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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 March 2010 (18.03.2010)

PCT

(10) International Publication Number
WO 2010/031061 A1

(51) International Patent Classification:
A61K 31/7004 (2006.01) *A61P 3/00* (2006.01)

(21) International Application Number:
PCT/US2009/057003

(22) International Filing Date:
15 September 2009 (15.09.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/097,023 15 September 2008 (15.09.2008) US

(71) Applicant *(for all designated States except US)*: **ELAN PHARMA INTERNATIONAL LIMITED** [IE/IE]; Monksland, Athlone, County Westmeath (IE).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **CEDARBAUM, Jesse** [US/US]; Elan Pharmaceuticals, Inc., 700 Gateway Blvd., South San Francisco, California 94080 (US).

(74) Agents: **ZELANO, Anthony, J.** et al.; Millen, White, Zelano & Branigan, P.C., 2200 Clarendon Boulevard, Suite 1400, Arlington, Virginia 22201 (US).

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

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

Published:

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

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2010/031061 A1

(54) Title: METHODS OF TREATMENT OF HYPERURICEMIA AND ASSOCIATED DISEASE STATES

(57) Abstract: The invention relates to compounds, compositions and methods for reducing uric acid levels in a subject. In particular, the invention relates to the treatment of hyperuricemia and diseases associated with high uric acid levels in mammals using scyllo-inositol.

Methods of Treatment of Hyperuricemia and Associated Disease States

This application claims the benefit of U.S. Provisional Application No. 61/097,023, filed September 15, 2008, the disclosure of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The invention generally relates to compounds, compositions and methods for reducing uric acid levels in a subject. In particular, the invention relates to the treatment of hyperuricemia and diseases associated with high uric acid levels in mammals using scyllo-inositol.

BACKGROUND OF THE INVENTION

Uric acid (7,9-dihydro-1*H*-purine-2,6,8(3*H*)-trione; UA) has been implicated as a risk factor for several diseases or disease states. Kutzing, M.K. et al., JPET Vol. 324, No. 1, 1-7 (2008) (doi:10.1124/jpet.107.129031).

Abnormally high UA levels (i.e., hyperuricemic levels) in the blood contribute to a number of disease states, for example, gout, renal disease (Johnson, R.J., et al., Hypertension. 2003 Jun;41(6):1183-90), atherosclerosis (Hayden, M.R., Nutr Metab (Lond). 2004 Oct 19;1(1):10), cardiovascular disease (Hayden 2004; Alderman, M., Curr Med Res Opin. 2004 Mar; 20(3):369-79), metabolic syndrome (Hayden, 2004; Lin, J.D., Metabolism, 2007 Jun;56(6):751-6), urate lithiasis (Shekarriz B. et al., J Urol., 2002 Oct;168(4 Pt 1):1307-14) and hypertension (Johnson 2003). Although the art is not entirely settled on whether hyperuricemia is a cause or effect of some of those disease states mentioned above, there is mounting opinion and evidence that UA is a risk factor in these diseases, rather than the presence of UA as a biological marker (i.e., indicator) consequent to the disease state.

A number of studies demonstrate a link between hyperuricemia and gout (see for example, Lin, K.C. et al., J. Rheumatol., 2000; 27:1501-1505; Choi, H.K. et al., Ann Intern Med., 2005; 143:499-516), an inflammatory arthritis that results from the crystallization of UA within the joints (Choi et al., 2005). Further, studies report a direct positive association between serum urate levels and a future risk for gout. Specifically, as urate concentration increases, the risk for crystal formation increases, raising a patient's susceptibility to the development of gout (Lin et al., 2000).

It is generally accepted that gout and urate lithiasis are linked to hyperuricemia among other risk factors. Some studies have linked primary gout and urate lithiasis. (Pak, C.Y. et al., Kidney Int., 2001 Aug; 60(2):757-61)

Hyperuricemia for men, can be a UA concentration greater than 386 μM (which is micromoles per liter or micromolar) in serum in one study (Klemp P. et al., Ann Rheum Dis. 56:22–26(1997)) and greater than 420 μM in a separate study (Johnson, R.J. et al., Hypertension 41:1183-1190(2003)). For women, most studies define hyperuricemia as a concentration greater than approximately 360 μM (Klemp 1997 and Johnson 2003). The normal range of UA concentrations falls somewhere between about 120 μM and about 380 μM, varying slightly depending on gender (Kutzing 2008). In some instances uric acid concentration in blood or serum is expressed in milligrams per deciliter (mg/dL); to convert a uric acid value from micromoles per liter to mg/dL, divide the value by 59.48.

After modification of diet, alcohol intake, and exercise levels for afflicted individuals, currently favored treatments for hyperuricemia include two types of drugs: xanthine oxidase inhibitors and uricosuric drugs. For example, those are presently the treatments of choice for gout. Xanthine oxidase inhibitors such as allopurinol, inhibit the production of UA by blocking the final two steps of urate synthesis. As a result, there is an increase in the pool of urate precursors, xanthine and hypoxanthine. Xanthine oxidase inhibitors are primarily used in patients who have an increased urate production compared to the norm.

Alternatively, if elevated UA concentrations are secondary to low urate clearance, uricosuric drugs, such as probenecid, sulfinpyrazone, and benzpromarone are used to reduce the serum UA concentration through the inhibition of a renal transporter that reabsorbs UA from the tubules which results in an increase in UA excretion (Emmerson, 1996; Choi et al., 2005). However, treatment of gout with some uricosuric drugs can lead to uric acid nephrolithiasis (kidney stones). Another older, less used treatment for gout is administration of colchicine. Side effects have been reported for these existing treatments, and there is still an unmet need for safe and effective treatments for hyperuricemia and for diseases associated with hyperuricemia.

SUMMARY OF THE INVENTION

Scyllo-inositol has been found to lower uric acid levels in patients, and in particular it has been found that scyllo-inositol lowers the amount of uric acid in the blood in a dose dependent manner. Therefore, scyllo-inositol is useful in lowering uric acid levels in tissues or organs, blood, serum, urine, or combinations thereof, and has utility in treating conditions associated with aberrant levels of uric acid, such as conditions characterized by elevated levels of uric acid. Conditions associated with aberrant levels of uric acid may involve

overproduction of uric acid, low excretion of uric acid, tumor lysis, a blood disorder, or a combination thereof.

Scyllo-inositol has particular utility in lowering abnormally high levels of uric acid in the blood (hyperuricemia) and has utility in treating diseases associated with hyperuricemia or having hyperuricemia as a risk factor, or diseases, which are exacerbated by the presence of hyperuricemia. Such diseases include, but are not limited to, gout, atherosclerosis, renal disease, cardiovascular disease, metabolic syndrome, urate lithiasis, and hypertension.

The present invention relates to a method of decreasing uric acid levels in one or more tissues or organs, blood, serum, urine, or combinations thereof of an individual in need of decreased uric acid levels comprising administering to the individual a therapeutically effective amount of scyllo-inositol. In one embodiment, the invention relates to a method of decreasing uric acid levels or maintaining uric acid levels in one or more tissues or organs, blood, serum, urine, or combinations thereof of an individual in need of decreased uric acid levels or maintaining uric acid levels, comprising administering to the individual a uric acid level lowering amount of scyllo-inositol.

The invention also provides a method of decreasing uric acid production, increasing uric acid excretion, or both, or maintaining uric acid levels in an individual comprising administering a therapeutically effective amount of scyllo-inositol.

The invention also relates to a method of treating an individual suffering from a condition associated with aberrant levels of uric acid comprising administering to the individual a therapeutically effective amount of scyllo-inositol. In at least one embodiment, the condition is chosen or selected from the group consisting of gout; a recurrent gout attack; gouty tophus; gouty arthritis; gouty nephropathy; eclampsia; metabolic syndrome; diseases that involve accelerated formation and destruction of blood cells; hyperuricaemia; secondary hyperuricemia; drug related hyperuricaemia; secondary chronic hyperuricemia of polycythermia vera, of myeloid metaplasia, or of blood dyscrasia; atherosclerosis; hyperuricaemia related to medical conditions such as nephropathies, myeloproliferative disorders; conditions associated with insulin resistance; conditions associated with transplantations; hypertension; cardiovascular disease; coronary heart disease; Lesch-Nyhan syndrome, Kelley-Seegmiller syndrome, renal disease, kidney stones, renal failure; acute renal failure; joint inflammation; arthritis; artherosclerosis; arteriolosclerosis; diabetes; diabetes related disorders; urolithiasis; urate lithiasis; plumbism; hyperparathyroidism; hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency; psoriasis; and sarcoidosis.

The invention further relates to a method of treating a condition associated with aberrant levels of uric acid in an individual at increased risk of developing the condition comprising administering to the individual a therapeutically effective amount of scyllo-inositol.

The invention relates to a method of reducing serum uric acid levels and/or increasing renal clearance of uric acid in an individual comprising administering a therapeutically effective amount of scyllo-inositol.

The invention relates to a method of reducing serum uric acid levels in an individual in need thereof by administering a serum uric acid level lowering amount of scyllo-inositol. In aspects of the invention, the individual to be treated has serum uric acid levels before treatment equal to or greater than 7 mg/dL (420 μmol/L). At least one condition treated using a method of the invention is gout or any condition brought about by high levels of uric acid in the joints or kidneys or a serum uric acid level over 9 mg/dL (530 μmol/L).

In another aspect, the invention relates to a method of preventing or reducing the formation of tophi/tophus in an individual comprising administering to the individual a therapeutically effective amount of scyllo-inositol.

The invention relates to a method of lowering hyperuricemia in a hyperuricemic patient comprising administering scyllo-inositol to the patient in an amount effective to lower the uric acid level in the blood.

The invention relates to a method for treating or preventing hyperuricemia in an individual comprising administering a blood uric acid level lowering amount of scyllo-inositol to the individual.

In another aspect, the invention relates to a method of treating a disease mediated at least in part by hyperuricemia by administering a therapeutically effective amount of scyllo-inositol to a patient having hyperuricemia and such a disease state or states.

In another aspect, the invention provides a method of lowering hyperuricemia in a hyperuricemic patient comprising administering scyllo-inositol to the patient in an amount effective to lower the uric acid level in the blood, wherein the uric acid in the blood prior to administering scyllo-inositol is greater than or equal to about 360 μM as measured in blood serum.

In another aspect of the invention, the amount of scyllo-inositol administered to the hyperuricemic patient ranges from about 100 mg/day to 7000 mg/day, 150 mg/day to 6000

mg/day, and within that range from about 200 mg/day to 6000 mg/day, from 400 mg/day to 6000 mg/day, from 150 mg/day to about 4000 mg/day, or from 200 mg/day to 3000 mg/day.

In another aspect, the scyllo-inositol is administered to an individual, such as a hyperuricemic patient, in a unit dosage form. In an aspect, the unit dosage form is an immediate release dosage form. In another aspect, the unit dosage form is an extended release dosage form In another aspect, the unit dosage form is a gastric retentive dosage form. In anaspect of the invention the unit dosage form comprises 150 mg, 250 mg, 500 mg, 750 mg, 800 mg, 1000 mg or 2000 mg of scyllo-inositol.

In another aspect of the invention, a method of preventing or treating gout in a patient in need of such treatment comprising administering to the patient a therapeutically effective amount of scyllo-inositol is provided. In another aspect, the invention provides a method of treating or preventing gout, wherein the amount of scyllo-inositol administered to the patient ranges from about 100 mg/day to about 7000 mg/day, in particular about 150 mg/day to about 6000 mg/day, and more particularly about 150 mg/day to about 4000 mg/day. In another aspect, scyllo-inositol is administered to the patient in the treatment or prevention of gout in a unit dosage form. In another aspect, the unit dosage form is an immediate release dosage form. In another aspect, the unit dosage form is an extended release dosage form In another aspect, the unit dosage form is a gastric retentive dosage form. In an aspect of the invention the prevention or treatment of gout is performed with a unit dosage form comprising 150 mg, 250 mg, 500 mg, 750 mg, 800 mg, or 1000 mg of scyllo-inositol.

Another aspect of the invention provides a method of treating a disease state in which hyperuricemia is a risk factor in a patient in need of such treatment comprising administering a uric acid level lowering amount or uric acid level maintaining amount of scyllo-inositol to the patient. In another aspect, the disease state in which hyperuricemia is a risk factor being treated is chosen or selected from the group consisting of atheroscleropathy, renal disease, cardiovascular disease, metabolic syndrome, urate lithiasis, and hypertension. In another aspect, the patient having a disease state wherein hyperuricemia is a risk factor is administered an amount of scyllo-inositol from about 100 mg/day to about 7000 mg/day, in particular 150 mg/day to about 6000 mg/day, more particularly 150 mg/day to about 4000 mg/day. In another aspect in the method of treatment of the disease states, scyllo-inositol is administered in a unit dosage form. In another aspect, the unit dosage form is an immediate release dosage form. In another aspect, the unit dosage form is an extended release dosage form In another aspect, the unit dosage form is a gastric retentive dosage form. In the

methods of treatment of the disease states, the unit dosage form may comprise 150 mg, 250 mg, 500 mg, 750 mg, 800 mg, or 1000 mg of scyllo-inositol.

The invention also relates to a method of treating a condition associated with aberrant levels of uric acid in an individual comprising determining the individual's average serum uric acid level and administering to the individual scyllo-inositol according to a regimen effective to maintain the individual's serum uric acid level at or below 5 mg/dL or 6 mg/dL. The average serum uric acid level is generally the average of two or more uric acid readings obtained from the individual. The readings may be taken within hours, days, or weeks of each other. In an aspect of the invention, the two or more readings are obtained at least a week apart.

A method of the invention may also comprise administering in combination with scyllo-inositol, a second treatment, such as a second therapeutic agent, effective for the treatment or prevention of a condition associated with aberrant levels of uric acid, such as a disease mediated in part by hyperuricemia. Therefore, the invention relates to a combination treatment for a condition associated with aberrant levels of uric acid comprising administering therapeutically effective amounts of scyllo-inositol and a second therapeutic agent. In embodiments of the invention, the second therapeutic agent is a uric acid lowering agent, such as a xanthine oxidase inhibitor. Therefore, the invention also relates to a method for decreasing uric acid production, increasing uric acid excretion, or bothor maintaining uric acid levels comprising administering therapeutically effective amounts of scyllo-inositol and a uric acid lowering agent. In aspects of the invention, the uric acid lowering agent is allopurinol, febuxostat, 4-(5-pyridin-4-yl-l/f-[l,2,4]triazol-3-yl)pyridine-2-carbonitrile (FYX-051), or combinations thereof.

In particular aspects the invention provides a method for treating edema and hypertension in a subject comprising administering an antihypertensive agent and a uric acid level maintaining amount or uric acid level lowering amount of a scyllo-inositol.

In aspects the invention provides a method for treating cancer in a subject comprising administering an anticancer agent and a uric acid level maintaining amount or uric acid level lowering amount of a scyllo-inositol.

In aspects the invention provides a method for reducing the side effects of chemotherapy in a cancer individual comprising administering a uric acid level maintaining amount or uric acid level lowering amount of a scyllo-inositol, wherein said side effects are related to elevated uric acid levels.

The invention also relates to a pharmaceutical composition for treating a condition associated with aberrant levels of uric acid comprising therapeutically effective amounts of scyllo-inositol and a pharmaceutically acceptable carrier, excipient, or vehicle. In additional embodiments, the pharmaceutical compositions comprise uric acid level lowering amounts of scyllo-inositol. In additional embodiments, the pharmaceutical compositions of the invention contain adjuvants, excipients, vehicles, preservatives, agents for delaying absorption, fillers, binders, adsorbents, buffers, disintegrating agents, solubilizing agents, other carriers, other inert ingredients, or combinations thereof. In further or additional embodiments, the pharmaceutical composition is in a form suitable for oral administration. In further or additional embodiments, the pharmaceutical composition is in the form of a tablet, capsule, pill, powder, sustained release formulation, solution, suspension, for parenteral injections as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

In embodiment, the invention relates to a pharmaceutical composition comprising an amount of scyllo-inositol effective to lower the uric acid level in a mammal's blood compared to a baseline level and at least one pharmaceutically acceptable component chosen from a carrier, an excipient, and a vehicle.

In embodiments, the pharmaceutical compositions of the invention are useful for treating or preventing gout. In additional embodiments, the pharmaceutical compositions are useful for reducing hypertension or cardiovascular events. In additional embodiments, the pharmaceutical compositions are used as a medicament for use in the amelioration of symptoms related to a high level of uric acid, or as a dietary supplement.

A pharmaceutical composition of the invention can be in a unit dosage form suitable for single administration of precise dosages. In additional embodiments, the amount of scyllo-inositol present in the unit dosage form ranges from about 150 mg to 2000 mg and in particular within that range from about 150 mg to 1500 mg, from about 100 mg to 2000 mg, from about 100 mg to 1500 mg, or from about 100 mg to 1000 mg. In additional embodiments, scyllo-inositol is administered in a single dose, once daily. In additional embodiments, scyllo-inositol is administered twice daily. In further or additional embodiments, scyllo-inositol is administered three times per day. In additional embodiments, scyllo-inositol is administered four times per day.

A pharmaceutical composition of the invention may also comprise a second therapeutic agent, such as a uric acid lowering agent. Combinations of a scyllo-inositol and a second therapeutic agent, such as a uric acid lowering agent, in compositions of the invention

may be selected to provide additive effects or greater than additive effects, for example, synergistic effects. In an aspect, the invention relates to a pharmaceutical composition comprising a scyllo-inositol and a second therapeutic agent, such as a uric acid lowering agent, in combination with at least one pharmaceutically acceptable component chosen from a carrier, an excipient, and a vehicle, wherein the amounts of scyllo-inositol and second therapeutic agent are selected to provide an additive or synergistic effect in treating or preventing a condition disclosed herein. In an aspect, the invention relates to a pharmaceutical composition comprising scyllo-inositol and a second therapeutic agent in combination with at least one pharmaceutically acceptable component chosen from a carrier, an excipient, and a vehicle, wherein the scyllo-inositol and second therapeutic agent are selected to provide a synergistic effect, as a combined preparation for simultaneous, separate, or sequential use in treatment of a condition associated with aberrant levels of uric acids. In an aspect, the invention relates to a pharmaceutical composition comprising scyllo-inositol and a second therapeutic agent, wherein said composition achieves a synergistic effect for treating a disease state in which hyperuricemia is a risk factor in a mammal in need thereof. The invention also relates to a pharmaceutical composition in separate containers and intended for simultaneous or sequential administration to a subject, comprising a scyllo-inositol and a second therapeutic agent, such as a uric acid lowering agent, both optionally together with pharmaceutically acceptable carriers, excipients, or vehicles. In aspects of the invention, the scyllo-inositol is in a unit dosage form. In a particular aspect, the unit dosage from comprises a suboptimal dose of scyllo-inositol and optionally a suboptimal dose of the second therapeutic agent.

In aspects of the invention, a pharmaceutical composition of the invention comprises: (i) a scyllo-inositol; (ii) allopurinol, febuxostat, 4-(5-pyridin-4-yl-l/f-[l,2,4]triazol-3-yl)pyridine-2-carbonitrile (FYX-051), or combinations thereof; and (iii) optionally one or more pharmaceutically acceptable carriers, excipients, or vehicle. In particular aspects of the invention, a pharmaceutical composition of the invention comprises: (i) a scyllo-inositol; (ii) allopurinol; and (iii) optionally one or more pharmaceutically acceptable carriers, excipients, or vehicle. In further or additional embodiments, the amount of scyllo-inositol is in the range of about 100-2000 mg and in particular within that range about 100-1500 mg or 100-1000 mg, and the amount of allopurinol is in the range of about 50-500 mg and in particular within that range about 50-400 mg, 200-500 mg, 200-400 mg, or 100-300 mg.

In particular aspects of the invention, a pharmaceutical composition of the invention comprises: (i) a scyllo-inositol; (ii) febuxostat; and (iii) optionally one or more

pharmaceutically acceptable carriers, excipients, or vehicle. In further or additional embodiments, the amount of scyllo-inositol is in the range of about 100-2000 mg and in particular within that range about 100-1500 mg or 100-1000 mg, and the amount of febuxostat is in the range of about 40-200 mg and in particular within that range about 40-150 mg, 40-120 mg, 40-80 mg, or 80-120 mg.

In aspects the invention provides a pharmaceutical composition useful in the treatment of gout comprising: (i) a uric acid lowering agent; (ii) a uric acid level maintaining amount or lowering amount of a scyllo-inositol; and (iii) optionally one or more pharmaceutically acceptable carriers, excipients, or vehicle. In particular aspects of the invention, the uric acid lowering agent is allopurinol or febuxostat.

In aspects the invention provides a pharmaceutical composition useful in the treatment of edema and hypertension which also maintains uric acid levels at pretreatment levels or causes a decrease in uric acid levels comprising: (i) an antihypertensive agent; (ii) a uric acid level maintaining amount or lowering amount of a scyllo-inositol; and (iii) optionally one or more pharmaceutically acceptable carriers, excipients, or vehicle.

In aspects the invention provides a pharmaceutical composition useful in the treatment of cancer which also maintains uric acid levels at pretreatment levels or causes a decrease in uric acid levels comprising: (i) an anticancer agent; (ii) a uric acid level maintaining amount or lowering amount of a scyllo-inositol; and (iii) optionally one or more pharmaceutically acceptable carriers, excipients, or vehicle.

In aspects the invention provides a pharmaceutical composition useful for reducing the side effects of chemotherapy in a cancer individual comprising: (i) a uric acid level maintaining amount or lowering amount of a scyllo-inositol; and (iii) optionally one or more pharmaceutically acceptable carriers, excipients, or vehicle, wherein said side effects are related to elevated uric acid levels.

The invention relates to the use of scyllo-inositol in the preparation of a medicament for decreasing uric acid levels in one or more tissues or organs, blood, serum, urine, or combinations thereof. The invention also relates to the use of scyllo-inositol in the preparation of a medicament for decreasing uric acid production, increasing uric acid excretion, or both. The invention further relates to the use of scyllo-inositol in the preparation of a medicament for treating or preventing a condition associated with aberrant levels of uric acid. The invention still further relates to the use of scyllo-inositol in the preparation of a medicament for treating a condition chosen or selected from the group consisting of gout; a recurrent gout attack; gouty tophus; gouty arthritis; gouty nephropathy;

eclampsia; metabolic syndrome; diseases that involve accelerated formation and destruction of blood cells; hyperuricaemia; secondary hyperuricemia; drug related hyperuricaemia; secondary chronic hyperuricemia of polycythermia vera, of myeloid metaplasia, or of blood dyscrasia; atheroscleropathy; arteriolosclerophathy; hyperuricaemia related to medical conditions such as nephropathies, myeloproliferative disorders; conditions associated with insulin resistance; conditions associated with transplantations; hypertension; cardiovascular disease; coronary heart disease; Lesch-Nyhan syndrome, Kelley-Seegmiller syndrome, renal disease, kidney stones, renal failure; acute renal failure; joint inflammation; arthritis; artherosclerosis; diabetes; diabetes related disorders; urolithiasis; urate lithiasis; plumbism; hyperparathyroidism; hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency; psoriasis; and sarcoidosis.

The invention also relates to the use of a scyllo-inositol and at least one second therapeutic agent, composition, or combination treatment of the present disclosure for ameliorating disease severity, disease symptoms, and/or periodicity of recurrence of a condition disclosed herein. Further, the invention relates to the use of a scyllo-inositol and a second therapeutic agent as a medicament. The medicament may be suitable for use in treating a condition disclosed herein or is suitable for use in patients who are at risk of developing a condition disclosed herein.

Still further the invention contemplates pharmaceutical packs or kits comprising scyllo-inositol or a pharmaceutical composition disclosed herein, and optionally a second therapeutic agent. In an aspect, the invention is directed to a kit comprising a first container comprising a pharmaceutical composition comprising an amount of scyllo-inositol effective to lower a mammal's uric acid level in blood compared to a baseline level and at least one pharmaceutically acceptable component chosen from a carrier, an excipient, and a vehicle scyllo-inositol. The kit may further comprise a second container comprising a second therapeutic agent.

These and other aspects, features, and advantages of the present invention should be apparent to those skilled in the art from the following drawings and detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a plot of serum levels of UA vs. time under administration of different dosages of scyllo-inositol to healthy human subjects. The legend shows doses that were 0 mg (control), 200 mg, 700 mg, 1500 mg, and 3000mg per day. Measurements were taken at days 0 (baseline), 4, 7, and 12.

Figure 2 shows the change in serum uric acid levels in subjects in the same study as summarized in Figure 1.

DETAILED DESCRIPTION OF THE INVENTION

Unless defined otherwise, 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. Particular aspects of the disclosure are described in greater detail below. The terms and definitions as used in the present application and as clarified herein are intended to represent the meaning within the present disclosure. The patent and scientific literature referred to herein and referenced above are hereby incorporated by reference. The terms and definitions provided herein control, if in conflict with terms and/or definitions incorporated by reference.

Numerical ranges recited herein by endpoints include all numbers and fractions subsumed within that range (for example, from 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.90, 4, and 5). It is also to be understood that all numbers and fractions thereof are presumed to be modified by the term "about." The term "about" means plus or minus 0.1 to 50%, 5-50%, or 10-40%, preferably 10-20%, more preferably 10% or 15%, of the number to which reference is being made. Further, it is to be understood that "a," "an," and "the" include plural referents unless the content clearly dictates otherwise. Aspects of the present disclosure requiring a particular value in a subject are substantially supported herein by population data in which the relevant value is assessed to be a meaningful delimitation of the subject population.

A "condition(s) associated with aberrant levels of uric acid" may be characterized by levels of uric acid which are greater than or below normal levels in at least one tissue or organ, blood, serum, urine, or combinations thereof. Normal levels of uric acid generally range from between about 120μM and about 380 μM or from about 2.0 and 8.0 mg/dL, varying slightly depending on gender. In aspects of the invention the condition is characterized by elevated levels of uric acid, that is, levels greater than normal, for example, levels greater than 5.0, 6.0, 7.0 or 8.0 mg/dL. The aberrant levels may result from overproduction of uric acid, low excretion of uric acid, tumor lysis, a blood disorder, or a combination thereof. Examples of conditions associated with aberrant levels of uric acid include without limitation gout; a recurrent gout attack; gouty tophus; gouty arthritis; gouty nephropathy; eclampsia; metabolic syndrome; diseases that involve accelerated formation and destruction of blood cells; hyperuricaemia; secondary hyperuricemia; drug related

hyperuricaemia; secondary chronic hyperuricemia of polycythermia vera, of myeloid metaplasia, or of blood dyscrasia; atheroscleropathy; hyperuricaemia related to medical conditions such as nephropathies, myeloproliferative disorders; conditions associated with insulin resistance; conditions associated with transplantations; hypertension; cardiovascular disease; coronary heart disease; Lesch-Nyhan syndrome, Kelley-Seegmiller syndrome, renal disease, kidney stones, renal failure; acute renal failure; joint inflammation; arthritis; artherosclerosis; arteriolosclerosis; diabetes; diabetes related disorders; urolithiasis; urate lithiasis; plumbism; hyperparathyroidism; hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency psoriasis; and sarcoidosis.

In an aspect, the condition is chosen or selected from the group consisting of gout, a recurrent gout attack, gouty arthritis, gouty nephritis, eclampsia, secondary hyperuricemia, and secondary chronic hyperuricemia of polycythermia vera, of myeloid metaplasia, or of blood dyscrasia.

In an aspect, the condition is a drug related hyperuricaemia where the drug may be one or more of nucleic acid metabolic antagonists, hypotensive diuretics, anti-tuberculosis drugs, anti-inflammatory analgesic drugs, hyperlipidemic drugs, therapeutic drugs for asthma, immunosuppressants, cytotoxic drugs, salicylic acid, pyrazinamide, ethambutol, nicotinic acid, ethanol, cyclosporine and the like.

In aspects of the invention, the condition is a disease state in which hyperuricemia is a risk factor. A risk factor is a characteristic that has been implicated or demonstrated to be associated with (although not necessarily the direct cause of) a particular disease or syndrome. Risk factors can be used for targeting treatment and preventive efforts of individuals who may be particularly in danger of the disease or syndrome based on having a particular risk factor or combination of risk factors. Disease states in which hyperuricemia is a risk factor include without limitation atheroscleropathy, renal disease, cardiovascular disease, metabolic syndrome, urate lithiasis, and hypertension. It will be recognized by those of skill in the art that renal disease, atheroscleropathy, cardiovascular disease, metabolic syndrome, and hypertension are complex disease states in which there are more than one risk factor and an array of pathological processes. Treatment of those disease states by administration of scyllo-inositol is intended to treat that portion of the disease state that is mediated or affected by hyperuricemia.

In an embodiment of the invention, the condition is gout and related symptoms.

In another embodiment of the invention, the condition is hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency.

In another embodiment of the invention, the condition is hypertension or edema.

In another embodiment of the invention, the condition is acute renal failure.

The term "treating" refers to reversing, alleviating, or inhibiting the progress of a condition, or one or more symptoms of such condition, to which such term applies. Depending on the state of the subject, the term in some aspects of the invention may refer to preventing a condition, and includes preventing the onset, or preventing the symptoms associated with a condition. The term also includes maintaining the condition and/or symptom such that the condition and/or symptom does not progress in severity. A treatment may be either performed in an acute or chronic way. The term also refers to reducing the severity of a condition or symptoms associated with such condition prior to affliction with the disease. Such prevention or reduction of the severity of a condition prior to affliction refers to administration of scyllo-inositol, or composition, or combination of the present invention to a subject that is not at the time of administration afflicted with the condition. "Preventing" also refers to preventing the recurrence of a condition, or of one or more symptoms associated with such condition. The terms "treatment" and "therapeutically," refer to the act of treating, as "treating" is defined above. The purpose of intervention is to combat the condition and includes the administration of an active compound to prevent or delay the onset of the symptoms or complications, or alleviating the symptoms or complications, or eliminating the condition. For example, a compound, composition, or combination disclosed herein may be used to ameliorate symptoms associated with elevated levels of uric acid such as muscle spasm, localized swelling, inflammation, joint pains, muscle fatigue, stress feelings, or myocardial infarction.

The term "administering" or "administration" refers to the process by which scyllo-inositol, compositions, and/or combinations disclosed herein are delivered to a subject for treatment or prophylactic purposes. Scyllo-inositol, compositions, and/or combinations are administered in accordance with good medical practices taking into account the subject's clinical condition, the site and method of administration, dosage, subject age, sex, body weight, and other factors known to the physician. For example, the terms "administering" or "administration" as used herein refer to (1) providing, giving, dosing and/or prescribing by either a health practitioner or his authorized agent or under his direction scyllo-inositol, and (2) putting into, taking or consuming by the patient or person himself or herself, scyllo-inositol.

A "combination treatment," "administering in combination" or "administered in combination" means use of multiple pharmaceutical agents in combination as active

ingredients administered concurrently to a patient being treated. The terms include use as a combination drug, use as a kit, and use in a combination characterized by independent administration of each by the same or different administration routes and the like. When administered in combination each component may be administered at the same time, or sequentially in any order at different points in time. Therefore, each component may be administered separately, but sufficiently close in time to provide a desired effect, such as an additive or synergistic effect. The first compound may be administered in a regimen that additionally comprises treatment with a second therapeutic agent. In aspects of the invention, the terms refer to the administration of scyllo-inositol and a second therapeutic agent including separate administration of medicaments each containing one of the compounds, as well as simultaneous administration whether or not the compounds are combined in one formulation or whether they are in separate formulations.

An "additive effect" of a scyllo-inositol and a second therapeutic agent refers to an effect that is equal to the sum of the effects of the two individual agents.

A "synergistic effect" of a scyllo-inositol and a second therapeutic agent refers to an effect that is greater than the additive effect that results from the sum of the effects of the two individual agents.

A "uric acid lowering agent" refers to an agent effective in reducing uric acid levels in tissues or organs, blood, serum, urine, or combinations thereof and in particular refers to an agent known to reduce blood or serum uric acid levels. Uric acid lowering agents, include without limitation, NSAIDs, colchicine, cinchophan, bucolome,corticosteroids, adenocorticotropic hormones (ACTH), sulfinpyrazone, Arcalyst™ (rilonacept), XOMA 052, xanthine oxidoreductase inhibitors such as 4-(5-pyridin-4-yl-l/f-[l,2,4]triazol-3-yl)pyridine-2-carbonitrile (FYX-051), xanthine oxidase inhibitors such as allopurinol, tisopurine, hydroxyakalone, TEI-6720, febuxostat (Adenuric™, Uloric®),™), and Y-700; uricosurics such as benziodarone, benzbromarone, probenecid and RDEA594; supplements of the uricase protein, an inhibitor of the organic anion transport channels and/or voltage sensitive transport channels acting in the kidney, including but not limited to losartan, benzbromaraone, benziodarone, probenicid, sulfinpyrazone ethebencid, orotic acid, ticrynafen and zoxazolamine; a supplement of the uricase protein which may be delivered as a conjugate with polyethylene glycol or another delivery system, a urate channel inhibitor, uricase derivatives such as Rasburicase and Pegylated uricase; and gene based therapies such as uricase overexpression or blockade of URAT-1, or combinations thereof.

The terms "subject," "individual," and "patient" refer to an animal including a warm-blooded animal, such as a mammal. Mammal includes without limitation any members of the kingdom Mammalia. Mammal includes humans, but the term also includes domestic animals bred for food or as pets, such as horses, cows, sheep, poultry, fish, pigs, cats, dogs, and zoo animals, goats, apes (e.g. gorilla or chimpanzee), and rodents such as rats and mice. Subjects for treatment include mammals, such as humans, susceptible to, suffering from, suspected of having, being pre-disposed or that have suffered a condition disclosed herein.

The phrase "at least one pharmaceutically acceptable component chosen from a carrier, an excipient, and a vehicle" refers to a medium which is useful for preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable. It is generally selected so that it does not interfere with the effectiveness or activity of an active ingredient and is not toxic to the hosts to which it is administered. The phrase as used in the specification and claims include both one and more than one such carrier, excipient, or vehicle. Acceptable carriers, excipients, or vehicles may be chosen or selected from any of those commercially used in the art. By way of example, a carrier, excipient, or vehicle includes diluents, binders, adhesives, lubricants, disintegrates, bulking agents, wetting or emulsifying agents, pH buffering agents, and miscellaneous materials such as absorbants that may be needed in order to prepare a particular composition. Examples of carriers, excipients, and vehicles include but are not limited to saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof. The use of such media and agents for an active substance is well known in the art.

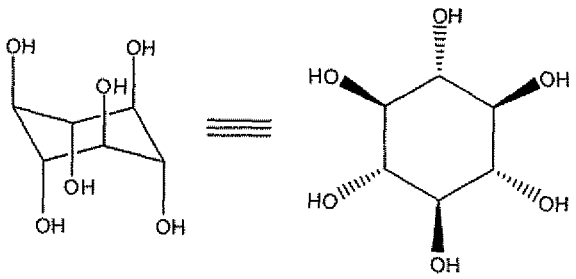
"Therapeutically effective amount" refers to the amount or dose of active compound(s) or a composition of the invention that will lead to one or more desired effects, in particular therapeutic effects. A therapeutically effective amount of a substance can vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the substance to elicit a desired response in the individual. A dosage regimen may be adjusted to provide the optimum therapeutic response (such as sustained therapeutic or beneficial effects). For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

In some aspects, a therapeutically effective amount is a "uric acid level maintaining amount". Preferably, the uric acid level maintaining amount maintains the uric acid levels in the individual at about normal levels, more preferably uric acid levels at or below 5 mg/dL, 6 mg/dL, 7 mg/dL or 8 mg/dL.

In some aspects, a therapeutically effective amount is a "uric acid level lowering amount". The uric acid level lowering amount may decrease the serum levels of uric acid to achieve normal serum uric acid levels. A uric acid lowering amount may decrease the uric acid level in an individual compared to the individual's uric acid level before administration. A uric acid level lowering amount can decrease uric acid levels by at least about 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 75%, 80%, 85%, 90%, or 95%, preferably at least 10%, or any percentage in between. In embodiments of the invention, the uric acid lowering amount decreases uric acid from about 5% to 50%, 5% to 95% and in particular within that range about 5% to 50%, 10% to 50%, 10% to 20%, 10% to 30%, 10% to 40%, 10% to 50%, 10% to 60%, 10% to 70%, 10% to 95%, 15-% to 50%, 15% to 95%, 20-40%, or 20-60%. Alternatively, a uric acid level lowering amount can decrease serum uric acid levels by at least about 0.5 mg/dL (about 30 μM), 1 mg/dL (about 60 μM), 2 mg/dL (about 119 μM), 2.5 mg/dL (about 149 μM) or 3 mg/dL (about 178 μM). In embodiments of the invention, the uric acid level lowering amount can decrease blood uric acid levels from about 0.5 mg/dL (about 30 μM) to 3 mg/dL (about 178 μM), from 1 mg/dL (about 60 μM) to 3 mg/dL (about 178 μM), or from 2mg/dL (about 119 μM) to 3 mg/dL (about 178 μM).

"Suboptimal dose" refers to a dose of an active compound which is less than the optimal dose for that compound when used in monotherapy.

Scyllo-inositol is a cyclohexane polyol, isomeric with myo-inositol, but differing in the orientation of the six hydroxyl groups around the ring. The structural formula of scyllo-inositol is depicted below in both 3-dimensional and planar drawings.



It is also known as scyllitol, quercinitol, and 1,2,3,4,5,6-cyclohexanehexol, (1alpha,2beta,3alpha,4beta,5alpha,6beta). Scyllo-inositol is commercially available in the SigmaAldrich catalog under CAS no. 488-59-5 or may be made by oxidation of myo-inositol to scyllo-inosose and stereospecific reduction using a metal catalyst and hydrogen

following known procedures. Scyllo-inositol may alternatively be produced using process steps described by Sarmah M. and Shashidhar, M., Carbohydrate Research, 2003, 338, 999-100, Husson, C., et al, Carbohydrate Research 307 (1998) 163-165, Weissbach, A., J Org Chem (US), 1958, 23:329-330; Chung, S.K. et al., Bioorg Med Chem. 1999, 7(11):2577-89; or Kiely D.E., and Fletcher, H.G., J. American Chemical Society (US) 1968, 90:3289-3290; and described in DE 3,405,663 (Merck Patent GMBH). Scyllo-inositol may also be made according to the procedures in U.S. Patent Application Publication No. 2006/0240534 (see also WO05035774, EP1674578, JP2003102492, and JP09140388) assigned to Hokko Chemical Industries.

In some embodiments of the invention, the scyllo-inositol is the compound designated AZD-103/ ELND005 (Elan Corporation).

In some aspects of the invention, the methods, compositions, and combinations disclosed herein may comprise an analog or derivative of scyllo-inositol, for example, an analog or derivative as disclosed in International Published Applications WO 2007/041855 and WO 2007/119108.

Uric acid is denoted by the following systematic nomenclature: 7,9-dihydro-1*H*-purine-2,6,8(3*H*)-trione. Urate is the anion of uric acid and may be found physiologically as the ammonium, calcium, or sodium salt, among other possible physiological counterions. Uric acid exists along with the ionized urate form physiologically. Unless otherwise constrained by the context in which it is used, uric acid includes urate salts.

Scyllo-inositol may be administered by any of the accepted modes of systemic administration including oral, subdermal, intramuscular, parenteral, and other systemic routes of administration. Any pharmaceutically acceptable mode of administration can be used, including solid, semi-solid, or liquid dosage forms, such as for example, tablets, pills, capsules, powders, liquids, suspensions, or the like. Those dosage forms may be in a unit dosage form suitable for administration of precise dosages, or in sustained or controlled, such as extended, release forms for the prolonged administration of the compound at a predetermined rate. Sustained or continuous release compositions containing scyllo-inositol are described, for example, in WO 2007/101353.

Compositions of scyllo-inositol may be formulated as sterile, substantially isotonic and in full compliance with all Good Manufacturing Practice (GMP) regulations of appropriate regulatory authorities such as the US Food and Drug Administration. The compositions will typically include at least one pharmaceutically acceptable component chosen from a carrier, an excipient, and a vehicle and the active compound and, in addition,

may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, and the like. Carriers, excipients, and vehicles are generally selected based on the intended form of administration, and consistent with conventional pharmaceutical practices. Suitable pharmaceutical carriers, excipients, and vehicles are described in the standard text, *Remington: The Science and Practice of Pharmacy* (21st Edition, Popovich, N (eds), Advanced Concepts Institute, University of the Sciences in Philadelphia, Philadelphia, PA. 2005).

Parenteral administration is generally characterized by injection, whether subcutaneously or intramuscularly. Injectables can be prepared in conventional forms, either as liquid solutions or suspension, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients include, for example, water, saline, aqueous dextrose, glycerol, ethanol or the like. In addition, if desired, the pharmaceutical compositions may also contain minor amounts of non-toxic substances such as wetting or emulsifying agents, auxiliary pH buffering agents and the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate, and the like.

Scyllo-inositol may be admixed, encapsulated, conjugated or otherwise associated with molecules to facilitate uptake, distribution and/or absorption of the compound. Various known delivery systems can be used to administer a medicament of the invention, e.g. encapsulation in liposomes, microparticles, microcapsules, and the like. Medicaments can also be formulated as pharmaceutically acceptable salts.

For delayed release, scyllo-inositol may be included in a pharmaceutical composition formulated for slow release, such as in microcapsules formed with biocompatible polymers, polymer coated multiparticulates or in liposomal carrier systems according to methods known in the art. The compositions may also be advantageously administered as bi-layer tablets containing an immediate release component and a delayed release component.

For extended release of active agent, the scyllo-inositol may be covalently conjugated to a water soluble polymer, such as a polylactide or biodegradable hydrogel derived from an amphipathic block copolymer, as described in U.S. Pat. No. 5,320,840. The scyllo-inositol may also be incorporated into a polymer or multi-polymer matrix having properties that release the active compound through diffusion from the matrix, erosion of the matrix or a combination of diffusion and erosion.

Scyllo-inositol may be administered in substantially pure form as a powder or a powder contained in, for example, a gelatin capsule. It may also be administered in solid compositions with conventional non-toxic carriers, for example, mannitol, lactose, starch,

magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like may be used. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc. scyllo-inositol as defined above and optional pharmaceutical adjuvants in a sterile carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol, mineral or vegetable oils and the like to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of non-toxic auxiliary pH buffering agents and the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 15th Edition, 1975.

The compositions are advantageously compounded into unit dosage forms containing a predetermined, standard amount of the active compound, to make dosing and patient compliance simpler. For example, capsules, tablets or controlled release delivery forms may be formulated and manufactured to contain, for example, 200 mg, 250 mg, 350 mg, 500 mg, 750 mg, 800 mg, 1000 mg, or 2000 mg of scyllo-inositol. Such tablets or controlled release delivery forms may be used for administration of one unit dosage form or any combination of unit dosage forms, that is more than one unit dosage form, to achieve the total dosage required as determined by the prescribing physician.

The amount of active compound administered will be dependent on the subject being treated, the amount or severity of the condition (e.g. hyperuricemia), the particular disease state being treated in particular in which hyperuricemia is a cause or risk factor, the manner of administration and the judgment of the prescribing physician. However, an effective dosage is in the range of about 100 mg/day to about 7000 mg/day, and in particular within that range, about 150 mg/day to about 6000 mg/day, about 150 mg/day to about 4000 mg/day, about 150 mg/day to about 3000 mg/day, 150 mg/day to about 2000 mg/day, 200 mg/day to about 3000 mg/day, 150 mg/day to about 4000 mg/day, 200 mg/day to about 4000 mg/day, or 500 mg/day to about 3000 mg/day. Daily dosages may be achieved by once a day, twice a day or three times daily administration. The duration of treatment can be adapted to the conditions of the patient, preferably with the aim to obtain long term normal uric acid levels.

Dosage forms or compositions containing scyllo-inositol in the range of 0.25 to 100%, with the balance when less than 100% made up from non-toxic excipients and carriers may be prepared. For oral administration, a pharmaceutically acceptable non-toxic composition is

formed, optionally with the incorporation of any of the normally employed pharmaceutical excipients, and may contain 1%-100% active ingredient, preferably 25%-75%. Percentages recited in the compositions in the specification and claims are weight percentages or w/w.

Scyllo-inositol may be administered in combination with other medications (such as second therapeutic agents) or other medical procedures to treat the same or other aspects of the disease state being treated. A second therapeutic agent may either be within the same pharmaceutical composition (combination compositions), or the two agents may be administered in separate compositions at substantially the same time or at different times as required in the judgment of the prescribing physician. In aspects of the invention, the second therapeutic agent can be an agent for the prophylaxis and/or treatment of hyperuricemia; gout arthritis; gouty kidney; urolithiasis; hypertension or hypertensive complications; hyperlipidemia or hyperlipidemic complications, diabetes or diabetes complications, obesity or obesity complications,; kidney failure; cardiovascular disorder; cancer; or a cerebrovascular disorder. In aspects of the invention, the second therapeutic agent can be an agent that increases uric acid levels in a subject. In particular aspects of the invention, the second therapeutic agent is chosen or selected from the group consisting of a diuretic (e.g. hydrochlorothiazide, furosemide), loop diuretics, angiotension-convertase inhibitors, angiotensin II receptor antagonists, renin angiotensin systems inhibitor (e.g. captopril, cilazapril, enalapril, fosinopril, lisinopril, quinapril, ramapril, zofenopril, candesartan cilexetil, eprosartan, irbesartan, losartan, tasosartan, telmisartan, and valsartan), CA antagonists, β-blockers, α,β-blockers, α-blockers, statins, anion exchange resins, probucol, fibrate agents, eicosapentaenoic acid preparations, thromboxane synthetase inhibitor, thromboxane receptor antagonist, alkalinizing urine agents such as citric acid preparations, and sodium bicarbonate, cation exchange resins, aluminum hydroxide, alfacalcidol, ACE inhibitors, salicylate, pyrazinamide, ethambutol, NSAID (e.g., indomethacin, naproxen, fenbufen, pranoprofen, oxaprozin, colchicine, corticosteroid and the like), nicotinic acid, cyclosporine, 2-ethylamino-1,3,4-thiadiazole, antineoplastic agent, immunosuppressive agent, cytotoxic agent, anti-hypertensive agent and uric acid lowering agent.

In aspects of the invention, the second therapeutic agent is an agent for treatment of hyperlipidemia or hyperlipidemic complications including without limitation lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, colestimide, colestyramine, niceritrol, nicomol, fenofibrate, bezafibrate, clinofibrate, clofibrate, ethyl icosapentate and the like.

In aspects of the invention, the second therapeutic agent is an agent for treatment of diabetes and diabetes complications including without limitation, insulin preparations, sulfonylureas, insulin secretagogues, sulfonamides, biguanides, α glucosidase inhibitors, insulin sensitizers, angiotensin-convertase inhibitors, aldose reductase inhibitors, antiarrhythmic drugs and the like, in particular, insulin, chlorpropamide, glibenclamide, glipizide, tolbutamide, glyclopyramide, acetohexamide, glimepiride, tolazamide, gliclazide, nateglinide, glybuzole, metformin hydrochloride, buformin hydrochloride, voglibose, acarbose, pioglitazone hydrochloride, mexiletine and the like.

In aspects of the invention, the second therapeutic agent is an agent for treatment of kidney failure, cardiovascular disorder, cerebrovascular disorder caused by hyperuricemia including without limitation loop diuretics (e.g., furosemide), citric acid preparations, sodium bicarbonate, cation exchange resins, aluminum hydroxide, alfacalcidol, β-blockers (e.g., propranolol hydrochloride), ACE inhibitors (e.g., captopril), cardiac stimulants (e.g., digoxin), angina pectoris therapeutic agents (e.g., isosorbide nitrate), Ca antagonists (e.g., diltiazem hydrochloride), uric acid production suppressants (e.g., allopurinol), amino acid preparations, hyperammonemia improvers, therapeutic agents for antiarrhythmia (e.g., mexiletine) and therapeutic agents for anemia (e.g., mepitiostane, erythropoietin).

The dose of the second therapeutic agent can be determined according to the dose employed clinically, and having regard to the age and body weight of the subject of administration, condition, administration time, dosage form, administration method, combination and the like. The mode of administration of the second therapeutic agent is not particularly limited.

Medical procedures which may be used in combination with scyllo-inositol include, without limitation, surgical procedures which are likely to lead to post-operative elevation in serum uric acid levels such as cardiovascular surgery, prolonged orthopedic surgeries, organ transplantation, abdominal/GI-related surgery, gynecological-related surgery, among others, and procedures such as administration of contrast agents or nephrotoxins which can increase the risk for acute renal failure.

According to the invention, a kit is provided comprising a scyllo-inositol or pharmaceutical composition disclosed herein, and optionally one or more second therapeutic agent. The kit can be a package which houses a container which contains a scyllo-inositol or pharmaceutical composition disclosed herein, and also houses instructions for administering the scyllo-inositol or pharmaceutical composition disclosed herein. The invention further relates to a commercial package comprising a scyllo-inositol or pharmaceutical composition

disclosed herein together with instructions for simultaneous, separate or sequential use. In particular a label may include amount, frequency, and method of administration.

In embodiments of the invention, a kit is provided comprising a first container comprising a pharmaceutical composition comprising an amount of scyllo-inositol effective to lower a mammal's uric acid level in blood compared to a baseline level and at least one pharmaceutically acceptable component chosen from a carrier, an excipient, and a vehicle scyllo-inositol. The kit further comprises a second container comprising a second therapeutic agent.

In embodiments of the invention, a pharmaceutical pack or kit is provided comprising one or more containers filled with one or more of the ingredients of a composition disclosed herein, optionally with a second therapeutic agent. Associated with such container(s) can be various written materials such as instructions for use, or a notice in the form prescribed by a governmental agency regulating the labeling, manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use, or sale for human administration.

The invention also relates to articles of manufacture and kits containing materials useful for treating a condition associated with aberrant levels of uric acid. An article of manufacture may comprise a container with a label. Examples of suitable containers include bottles, vials, and test tubes which may be formed from a variety of materials including glass and plastic. A container holds a medicament or formulation of the invention comprising a scyllo-inositol or pharmaceutical composition disclosed herein, and optionally a second therapeutic agent which is effective for treating a condition associated with aberrant levels of uric acid. The label on the container indicates that the medicament or formulation is used for treating a condition associated with aberrant levels of uric acid, and may also indicate directions for use. In aspects of the invention, a medicament or formulation in a container may comprise any of the medicaments or formulations disclosed herein.

The invention also contemplates kits comprising scyllo-inositol and optionally one or more second therapeutic agent for treating a condition associated with aberrant levels of uric acid. In aspects of the invention, a kit of the invention comprises a container described herein. In particular aspects, a kit of the invention comprises a container described herein and a second container comprising a buffer. A kit may additionally include other materials desirable from a commercial and user standpoint, including, without limitation, buffers, diluents, filters, needles, syringes, and package inserts with instructions for performing any methods disclosed herein (e.g., methods for treating a polyglutamine disease). A medicament

or formulation in a kit of the invention may comprise any of the formulations or compositions disclosed herein.

The present invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of parameters which can be changed or modified to yield essentially the same results.

EXAMPLES

Example 1

A Phase 1 single site, open-label multiple dosing study evaluating a scyllo-inositol formulation was conducted in healthy adult subjects. Approximately 8 healthy male subjects received 2000 mg of scyllo-inositol twice daily (4 - 500 mg tablets orally administered twice a day) for 10 days. Blood samples were collected 12 hours prior to the first dose (day 0) and on days 6, 14, and 21.

Scyllo-inositol 500 mg capsules were BSE/TSE-free soft gelatin, white, opaque capsules and no excipients were used in the finished product. Capsules were supplied in 60-mL, oblong, white pharmaceutical highdensity polyethylene (HDPE) bottles with white caps. Each 60-mL bottle contained 30 capsules of 500 mg strength scyllo-inositol.

In all 8 subjects, uric acid decreased between Day 0 and Day 6; this decrease ranged from approximately 12 to 175 μmol/L, then returned to Day 0 values by Day 21, the last follow-up visit. Serum uric acid levels decreased in all subjects following the start of treatment, although mean uric acid levels remained within the normal range during the study. Maximal decreases were seen at Day 6, and ranged from approximately 12 to approximately 172 μmol/L between Day 0 and Day 6, and returned towards baseline by Day 21.

The mean uric acid values and change from baseline values are provided in Table 1 for all the subjects. Overall, a decrease in serum uric acid levels was observed in all subjects following scyllo-inositol administration.

Table 1: Summary of uric acid values in micromole per liter.

	Baseline	Day 6	Day 14	Day 21
N	8	8	8	8
Mean	305.6	216.8	243.9	289.2
SD	38.54	29.94	22.48	30.48
Median	300.4	226.0	237.9	291.5
Min, Max	256, 375	155, 250	196, 274	250, 333
N	-	8	8	8
Mean Change	-	-88.8	-70.6	-16.4
SD Change	-	51.85	43.06	44.25
Median Change	-	-72.6	-74.4	-23.8
Min, Max Change	-	-172, -12	-131, -12	-83, 65

Note: (1) Baseline is defined as the evaluation performed on Day 0; and Change from Baseline equals value at indicated time point - value at Baseline.

Example 2 - Multiple Ascending Dose Study of Orally Administered *scyllo inositol* Every Twelve Hours for Seven Days in Healthy Elderly Subjects

A single-center, randomized, placebo-controlled, multiple ascending dose study evaluating a scyllo-inositol formulation was conducted in healthy elderly subjects. Approximately 32 healthy subjects (men and women) participated in one or four cohorts consisting of 8 subjects each (i.e., 6 on active drug and 2 on placebo). Subjects received drug twice daily (BID) (every 12 hours) for 7 days. The dosage levels of the scyllo-inositol were 200 mg BID (400 mg/d total), 700 mg BID (1400 mg/d total), 1500 mg BID (3000 mg/d total) and 3000 mg BID (6000 mg/d total) given every 12 hours. Blood samples were collected from each subject on days 0, 4, 7, and 12. Uric acid levels were measured in the blood samples and the results are shown in Figures 1 and 2.

Scyllo-inositol 200 and 500 mg capsules were bovine spongiform encephalopathy (BSE)/transmissible spongiform encephalopathy (TSE)-free soft gelatin, white, opaque

capsules and no excipient was used in the finished product. Capsules were supplied in 60-mL, oblong, white pharmaceutical high density polyethylene (HDPE) bottles with white caps. Each 60-mL bottle contained 30 capsules of 200 or 500 mg scyllo-inositol.

A dose-related decrease in mean uric acid levels was observed at Days 4 and 7, which partially resolved by Day 12. The baseline mean uric acid for all subjects treated with scyllo-inositol was 297.2 μmol/L-5mg/dL (normal range: 269.6 to 316.2 μmol/L) and for placebo subjects was 270.3 μmol/L. At Day 4, mean decreases from baseline across all scyllo-inositol treatment groups were observed: 200 mg (-7.9 μmol/L-0.1mg/dL), 700 mg (-51.5 μmol/L-0.87mg/dL), 1500 mg (-70.4 μmol/L-1.2mg/dL), and 3000 mg (-83.3 μmol/L-1.4mg/dL). A mean decrease from baseline of –9.9 μmol/L-0.1mg/dL was observed in the placebo group at this time point.

By Day 7, decreases from baseline continued among subjects treated with scyllo-inositol, but a dose-response effect was not as apparent: 200 mg (-25.8 μmol/L), 700 mg (-70.4 μmol/L), 1500 mg (-88.2 μmol/L), and 3000 mg (-85.3 μmol/L). At Day 7, the mean decrease from baseline in subjects treated with placebo was -24.5 μmol/L.

By Day 12, mean increases from baseline in uric acid were seen in the scyllo-inositol 200 mg group (+25.8 μmol/L) and the placebo group (+29.0 μmol/L). Mean decreases in the scyllo-inositol 700 mg, 1500 mg, and 3000 mg groups at Day 12 were –1.0, -27.8, and -29.7 μmol/L, respectively. Results are summarized at Tables 2-5.

Table 2: Summary of uric acid results at Baseline in micromole per liter.

	Placebo	200 mg	700 mg	1500 mg	3000 mg
N	9	6	6	6	6
Mean	270.3	316.2	269.6	303.3	299.4
SD	67.43	108.08	104.02	76.54	51.81
Median	285.5	318.2	258.7	279.6	300.4
Min, Max	167, 381	149, 458	161, 410	220, 434	226, 363

Table 3: Summary of uric acid results at Day 4 in micromole per liter.

	Placebo	200 mg	700 mg	1500 mg	3000 mg
N	9	6	6	6	6
Mean	260.4	308.3	218.1	233.0	216.1
SD	69.29	106.76	86.66	52.86	44.77
Median	243.9	330.1	175.5	237.9	226.0
Min, Max	161, 357	143, 410	143, 351	155, 291	161, 262
N	9	6	6	6	6
Mean Change	-9.9	-7.9	-51.5	-70.4	-83.3
SD Change	30.76	33.58	36.60	50.11	20.26
Median Change	-5.9	-11.9	-62.5	-71.4	-83.3
Min, Max Change	-48, 24	-48, 54	-101, 0	-143, 12	-107, -59

Table 4: Summary of uric acid results at Day 7 in micromole per liter.

	Placebo	200 mg	700 mg	1500 mg	3000 mg
N	9	6	6	6	6
Mean	258.7	290.5	199.3	215.1	214.1
SD	64.06	102.29	74.17	38.26	45.61
Median	229.0	333.1	169.5	229.0	214.1
Min, Max	190, 369	143, 387	125, 309	155, 256	149, 268
N	8	6	6	6	6
Mean Change	-24.5	-25.8	-70.4	-88.2	-85.3
SD Change	28.87	41.15	38.81	61.86	23.39
Median Change	-17.8	-17.8	-83.3	-77.3	-74.4
Min, Max Change	-65, 18	-77, 18	-107, -12	-196, -24	-131, -71

Table 5: Summary of uric acid results at Day 12 in micromole per liter.

	Placebo	200 mg	700 mg	1500 mg	3000 mg
N	8	6	6	6	6
Mean	312.3	342.0	268.7	275.6	269.6
SD	81.12	108.75	99.20	71.14	51.40
Median	294.4	368.8	237.9	279.6	270.6
Min, Max	214, 428	184, 476	167, 410	196, 399	208, 345
N	8	6	6	6	6
Mean Change	29.0	25.8	-1.0	-27.8	-29.7
SD Change	49.91	25.14	28.00	29.06	37.24
Median Change	14.9	26.8	3.0	-29.7	-23.8
Min, Max Change	-24, 101	-12, 59	-54, 30	-65, 18	-83, 18

The mean change from baseline to day 7 versus placebo was used to determine statistical significance. The ANCOVA model and a simple t-test resulted in $p<0.003$ for both, 95% confidence interval (CI) for mean difference (PLC-TRT) was (0.34, 1.37), with point estimate of 0.85. The ANCOVA looked at the change of uric acid levels in controls from starting levels of uric acid; the software used was SAS 9.1.3. The confidence interval did not include 0 and the 95% CI difference between treatment and placebo demonstrated statistical significance. The point estimate of 0.85 is a population parameter in dosed subjects. The simple t-test did not control for variables.

The present invention and manner and process of using it, are now described in such full, clear and concise terms so as to enable a person skilled in the art to which it pertains to make and use the same. It is also to be understood that the foregoing description is of exemplary embodiments of the invention and that modifications may be made hereof without departing from the scope or spirit of the invention as set forth in the claims.

WHAT IS CLAIMED IS:

1. A method of decreasing uric acid levels in one or more tissues or organs, blood, serum, urine, or combinations thereof of an individual in need of decreased uric acid levels comprising administering to the individual a therapeutically effective amount of scyllo-inositol.

2. A method of decreasing uric acid levels of a patient in need thereof in one or more tissues or organs, blood, serum, urine or combinations thereof comprising administering to the patient a therapeutically effective amount of scyllo-inositol to decrease the uric acid level in the patient compared to the patient's uric acid level before administration.

3. The method of claim 1, wherein the scyllo-inositol is administered in combination with a second therapeutic agent.

4. A method of treating an individual suffering from a condition associated with aberrant levels of uric acid comprising administering to the individual a therapeutically effective amount of scyllo-inositol.

5. The method of claim 4 wherein the therapeutically effective amount is a uric acid lowering amount which decreases the uric acid level in the individual compared to the individual's uric acid level before administration.

6. The method of claim 4 wherein the therapeutically effective amount is a uric acid level maintaining amount which maintains the uric acid level in the individual at about a normal level.

7. The method of claim 4, wherein the condition is chosen from gout; recurrent gout attack; gouty tophus; gouty arthritis; gouty nephropathy; eclampsia; atherosclerosis; metabolic syndrome; diseases that involve accelerated formation and destruction of blood cells; hyperuricaemia; secondary chronic hyperuricemia of polycythermia vera, of myeloid metaplasia, or of blood dyscrasia; atherosclerosis; hypertension; cardiovascular disease; coronary heart disease; Lesch-Nyhan syndrome; Kelley-Seegmiller syndrome; renal disease; kidney stones; renal failure; acute renal failure; joint inflammation; arthritis; urolithiasis; urate lithiasis; metabolic syndrome; plumbism; hyperparathyroidism; psoriasis; and sarcoidosis.

8. A method of treating hyperuricemia in a patient in need of such treatment comprising administering scyllo-inositol to the patient in an amount effective to lower the uric acid level in the blood.

9. The method of claim 8, wherein the uric acid level in the blood of the patient in need of such treatment is greater than or equal to about 360 μM, as measured in blood serum.

10. The method of claim 8, wherein the amount of scyllo-inositol administered ranges from about 150 mg/day to about 7000 mg/day.

11. The method of claim 8, wherein scyllo-inositol is administered in a unit dosage form.

12. The method of claim 11, wherein the unit dosage form is an immediate release dosage form or an extended release dosage form.

13. The method of claim 11, where the unit dosage form is a gastric retentive dosage form.

14. The method of claim 11, wherein the unit dosage form contains 150 mg, 250 mg, 500 mg, 750 mg, 800 mg, 1000 mg or 2000 mg of scyllo-inositol.

15. A method of treating gout in a patient in need of such treatment comprising administering to the patient a therapeutically effective amount of scyllo-inositol.

16. The method of claim 15, wherein the amount of scyllo-inositol administered ranges from about 150 mg/day to about 7000 mg/day.

17. The method of claim 15, wherein scyllo-inositol is administered in a unit dosage form.

18. The method of claim 17, wherein the unit dosage form is an immediate release dosage form or an extended release dosage form.

19. The method of claim 17, wherein the unit dosage form is a gastric retentive dosage form.

20. The method of claim 17, wherein the unit dosage form contains 150 mg, 250 mg, 500 mg, 750 mg, 800 mg, 1000 mg or 2000 mg of scyllo-inositol.

21. A method of treating a disease state in which hyperuricemia is a risk factor in a patient in need of such treatment comprising administering a uric acid lowering amount of scyllo-inositol to the patient.

22. The method of claim 21, wherein the disease state is chosen from atherosclerosis, arteriolosclerosis, renal disease, cardiovascular disease, metabolic syndrome, urate lithiasis, and hypertension.

23. The method of claim 21, wherein the amount of scyllo-inositol administered ranges from about 150 mg/day to about 7000 mg/day.

24. The method of claim 21, wherein scyllo-inositol is administered in a unit dosage form.

25. The method of claim 24, wherein the unit dosage form is an immediate release dosage form or an extended release dosage form.

26. The method of claim 25, wherein the extended release dosage form is a gastric retentive dosage form.

27. The method of claim 24, wherein the unit dosage form contains 150 mg, 250 mg, 500 mg, 750 mg, 800 mg, 1000 mg or 2000 mg of scyllo-inositol.

28. A pharmaceutical composition for decreasing or maintaining uric acid levels in at least one tissue or organ, blood, serum, urine, or combinations thereof or treating a condition associated with aberrant levels of uric acid comprising therapeutically effective amounts of scyllo-inositol and at least one pharmaceutically acceptable component chosen from a carrier, an excipient, and a vehicle.

29. A pharmaceutical composition comprising an amount of scyllo-inositol effective to lower the uric acid level in a mammal's blood compared to a baseline level and at least one pharmaceutically acceptable component chosen from a carrier, an excipient, and a vehicle.

30. Use of scyllo-inositol in the preparation of a medicament for decreasing or maintaining uric acid levels in one or more tissues or organs, blood, serum, urine or combinations thereof or for treating a condition associated with aberrant levels of uric acid.

31. A kit for decreasing or maintaining uric acid levels in one or more tissues or organs, blood, serum, urine or combinations thereof or treating a condition associated with aberrant levels of uric acid comprising scyllo-inositol, and optionally one or more second therapeutic agent

Figure 1

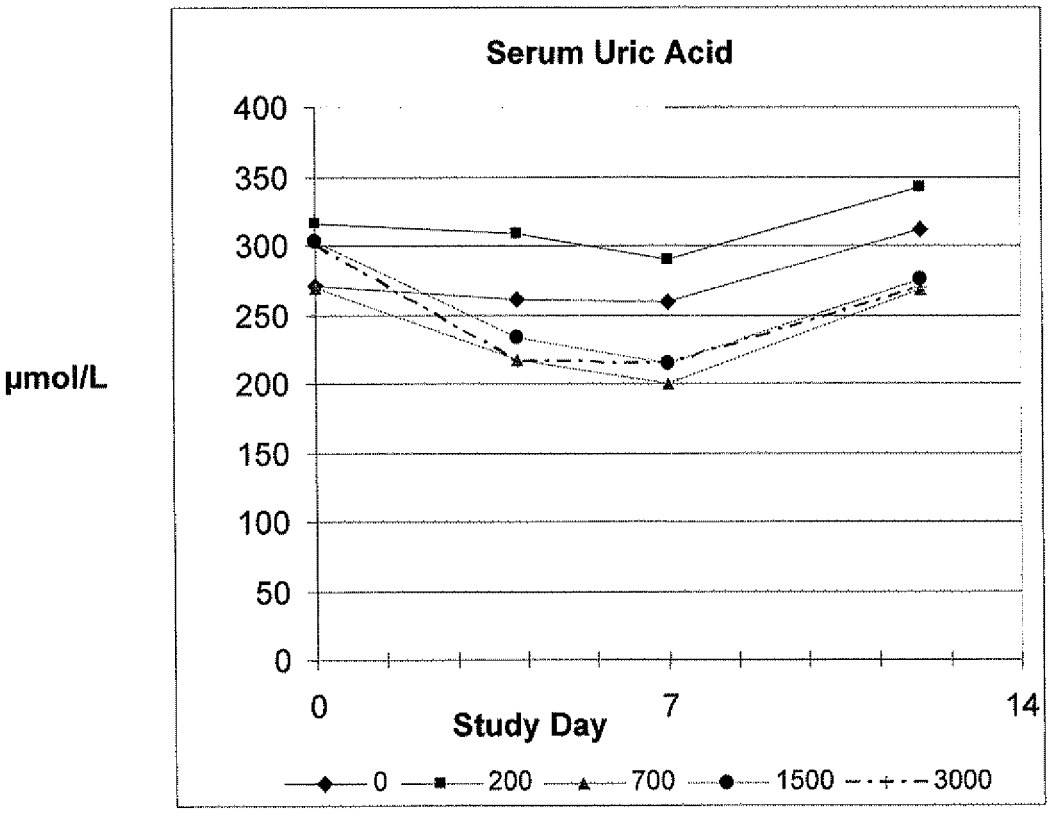
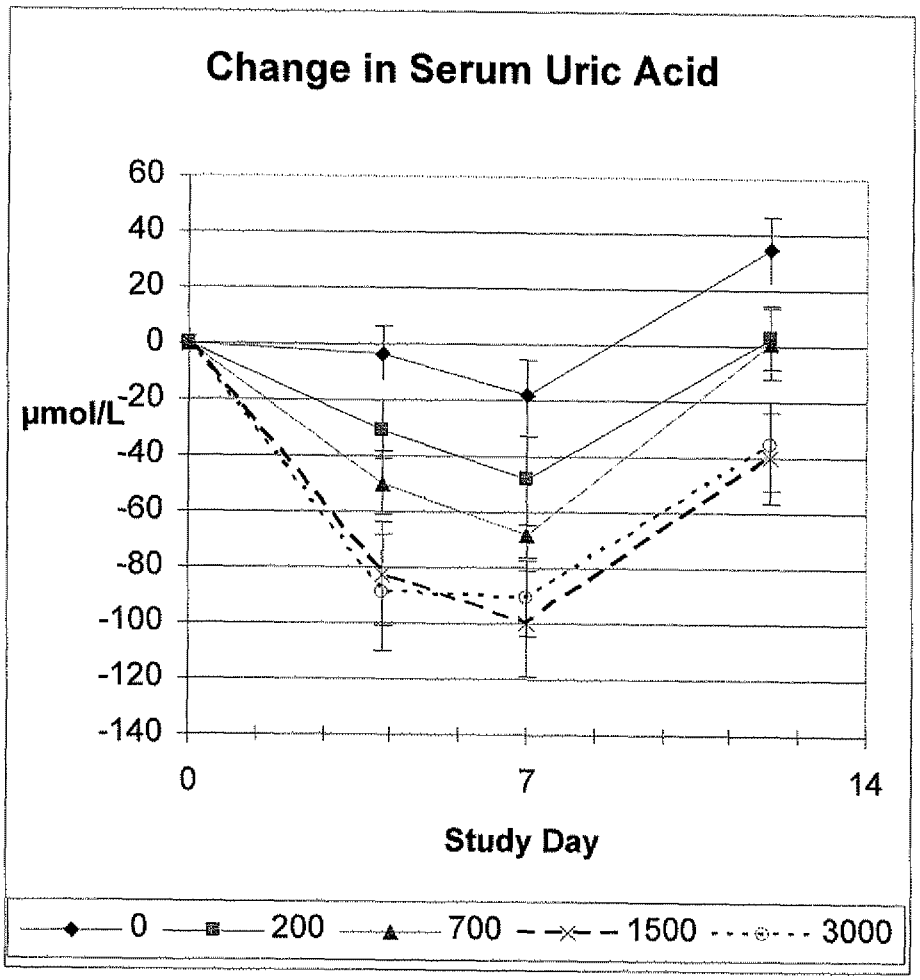

Serum Uric Acid
µmol/L
400
350
300
250
200
150
100
50
0
0
7
14
Study Day
0
200
700
1500
3000

Figure 2


Change in Serum Uric Acid
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
µmol/L
0
7
14
Study Day
0
200
700
1500
3000

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/057003

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/7004 A61P3/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/053428 A (MCLAURIN JOANNE [CA]) 26 May 2006 (2006-05-26) claims; examples	28-29,31
X	WO 98/57620 A (CEDARS SINAI MEDICAL CENTER [US]) 23 December 1998 (1998-12-23) page 5, lines 16-19; claims	28-29,31

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 February 2010	17/02/2010

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/057003

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006053428 A	26-05-2006	AU 2005306531 A1	26-05-2006
		BR PI0517733 A	21-10-2008
		CA 2588423 A1	26-05-2006
		CN 101102779 A	09-01-2008
		EP 1824496 A1	29-08-2007
		JP 2008520589 T	19-06-2008
		US 2008306166 A1	11-12-2008
		ZA 200704872 A	31-12-2008
WO 9857620 A	23-12-1998	AU 7968398 A	04-01-1999
		US 5998485 A	07-12-1999