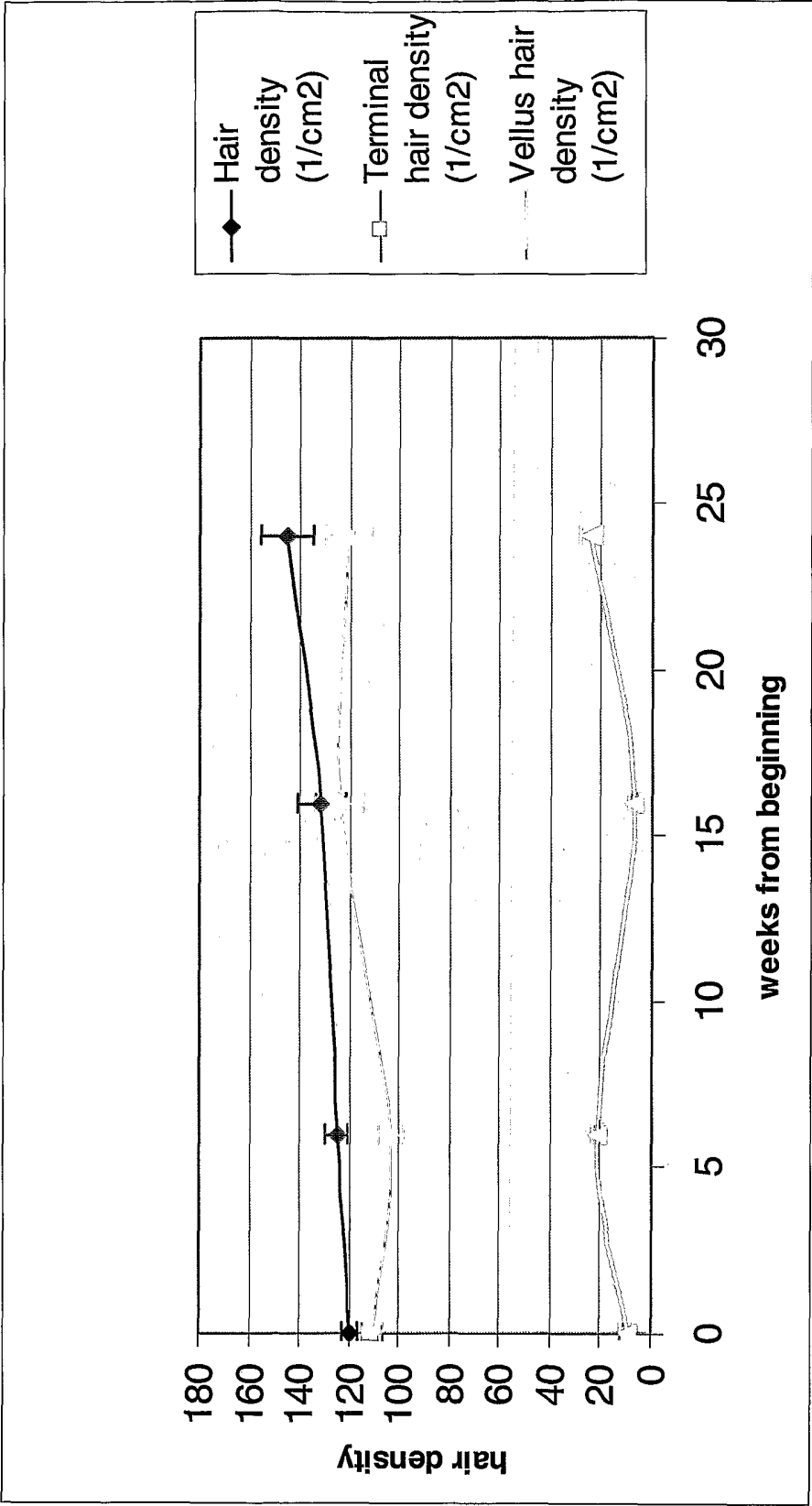


Figure 3

