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(54) Title: COMPOSITIONS AND METHODS FOR IMPROVING SKIN APPEARANCE

(57) Abstract: Disclosed herein are injectable compositions and methods of treating skin to improve hydration, elasticity and/or texture. The compositions are based on crosslinked hyaluronic acid matrices made with low molecular weight hyaluronic acids.



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## **COMPOSITIONS AND METHODS FOR IMPROVING SKIN APPEARANCE**

**By Inventors: Pierre Lebreton and Olivier Guetta**

**[0001]** The present invention generally relates to injectable compositions and more specifically relates to hyaluronic acid-based compositions for treatment of fine lines in skin.

Current injectable treatment options for improving skin quality over the full-face or other significant surface area of skin require multiple treatment sessions (typically 3-4 treatments, every three to four weeks) and have a relatively short duration of effect.

Skin is composed of the epidermis and the dermis. The outermost epidermis is made up of stratified squamous epithelium with an underlying basement membrane. It contains no blood vessels, and is nourished by diffusion from the dermis. The main type of cells which make up the epidermis are keratinocytes, with melanocytes and langerhans cells also present. This layer of skin is responsible for keeping water in the body and keeping harmful chemicals and pathogens out.

**[0002]** The dermis lies below the epidermis and contains a number of structures including blood vessels, nerves, hair follicles, smooth muscle, glands and lymphatic tissue. The dermis (or corium) is typically 3-5 mm thick and is the major component of human skin. It is composed of a network of connective tissue, predominantly collagen fibrils providing support and elastic tissue providing flexibility. The main cell types are fibroblasts, adipocytes (fat storage) and macrophages. Hyaluronic acid (HA) is a part of the dermis composition and is a major component of the extra cellular matrix.

**[0003]** Facial aging occurs as the result of several factors: inherent changes within the skin, effects of gravity, facial muscles acting on the skin (dynamic lines), soft tissue loss or shift and bone loss and loss of tissue elasticity. The skin ages when the epidermis begins to thin, causing the junction with the dermis to flatten. Collagen decreases as a person ages and the bundles of collagen, which gives the skin turgor, become looser and lose strength. When the skin loses elasticity, it is less able to resist

stretching. Coupled with gravity, muscle pull and tissue changes, the skin begin to wrinkle. Water loss and breakdown of bonds between cells also reduces the barrier function of the skin, which can cause the skin's pore size to increases.

**[0004]** It is well known that the eyes are often the first facial feature to show signs of aging. Skin changes around the eyes occur earlier than in the rest of the face since the skin is thinner around the eyes. The skin here contains fewer glands and is subjected to constant blinking, squinting, rubbing, and pulling. The midface ages when the cheeks begin to droop, causing nasolabial folds. Nasolabial folds are the lines that run from the sides of the nose to the corners of the mouth. In the lower face area, as the face ages, facial tissues descend. This results in the so-called "laugh lines". These and other folds and wrinkles are now commonly treated with subdermal and dermal injections of aesthetic facial fillers which add lost volume to the skin thereby reducing the appearance of the folds and wrinkles.

**[0005]** Hyaluronic acid (HA), also known as hyaluronan, is now one of the most commonly used components of dermal fillers. Hyaluronic acid is a naturally occurring, water soluble polysaccharide, specifically a glycosaminoglycan, which is a major component of the extra-cellular matrix and is widely distributed in animal tissues. The identical structure of hyaluronic acid in all species and tissues makes this polysaccharide an ideal substance for use as a bio-material in health and medicine.

**[0006]** HA has excellent biocompatibility and, unlike collagen, does not require any skin testing before implantation. In addition, HA has the ability to bind to large amounts of water, making it an excellent volumizer of soft tissues.

**[0007]** To enhance its longevity in vivo, the HA in dermal fillers is commonly crosslinked. Chemically crosslinked HA is formed by reacting uncrosslinked HA with a crosslinking agent under suitable reaction conditions.

**[0008]** It is generally accepted that HA-based dermal fillers having a high viscosity, for example, those that are highly crosslinked and/or made of high molecular weight HA and/or having a high HA concentration tend to last longer in the body. Conversely, it is

generally accepted that HA-based dermal fillers having a low viscosity, for example, those that are more lightly crosslinked and/or made up of low molecular weight HA and/or have a low HA concentration, may have a shorter duration in the body. Naturally, injection of a high viscosity material through a needle is relatively more difficult, and generally requires a lower gauge needle (for instance, 21G or 23G compared to 27G or 30G) than injection of a relatively low viscosity material. It has proven difficult to develop an HA based composition that is both easy to inject through a high gauge needle (i.e. thin needle) and which has extended duration in the body.

### **Summary**

**[0009]** The present invention relates to injectable compositions, and more specifically, to injectable compositions for superficial injection into skin. The compositions and methods provide improved skin appearance and quality by filling of superficial skin depressions, and/or improving skin quality and appearance. In one aspect, the compositions and methods provide at least one of improved skin texture, increased skin hydration and increased elasticity.

**[0010]** In one aspect, the present compositions are based on hyaluronic acid (HA) and pharmaceutically acceptable salts of HA, for example, sodium hyaluronate (NaHA). Many of the long lasting, highly injectable compositions of the present invention include a crosslinked HA matrix made with relatively low molecular weight HA. In some embodiments, the compositions have a relatively low concentration of HA. Advantageously, many of the compositions provided herein have an extended duration of effect. For example, rather than requiring multiple repeated treatments every three to four weeks, as is common with conventional superficial injection treatment methods, many of the present compositions and methods provided herein have a duration of effect of three months, four months, six months, to a year or more.

**[0011]** In a broad aspect of the invention, a composition is provided which generally comprises an HA gel containing, or consisting essentially of, a low molecular weight HA material. The HA component includes more than 50%, for example, at least 70%, for

example, about 90% by weight of the low molecular weight HA. The low molecular weight HA material has a weight average molecular weight of no greater than about 0.20 MDa and about 0.99 MDa.

**[0012]** In some embodiments, the HA gel may further contain a high molecular weight HA, that is, an HA material having a molecular weight of at least about 1.0 MDa to about 4.0 MDa. Generally, in embodiments of the invention including high molecular weight HA material, the weight average molecular weight of the high molecular weight HA material is at least twice that of the low molecular weight HA material.

**[0013]** The HA of the HA gel may be crosslinked. For example, the HA may be chemically crosslinked by a suitable crosslinking agent. In some embodiments, the crosslinking agent is selected from the group consisting of 1,4-butanediol diglycidyl ether (BDDE), 1,4-bis(2,3-epoxypropoxy)butane, 1,4-bisglycidyoxybutane, 1,2-bis(2,3-epoxypropoxy)ethylene and 1-(2,3-epoxypropyl)-2,3-epoxycyclohexane.

**[0014]** In some embodiments, the composition has an HA concentration of about 10.0 mg/g up to about 17.0 mg/g. In some embodiments, the HA concentration is less than about 17.0 mg/g, for example, less than about 15.0 mg/g. In some embodiments, the HA concentration is between about 10.0 mg/g and about 14.0 mg/g. In some embodiments, the HA concentration is about 10.0 mg/g, about 11.0 mg/g, about 12.0 mg/g, about 13.0mg/g, or about 14.0 mg/g.

**[0015]** In another aspect of the invention, methods of treating skin using the present compositions are provided. For example, methods of improving one or more qualities of skin, or improving appearance or texture of skin, are provided.

**[0016]** In one aspect, methods of treating dryness, texture or roughness, and/or elasticity in skin are provided. The methods generally comprise treating an area of skin by introducing, into the area, multiple, spaced apart injections of a composition comprising a hyaluronic acid (HA) gel containing crosslinked HA, wherein the treated skin maintains an improved hydration, smoother texture or increased elasticity, due to the treatment for an extended duration, for example, for at least about 3 months to

about a year or more. In a particularly advantageous embodiment, the step of introducing is performed in only a single treatment session, thereby eliminating the need for repeated treatments to maintain the duration of effect.

**[0017]** In some embodiments, the step of introducing comprises introducing the composition in injections spaced apart by a distance of between about 2 mm to about 30 mm. For example, the step of introducing comprises introducing the composition in injections spaced apart by a distance of between about 5 mm to about 20 mm, or about 10 mm to about 15 mm. In some embodiments, the compositions are introduced at a depth of between about 500 microns and about 2000 microns, for example, a depth of about 1000 microns.

**[0018]** In another aspect, the invention provides a method of treating roughness in skin comprising treating an area of skin by introducing, into the area, multiple, spaced apart injections of a composition comprising a hyaluronic acid (HA) gel containing crosslinked HA, wherein the treated skin maintains a smoother texture due to the treatment for at least about 3 months, at least about 4 months, at least about 6 months, or at least about 12 months.

### **Detailed Description**

**[0019]** The term “about” in the context of numerical values will be readily understood by a person skilled in the art, and preferably means that specific values may be modified by +/- 10%. As regards endpoints of ranges, the modifier “about” preferably means that the lower endpoint may be reduced by 10% and the upper endpoint increased by 10%. It is also contemplated that each numerical value or range disclosed in this application can be absolute, i.e. that the modifier “about” can be deleted.

**[0020]** All numbers herein expressing “molecular weight” of HA are to be understood as indicating the weight average molecular weight (Mw) in Daltons.

**[0021]** The molecular weight of HA is calculated from an intrinsic viscosity measurement using the following Mark Houwink relation:

$$\text{Intrinsic Viscosity (m}^3\text{/kg)} = 9.78 \times 10^{-5} \times \text{Mw}^{0.690}$$

**[0022]** The intrinsic viscosity is measured according to the procedure defined European Pharmacopoeia (HA monograph N°1472, 01/2009).

**[0023]** High molecular weight HA as used herein describes a HA material having a molecular weight of at least about 1.0 million Daltons ( $\text{Mw} \geq 10^6$  Da or 1 MDa) to about 5.0 MDa. For example, the high molecular weight HA in the present compositions may have a molecular weight in the range about 1.5 MDa to about 3.0 MDa, or the high molecular weight HA may have a weight average molecular weight of about 2.0 MDa. In another example, the high molecular weight HA may have a molecular weight of about 3.0 MDa.

**[0024]** Low molecular weight HA as used herein describes a HA material having a molecular weight of less than about 1.0 MDa. Low molecular weight HA can have a molecular weight of between about 200,000 Da (0.2 MDa) to less than 1.0 MDa, for example, between about 400,000 Da and about 800,000 Da, for example about 386,000 Da (0.386 MDa) to about 740,000 Da (0.74 MDa). In some embodiments the low molecular weight HA used to make the crosslinked HA matrix does not exceed 0.99 MDa.

**[0025]** Preferably, the mixture of the low molecular weight HA and high molecular weight HA has a bimodal molecular weight distribution. The mixture may also have a multi-modal distribution.

**[0026]** In one aspect of the invention, the compositions comprise HA having a high molecular weight component and a low molecular weight component, and the high molecular weight component has a weight average molecular weight at least twice the weight average molecular weight of the low molecular weight component.

**[0027]** For example, a composition in accordance with this aspect of the invention may include a low molecular weight component having a weight average molecular

weight of about 500,000 Da, and a high molecular weight component having a weight average molecular weight of about, or at least about, 1.0 MDa.

**[0028]** In another example, a composition in accordance with the invention may include a low molecular weight component having a weight average molecular weight of about 800,000 Da, and a high molecular weight component having a weight average molecular weight of about, or at least about, 1.6 MDa.

**[0029]** Degree of crosslinking is measured by the final weight ratio of crosslinker to HA disaccharide units.

**[0030]** Uncrosslinked HA as used herein refers to individual HA polymer molecules that are not crosslinked to one another. Uncrosslinked HA generally remains water soluble.

**[0031]** Provided herein are compositions for treating skin, for example, injectable compositions that can be introduced intradermally to improve the appearance or quality of skin, for example, to improve hydration, texture and/or elasticity. The compositions may also be effective for treatment of fine lines in skin and for reducing superficial cutaneous depressions. Methods of making these compositions are also provided, as well as methods of treatment using these compositions. The compositions are based on hyaluronic acids (HA) and pharmaceutically acceptable salts of HA, for example, sodium hyaluronate (NaHA).

**[0032]** As used herein, hyaluronic acid (HA) can refer to any of its hyaluronate salts, and includes, but is not limited to, sodium hyaluronate (NaHA), potassium hyaluronate, magnesium hyaluronate, calcium hyaluronate, and combinations thereof. Both HA and pharmaceutically acceptable salts thereof can be used in this invention.

**[0033]** Generally, the concentration of HA in some of the present compositions is about 10.0 mg/g up to about 17.0 mg/g. In some embodiments, the HA concentration is less than about 17.0 mg/g, for example, less than about 15.0 mg/g. In some embodiments, the HA concentration is between about 10.0 mg/g and about 14.0 mg/g.

In some embodiments, the HA concentration is about 10.0 mg/g, about 11.0 mg/g, about 12.0 mg/g, about 13.0mg/g, or about 14.0 mg/g.

**[0034]** Some of the compositions of the invention include additional agents, for example, anesthetic agents in an amount effective to mitigate pain experienced upon injection of the composition. The anesthetic agent may be selected from the group of ambucaine, amolanone, amylocaine, benoxinate, benzocaine, betoxycaine, biphenamine, bupivacaine, butacaine, butamben, butanilcaine, butethamine, butoxycaine, carticaine, chloroprocaine, cocaethylene, cocaine, cyclomethycaine, dibucaine, dimethisoquin, dimethocaine, diperodon, dicyclomine, ecgonidine, ecgonine, ethyl chloride, etidocaine, beta-eucaine, euprocine, fenalcomine, formocaine, hexylcaine, hydroxytetracaine, isobutyl p-aminobenzoate, leucinocaine mesylate, levexadol, lidocaine, mepivacaine, meprylcaine, metabutoxycaine, methyl chloride, myrtecaine, naepaine, octocaine, orthocaine, oxethazaine, parethoxycaine, phenacaine, phenol, piperocaine, piridocaine, polidocanol, pramoxine, prilocaine, procaine, propanocaine, proparacaine, propipocaine, propoxycaine, pseudococaine, pyrrocaine, ropivacaine, salicyl alcohol, tetracaine, tolycaine, trimecaine, zolamine, and salts thereof. In one embodiment, at least one anesthetic agent is lidocaine, such as in the form of lidocaine HCl. The compositions described herein may have a lidocaine concentration of between about 0.1% and about 5% by weight of the composition, for example, about 0.2% to about 1.0% by weight of the composition. In one embodiment, the composition has a lidocaine concentration of about 0.3% by weight (w/w %) of the composition.

**[0035]** In some embodiments, the compositions further comprise a beneficial additive, for example, an antioxidant. In some embodiments, the compositions include, for example, mannitol. The mannitol may be present in an amount of between about 0.1% w/w to about 2.0% w/w, or between about 0.3% to about 0.9%. In some embodiments, the mannitol is present in an amount of less than, no greater than, or about 1.0%. In some embodiments, the mannitol is present in an amount of about 0.9 % w/w. In other embodiments, the mannitol is present in an amount of about 0.1%, or about 0.2%, or about 0.3%, or about 0.4%, or about 0.5%, or about 0.6%, or about

0.7%, or about 0.8%, or about 0.9%, or about 1.0%. In other embodiments, the mannitol is present in an amount of greater than about 1.0%. In some embodiments, the mannitol is present in an amount of between about 1.0% to about 5.0% w/w.

**[0036]** In some embodiments, the compositions further comprise a vitamin, for example, Vitamin C. In a more preferred embodiment, the vitamin is a derivative or a stabilized form of Vitamin C, for example, ascorbic acid 2-glucoside. The vitamin may be present in an amount of between about 0.1% to about 2.0%, or between about 0.2% and about 1.0%, or between about 0.3% to about 0.6%. In some embodiments, the Vitamin C is present in an amount of about 0.6% w/w. In other embodiments, the Vitamin C derivative is present in an amount of about 0.1%, or about 0.2%, or about 0.3%, or about 0.4%, or about 0.5%, or about 0.6%, or about 0.7%, or about 0.8%, or about 0.9%, or about 1.0%. In other embodiments, the Vitamin C derivative is present in an amount of greater than 1.0%. In some embodiments, the Vitamin C derivative is present in an amount of between about 1.0% to about 5.0% w/w.

**[0037]** In some embodiments, the compositions further comprise a combination of mannitol and ascorbic acid 2-glucoside. In some of these embodiments, the mannitol is present in an amount of no greater than 1.0% w/w, for example, 0.9 % w/w and the ascorbic acid 2-glucoside is present in an amount of about 0.6% w/w.

**[0038]** In some embodiments, the compositions do not include an antioxidant or a vitamin. For example, in some embodiments, the compositions comprise or consist essentially of hyaluronic acid crosslinked with a crosslinking agent and water. These compositions may or may not include an anesthetic agent such as lidocaine.

**[0039]** The present products and compositions are preferably provided in a sterile form. The compositions may be sterilized using conventional methods, for example, autoclaving. For example, the compositions may be sterilized by exposing the compositions to temperatures of at least about 120°C to about 130°C and/or pressures of at least about 12 pounds per square inch (PSI) to about 20 PSI for a period of at least about 1 minute to about 15 minutes.

**[0040]** Method of making the composition comprise the steps of providing raw HA material in the form of dry HA fibers or powder. The raw HA material may be HA, its salts and/or mixtures thereof. In a preferred embodiment, the HA material comprises fibers or powder of NaHA, for example, bacterial-sourced NaHA fibers. In some aspects of the present description, the HA material may be animal derived. The HA material may be a combination of raw materials including HA and at least one other polysaccharide, for example, glycosaminoglycan (GAG).

**[0041]** In a broad aspect of the invention, the HA material of the compositions may comprise a crosslinked HA matrix made with between about 5% to about 95% low molecular weight HA with the balance of the HA material including high molecular weight HA.

**[0042]** In some embodiments of the invention, the HA material used to make the present compositions nearly entirely comprises or consists of low molecular weight HA. In some embodiments, nearly 100% of the HA material used to make the present compositions may be low molecular weight HA as defined above. In other embodiments, the HA material used to make the compositions comprises a combination of relatively high molecular weight HA and relatively low molecular weight HA, as defined above. In certain embodiments, at least about 50%, for example, at least about 70%, for example, at least about 90% or greater of the HA material in the compositions is a low molecular weight HA as defined above, with the remaining portion of HA being high molecular weight HA. In one embodiment, the compositions are made using a 90:10 ratio of low molecular weight HA to high molecular weight HA. That is, the compositions of these embodiments are made with a combination of high and low molecular weight HA, with about 90% of the HA being the low molecular weight HA.

**[0043]** In one embodiment, the pure, dry NaHA fibers are hydrated in an alkaline solution to produce an uncrosslinked NaHA gel. Any suitable alkaline solution may be used to hydrate the NaHA in this step, for example, but not limited to aqueous solutions containing sodium hydroxide (NaOH), potassium hydroxide (KOH), sodium bicarbonate (NaHCO<sub>3</sub>), lithium hydroxide (LiOH), and the like. In another embodiment, the suitable

alkaline solution is aqueous solutions containing NaOH. The resulting alkaline gel will have a pH above 7.5. The pH of the resulting alkaline gel can have a pH greater than 9, or a pH greater than 10, or a pH greater than 11, or a pH greater than 12, or a pH greater than 13.

**[0044]** The next step in the manufacturing process involves the step of crosslinking the hydrated, alkaline NaHA gel with a suitable crosslinking agent. The crosslinking agent may be any agent known to be suitable for crosslinking polysaccharides and their derivatives via their hydroxyl groups. Suitable crosslinking agents include but are not limited to, 1,4-butanediol diglycidyl ether (or 1,4-bis(2,3-epoxypropoxy)butane or 1,4-bisglycidyl oxybutane, all of which are commonly known as BDDE), 1,2-bis(2,3-epoxypropoxy)ethylene and 1-(2,3-epoxypropyl)-2,3-epoxycyclohexane. The use of more than one crosslinking agent or a different crosslinking agent is not excluded from the scope of the present disclosure. In one embodiment, the HA gels described herein are crosslinked using BDDE.

**[0045]** The step of crosslinking may be carried out using any means known to those of ordinary skill in the art. Those skilled in the art appreciate how to optimize conditions of crosslinking according to the nature of the HA, and how to carry out crosslinking to an optimized degree.

**[0046]** In another embodiment, the crosslinking of the HA is accomplished during hydration of the HA fibers, by hydrating the combined high and low molecular weight fibers in an alkaline solution containing a crosslinking agent, for example, BDDE.

**[0047]** The degree of crosslinking in the HA component of the present compositions is at least about 1% and is up to about 20% BDDE/HA, w/w, for example, between about 4% and about 12%, for example, about 10 %, for example, about 8%, for example, about 6%, for example, about 5%, for example, about 4%.

**[0048]** The hydrated crosslinked, HA gels may be swollen to obtain the desired HA concentration. This step can be accomplished by neutralizing the crosslinked, hydrated

HA gel, for example by adding an aqueous solution containing of an acid, such as HCl. The gels are then swelled in a phosphate buffered saline (PBS) solution.

**[0049]** The gels may be purified by conventional means such as, dialysis against a phosphate buffer, or alcohol precipitation, to recover the crosslinked material, to stabilize the pH of the material and to remove any un-reacted crosslinking agent. The compositions are mixed to achieve homogeneity. Preferably, the homogenization step comprises mixing, stirring, or beating the gels with a controlled shearing force obtaining substantially homogenous mixtures. In some embodiments, during or after the mixing, a phosphate buffer is added to reach the desired concentration of HA in the final composition.

**[0050]** In some embodiments, lidocaine, or another suitable anesthetic, is added to the compositions. For example, the pH of the purified, substantially pH neutral, gel is adjusted to cause the gel to become slightly alkaline such that the gels have a pH of greater than about 7.2, for example, about 7.5 to about 8.0. This step may be accomplished by any suitable means, for example, by adding to the gels a suitable amount of dilute NaOH, KOH, NaHCO<sub>3</sub> or LiOH, or any other alkaline molecule, solution and/or buffering composition known by one skilled in the art. For example, in some embodiments, the lidocaine HCl is provided in a powder form which is solubilized using water for injection (WFI). The lidocaine is then added to the slightly alkaline gel. For example, in one embodiment, the desired HA concentration is about 12.0 mg/g. The compositions including lidocaine may have a lidocaine concentration of between about 0.1% and about 5% by weight of the composition, for example, about 0.3%.

**[0051]** The compositions are introduced into delivery devices, for example, syringes. Syringes useful according to the present description include any syringe known in the art capable of delivering viscous dermal filler compositions. The syringes may have an internal volume of about 0.4 mL to about 3 mL, between about 0.5 mL and about 1.5 mL or between about 0.8 mL and about 1.0 mL.

**[0052]** In other embodiments, the compositions are introduced into injection devices suitable for delivering the compositions using multiple microdepot injections, into relatively shallow, superficial, surfaces of skin.

**[0053]** The gauges of needles used to deliver the present compositions includes gauges of between about 18G and about 40G. In some embodiments, the needles for delivering the compositions are between about 25G to about 33G. In some embodiments, the compositions are delivered using a needle having a gauge of 28G, 29G, 30G, 32G or 33G.

**[0054]** In another aspect of the invention, methods of treating skin using the present compositions are provided. For example, methods of improving one or more qualities of skin, or improving appearance or texture of skin, are provided.

**[0055]** In one aspect, methods of treating dryness, texture or roughness, and/or elasticity in skin are provided. The methods generally comprise treating an area of skin by introducing, into the area, multiple, spaced apart injections of a composition comprising a hyaluronic acid (HA) gel containing crosslinked HA, wherein the treated skin maintains an improved hydration, smoother texture or increased elasticity, due to the treatment for an extended duration, for example, for at least about 3 months to about a year or more.

**[0056]** In a particularly advantageous embodiment, the step of introducing is performed in only a single treatment session, thereby eliminating the need for repeated treatments to maintain the duration of effect.

**[0057]** In one aspect of the invention, a method of treating skin is provided comprising introducing the composition into the skin during a treatment session comprising multiple injections of the composition into a skin region.

**[0058]** In one embodiment, a treatment session comprises a single visit by the patient to a practitioner. During the treatment session, multiple injections into the skin, for example into a particular skin region, may be administered.

**[0059]** The multiple injections of a single treatment session may comprise, for example, from 2 to about 500 injections, from about 50 to about 200 injections. In some embodiments, a treatment session comprises, for example, at least 2 injections, at least 10 injections, at least 20 injections, at least 40 injections, at least 60 injections, at least 80 injections, at least 100 injections, at least 140 injections, at least 180 injections, at least 200 injections, at least 300 injections, at least 400 injections at least 500 injections, or more, into the skin region.

**[0060]** In some embodiments, the treatment session takes no longer than about 45 minutes, no longer than about 30 minutes, no longer than about 15 minutes, or no longer than about 10 minutes per treatment area. Treatment area is defined as a skin region being treated with the present compositions and methods. The treatment area may comprise or consist of a skin region of at least one of a face, a neck, or a décolletage. The treatment area may also comprise or consist of a region of skin other than a face, neck or décolletage, for example, a skin region of the top of the hand, a knee, an elbow, a forearm, a calf, a thigh, a back, or any other region of skin that can be treated using the present compositions and methods and can be benefitted or improved thereby.

**[0061]** In some embodiments, the step of introducing comprises introducing the composition in injections spaced apart by a distance of between about 2 mm to about 30 mm. For example, the step of introducing comprises introducing the composition in injections spaced apart by a distance of between about 5 mm to about 20 mm. In some embodiments, the step of introducing comprises introducing the composition in injections spaced apart by a distance of between about 10 mm to about 15 mm.

**[0062]** In some embodiments, the injections are provided at a very superficial depth in the skin. For example, in some embodiments, the compositions are introduced at a depth of no greater than about 2000 microns. For example, the injections may be provided at a depth of about 500 microns to about 2000 microns, about 800 microns to about 1600 microns, about 1000 microns to about 1200 microns. In one embodiment, the injections are introduced in an amount of about 1  $\mu$ L to about 200  $\mu$ L, for example,

about 5  $\mu$ L to about 100  $\mu$ L per injection, for example, between about 20  $\mu$ L to about 80  $\mu$ L, for example, about 40  $\mu$ L to about 60  $\mu$ L per injection. In some embodiments, the injections are introduced in an amount of about 5  $\mu$ L to about 500  $\mu$ L per injection, about 10  $\mu$ L to about 400  $\mu$ L, about 50  $\mu$ L to about 200  $\mu$ L, or about 100  $\mu$ L per injection.

**[0063]** In some embodiments, the injections are delivered through a needle having a gauge of at least 27 G, for example, 28 G, 30 G or 32 G.

**[0064]** Advantageously, method of treatment may comprise or consist of a single treatment session lasting a relatively short amount of time. In some embodiments, the treatment session covering the region of skin being treated, comprises multiple, superficial injections into the skin region, and takes no longer than about 45 minutes. In some embodiments, the treatment session takes no longer than about 30 minutes. In yet other embodiments, the treatment session takes no longer than about 20 minutes, or no longer than about 15 minutes, or no longer than about 10 minutes.

**[0065]** A method of treating roughness in skin is also provided, wherein the method comprises treating an area of skin by introducing, into the area, multiple, spaced apart injections of a composition comprising a hyaluronic acid (HA) gel containing crosslinked HA wherein the treated skin maintains a smoother texture due to the treatment for at least about 3 months, for at least about 4 months, for at least about 6 months, for at least about 9 months, or for at least about 12 months.

**[0066]** In a particular embodiment, the compositions of the invention comprise a sterile physiological solution of hyaluronic acid (HA) gel of non-animal origin cross-linked with 1,4-Butanediol Diglycidyl ether (BDDE) at a concentration of 12mg/mL. The compositions are useful for treatment of superficial skin depressions as measured by improvement in skin texture and improvement of skin quality, such as smoothness, hydration and elasticity. In a particular embodiment, methods of treatment include injections, for example, depot injections, into the dermis using a 32G needle across the target anatomic region(s). The target anatomic regions include skin regions of the face, and skin regions of the neck. The improvement of skin appearance, for example,

reduced appearance of depressions, fine lines and uneven or rough texture, may be markedly noticeable by the patient, and the improvement may last for a duration of at least 4 months, 6 months, 9 months or even 12 months, after a single treatment session lasting only 45 minutes, or only 30 minutes, or only 20 minutes, or only 15 minutes, or less. Improvement of skin texture can be evaluated using appropriate scales. Skin quality measurements of hydration and elasticity can be performed, using appropriate instrumentation, and compared to baseline. Other evaluation methods, for example, FACE Q and GAIS can be utilized to assess subject and investigator satisfaction, respectively. In a specific embodiment, the duration of action of the product after the treatment is at least about 4 months for example, about 6 months.

**[0067]** The addition of lidocaine to the compositions in some embodiments, reduces pain in the treatment area. However, in some embodiments, the compositions do not include lidocaine, in order to address patient need with regard to pain sensitivity and allergy to lidocaine.

**[0068]** Another embodiment provides a method of increasing at least one of smoothness, hydration, and elasticity in skin comprising introducing, into a skin region at a depth of between about , in a single treatment session, multiple, spaced apart injections of a composition comprising a hyaluronic acid (HA) gel containing BDDE-crosslinked HA and uncrosslinked HA, wherein the injections are introduced in an amount of about 5  $\mu$ L to about 100  $\mu$ L per injection, wherein the injections are delivered through a needle having a gauge of from 28 G to 33 G, wherein the injections are spaced apart by a distance of between about 5 mm to about 20 mm.

**[0069]** In some embodiments, the skin region maintains an increased smoothness, hydration, and/or elasticity due to the treatment for at least about 3 months, about 4 months, about 5 months, about 6 months, 9 months, 12 months, or longer.

**[0070]** In another embodiment, a composition for increasing at least one of smoothness, hydration, and elasticity in skin is provided comprising a hyaluronic acid (HA) gel comprising a crosslinked HA matrix made with a low molecular weight HA

material having a weight average molecular weight of between about 400,000 Da and about 800,000 Da; wherein the HA concentration of the composition is from about 10.0 mg/g to about 14.0 mg/g; and wherein the composition maintains the increased smoothness, hydration, and/or elasticity due to the treatment for at least about 6 months from being introduced into the skin in a single treatment session comprising multiple, spaced apart injections of the composition in which the injections are introduced in an amount of about 5  $\mu$ L to about 100  $\mu$ L per injection, delivered through a needle having a gauge of from 28 G to 33 G and are spaced apart by a distance of between about 5 mm to about 20 mm. The skin region may maintain an increased smoothness, hydration, and/or elasticity due to the treatment for at least about 3 months, about 4 months, about 5 months, about 6 months, 9 months, 12 months, or longer. The compositions may further include at least one of a mannitol and a Vitamin C. In some embodiments, both mannitol and a Vitamin C derivative are present in the compositions.

### **EXAMPLE**

The free radical degradation test allows to evaluate the resistance of a gel sample toward the degradation of the HA chains by the free radicals (one of the main degradation pathway of HA). Free radical degradation tests was carried out on 3 different batches of the present compositions. The results obtained are presented on the Table1. All measures were found to conform (CVr<10%).

Gel	References	m gel (g)	r <sup>2</sup>	initial viscosity (Pa.s)	slope	degradation time (s)	Conformity
LBA2-214		0.9985	0.9959	17.7	-0.0027	4572	CF
		0.9950	0.9953	15.5	-0.0023	4858	
		0.9972	0.9945	16.1	-0.0021	5044	
	Mean			16.4	-0,0024	4825	
	STD			1.1	0,0003	238	
	CVr (%)			7%	/	5%	
LBA2-263		0.9962	0.9975	12.5	-0.0016	5377	CF

		1.0039	0.9976	13.8	-0.0018	5009	
		0.9989	0.9953	13.9	-0.0019	4882	
	<b>Mean</b>			<b>13.4</b>	<b>-0.0018</b>	<b>5090</b>	
	STD			0,8	0.0002	257	
	CVr (%)			6%	/	5%	
LBA2-288		0.9952	0.9951	13.7	-0.0018	5057	CF
		0.9984	0.9966	14.1	-0.0018	5189	
		1.0063	0.9951	13.7	-0.0020	4878	
	<b>Mean</b>			<b>13.8</b>	<b>-0.0019</b>	<b>5041</b>	
	STD			0.2	0.0001	156	
	CVr (%)			2%	/	3%	

TABLE 1 Free radical degradation results for the present compositions

The inter-batch variability is around 3% on the 3 different batches and the average value of degradation time is 4985 s (Table 2).

	<b>LBA2-214</b>	<b>LBA2-288</b>	<b>LBA2-263</b>	
<b>mes1</b>	4572	5057	5377	
<b>mes2</b>	4858	5189	5009	
<b>mes3</b>	5044	4878	4882	
<b>mean</b>	4825	5041	5089	<b>4985</b>
<b>STD</b>	238	156	257	<b>141</b>
<b>CVr</b>	5%	3%	5%	<b>3%</b>

TABLE 2 Inter-batch variability for the present compositions degradation times

### **EXAMPLE**

**[0071]** A 37-year old woman presents with rough, dry facial skin due to aging, dry climate and/or sun/wind exposure over the course of her lifetime. The physician administers, by superficial, micro-depot injections, the compositions described herein. The treatment consists of from 10 to about 100 shallow injections per skin region, with a 32 G/4 mm needle. The skin regions treated are the face, neck, and décolleté. The treatment session, over the total of all of the skin regions of the patient, lasts about 40 minutes from the initial injection to the final injection. Each treatment region receives an appropriate amount of the composition in spaced apart injections. The facial region for example, receives about 2 mL to about 3 mL of the composition, administered by shallow single injections spaced apart approximately every 10 mm to about 15 mm. The neck is treated with about 1 mL to 2 mL of the composition, the injections spaced apart approximately every 15 mm to about 20 mm. After the treatment, the areas of the skin treated are examined by the senses of sight, touch and pressure. A photographic evaluation is performed at the beginning and at the end of the treatment. The patient reports to the physician that the treatment has caused only minimum discomfort. The patient returns to her everyday activities immediately after the treatment. In a small area on the skin of her treated right hand, ecchymosis is found, but this resolves a few days after the application of an anti-inflammatory cream. The patient returns to the physician 4 months after the treatment for a follow up evaluation. Prior to the follow up evaluation visit, no further injections of fillers or mesotherapy treatments are performed on the patient. On objective examination at the follow up visit, the treatment has resulted in an improvement in the epidermal texture, and decreased dryness, and improved brightness of the skin. These improvements are evidenced in part by the photographic documentation. The treated skin regions are gently palpated and seem to have an increase in hydration, suppleness, elasticity and tone. The patient expresses a high degree of satisfaction with the treatment via the completion of a self-assessment questionnaire. The patient claims the treated areas have improved and she is very happy with the results. Interestingly, these good results are achieved based on only the single treatment session, with no repeated injections,

“top-ups”, or further injection treatment between the time of the treatment session and the follow up visit.

**[0072]** Although the invention has been described and illustrated with a certain degree of particularity, it is understood that the present disclosure has been made only by way of example, and that numerous changes in the combination and arrangement of parts, steps and elements can be resorted to by those skilled in the art without departing from the scope of the invention, as hereinafter claimed.

What is claimed is:

1. An injectable composition useful for reducing the appearance of superficial depressions in the skin, the composition comprising:

a hyaluronic acid (HA) gel comprising a crosslinked HA matrix made with a low molecular weight HA material having a weight average molecular weight of between 0.20 about MDa and about 0.99 MDa;

wherein the HA concentration of the composition is less than about 17.0 mg/g;

wherein the composition maintains the reduced appearance of superficial depressions in the skin for at least about 3 months from being introduced into the skin.

2. The composition of claim 1 wherein the composition maintains the reduced appearance of superficial depressions in the skin for at least about 6 months from being introduced into the skin.

3. The composition of claim 1 wherein the composition maintains the reduced appearance of superficial depressions in the skin for at least about 9 months from being introduced into the skin.

4. The composition of claim 1 further comprising at least one of mannitol and a vitamin C derivative.

5. The composition of claim 4 wherein the mannitol is present in an amount of between about 0.3% to about 0.9% w/w.

6. The composition of claim 4 wherein the vitamin C derivative is ascorbic acid 2-glucoside.

7. The composition of claim 6 wherein the ascorbic acid 2-glucoside is present in an amount of between about about 0.3% to about 0.6%w/w.

8. The composition of claim 1 further comprising about 0.9% w/w mannitol and about 0.6% w/w ascorbic acid 2-glucoside.
9. The composition of claim 1 wherein the weight average molecular weight of the low molecular weight HA material is between about 400,000 Da and about 800,000 Da.
10. The composition of claim 1 wherein the crosslinked HA matrix is crosslinked with a crosslinking agent selected from the group consisting of 1,4-butanediol diglycidyl ether (BDDE), 1,4-bis(2,3-epoxypropoxy)butane, 1,4-bisglycidylloxybutane, 1,2-bis(2,3-epoxypropoxy)ethylene and 1-(2,3-epoxypropyl)-2,3-epoxycyclohexane.
11. The composition of claim 1 wherein the HA concentration is about 10.0 mg/g to about 14.0 mg/g.
12. The composition of claim 1 wherein the HA concentration is about 12.0 mg/g.
13. An injectable composition useful for reducing the appearance of superficial depressions in the skin or for improving skin quality, the composition comprising:
  - a hyaluronic acid (HA) gel comprising a crosslinked HA matrix;
  - at least one of a mannitol and a Vitamin C derivative;
  - wherein the HA concentration of the composition is less than about 17.0 mg/g;
  - wherein the composition maintains the reduced appearance of superficial depressions in the skin or the improved skin quality for at least about 3 months from being introduced into the skin.
14. The composition of claim 13 wherein the composition maintains the reduced appearance of superficial depressions in the skin or the improved skin quality for at least about 6 months from being introduced into the skin.

15. The composition of claim 13 wherein the composition maintains the reduced appearance of superficial depressions in the skin or the improved skin quality for at least about 9 months from being introduced into the skin.
16. The composition of claim 13 wherein the mannitol is present in an amount of between about 0.3% to about 0.9% w/w.
17. The composition of claim 13 wherein the vitamin C derivative is ascorbic acid 2-glucoside.
18. The composition of claim 17 wherein the ascorbic acid 2-glucoside is present in an amount of between about about 0.3% to about 0.6% w/w.
19. The composition of claim 13 wherein the at least one of a mannitol and a Vitamin C derivative comprises both mannitol present at about 0.9% w/w and a Vitamin C derivative present at about 0.6% w/w.
20. The composition of claim 19 wherein the Vitamin C derivative is ascorbic acid 2-glucoside.
21. The composition of claim 13 wherein the HA concentration is about 10.0 mg/g to about 14.0 mg/g.
22. The composition of claim 13 wherein the HA concentration is about 12.0 mg/g.
23. A method of improving at least one of texture, hydration and elasticity of skin, the method comprising;  
treating an area of skin by introducing into a skin region, in a single treatment session, multiple, spaced apart injections of a composition comprising a hyaluronic acid (HA) gel containing crosslinked HA;  
wherein the HA concentration of the composition is less than about 17.0 mg/g;

wherein the treated skin maintains at least one of an improved texture, hydration and elasticity due to the treatment for at least about 3 months.

24. The method of claim 23 wherein the treated skin maintains the at least one of an improved texture, hydration and elasticity due to the treatment for at least about 6 months.

25. The method of claim 23 wherein the treated skin maintains the at least one of an improved texture, hydration and elasticity due to the treatment for at least about 12 months.

26. The method of claim 23 wherein the HA concentration is about 10.0 mg/g to about 14.0 mg/g.

27. The method of claim 23 wherein the HA concentration is about 12.0 mg/g.

28. The method of claim 23 wherein the injections are spaced apart by a distance of between about 5 mm to about 20 mm.

29. The method of claim 23 wherein the injections are introduced in an amount of about 5  $\mu$ L to about 100  $\mu$ L per injection.

30. The method of claim 23 wherein the treatment takes no longer than about 45 minutes.

31. The method of claim 23 wherein the injections are delivered through a needle having a gauge of from 28 G to 33 G.

32. The method of claim 23 wherein the composition further comprising at least one of mannitol and a vitamin C derivative.

33. The method of claim 23 wherein the mannitol is present in an amount of between about 0.3% and about 0.9% w/w.

34. The method of claim 23 wherein the vitamin C derivative is ascorbic acid 2-glucoside.

35. The method of claim 34 wherein the ascorbic acid 2-glucoside is present in an amount of between about 0.3% and about 0.6% % w/w.

36. A method of increasing at least one of smoothness, hydration, and elasticity in skin comprising;

introducing, into a skin region at a depth of between about , in a single treatment session, multiple, spaced apart injections of a composition comprising a hyaluronic acid (HA) gel containing BDDE-crosslinked HA and uncrosslinked HA;

wherein the injections are introduced in an amount of about 5  $\mu$ L to about 100  $\mu$ L per injection;

wherein the injections are delivered through a needle having a gauge of from 28 G to 33 G;

wherein the injections spaced apart by a distance of between about 5 mm to about 20 mm; and

wherein the skin region maintains an increased smoothness, hydration, and/or elasticity due to the treatment for at least about 6 months.

37. The method of claim 36 wherein the composition further comprises at least one of mannitol and a vitamin C derivative.

38. A composition for increasing at least one of smoothness, hydration, and elasticity in skin comprising:

a hyaluronic acid (HA) gel comprising a crosslinked HA matrix made with a low molecular weight HA material having a weight average molecular weight of between about 400,000 Da and about 800,000 Da;

wherein the HA concentration of the composition is from about 10.0 mg/g to about 14.0 mg/g; and

wherein the composition maintains the increased smoothness, hydration, and/or elasticity due to the treatment for at least about 6 months from being introduced into the skin in a single treatment session comprising multiple, spaced apart injections of the composition in which the injections are introduced in an amount of about 5  $\mu$ L to about 100  $\mu$ L per injection, delivered through a needle having a gauge of from 28 G to 33 G and are spaced apart by a distance of between about 5 mm to about 20 mm.

39. The composition of claim 38 wherein the composition further comprises at least one of mannitol and a vitamin C derivative.

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/IB2015/000347

A. CLASSIFICATION OF SUBJECT MATTER		
INV.	A61K8/34 C08J3/075	A61K8/60 A61K8/67
	A61K8/73	A61Q19/08
		C08B37/08
ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
A61K A61Q C08B C08J		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
EPO-Internal		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>"SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED) I. GENERAL INFORMATION Device Generic Name: Injectable Dermal Filler Device Trade Name: Restylane Silk Injectable Gel Device Procode: LMH Applicant's Name and Address: Valeant Pharmaceuticals North America",  13 June 2014 (2014-06-13), pages 1-33, XP055210777, Retrieved from the Internet: URL: <a href="http://www.accessdata.fda.gov/cdrh_docs/pdf4/P040024S072b.pdf">http://www.accessdata.fda.gov/cdrh_docs/pdf4/P040024S072b.pdf</a> [retrieved on 2015-09-02] Device Description, Preclinical Studies ----- -/-</p>	1,2,10
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> 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
23 October 2015		18/01/2016
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer  Skulj, Primoz

## INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2015/000347

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2006/194758 A1 (LEBRETON PIERRE [FR]) 31 August 2006 (2006-08-31) claims 1,9,10,12,13,16 -----	1-3,10, 11,23-26
X	US 2011/118206 A1 (LEBRETON PIERRE F [FR]) 19 May 2011 (2011-05-19)  paragraphs [0013] - [0016], [0018], [0024], [0036], [0045], [0050]; claims 1,5,10,15 -----	1-3, 9-11, 23-26,31
X	US 2011/172180 A1 (GOUSSE CECILE [FR] ET AL) 14 July 2011 (2011-07-14)  paragraph [0033]; claims 1-5; examples 2-5,20,33 -----	1-7, 13-18, 20,23-27 1-35,38, 39
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X	WO 2013/040242 A2 (ALLERGAN INC [US]; NJIKANG GABRIEL N [US]; YU XIAOJIE [US]; LIU FUTIAN) 21 March 2013 (2013-03-21)  pages 3,7,39; claims 37,34,38,39 -----	1-4,6, 10,11, 13-15, 17,20, 21, 23-27,34 1-35,38, 39
X	KABLIK JEFFREY ET AL: "Comparative physical properties of hyaluronic acid dermal fillers", DERMATOLOGIC SURGERY, WILEY-BLACKWELL PUBLISHING, INC, NEW YORK, US, vol. 35, no. Suppl.1, 1 February 2009 (2009-02-01), pages 302-312, XP009135280, ISSN: 1076-0512 the whole document pages 303,304; table 1 page 310 ----- -/--	1-3,10, 23-25

## INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2015/000347

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Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	<p>Weidmann: "Varioderm - Eine Innovation im Bereich der Hyaluronsäuren", Kosmetische Medizin, 30 June 2007 (2007-06-30), XP055210966, Retrieved from the Internet: URL:http://www.adoderm.com/literature/kosmetische-medizin-varioderm-dr.weidmann,06-2007.pdf [retrieved on 2015-09-03] page 275</p> <p>-----</p>	1-3, 9-12, 23-31,38
X	<p>J U: "VARIODERM es", 31 December 2011 (2011-12-31), XP055210889, Retrieved from the Internet: URL:http://www.cirugiadeavanzada.com/PDF/VARIODERM.PDF [retrieved on 2015-09-02] the whole document</p> <p>-----</p>	1
Y		1-35,38, 39
	-/--	

## INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2015/000347

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>"The European Aesthetic Guide",  31 December 2011 (2011-12-31),  XP055210886,  Retrieved from the Internet:  URL: <a href="http://cdn.coverstand.com/3708/63217/63217.5.pdf">http://cdn.coverstand.com/3708/63217/63217.5.pdf</a>  [retrieved on 2015-09-02]  pages 98-99</p> <p style="text-align: center;">-----</p>	1
X	<p>MARCIA RAMOS-E-SILVA ET AL: "STYLAGE : a  range of hyaluronic acid dermal fillers  containing mannitol. Physical properties  and review of the literature",  CLINICAL, COSMETIC AND INVESTIGATIONAL  DERMATOLOGY,  1 October 2013 (2013-10-01), page 257,  XP055211011,  DOI: 10.2147/CCID.S35251</p>	1-4, 13-15
Y	<p>the whole document</p> <p style="text-align: center;">-----</p>	1-35, 38, 39

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2015/000347

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
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			EP	2289945 A1		02-03-2011
			EP	2868669 A1		06-05-2015
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WO 2013040242	A2	21-03-2013	NONE			
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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IB2015/000347

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

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

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-35, 38, 39

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

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

1. claims: 1-35, 38, 39

HA dermal filler compositions with the concentration of HA below 17 mg/g and their uses

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2. claims: 36, 37

The administration technique of the HA dermal filler compositions

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