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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
2 February 2017 (02.02.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/017677 A1

(51) International Patent Classification:
A61K 31/20 (2006.01) *A61P 1/16* (2006.01)
A61K 31/59 (2006.01)

(21) International Application Number:
PCT/IL2016/050816

(22) International Filing Date:
26 July 2016 (26.07.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
240157 27 July 2015 (27.07.2015) IL

(71) Applicant: **GALMED RESEARCH AND DEVELOPMENT LTD.** [IL/IL]; 16 Ze'ev Tyomkin Street (4th Flr), 6578317 Tel Aviv (IL).

(72) Inventors: **BAHARAFF, Allen**; 7 Hayutman Street, 6215441 Tel Aviv (IL). **HALPERN, Maya**; 16 Barcan Street, 15241 Kfar Tavor (IL).

(74) Agents: **WEBB, Cynthia** et al.; WEBB & CO., P.O. Box 2189, 7612101 Rehovot (IL).

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

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

Published:

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

WO 2017/017677 A1

(54) **Title**: COMBINATION TREATMENT FOR LIVER DISEASE

(57) **Abstract**: Embodiments of the invention relate to combination therapy for liver disease comprising an amount of Aramchol or a pharmaceutically acceptable salt thereof in combination with an amount of vitamin D receptor (VDR) agonist to treat the disease. The liver disease may be non- alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH). Compositions comprising Aramchol and VDR agonist are also provided.

COMBINATION TREATMENT FOR LIVER DISEASE

FIELD OF THE INVENTION

Embodiments of the invention relate to compositions and methods for treatment of liver disease, in particular non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

BACKGROUND OF THE INVENTION

NAFLD is a liver disease in which excessive fat accumulates in the liver. It may be demonstrated histologically by presence of vesicular fat droplets in the liver tissue. NAFLD may be detected by blood tests indicating abnormal liver function.

NASH is a severe form of NAFLD, in which the fat accumulation in the liver is accompanied by inflammation, necrosis and eventually fibrosis of the liver. Both NASH and NAFLD are commonly associated with excessive dietary intake, obesity and a variety of other causes other than excess alcohol consumption. The excess fibrosis which is the result of inflammation and liver cell necrosis in NASH may lead to cirrhosis, potentially leading to liver dysfunction, hepatocarcinoma and/or death. Patients with NASH may also be prone to develop other complications such as myocardial infarction or stroke. NASH is a multi-factorial disease whose pathophysiology not completely understood. It is therefore difficult to predict which classes of drugs, through which mechanism of action, will improve the hepatic features and prevent complications associated with the disease.

Vitamin D is a secosteroid hormone regulating mineral metabolism. The two major forms of vitamin D are Vitamin D2 (ergocalciferol), produced by certain phytoplankton, invertebrates and yeast, and vitamin D3 (cholecalciferol), produced in the skin of most vertebrates following to ultraviolet (UV) irradiation. The vitamin D receptor (VDR), also known as the calcitriol receptor and NR1I1 (nuclear receptor subfamily 1, group I, member 1), is a member of the nuclear receptor family of transcription factors. VDR has four major domains that interact to confer ligand-activated transcription factor activity: a ligand-binding domain, a retinoid X receptor (RXR) heterodimerization domain, a DNA binding domain to vitamin D response elements, and a recruitment domain of VDR coregulators. Upon activation by vitamin D, the VDR forms a heterodimer with the retinoid-X receptor and binds to hormone response elements on DNA resulting in expression or trans-repression of specific gene products (Kwok *et al.*, Hepatology, Vol. 58, No. 3, 2013).

Although the leading physiological function of vitamin D is to regulate mineral and skeletal homeostasis, putative properties of this vitamin, in regulating cell proliferation, differentiation and apoptosis as well as immune-cells regulation, have been suggested. VDR has also been suggested as a negative regulator of the transforming growth factor beta (TGF-β)/Smad signaling and fibroblast activation in models of systemic sclerosis (Zerr *et al.*, Ann Rheum Dis 2014; 0:1-8) and in hepatic stellate cells (HSC) of certain genotypes. Various vitamin D analogs, acting as VDR agonists, have been developed and are available commercially. Some of these analogs have been suggested to suppress HSC proliferation in cultured HSC from rats (Eliades et al., World J Gastroenterol 2015; 21(6): 1718-1727).

Epidemiological studies (Eliades et al 2013, Aliment Pharmacol Ther 2013; 38: 246-254; Barchetta *et al* Hepatology 2012;56:2180-2187) suggested that serum 25-hydroxy-vitamin D3 [25(OH)D3] levels and/or VDR expression in hepatocytes are inversely associated with chronic liver diseases including NAFLD. These publications disclose that the directionality of this association cannot be determined from the cross-sectional studies, and that demonstration of a causal role is warranted. One of the confounders suggested relates to both NAFLD and vitamin D deficiency being associated with a sedentary indoor lifestyle (Kwok *et al.*, *ibid*).

Since patients with NAFLD may be more likely to be vitamin D deficient, and in view of pre-clinical studies suggesting the involvement of VDR in certain immunologic, hormonal and cellular pathways, it was suggested to evaluate the effects of vitamin D supplementation on disease progression. However, clinical trial results were largely inconclusive and controversial. In addition, clinical use of vitamin D repletion was considered to be limited by dose-limiting hypercalcemia that results from the pharmacological doses of vitamin D required to obtain similar immunologic, hormonal, and cellular effects seen in the pre-clinical studies (Eliades et al. 2015, *ibid,* Kwok et al., *ibid*).

Fatty acid bile salt conjugates, referred to also as Fatty Acid Bile Acid Conjugates (FABACs), are a family of synthetic molecules that may be used to improve conditions related to bile acids or cholesterol metabolism. FABACs are believed to lower blood cholesterol concentration, reduce liver fat levels and dissolve gallstones (Gilat et al., Hepatology 2003; 38: 436-442; and Gilat et al., Hepatology 2002; 35: 597-600). FABAC include *inter alia* 3β-arachidylamido-7α,12α-dihydroxy-5β-cholan-24-oic acid, also known as Aramchol.

US Patents 6,384,024, 6,395,722, 6,589,946 disclose use of certain FABACs in dissolving cholesterol gallstones in bile and treating arteriosclerosis. These and additional FABACs were disclosed in US Patents 7,501,403, 8,975,246 and 8,110,564 for use in treating fatty liver, in reducing blood cholesterol levels and in treating hyperglycemia, diabetes, insulin

resistance and obesity. Further therapeutic uses of FABACs are disclosed in Safadi *et al.* (*Clin Gastroenterol Hepatol.* 2014 Dec;12(12):2085-91) and in WO 2015/019358 and WO 2015/019359, and amine salts of certain FABACs are disclosed in WO 2015/083164.

Currently, there are few therapies suggested to slow down or alter the course of disease progression in NAFLD or NASH. For example, U.S. Pat. No. 8,865,641 discloses a method of treating a fatty liver disease in a subject, comprising administering to the subject an effective amount of a cholinergic pathway stimulating agent, such as a nicotinic receptor agonist, a muscarinic receptor agonist, a cholinesterase inhibitor and an antagonist of presynaptic acetylcholine autoreceptors. U.S. Pat. No. 9,012,509 discloses methods of treating NAFLD and/or NASH, and/or negative effects of each thereof by administering phenoxyalkylcarboxylic acids such as MN-001 and MN-002. WO 2015/053379 discloses methods for treating a fatty liver disease or disorder in a subject in need thereof, particularly in pre-menopausal women, comprising administering to the subject omega 3 fatty acids or derivatives thereof such as ethyl eicosapentanoate, eicosapentaenoic acid, or pharmaceutically acceptable amides, salts, ester or phospholipids thereof. This publication further suggests administering these agents in combination with various additional drugs, vitamins and antioxidants.

There is no approved treatment for NAFLD or NASH to date. Accordingly, there remains a medical need for providing effective treatment for these conditions.

SUMMARY OF THE INVENTION

Embodiments of the invention relate to compositions, methods, pharmaceutical packages and combined preparations for treatment of liver disease, in particular non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). The compositions, methods, pharmaceutical packages and combined preparations according to these embodiments employ the use of a combination of a Fatty Acid Bile Acid Conjugate (FABAC) with a vitamin D receptor (VDR) agonist, or salts thereof. According to advantageous embodiments, the use of Aramchol in combination with a VDR agonist such as vitamin D3 or a precursor, analog or active metabolite thereof is contemplated.

According to one aspect, the invention relates to a therapeutic combination of Aramchol or a pharmaceutically acceptable salt thereof and a VDR agonist (e.g. in the form of a pharmaceutically acceptable salt thereof), for use in the treatment of a liver disease selected from the group consisting of NASH and NAFLD in a patient in need thereof.

Aramchol (3β-arachidylamido-7α,12α-dihydroxy-5β-cholan-24-oic acid) is a bile acid/ fatty acid conjugate comprising an arachidic acid moiety and a cholic acid moiety. Aramchol is described in United States Patent Numbers 6,384,024, 6,395,722, 6,589,946, 7,501,403, 8,110,564 and 8,975,246, incorporated herein by reference.

The vitamin D receptor (VDR), also known as the calcitriol receptor, is a nuclear receptor known to be involved in, inter alia, mineral (such as calcium) metabolism, the neuromuscular system and the immune response. VDR agonists include, but are not limited to an agent or agents selected from the group consisting of: calciferol, alfacalcidol (1α(OH)D_3, 1-hydroxycholecalciferol), 1,25-dihydroxyvitamin D_3, ergocalciferol (Vitamin D_2), cholecalciferol (Vitamin D_3), calcitriol (1,25-dihydroxycholecalciferol), 22-dihydroergocalciferol (Vitamin D_4), sitocalciferol (Vitamin D_5), dihydrotachysterol, calcipotriol, tacalcitol 1,24-dihydroxyvitamin D_3 and paricalcitol.

Aramchol, as a monotherapy, may reduce liver fat infiltration in animals fed a high fat diet, through reduction of fatty acid synthesis and inhibition of stearoyl CoA desaturase activity. VDR agonists, as a monotherapy, may exert anti-fibrotic properties. Without being bound by theory, combination therapy comprising Aramchol with a VDR agonist according to the invention may provide an improved and preferably greater than additive effect in NAFLD and/or NASH patients, e.g. in treating and/or preventing development of hepatic fibrosis.

In another aspect, the invention provides a method for treatment of disease, selected from the group consisting of NAFLD and NASH, in a patient in need thereof, comprising administering to the patient an amount of Aramchol or a pharmaceutically acceptable salt thereof in combination with an amount of a VDR agonist or a pharmaceutically acceptable salt thereof to treat the disease.

According to another aspect, the invention relates to the use of Aramchol or a pharmaceutically acceptable salt thereof in combination with a VDR agonist, for the preparation of a medicament for the treatment of a liver disease selected from the group consisting of NASH and NAFLD in a patient in need thereof.

In another aspect, there is provided a pharmaceutical composition comprising Aramchol or a pharmaceutically acceptable salt thereof in combination with a VDR agonist as the active ingredients, and optionally pharmaceutically acceptable carriers, excipients and/or diluents.

In another aspect the invention provides a package comprising a) a first pharmaceutical composition comprising Aramchol or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier; b) a second pharmaceutical composition comprising a

VDR agonist and a pharmaceutically acceptable carrier; and c) instructions for use of the first and second pharmaceutical compositions in combination to treat a subject afflicted with a liver disease, preferably NAFLD or NASH.

In one embodiment, the liver disease treated by the compositions, methods and combinations of the invention is NAFLD. In another embodiment, the liver disease is NASH. In another embodiment, the medicament or combination consists of Aramchol and the VDR agonist as active ingredients.

In another embodiment, the combination may be for simultaneous, separate or sequential use in the treatment of the liver disease. In another embodiment, Aramchol and the VDR agonist are provided in a single dosage form. In a particular embodiment, Aramchol and the VDR agonist are provided in an oral dosage form. In another embodiment Aramchol and the VDR agonist are administered in the form of a single oral dosage form.

In other embodiments, the medicament or combination comprises between about 100 and 600 miligrams (mg) of Aramchol free acid or equivalent amount of salt thereof. In another embodiment, the method comprises administering a daily dose of 100-600 mg of Aramchol free acid or equivalent amount of salt thereof. In other embodiments, the medicament or combination comprises between about 50-15,000 International Units (IU) of the VDR agonist. In other exemplary embodiments, the method, medicament or combination is adapted for providing a daily dosage of between about 400 mg and 600 mg of Aramchol or equivalent amount of a salt thereof and a daily dose of between about 400-10,000 IU of the VDR agonist. In certain embodiments, the composition, medicament or combination is formulated for oral administration.

According to certain embodiments, Aramchol is in the form of Aramchol free acid. In other embodiments, Aramchol is in the form of an amine-based salt, including, but not limited to, meglumine, lysine and tromethamine Aramchol salt. Each possibility represents a separate embodiment of the invention.

According to particular embodiments, the VDR agonist may be selected from the group consisting of calciferol, alfacalcidol, 1,25-dihydroxyvitamin D_3, Vitamin D_2, Vitamin D_3, calcitriol, Vitamin D_4, Vitamin D_5, dihydrotachysterol, calcipotriol, tacalcitol 1,24-dihydroxyvitamin D_3 and paricalcitol. Each possibility represents a separate embodiment of the invention. In another embodiment the VDR agonist is vitamin D3 or a precursor, analog or active metabolite thereof. In another embodiment said VDR agonist is selected from the group consisting of: vitamin D3, a vitamin D metabolite, and a vitamin D3 precursor. In a particular

embodiment, the VDR agonist comprises cholecalciferol, e.g. at an amount of between about 400 and 5,000 IU. In another particular embodiment the method comprises (or the combination is adapted for) administering a daily dose of 400-5,000 IU of cholecalciferol (e.g. 500-4500, 1000-4000 or 1500-4000). In another particular embodiment, the VDR agonist comprises alfacalcidol, e.g. at an amount of between about 0.25 and 1 microgram. In another particular embodiment the method comprises (or the combination is adapted for) administering a daily dose 0.25 and 1 microgram of alfacalcidol.

In another embodiment the combinations of the invention may be administered in concurrent or sequential combination with calcium supplementation (e.g. in the form of a pharmacologically acceptable salt thereof such as calcium citrate). In some embodiments, the calcium supplementation may be adapted for providing a daily dose of 100-1000 mg. For example, without limitation, the calcium supplementation comprises 150-750 mg, e.g. 500 mg of elemental calcium in the form of calcium citrate. Thus, in other embodiments, the methods of the invention further comprise administering calcium to said patient. In another embodiment, the methods comprise, or the combinations, compositions and packages are adapted for administering a daily dose of 100-1000 mg of elemental calcium in the form of a carbonate, citrate, gluconate, succinate or citrate maleate. In another embodiment the methods comprise (or the combinations, compositions and packages are adapted for) administering a daily dose of 150-750 mg of elemental calcium in the form of calcium citrate.

In another particular embodiment, the methods comprise (or the combinations, compositions and packages are adapted for) administering a daily dose of 300-500 mg of Aramchol or an equivalent amount of a salt thereof, a daily dose of 400-5,000 IU of cholecalciferol and a daily dose of 150-750 mg of elemental calcium in the form of calcium citrate.

In other embodiments, the combination, medicament, composition or method may be used for the treatment of liver fibrosis in the patient. In a particular embodiment, the fibrosis is in a patient suffering from NASH.

This summary is provided to introduce a selection of concepts in a simplified form that are further described below in the detailed description. This summary is not intended to identify key features or essential features of the claimed subject matter, nor is it intended to be used to limit the scope of the claimed subject matter.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to compositions, methods, pharmaceutical packages, therapeutic combinations and combined preparations useful for treatment of liver disease, in particular non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). Embodiments of the invention include or employ the use of a combination of a Fatty Acid Bile Acid Conjugate (FABAC) such as Aramchol with a vitamin D receptor (VDR) agonist, or salts thereof. According to advantageous embodiments, the use of Aramchol or a pharmaceutically acceptable salt thereof in combination with vitamin D3 or a precursor, analog or active metabolite thereof is contemplated.

Compounds and combinations

Embodiments of the invention relate to treatments of disease using Aramchol or a pharmaceutically acceptable salt thereof in combination with a VDR agonist. Other embodiments of the invention relate to compositions and pharmaceutical packages comprising Aramchol or a pharmaceutically acceptable salt thereof in combination with a VDR agonist. "In combination" or "combination" refer to both drugs being substantially effective in the body at a same time. Both drugs can be administered substantially at the same time, or both drugs can be administered at different times but have effect on the body at the same time. For example, "in combination" includes administering Aramchol before the administration of the VDR agonist, and subsequently administering the VDR agonist while functioning of Aramchol in the body is substantially extant. In addition, "in combination" includes administering the VDR agonist before the administration of Aramchol, and subsequently administering the Aramchol while functioning of the VDR agonist in the body is substantially extant. When a pharmaceutical composition is described as containing Aramchol and a VDR agonist in combination, this term refers to both agents being concurrently present in the composition.

While subjects treated with the compositions and methods of the invention may optionally be under treatment with other therapeutic agents (e.g. for ameliorating other unrelated conditions), the invention surprisingly demonstrates that Aramchol, in combination with a VDR agonist, provides a surprisingly beneficial treatment for NAFLD/NASH patients in the absence of adjunct therapy. The terms "in combination" and "combination" may further relate to the advantageous use of Aramchol and a VDR agonist in the absence of concomitant treatment for liver diseases such as NAFLD or NASH. According to some embodiments, concomitant treatment with fatty acids such as ethyl eicosapentanoate, eicosapentaenoic acid, and their amides, salts and phospholipids is explicitly excluded. In other embodiment,

concomitant treatment with bile acids such as ursodeoxycholic acid and lithocholic acid is excluded. According to certain preferred embodiments, the combinations of the invention consist essentially of Aramchol and VDR agonists as active ingredients. For example, the composition may further contain calcium or other additives for enhancing the absorption of the VDR agonist and/or Aramchol. In other embodiments the combinations of the invention consist of Aramchol and VDR agonists as sole active ingredients.

VDR agonists referred to herein include vitamin D compounds (forms) as described herein and vitamin D analogs and active metabolites thereof that induce ligand-mediated VDR activation in vivo. As used herein, the term further includes vitamin D precursors (prodrugs), capable of being converted to an agonist of the VDR by one or more enzymes. In certain, non-limiting examples, that enzyme is CYP27B1. Specific, non-limiting examples of precursors include vitamin D3 (cholecalciferol), 25-hydroxy-vitamin D3 (25-OH-D3) (calcidiol), as well as vitamin D2 (ergocalciferol) and its precursors. Vitamin D active metabolites include VDR ligands (that activate the receptor directly upon binding) such as calcitriol, and other compounds formed by vitamin D metabolism that retain the ability to induce ligand-mediated VDR activation (either directly or upon further enzymatic processing).

Vitamin D analogs referred to herein are synthetic compounds comprising a vitamin D scaffold with side chain modifications and/or modifications of the scaffold itself, that exhibit a biological activity on the vitamin D receptor comparable to that of naturally occurring vitamin D compounds. This term may further refer specifically to a molecule having a 9,10-seco-steroidal structure, and similar chemical or biological activity to vitamin D3. Certain vitamin D analogs having improved properties, such as reduced risk for hypercalcemia, have been reported, non-limitative examples of which include alfacalcidol, calcipotriol (Dovonex), 19-nor-1,25(OH)(2)D(2) (Zemplar), doxercalciferol (Hectorol), and 22-oxacalcitriol (Maxacalcitol). In some embodiments, VDR agonist is a vitamin D3 analog that is a non-endogenous product of a chemical synthetic reaction which uses a substrate other than any of the naturally occurring following group: vitamin D3, a vitamin D metabolite, a vitamin D3 precursor. A non-limiting example of a vitamin D3 analog is calcipotriol.

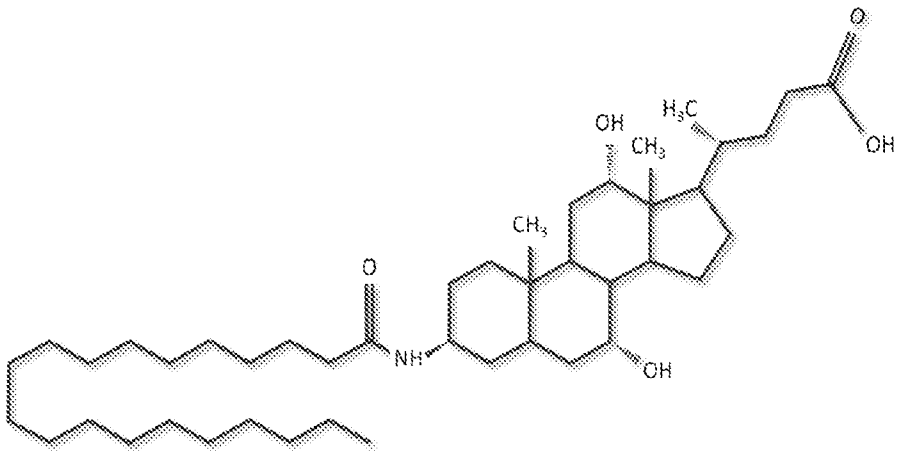
While the use of vitamin D compounds (e.g. vitamin D3) is preferred according to certain advantageous embodiments of the invention, the use of vitamin D analogs may be considered in other embodiments, for example in patients with renal dysfunction that may impair vitamin D metabolism.

According to certain embodiments, the VDR agonist is an agent or agents selected from the group consisting of: calciferol, alfacalcidol ($1\alpha(OH)D_3$, 1-hydroxycholecalciferol), 1,25-

dihydroxyvitamin D_3, ergocalciferol (Vitamin D_2), cholecalciferol (Vitamin D_3), calcitriol (1,25-dihydroxycholecalciferol), 22-dihydroergocalciferol (Vitamin D_4), sitocalciferol (Vitamin D_5), dihydrotachysterol, calcipotriol, tacalcitol 1,24-dihydroxyvitamin D_3 and paricalcitol. In another embodiment said VDR agonist is vitamin D3 or a precursor, analog or active metabolite thereof (e.g. calcitriol). In another embodiment said VDR agonist is selected from the group consisting of: vitamin D3, a vitamin D metabolite, and a vitamin D3 precursor. In a particular embodiment said VDR agonist is cholecalciferol (vitamin D3). Each possibility represents a separate embodiment of the invention.

VDR agonists may be synthesized by readily available methods. For example, without limitation, cholecalciferol may be synthesized by the ultraviolet irradiation of 7-dehydrocholesterol extracted from lanolin found in sheep's wool. Various VDR agonists are commercially available. For example, calcitriol is marketed under various trade names including Rocaltrol (Roche), Calcijex (Abbott), Decostriol (Mibe, Jesalis), Biowoz (Solmarc) and Vectical (Galderma), Rolsical (Sun Pharma). Ergocalciferol is manufactured and marketed under various names, including Deltalin (Eli Lilly and Company), Drisdol (Sanofi-Synthelabo) and Calcidol (Patrin Pharma). In addition, vitamin D formulations further comprising calcium supplements are commercially available.

Aramchol is chemically named 3β-arachidylamido-7α,12α-dihydroxy-5β-cholan-24-oic acid, and is represented by the following chemical structure:



According to an embodiment of the invention, the combinations, compositions, methods and packages of the invention may comprise Aramchol in its free acid form. According to an embodiment of the invention, Aramchol is in its salt form. The salt may be an amine-based salt.

The amine-based salt may be selected from the group consisting of meglumine, lysine and tromethamine salts.

According to an embodiment of the invention, an amount of Aramchol or a pharmaceutically acceptable salt thereof is provided in combination with an amount of VDR agonist in a single dosage form. According to an embodiment of the invention, an amount of Aramchol or a pharmaceutically acceptable salt thereof is provided in combination with an amount of VDR agonist in separate dosage forms.

Other embodiments of the invention relate to compositions, methods and packages for treatment of liver disease, in particular NAFLD and NASH, employing the use of a combination of a Fatty Acid Bile Acid Conjugate (FABAC) with a VDR agonist, or salts thereof. For example, in some embodiments, the compositions, methods and packages may comprise Aramchol and at least one additional FABAC in combination with one or more VDR agonists.

According to some embodiments, the FABAC is of Formula I:

W - X - G (I)

wherein G represents a bile acid or a bile salt radical thereof; W represents one or two fatty acid radicals having 6-22 carbon atoms; and X represents a bonding member selected from the group consisting of: a heteroatom, a direct C-C bond and a C=C bond. Each possibility represents a separate embodiment of the present invention.

According to some embodiments, the bonding member is selected from the group consisting of: NH, P, S, O and a direct C-C or C=C bond. Each possibility represents a separate embodiment of the present invention. According to some embodiments, the bonding member is NH.

According to some embodiments, each of said one or two fatty acid radicals is a radical of a fatty acid selected from the group consisting of: arachidylic acid, stearic acid, behenic acid, palmitic acid, arachidonic acid, eicosapentaenoic acid and oleic acid. Each possibility represents a separate embodiment of the present invention. According to some embodiments, said one or two fatty acid radicals are radicals of arachidylic acid. Each possibility represents a separate embodiment of the present invention.

According to some embodiments, W represents two fatty acid radicals, each independently comprises 6-22 carbon atoms; and wherein each of said fatty acid radicals is independently bound to a bonding member X selected from the group consisting of: a heteroatom, a direct C-C bond and a C=C bond. According to some embodiments, W represents a single fatty acid radical.

According to some embodiments, the bile acid is selected from the group consisting of: cholic acid, ursodeoxycholic acid, chenodeoxycholic acid, deoxycholic acid, lithocholic acid and derivatives thereof. Each possibility represents a separate embodiment of the present invention. In another embodiment the bile acid is cholic acid, chenodeoxycholic acid, or deoxycholic acid. In another embodiment the bile acid is other than ursodeoxycholic acid and lithocholic acid. According to some embodiments, the bile acid is cholic acid.

According to some embodiments, the FABAC is 3β-arachidylamido-7α, 12α-dihydroxy-5β-cholan-24-oic acid.

In another embodiment the combinations of the invention may be provided or administered in concurrent or sequential combination with calcium. In some embodiments, the calcium in the form of a pharmacologically acceptable salt thereof, including, but not limited to a carbonate, citrate, gluconate, succinate or citrate maleate. According to certain embodiments, the use of calcium citrate may be advantageous in providing enhanced absorption and/or improved safety, e.g. with respect to renal toxicity and kidney stone formation. According to other embodiments, the calcium is amorphous, e.g. amorphous calcium carbonate. In other embodiments, the calcium is at an amount (e.g. daily dose) of 100-1000 mg, e.g. 100-1000 mg, 150-750 or 250-500 mg of elemental calcium in the form of a carbonate, citrate, gluconate, succinate or citrate maleate. According to certain particular embodiments said calcium is 150-750, 250-650 or 350-550 mg of elemental calcium in the form of calcium citrate. Each possibility represents a separate embodiment of the invention.

Pharmaceutical compositions

Further embodiments of the invention relate to pharmaceutical compositions comprising Aramchol or a pharmaceutically acceptable salt thereof and a VDR agonist. Such pharmaceutical compositions may be administered to patients suffering from NAFLD and/or NASH according to embodiments of the invention.

According to an embodiment of the invention, a package comprising a pharmaceutical dosage form comprising Aramchol or a pharmaceutically acceptable salt thereof and a pharmaceutical dosage form comprising VDR agonist is provided. The package may further comprise instructions to administer the pharmaceutically dosage forms to a patient in need thereof.

Aramchol or a pharmaceutically acceptable salt thereof in combination with an amount of VDR agonist may be provided in a pharmaceutical composition or separate pharmaceutical compositions via oral administration.

The pharmaceutical compositions according to an embodiment of the invention may be conveniently presented in unit dosage form and may be prepared by any of methods well known in the art of pharmacy. In an embodiment of the invention, the unit dosage form is in the form of a tablet, capsule, lozenge, wafer, powder or liquid form. The compositions of the present invention are generally administered in the form of a pharmaceutical composition comprising at least one active component together with a pharmaceutically acceptable carrier or diluent.

For oral administration, a pharmaceutical composition can take the form of solutions, suspensions, tablets, pills, capsules, powders, and the like. Tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate are employed along with various disintegrants.

Suitable carriers for oral administration are well known in the art. Compositions 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 as desired, to obtain tablets or dragee cores. Non-limiting examples of suitable excipients include fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol, cellulose preparations such as, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, and sodium carbomethylcellulose, and/or physiologically acceptable polymers such as polyvinylpyrrolidone (PVP).

If desired, disintegrating agents, such as cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate, may be added. Capsules and cartridges of, for example, gelatin for use in a dispenser may be formulated containing a powder mix of the compound and a suitable powder base, such as lactose or starch.

Solid dosage forms for oral administration include without limitation capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as it normal practice, additional substances other than inert diluents, e.g., lubricating, agents. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings. The term “enteric coating”, as used herein, refers to a coating which controls the location of composition absorption within the digestive system. Non-limiting examples for materials used for enteric coating are fatty acids, waxes, plant fibers or plastics.

Liquid dosage forms for oral administration may further contain adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring and perfuming agents. The compositions according to embodiments of this invention may also be administered

in a controlled release formulation such as a slow release or a fast release formulation. Such controlled release dosage composition may be prepared using methods known to those skilled in the art.

Pharmaceutical compositions according to embodiments of the invention may contain an active amount of 0.1%-95% (by weight basis relative to total composition) of the Aramchol and VDR agonist, preferably 1%-70%.

In another embodiment there is provided a pharmaceutical composition comprising Aramchol or a pharmaceutically acceptable salt thereof in combination with a VDR agonist as the active ingredients, and optionally pharmaceutically acceptable carriers, excipients and/or diluents. In another embodiment said composition is formulated as an oral (e.g. solid) dosage form.

In another embodiment the VDR agonist is selected from the group consisting of calciferol, alfacalcidol, 1,25-dihydroxyvitamin D3, Vitamin D2, Vitamin D3, calcitriol, Vitamin D4, Vitamin D5, dihydrotachysterol, calcipotriol, tacalcitol 1,24-dihydroxyvitamin D3 and paricalcitol. In another embodiment the VDR agonist is vitamin D3 or a precursor, analog or active metabolite thereof. In another embodiment said VDR agonist is selected from the group consisting of: vitamin D3, a vitamin D metabolite, and a vitamin D3 precursor. In another embodiment the VDR agonist comprises cholecalciferol (vitamin D3). In another embodiment the composition comprises 400-5,000 IU of cholecalciferol in unit dosage form. In another embodiment the composition comprises 500-4,000, 750-4500, 1000-4000 or 2000-5000 IU of cholecalciferol in unit dosage form. In another embodiment the VDR agonist comprises alfacalcidol. In another embodiment the composition comprises alfacalcidol at an amount of between about 0.25 and 1 microgram.

In another embodiment Aramchol is in the form of Aramchol free acid. In another embodiment Aramchol is in the form of a meglumine, lysine or tromethamine Aramchol salt. In another embodiment the composition comprises 100-600 mg of Aramchol free acid or equivalent amount of salt thereof in unit dosage form.

In another embodiment the composition consists essentially of Aramchol and the VDR agonist. In another embodiment the composition further comprises calcium. In another embodiment said composition comprises 100-1000 mg, 150-750 or 250-500 mg of elemental calcium in the form of a carbonate, citrate, gluconate, succinate or citrate maleate. In another embodiment said composition comprises 150-750 mg of elemental calcium in the form of calcium citrate. In another embodiment said composition does not comprise calcium. In another

embodiment said composition consists of Aramchol and the VDR agonist (e.g. vitamin D3 or a precursor, analog or active metabolite thereof) as sole active ingredients.

In another embodiment said composition is adapted for providing a daily dosage of between about 400 mg and 600 mg of Aramchol or equivalent amount of a salt thereof and a daily dose of between about 400-10,000 IU of the VDR agonist.

As used herein, the term "about," when referring to a value or to an amount of mass, weight, time, volume, concentration or percentage is meant to encompass variations, as such variations are appropriate to perform the disclosed method or embodiment as determined by the skilled artisan. The term encompasses variations of up to ±20% and typically no more than ±10%. For example, in some embodiments, the variations may be of ±5%, ±1%, ±0.5%, or ±0.1% from the specified amount, as such variations are appropriate to perform the disclosed method.

In another embodiment said composition may comprise 300-500 mg of Aramchol or an equivalent amount of a salt thereof, 400-5,000 IU of cholecalciferol or a precursor, analog or active metabolite thereof. In another embodiment said composition may comprise 300-500 mg of Aramchol or an equivalent amount of a salt thereof, 400-5,000 IU of cholecalciferol or a precursor, analog or active metabolite thereof and 100-1000 mg of elemental calcium in the form of a carbonate, citrate, gluconate, succinate or citrate maleate. In another embodiment said composition may comprise 300-500 mg of Aramchol or an equivalent amount of a salt thereof, 400-5,000 IU of cholecalciferol and 150-750 mg of elemental calcium in the form of calcium citrate.

According to some embodiments, the composition may be used in the treatment of liver disease. According to some embodiments, the composition may be used in the treatment of NAFLD. According to some embodiments, the composition may be used in the treatment of NASH. In another embodiment said pharmaceutical composition is used in the preparation of a medicament for the treatment of liver disease, preferably NAFLD and NASH. In another embodiment the liver disease is NAFLD. In another embodiment the liver disease is NASH. In another embodiment said medicament is for the treatment of liver fibrosis in a patient in need thereof.

In another embodiment the invention provides a package comprising a) a first pharmaceutical composition comprising Aramchol or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier; b) a second pharmaceutical composition comprising a VDR agonist and a pharmaceutically acceptable carrier; and c) instructions for use

of the first and second pharmaceutical compositions in combination to treat a subject afflicted with a liver disease. In another embodiment the disease is selected from the group consisting of NAFLD and NASH. . In one embodiment the instructions are for use of the first and second pharmaceutical compositions in combination to treat a subject afflicted with NAFLD. In another embodiment the instructions are for use of the first and second pharmaceutical compositions in combination to treat a subject afflicted with NASH.

In another embodiment the VDR agonist is selected from the group consisting of calciferol, alfacalcidol, 1,25-dihydroxyvitamin D3, Vitamin D2, Vitamin D3, calcitriol, Vitamin D4, Vitamin D5, dihydrotachysterol, calcipotriol, tacalcitol 1,24-dihydroxyvitamin D3 and paricalcitol. In another embodiment the VDR agonist is vitamin D3 or a precursor, analog or active metabolite thereof. In another embodiment said VDR agonist is selected from the group consisting of: vitamin D3, a vitamin D metabolite, and a vitamin D3 precursor. In another embodiment the VDR agonist comprises cholecalciferol (vitamin D3). In another embodiment the package comprises 400-5,000 IU of cholecalciferol in unit dosage form. In another embodiment the package comprises 500-4,000, 750-4500, 1000-4000 or 2000-5000 IU of cholecalciferol in unit dosage form. In another embodiment the VDR agonist comprises alfacalcidol. In another embodiment the package comprises alfacalcidol at an amount of between about 0.25 and 1 microgram.

In another embodiment Aramchol is in the form of Aramchol free acid. In another embodiment Aramchol is in the form of a meglumine, lysine or tromethamine Aramchol salt. In another embodiment the composition comprises 100-600 mg of Aramchol free acid or equivalent amount of salt thereof in unit dosage form.

In another embodiment the package consists essentially of Aramchol and the VDR agonist. In another embodiment the package further comprises calcium. In another embodiment said package comprises 100-1000 mg, 150-750 or 250-500 mg of elemental calcium in the form of a carbonate, citrate, gluconate, succinate or citrate maleate. In another embodiment said package comprises 150-750 mg of elemental calcium in the form of calcium citrate. In another embodiment said package does not comprise calcium. In another embodiment said package consists of Aramchol and the VDR agonist (e.g. vitamin D3 or a precursor, analog or active metabolite thereof) as sole active ingredients.

In another embodiment said package is adapted for providing a daily dosage of between about 400 mg and 600 mg of Aramchol or equivalent amount of a salt thereof and a daily dose of between about 400-10,000 IU of the VDR agonist. In another embodiment said package may comprise 300-500 mg of Aramchol or an equivalent amount of a salt thereof, and 400-5,000 IU

of cholecalciferol or a precursor, analog or active metabolite thereof. In another embodiment said package may comprise 300-500 mg of Aramchol or an equivalent amount of a salt thereof, 400-5,000 IU of cholecalciferol or a precursor, analog or active metabolite thereof and 100-1000 mg of elemental calcium in the form of a carbonate, citrate, gluconate, succinate or citrate maleate. In another embodiment said package may comprise 300-500 mg of Aramchol or an equivalent amount of a salt thereof, 400-5,000 IU of cholecalciferol and 150-750 mg of elemental calcium in the form of calcium citrate.

In another embodiment, the package is used in the treatment of a liver disease selected from the group consisting of NASH and NAFLD. In another embodiment the package consists of Aramchol and the VDR agonist as the active ingredients. In another embodiment said package is for use in the treatment of liver disease, preferably NAFLD and NASH. In another embodiment the liver disease is NAFLD. In another embodiment the liver disease is NASH. In another embodiment said medicament is for the treatment of liver fibrosis in a patient in need thereof.

Subjects

The subject to be treated by the compositions and methods of the invention, also referred to herein as a patient in need thereof, is a mammalian and preferably a human subject. In certain embodiments, the subject has been diagnosed as suffering from NAFLD or NASH.

According to certain embodiments, the invention relates to treatments of liver disease with Aramchol or a pharmaceutically acceptable salt thereof in combination with VDR agonist. According to an embodiment of the invention, the liver disease is NAFLD. According to an embodiment of the invention, the liver disease is NASH. Determining the presence of liver diseases such as NAFLD and NASH is readily performed by well known diagnostic methods. For example, without limitation, the liver disease may be confirmed by one or more than one of: liver enzyme level in serum, ultrasound, liver biopsy, magnetic resonance imaging (MRI), and by known genetic and metabolic markers. According to an embodiment of the invention, the liver disease is associated with fibrosis.

Certain non-limitative examples for diagnosing NAFLD and NASH, e.g. by evaluating liver fat content and liver stiffness are presented in the Examples below. According to some non-limitative exemplary embodiments, the subject is diagnosed with proton density fat fraction (PDFF) $\geq$ 5.5% as measured by magnetic resonance imaging (MRI) using multiecho Dixon methods. In other non-limitative exemplary embodiments, said subject is afflicted with liver

fibrosis exhibiting liver stiffness (e.g. at least 3.9 kPa) measured by magnetic resonance elastography (MRE).

25-hydroxyvitamin D (25(OH)D), also known as calcifediol, is a metabolite of vitamin D, produced by hydroxylation of cholecalciferol (Vitamin D_3). According to an embodiment of the invention, a 25-hydroxyvitamin D serum level below a threshold of 12 nanograms/milliliter (ng/ml) in a subject indicates that the subject is vitamin D deficient. According to an embodiment of the invention, the threshold is 20 ng/ml of 25-hydroxyvitamin D in serum. According to some embodiments, the compositions and methods of the invention may be particularly advantageous in vitamin D deficient patients. Thus, e.g. according to these embodiments, the methods of the invention may include a step of determining whether the patient is vitamin D deficient, as described herein. Yet, according to certain other advantageous embodiments, the compositions and methods of the invention may be surprisingly effective even in vitamin D non-deficient patients, not hitherto considered to be amenable for vitamin D supplement treatment. Thus, according to certain embodiments of the invention, the patient has not been diagnosed with vitamin D deficiency. In other embodiments, the patient is vitamin D non-deficient.

According to an embodiment of the invention, methods are provided for treatment of NAFLD or NASH wherein a patient suffers from an additional condition. According to an embodiment of the invention, the additional condition is selected from the group consisting of: insulin resistance, diabetes, arteriosclerosis, metabolic syndrome, elevated triglycerides, low high density lipoprotein (HDL) levels, elevated fasting glucose levels, hypertension, acquired lipodystrophy, human immunodeficiency virus (HIV)-associated lipodystrophy and obesity. Yet according to other embodiments, the patient is not concomitantly afflicted with another condition, e.g. the conditions as detailed above. Each possibility represents a separate embodiment of the invention.

In another embodiment, the subject is not afflicted with impaired renal function or kidney stones. In another embodiment said subject is not afflicted with primary hypercalcemia or another condition that carries a risk of hypercalcemia (e.g. sarcoid, tuberculosis). In another embodiment said subject is not afflicted with inflammatory bowel disease (IDB), chronic pancreatic disease, or celiac disease. In another embodiment, said patient is not afflicted with an additional liver disease, such as autoimmune hepatitis, hepatitis B, hepatitis C, alcoholic liver disease, or hepatocellular carcinoma (HCC). In another embodiment, said patient is not afflicted with HIV. In another embodiment, said subject is not under concomitant treatment for an additional liver disease, e.g. interferon-gamma or other immunomodulating or antiviral

treatments. In another embodiment, said subject is characterized by the bAt (CCA) VDR haplotype. In another embodiment, said subject is characterized by the bat (CAA) and/or BaT (TAG) VDR haplotype. Each possibility represents a separate embodiment of the invention.

Therapeutic use

In another embodiment there is provided a method for treatment of disease, selected from the group consisting of NAFLD and NASH, in a patient in need thereof comprising administering to the patient, an amount of Aramchol or a pharmaceutically acceptable salt thereof in combination with an amount of a VDR agonist or a pharmaceutically acceptable salt thereof to treat the disease. According to an embodiment of the invention, the liver disease is fibrotic NASH. In another embodiment the invention relates to a therapeutic combination of Aramchol or a pharmaceutically acceptable salt thereof and a VDR agonist, for use in the treatment of a liver disease selected from the group consisting of NASH and NAFLD in a patient in need thereof.

Embodiments of the invention comprise administering Aramchol or a pharmaceutically acceptable salt thereof in combination with a VDR agonist (which combination may be referred to hereinafter as "the active pharmaceutical agents") in amounts (e.g. daily doses) in which there is a synergistic effect on treatment of liver disease. Methods and therapeutic uses according to embodiments of the invention comprise administering the active pharmaceutical agents in amounts in which there is a complementary effect on treatment of NAFLD and/or NASH.

According to an embodiment of the invention, the method comprises administering Aramchol or a pharmaceutically acceptable salt thereof in combination with a VDR agonist in amounts in which there is a greater than additive effect relative to treatment with one of the active pharmaceutical agents individually. It is suggested that embodiments of the invention using VDR agonists in combination with Aramchol, may show at least an additive or greater than additive effect on non-alcoholic liver disease (NAFLD and/or NASH) in treatment of fibrosis of the liver in the patient. It is suggested that embodiments of the invention using VDR agonists in combination with Aramchol, may show at least an additive or greater than additive effect on non-alcoholic liver disease (NAFLD and/or NASH) in treatment of inflammation of the liver in the patient.

In other embodiments, the use of VDR agonists in combination with Aramchol or a pharmaceutically acceptable salt thereof may provide improved therapy of NAFLD and/or NASH patients with respect to therapeutic potency and/or safety. In another embodiment, the

use of VDR agonists in combination with Aramchol or a pharmaceutically acceptable salt thereof as described herein may provide reduced risk for hypercalcemia.

According to certain embodiments, the treatment is provided in a chronic manner, as needed e.g. once, twice, three times or four times daily or weekly.

According to some embodiments, the methods and therapeutic uses are effective in improving one or more symptoms of fatty liver disease, such as reducing liver fat content and/or liver stiffness. For example, without limitation, the methods and therapeutic uses are effective in reducing PDFF to a level lower than 5.5% as measured by MRI using a multiecho Dixon method. In another non-limitative example, the methods and therapeutic uses are effective in reducing liver stiffness to a level lower than 3.9 kPa measured by MRE.

According to an embodiment of the invention, the method is effective to reduce one, or more than one of the following histological features: steatosis, lobular inflammation, hepatocellular ballooning and liver fibrosis. According to an embodiment of the invention, the method is effective in lowering alanine aminotransferase (ALT) levels. According to other embodiments, the methods of the invention may be effective in improving one or more additional parameters in a patient afflicted with fatty liver disease, e.g. parameters associated with co-morbidities of the disease. According to an embodiment of the invention, the method is effective in improving insulin resistance. The insulin resistance is optionally determined by HOMA score. According to an embodiment of the invention, the method is effective in reducing glycated haemoglobin (HbA1c) levels. According to an embodiment of the invention, the method is effective in reducing leptin adiponectin ratio. According to an embodiment of the invention, the method is effective in reducing inflammation or fibrosis in a patient. Optionally, the inflammation or fibrosis is reduced as evident from a reduction of a biomarker selected from the group consisting of: Fibrinogen, CK-18, C-reactive protein (CRP), TNFα and IL-6. According to an embodiment of the invention, the method is effective in reducing body weight in a patient. According to an embodiment of the invention, the method is effective in reducing waist circumference in a patient. According to an embodiment of the invention the combination is effective in reducing the incidence of myocardial infarction or stroke

According to an embodiment of the invention, the method or treatment comprises administering 400 mg daily of Aramchol or an equivalent amount of a pharmaceutically acceptable salt thereof. Optionally, the method or treatment comprises administering at least 600 mg daily of Aramchol or an equivalent amount of a pharmaceutically acceptable salt thereof. According to an embodiment of the invention, the method or treatment comprises administering less than 400 mg daily of Aramchol or an equivalent amount of a

pharmaceutically acceptable salt thereof. According to an embodiment of the invention, Aramchol is administered once daily.

According to an embodiment of the invention, VDR agonist is administered to a patient in need thereof in an amount of between 50-15,000 International Units (IU) per day. According to an embodiment of the invention, the VDR agonist is Vitamin D_3, and the amount administered per day is between 400 IU and 5,000 IU per day. According to an embodiment of the invention, Vitamin D_3 is administered in an amount of 500-4,000, 750-4500, 1000-4000, 1000-3000, 2000-5000 or 3000-5000 IU, e.g. 400, 600, 800, 1000, 2,000, 4,000 or 5,000 IU per day. According to an embodiment of the invention, 50,000 IU of Vitamin D_3 is administered once every 14 days. An international unit of VDR agonist is equivalent to 0.025 micrograms of cholecalciferol. According to an embodiment of the invention, the VDR agonist is alfacalcidol and the amount administered is between 0.25 and 1 microgram per day.

In some embodiments, the dose of the VDR agonist to be administered may be adjusted by the treating physician according to the change in serum 25(OH)D levels. For example, without limitation, a daily dose of 3000-5000 IU of Vitamin D_3 may be administered to a patient having a serum 25(OH)D level lower than 20 ng/ml, and a daily dose of 1000-3000 IU of Vitamin D_3 may be administered to a patient having a serum 25(OH)D level of 20 ng/ml or more.

The aforementioned daily doses may be administered at intervals less regular than once daily. The daily dosage should be multiplied by the number of days between administrations.

In another embodiment there is provided a combined preparation of Aramchol, or a pharmaceutically acceptable salt thereof, and a VDR agonist for simultaneous, separate or sequential use in therapy of liver disease, preferably NAFLD or NASH. In another embodiment, Aramchol or pharmaceutically acceptable salt thereof and the VDR agonist are provided in a single dosage form. In another embodiment Aramchol or pharmaceutically acceptable salt thereof and the VDR agonist are provided in separate dosage forms. In another embodiment, the preparation comprises between about 400 mg and 600 mg of Aramchol or equivalent amount of a salt thereof and between about 400-10,000 IU of the VDR agonist.

In another embodiment the invention provides a method for treatment of disease, selected from the group consisting of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), in a patient in need thereof, comprising administering to the patient an amount of Aramchol or a pharmaceutically acceptable salt thereof in combination with an amount of a VDR agonist or a pharmaceutically acceptable salt thereof to treat the

disease. In another embodiment the method is for use in the treatment of liver fibrosis in said patient. In another embodiment Aramchol and the VDR agonist are administered in the form of a single oral dosage form.

In another embodiment the VDR agonist is selected from the group consisting of calciferol, alfacalcidol, 1,25-dihydroxyvitamin D3, Vitamin D2, Vitamin D3, calcitriol, Vitamin D4, Vitamin D5, dihydrotachysterol, calcipotriol, tacalcitol 1,24-dihydroxyvitamin D3 and paricalcitol. In another embodiment the VDR agonist is vitamin D3 or a precursor, analog or active metabolite thereof. In another embodiment said VDR agonist is selected from the group consisting of: vitamin D3, a vitamin D metabolite, and a vitamin D3 precursor. In another embodiment the VDR agonist comprises cholecalciferol (vitamin D3). In another embodiment the method comprises administering a daily dose of 400-5,000 IU of cholecalciferol (e.g. 500-4,000, 750-4500, 1000-4000 or 2000-5000 IU).

In another embodiment Aramchol is in the form of Aramchol free acid. In another embodiment Aramchol is in the form of a meglumine, lysine or tromethamine Aramchol salt. In another embodiment the method comprises administering a daily dose of 100-600 mg of Aramchol free acid or equivalent amount of salt thereof.

In another embodiment the method is adapted for providing a daily dosage of between about 400 mg and 600 mg of Aramchol or equivalent amount of a salt thereof and a daily dose of between about 400-10,000 IU of the VDR agonist.

In another embodiment the method further comprises administering calcium to said patient. In another embodiment said method comprises administering a daily dose of 100-1000 mg of elemental calcium in the form of a carbonate, citrate, gluconate, succinate or citrate maleate. In another embodiment said method comprises administering a daily dose of 150-750 mg of elemental calcium in the form of calcium citrate.

In another embodiment the method comprises administering a daily dose of 300-500 mg of Aramchol or an equivalent amount of a salt thereof, a daily dose of 400-5,000 IU of cholecalciferol and a daily dose of 150-750 mg of elemental calcium in the form of calcium citrate.

In another embodiment there is provided a therapeutic combination of Aramchol or a pharmaceutically acceptable salt thereof and a VDR agonist, for use in the treatment of a liver disease selected from the group consisting of NASH and NAFLD in a patient in need thereof. In another embodiment the liver disease is NAFLD. In another embodiment the liver disease is

NASH. In another embodiment the combination is for use in the treatment of liver fibrosis in the patient. In a particular embodiment the fibrosis is in a patient suffering from NASH.

In another embodiment the combination consists of Aramchol and the VDR agonist as active ingredients. In another embodiment the combination is for simultaneous, separate or sequential use in the treatment of the liver disease. In another embodiment Aramchol and the VDR agonist are provided in a single dosage form. In a particular embodiment Aramchol and the VDR agonist are provided in an oral dosage form.

In another embodiment the VDR agonist is selected from the group consisting of calciferol, alfacalcidol, 1,25-dihydroxyvitamin D3, Vitamin D2, Vitamin D3, calcitriol, Vitamin D4, Vitamin D5, dihydrotachysterol, calcipotriol, tacalcitol 1,24-dihydroxyvitamin D3 and paricalcitol. In another embodiment said VDR agonist is selected from the group consisting of: vitamin D3, a vitamin D metabolite, and a vitamin D3 precursor.

In another embodiment the combination comprises between about 100 and 600 mg of Aramchol free acid or equivalent amount of salt thereof. In another embodiment the combination comprises between 100 and 600 mg of Aramchol free acid or equivalent amount of salt thereof. In another embodiment the combination comprises between about 50-15,000 International Units (IU) of the VDR agonist. In another embodiment the combination is adapted for providing a daily dosage of between about 400 mg and 600 mg of Aramchol or equivalent amount of a salt thereof and a daily dose of between about 400-10,000 IU of the VDR agonist.

In another embodiment Aramchol is in the form of Aramchol free acid. In another embodiment Aramchol is in the form of an amine-based salt. In another embodiment the salt is a meglumine, lysine or tromethamine Aramchol salt.

In another embodiment the VDR agonist comprises cholecalciferol (vitamin D3). In another embodiment the combination comprises cholecalciferol at an amount of between about 400 and 5,000 IU. In another embodiment the VDR agonist comprises alfacalcidol. In another embodiment the combination comprises alfacalcidol at an amount of between about 0.25 and 1 microgram.

In another embodiment the combination further comprises calcium. In another embodiment the combination comprises a daily dose of 100-1000 mg of elemental calcium in the form of a carbonate, citrate, gluconate, succinate or citrate maleate. In another embodiment the combination comprises a daily dose of 150-750 mg of elemental calcium in the form of calcium citrate.

In another embodiment the combination comprises a daily dose of 300-500 mg of Aramchol or an equivalent amount of a salt thereof, a daily dose of 400-5,000 IU of cholecalciferol and a daily dose of 150-750 mg of elemental calcium in the form of calcium citrate.

EXAMPLES

Example 1: Mouse model of Methionine-choline deficient (MCD) diet.

The MCD diet is a diet deficient in methionine/choline in which test animals such as mice develop serologic and histological features of NASH including fat deposition, inflammation, necrosis and fibrosis.

Male mice (C57BL/6J, 8 wks) are housed in a pathogen-free barrier facility. All mice are fed MCD diet for 21 days.

Mice are weighed and separated into 7comparable groups (1 control group and 6 test compound groups) upon starting the testing.

The study is composed of two phases, a dose selection phase and a combination phase. At the first phase a dose of each treatment is been selected for the combination treatment phase.

Phase 1- dose selection

Group Number	Treatment
1 (control)	Vehicle alone
2 Aramchol high dose	Aramchol 100mg/kg
3 Aramchol medium dose	Aramchol 30mg/kg
4 Aramchol low dose	Aramchol 10mg/kg
5 VDR agonist high dose	VDR agonist, vitamin D_3 200ng/kg
6 VDR agonist medium dose	VDR agonist, vitamin D_3 50ng/kg
7 VDR agonist low dose	VDR agonist, vitamin D_3 12.5ng/kg

Phase 2- combination treatment

Group Number	Treatment
1 (control)	Vehicle alone
2 Aramchol	Aramchol selected doses

3 VDR	VDR, vitamin D_3 selected doses
4 combination treatment	Aramchol selected dose and VDR agonist, vitamin D_3 selected dose

Test compounds are administered for 2 weeks, daily, via oral gavage. After the treatment periods, mice are sacrificed. Serum and liver samples are processed for alanine aminotransferase (ALT) and Hematoxylin and eosin (H&E) staining. Inflammatory cell infiltration is examined by myeloperoxidase staining, and Sirius red staining is used to monitor fibrosis. Researchers blinded as to the grouping of the mice assess tissue samples.

Treated mice are examined for additive or greater than additive effects in at least one of the parameters of fat deposition, inflammation, necrosis, fibrosis, weight, blood cholesterol and glucose levels relative to the control group.

Example 2: Clinical use of Aramchol and VDR agonist combination

A double-blinded study is performed using about 200 patients diagnosed with NAFLD or NASH. Patients are weighed and tested for diabetes and metabolic syndrome, and a liver biopsy is performed before the treatment is initiated. Patients' disease severity is determined and patients are randomly designated to one of three groups:

Group	Treatment
1	VDR agonist alfacalcidol, 0.25 microgram, oral capsule, once daily
2	Aramchol 400 mg, oral tablet, once daily
3	VDR agonist alfacalcidol, 0.25 microgram, oral capsule, once daily, and Aramchol 400 mg, oral tablet, once daily

Groups 1 and 2 are also administered one placebo tablet once daily. Administration is continued for 52 weeks. Administration is terminated if adverse reactions occur.

All patients are tested for a variety of parameters at baseline, week 24 and week 52, including a liver biopsy to determine the presence of NASH and the degree of steatosis, lobular inflammation, liver fat concentration and hepatocellular ballooning, ALT levels, insulin resistance, HOMA score, glycated haemoglobin (HbA1c) levels, leptin adiponectin ratio, liver inflammation, liver fibrosis, fibrinogen, CK-18, CRP, TNFα and IL-6. Patient body weight and waist circumference are also measured.

Patients are examined for the presence of additive or greater than additive effects with respect to NASH presence, NAFLD activity score in a repeated biopsy after 52 weeks of treatment and/or one or more of the aforementioned parameters.

Example 3: Four arms clinical study

This study is a single-blind, placebo-controlled randomized trial of Aramchol {cholan-24-oic acid, 7, 12-dihydroxy-3-[(1-oxoeicosyl) amino]-, (3β, 5β, 7α, 12 α, tested alone and in combination with vitamin D_3 and calcium in patients with vitamin D deficiency and non-alcoholic fatty liver disease (NAFLD) and liver stiffness. Study drugs are given for 24 weeks. The main comparison is between baseline and end of treatment measurements of liver stiffness and liver fat. This study has four arms: Aramchol at 400 mg/day combined with vitamin D-placebo (Aramchol/ placebo), Aramchol at 400 mg/day combined with 4000 IU/day of vitamin D_3 (Aramchol/ vitamin D), Aramchol-placebo combined with 4000 IU/day of vitamin D_3 (placebo/ vitamin D), and Aramchol-placebo combined with vitamin D-placebo (placebo/ placebo).

The trial includes 80 adult patients (18 years of age or older) diagnosed with NAFLD (fatty liver) and increased liver stiffness (correlated with liver fibrosis). Parameters confirmed prior to treatment include, inter alia:

- MRI using multiecho Dixon methods indicating proton density fat fraction (PDFF) ≥ 5.5%;
- liver stiffness measured with MRE indicating ≥ stage 2 fibrosis (> 3.9 kPa);
- 25(OH)D measurement ≤ 20 ng/mL;
- serum calcium in the normal range;
- no history of kidney stones;
- estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73m2 and no history of renal dysfunction;
- platelets ≥ 100,000 cells/μL;
- albumin ≥ 3.5 mg/dL;
- INR (coagulation) in the normal range;
- No history of primary hyperparathyroidism or sarcoid;
- no history of decompensated cirrhosis, e.g., no esophageal varices, no ascites;
- no recorded diagnosis of an additional liver disease, such as autoimmune hepatitis, hepatitis B, hepatitis C, alcoholic liver disease, hepatocellular carcinoma (HCC) or HIV, as indicated by negative serum tests for markers of viral hepatitis and HIV;

- patients taking medications for diabetes must be on a stable regimen for at least 6 months prior to randomization;
- patients taking herbal supplements, fish oil, homeopathic medications, or other alternative treatments, are on a stable regimen for at least 6 months prior to randomization;
- patients taking dietary supplements containing > 400 IU/day vitamin E and/or > 2 g/day polyunsaturated fatty acid or ursodeoxycholic acid are on a stable regimen for at least 6 months prior to randomization; and
- patients with a history of hypertension are on a stable dose of anti-hypertensive medication for at least 2 months prior to screening.

Patients with impaired renal function or history of kidney stones, eGFR< 60 mL/min/1.73m2, a history of primary hypercalcemia or another condition that carries a risk of hypercalcemia if the patient is prescribed vitamin D (e.g. sarcoid, tuberculosis), inflammatory bowel disease (IDB), previous intestinal (ileal or colonic) operation, chronic pancreatic, celiac disease or previous vagotomy, and previous bariatric surgery are excluded.

Aramchol/vitamin D, Aramchol/placebo (vitamin D), placebo (Aramchol)/vitamin D, placebo (Aramchol)/placebo (vitamin D) are taken by mouth once daily for 24 weeks. Calcium (500 mg) in the form of calcium citrate (two tablets of 250 mg, Douglas Laboratories) is taken by mouth once daily for 24 weeks.

Height, weight and waist/hip ratio are measured. In addition to standard clinical tests, blood/plasma is collected for analysis of CK 18, metabolomics, genomic DNA, and other factors (e.g., miRNA). Additional parameters monitored include: HCG (in women of child bearing potential), fasting insulin, hemoglobin A1c, CBC with platelets, hsCRP, Transplant Monitoring Panel (fasting glucose, sodium, potassium, chloride, CO_2, urea nitrogen, creatinine, phosphorus, protein total, albumin, calcium, alkaline phosphatase, ALT, AST, gamma GT, bilirubin total, bilirubin direct, LDH, amylase, magnesium), and Lipid Panel (cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, cholesterol/HDL ratio, LDL/HDL ratio).

Liver fat content and liver stiffness are measured using MRI/MRE (magnetic resonance imaging/magnetic resonance elastography) and FibroScan (Echosens, France)/FibroScan with the Controlled Attenuation Parameter (CAP). CAP reports the degree of ultrasound attenuation, which correlates with hepatic fat content. FibroScan and FibroScan/CAP tests, measuring liver stiffness and PDFF, respectively, are performed five times: twice prior to the start of treatment, twice near and at the end of treatment (at weeks 20 and 24), and at the 4 week follow up visit.

MRI/MRE and ultrasound (US) are performed at the second screening visit and at the end of treatment (at week 24).

The primary outcome is the difference in the change in liver stiffness (baseline to end of treatment), measured by MRE comparing placebo/ placebo to Aramchol/ placebo and comparing placebo/ placebo to Aramchol/ vitamin D, analyzed by t-tests, or Mann-Whitney U tests, without correction for multiple testing. Secondary endpoints include (1) changes in PDFF (measured by MRI and FibroScan/CAP), (2) changes in liver stiffness measured by FibroScan, (3) comparison placebo/ vitamin D to placebo/ placebo, (4) changes levels of factors in blood, including, but not limited to the AST/ALT ratio and total bilirubin, (5) changes in serum levels of 25(OH)D and calcium, (6) the difference in the change in liver stiffness (baseline to end of treatment) Aramchol/placebo versus Aramchol/ vitamin D, (7) safety/adverse events.

In the description and claims of the present application, each of the verbs, "comprise", "include" and "have", and conjugates thereof, are used to indicate that the object or objects of the verb are not necessarily a complete listing of components, elements or parts of the subject or subjects of the verb.

Descriptions of embodiments of the invention in the present application are provided by way of example and are not intended to limit the scope of the invention. The described embodiments comprise different features, not all of which are required in all embodiments of the invention. Some embodiments utilize only some of the features or possible combinations of the features. Variations of embodiments of the invention that are described, and embodiments of the invention comprising different combinations of features noted in the described embodiments, will occur to persons of the art. The scope of the invention is limited only by the claims.

CLAIMS

1. A method for treatment of disease, selected from the group consisting of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), in a patient in need thereof, comprising administering to the patient an amount of Aramchol or a pharmaceutically acceptable salt thereof in combination with an amount of a vitamin D receptor (VDR) agonist or a pharmaceutically acceptable salt thereof to treat the disease.

2. The method of claim 1, wherein Aramchol and the VDR agonist are administered in the form of a single oral dosage form.

3. The method of claim 1, wherein the VDR agonist is selected from the group consisting of calciferol, alfacalcidol, 1,25-dihydroxyvitamin D_3, Vitamin D_2, Vitamin D_3, calcitriol, Vitamin D_4, Vitamin D_5, dihydrotachysterol, calcipotriol, tacalcitol 1,24-dihydroxyvitamin D_3 and paricalcitol.

4. The method of claim, wherein the VDR agonist is vitamin D3 or a precursor, analog or active metabolite thereof.

5. The method of claim 4, wherein the VDR agonist comprises cholecalciferol (vitamin D3).

6. The method of claim 5 comprising administering a daily dose of 400-5,000 IU of cholecalciferol.

7. The method of claim 1, wherein Aramchol is in the form of Aramchol free acid.

8. The method of claim 1, wherein Aramchol is in the form of a meglumine, lysine or tromethamine Aramchol salt.

9. The method of claim 1, comprising administering a daily dose of 100-600 mg of Aramchol free acid or equivalent amount of salt thereof.

10. The method of claim 1, adapted for providing a daily dosage of between about 400 mg and 600 mg of Aramchol or equivalent amount of a salt thereof and a daily dose of between about 400-10,000 IU of the VDR agonist.

11. The method of claim 1, further comprising administering calcium to said patient.

12. The method of claim 11, comprising administering a daily dose of 100-1000 mg of elemental calcium in the form of a carbonate, citrate, gluconate, succinate or citrate maleate.

13. The method of claim 12 comprising administering a daily dose of 150-750 mg of elemental calcium in the form of calcium citrate.

14. The method of claim 1, comprising administering a daily dose of 300-500 mg of Aramchol or an equivalent amount of a salt thereof, a daily dose of 400-5,000 IU of cholecalciferol and a daily dose of 150-750 mg of elemental calcium in the form of calcium citrate.

15. The method of claim 1 for use in the treatment of liver fibrosis in said patient.

16. A therapeutic combination of Aramchol or a pharmaceutically acceptable salt thereof and a VDR agonist, for use in the treatment of a liver disease selected from the group consisting of NASH and NAFLD in a patient in need thereof.

17. The combination of claim 16, consisting of Aramchol and the VDR agonist as active ingredients.

18. The combination according to any one of the previous claims, for simultaneous, separate or sequential use in the treatment of the liver disease.

19. The combination according to any one of the previous claims, wherein Aramchol and the VDR agonist are provided in a single dosage form.

20. The combination of claim 19, wherein Aramchol and the VDR agonist are provided in an oral dosage form.

21. The combination according to any one of the previous claims, wherein the VDR agonist is selected from the group consisting of calciferol, alfacalcidol, 1,25-dihydroxyvitamin D_3, Vitamin D_2, Vitamin D_3, calcitriol, Vitamin D_4, Vitamin D_5, dihydrotachysterol, calcipotriol, tacalcitol 1,24-dihydroxyvitamin D_3 and paricalcitol.

22. The combination according to any one of the previous claims comprising between about 100 and 600 mg of Aramchol free acid or equivalent amount of salt thereof.

23. The combination according to any one of the previous claims comprising between about 50-15,000 International Units (IU) of the VDR agonist.

24. The combination according to any one of the previous claims adapted for providing a daily dosage of between about 400 mg and 600 mg of Aramchol or equivalent amount of a salt thereof and a daily dose of between about 400-10,000 IU of the VDR agonist.

25. The combination according to any one of the previous claims wherein Aramchol is in the form of Aramchol free acid.

26. The combination according to any one of claims 16-24 wherein Aramchol is in the form of a meglumine, lysine or tromethamine Aramchol salt.

27. The combination according to any one of the previous claims wherein the VDR agonist comprises cholecalciferol (vitamin D3).

28. The combination according to claim 27 comprising cholecalciferol at an amount of between about 400 and 5,000 IU.

29. The combination according to claim 1 wherein the VDR agonist comprises alfacalcidol.

30. The combination according to claim 29 comprising alfacalcidol at an amount of between about 0.25 and 1 microgram.

31. The combination according to any one of the previous claims for use in the treatment of liver fibrosis in the patient.

32. The combination according to claim 31 wherein the fibrosis is in a patient suffering from NASH.

33. The combination according to any one of the previous claims further comprising calcium.

34. The combination of claim 33 comprising a daily dose of 100-1000 mg of elemental calcium in the form of a carbonate, citrate, gluconate, succinate or citrate maleate.

35. The combination of claim 33 comprising a daily dose of 150-750 mg of elemental calcium in the form of calcium citrate.

36. The combination of claim 35 comprising a daily dose of 300-500 mg of Aramchol or an equivalent amount of a salt thereof, a daily dose of 400-5,000 IU of

cholecalciferol and a daily dose of 150-750 mg of elemental calcium in the form of calcium citrate.

37. A pharmaceutical composition comprising Aramchol or a pharmaceutically acceptable salt thereof in combination with a VDR agonist as the active ingredients, and optionally pharmaceutically acceptable carriers, excipients and/or diluents.

38. The pharmaceutical composition of claim 37, wherein the VDR agonist is selected from the group consisting of calciferol, alfacalcidol, 1,25-dihydroxyvitamin D_3, Vitamin D_2, Vitamin D_3, calcitriol, Vitamin D_4, Vitamin D_5, dihydrotachysterol, calcipotriol, tacalcitol 1,24-dihydroxyvitamin D_3 and paricalcitol.

39. The composition of claim 38, wherein the VDR agonist is vitamin D3 or a precursor, analog or active metabolite thereof.

40. The composition of claim 38, wherein the VDR agonist comprises cholecalciferol (vitamin D3).

41. The composition of claim 40 comprising 400-5,000 IU of cholecalciferol in unit dosage form.

42. The composition of claim 37, wherein Aramchol is in the form of Aramchol free acid or in the form of a meglumine, lysine or tromethamine Aramchol salt.

43. The composition of claim 37, comprising 100-600 mg of Aramchol free acid or equivalent amount of salt thereof in unit dosage form.

44. The composition of claim 37, comprising 300-500 mg of Aramchol or an equivalent amount of a salt thereof and 400-5,000 IU of cholecalciferol or a precursor, analog or active metabolite thereof.

45. The composition of claim 37, further comprising calcium.

46. The pharmaceutical composition according to claim 21 for the preparation of a medicament for use in the treatment of liver disease selected from the group consisting of NAFLD and NASH.

47. A pharmaceutical composition according to claims 37, formulated as an oral dosage form.

48. The pharmaceutical composition of claim 37, consisting essentially of Aramchol and the VDR agonist.

49. A package comprising a) a first pharmaceutical composition comprising Aramchol or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier; b) a second pharmaceutical composition comprising a VDR agonist and a pharmaceutically acceptable carrier; and c) instructions for use of the first and second pharmaceutical compositions in combination to treat a subject afflicted with a liver disease selected from the group consisting of NAFLD and NASH.

50. The package of claim 49, consisting of Aramchol and the VDR agonist as the active ingredients.

51. The package of claim 49, wherein the VDR agonist is selected from the group consisting of calciferol, alfacalcidol, 1,25-dihydroxyvitamin D_3, Vitamin D_2, Vitamin D_3, calcitriol, Vitamin D_4, Vitamin D_5, dihydrotachysterol, calcipotriol, tacalcitol 1,24-dihydroxyvitamin D_3 and paricalcitol.

52. The package of claim 51, wherein the VDR agonist is vitamin D3 or a precursor, analog or active metabolite thereof.

53. The package of claim 52, wherein the VDR agonist comprises cholecalciferol (vitamin D3).

54. The package of claim 53 comprising 400-5,000 IU of cholecalciferol in unit dosage form.

55. The package of claim 49, wherein Aramchol is in the form of Aramchol free acid or in the form of a meglumine, lysine or tromethamine Aramchol salt.

56. The package of claim 49, comprising 100-600 mg of Aramchol free acid or equivalent amount of salt thereof in unit dosage form.

57. The package of claim 49 comprising 300-500 mg of Aramchol or an equivalent amount of a salt thereof and 400-5,000 IU of cholecalciferol or a precursor, analog or active metabolite thereof.

58. The package of claim 49, further comprising calcium.

59. The package of claim 58, comprising 100-1000 mg of elemental calcium in the form of a carbonate, citrate, gluconate, succinate or citrate maleate.

60. The package of claim 49, comprising 300-500 mg of Aramchol or an equivalent amount of a salt thereof, 400-5,000 IU of cholecalciferol and 150-750 mg of elemental calcium in the form of calcium citrate.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2016/050816

A. CLASSIFICATION OF SUBJECT MATTER
IPC (2016.01) A61K 31/20, A61K 31/59, A61P 1/16

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)
IPC (2016.01) A61K 31/20, A61K 31/59, A61P 1/16

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Databases consulted: THOMSON INNOVATION, Esp@cenet, Google Patents, MEDLINE, Google Scholar
Search terms used: Aramchol, C-20 FABAC, VDR, fatty liver disease, NAFLD, NASH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Rifaat Safadi et. al. "The fatty acid-bile acid conjugate Aramchol reduces liver fat content in patients with nonalcoholic fatty liver disease."Clinical gastroenterology and hepatology Volume 12, Issue 12, Pages 2085–2091.e1 Epub 2014 May 9, http://www.ncbi.nlm.nih.gov/pubmed/24815326 Rifaat Safadi et. al 09 May 2014 (2014/05/09) abstract, p. 2085-2086	1-60
Y	WO 2015083164 A1 GALMED RES & DEV LTD[IL] 11 Jun 2015 (2015/06/11) p.2, cl 24	1-60
Y	US 2011014126 A1 EVANS RONALD M[US]; DOWNES MICHAEL[US]; LIDDLE CHRISTOPHER[AU]; SUBRAMANIAM NANTHAKUMAR[AU]; SAMER CAROLINE FLORA[CH] 20 Jan 2011 (2011/01/20) para 0003-0004, para 0039-0040, ex 7, cl 2, 3-4, 7	1-60
Y	WO 2015053379 A1 Mochida pharm co LTD [JP] Suzuki Ayako [US] 16 Apr 2015 (2015/04/16) para 00118, 00220, 00239,00249	11-14,33-36,45, 58-60

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

[X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
03 Nov 2016	07 Nov 2016
Name and mailing address of the ISA: Israel Patent Office Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel Facsimile No. 972-2-5651616	Authorized officer SHAPIRA Elena Telephone No. 972-2-5657823

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2016/050816

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	Claudia D. Fuchs et al.. "Nuclear Receptor Modulation for the Treatment of Nonalcoholic Fatty Liver Disease" 36(1):69-86. doi: 10.1055/s-0036-1571296, Claudia D. Fuchs et al 12 Feb 2016 (2016/02/12) whole document	1-60

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2016/050816

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
WO 2015083164 A1	11 Jun 2015	WO 2015083164 A1	11 Jun 2015
		AU 2014358668 A1	02 Jun 2016
		CA 2930232 A1	11 Jun 2015
		EP 3077047 A1	12 Oct 2016
		IL 245452 D0	30 Jun 2016
		KR 20160093051 A	05 Aug 2016
		US 2016304553 A1	20 Oct 2016
US 2011014126 A1	20 Jan 2011	US 2011014126 A1	20 Jan 2011
		US 8318708 B2	27 Nov 2012
		AU 2008323903 A1	14 May 2009
		AU 2008323903 B2	05 Dec 2013
		CA 2703994 A1	14 May 2009
		EP 2209377 A1	28 Jul 2010
		EP 2209377 A4	08 Dec 2010
		US 2009209500 A1	20 Aug 2009
		WO 2009061961 A1	14 May 2009
WO 2015053379 A1	16 Apr 2015	WO 2015053379 A1	16 Apr 2015
		EP 3054940 A1	17 Aug 2016
		US 2016213639 A1	28 Jul 2016