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(54) Title: COMPOSITIONS OF EMPTY NANOPARTICLES AND THEIR USE FOR TREATING DERMATOLOGICAL CONDITIONS

(57) Abstract: The present invention describes systems and methods for treating disorders and/or conditions associated with the dermal level of the skin. Such disorders include acne, hyperhidrosis, bromhidrosis, chromhidrosis, rosacea, hair loss, dermal infection, and/or actinic keratosis, among others. Methods generally involve administering provided compositions to the skin.



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COMPOSITIONS OF EMPTY NANOPARTICLES AND THEIR USE FOR TREATING DERMATOLOGICAL CONDITIONS

Related Applications

[0001] This application claims priority to and benefit of U.S. provisional application serial number 61/435,749 filed January 24, 2011, the entire contents of which are incorporated herein by reference.

Background

[0002] Conditions or disorders associated with sweat glands or sebaceous glands can be both physically and psychologically debilitating to those who suffer from them. Current treatments are not very successful and often have undesirable side effects. For example, according to studies, acne often leads to reduced self esteem, and sometimes even to depression or suicide (see, *e.g.*, Goodman, 2006, *Aust. Fam. Physician* 35:503, 2006; Purvis *et al.*, 2006, *J. Paediatr. Child. Health* 42:793; both of which are incorporated herein by reference). Similar challenges are observed with hyperhidrosis (excessive sweating), bromhidrosis (body odor), chromhidrosis (colored sweat), psoriasis, dermal infection (*e.g.*, bacterial infection, viral infection, fungal infection, *etc.*), hair loss, actinic keratosis, rosacea, and other afflictions of the skin.

Summary of the Invention

[0003] The present invention encompasses the surprising finding that nanoparticle compositions, applied topically, can have beneficial effects on dermal structures even when prepared without a known therapeutic agent. Provided compositions are useful in medicine, for example to treat or prevent (*e.g.*, reduce the intensity and/or frequency of, and/or delay onset of, one or more symptoms or side effects of) diseases, disorders, or conditions associated with dermal structures. Provided compositions may also be useful to treat or prevent other diseases, disorders or conditions. Provided novel compositions may be used in accordance with the present invention for any purpose, and in particular for any topical administration to skin of a subject.

[0004] The present invention specifically encompasses use of nanoparticle compositions as described, for example, in U.S. patent number 7,763,663, issued on July 27, 2010, and entitled "POLYSACCHARIDE-CONTAINING BLOCK COPOLYMER PARTICLES AND USES THEREOF"; PCT patent application number PCT/US06/026918, filed July 11, 2006,

published as WO 08/010788 on January 24, 2008, and entitled “COMPOSITIONS AND METHODS FOR MAKING AND USING NANOEMULSIONS”; PCT patent application number PCT US06/46236, filed December 1, 2006, published as WO 08/045107 on April 17, 2008, and entitled “BOTULINUM NANOEMULSIONS; in PCT patent application number PCT US07/86018, filed November 30, 2007, published as WO 08/070538 on June 12, 2008, and entitled “AMPHIPHILIC ENTITY NANOPARTICLES”; PCT patent application number PCT/ US07/86040, filed November 30, 2007, published as PCT publication WO 08/140594 on November 20, 2008, and entitled “PEPTIDE NANOPARTICLES AND USES THEREFOR”; PCT application serial number PCT/US08/65329, filed May 30, 2008, published as PCT publication WO 08/151022 on December 11, 2008, and entitled “NUCLEIC ACID NANOPARTICLES AND USES THEREFOR”; and/or in PCT patent application number PCT US09/48972, filed June 26, 2009, published as WO 09/158687 on December 30, 2009, and entitled “DERMAL DELIVERY”; the contents of all of which are incorporated herein by reference. As described, such compositions may or may not include a biologically active agent. The present invention specifically addresses use of nanoparticle compositions that do not include as a biologically active agent a known therapeutic agent (*e.g.*, a therapeutic agent known to affect a dermal structure such as sweat glands, sebaceous glands, hair follicles, *etc.*) and/or an independently active biologically active agent (*e.g.*, an agent that shows biological activity whether or not the agent is present in a nanoparticle composition as described herein). Such nanoparticle compositions are referred to herein as “empty nanoparticle compositions.” It should be appreciated, however, that to the extent the present disclosure establishes one or more biological effects achieved with such empty nanoparticle compositions, the empty nanoparticle compositions themselves are demonstrated to be or contain (*e.g.*, through combination and/or structural arrangement of component ingredients) one or more biologically active agents. A nanoparticle composition is nonetheless referred to herein as an empty nanoparticle composition so long as the composition (i) is prepared without inclusion of a single particular ingredient known in advance to achieve by itself the biological effect ultimately observed with the empty nanoparticle composition; and/or (ii) without inclusion of a single particular ingredient that shows biological activity whether or not the agent is present in a nanoparticle composition as described herein.

[0005] The present invention therefore provides use of provided compositions (*e.g.*, empty nanoparticle compositions and/or individual components thereof) as described herein in

medicine, and in particular for the treatment of conditions or disorders associated with dermal structures (*e.g.*, sweat glands, sebaceous glands, hair follicles, *etc.*). The present invention further provides technologies for identifying the component or components present in the provided compositions that are responsible for the observed activity of the composition. To the extent that such technologies identify component(s) that can achieve the observed results independent of a nanoparticle structure, the present invention also provides use in medicine, and in particular in the treatment of conditions or disorders associated with dermal structures (*e.g.*, sweat glands, sebaceous glands, hair follicles, *etc.*), of compositions containing one or more empty nanoparticle components.

[0006] The present invention particularly provides uses that involve topical application (*e.g.*, to a skin surface) of a composition comprising an empty nanoparticle composition (or one or more individual components thereof) as described herein, to a subject suffering from or susceptible to a condition or disorder associated with dermal structures (*e.g.*, sweat glands, sebaceous glands, hair follicles, *etc.*). In some embodiments, administration of such a composition partially or completely treats, alleviates, ameliorates, relieves, inhibits, delays onset of, reduces severity of and/or reduces incidence of one or more symptoms of a condition or disorder associated with dermal structures (*e.g.*, sweat glands, sebaceous glands, hair follicles, *etc.*). Exemplary conditions or disorders associated with dermal structures include, but are not limited to, acne, hyperhidrosis, unwanted sweating, bromhidrosis, body odor, chromhidrosis, rosacea, hair loss, psoriasis, dermal infection (*e.g.*, herpes simplex virus infection, human papillomavirus infection, fungal infection, *etc.*), actinic keratosis, eczematous dermatitis (*e.g.*, atopic dermatitis, *etc.*), excess sebum-producing disorders (*e.g.*, seborrhea, seborrheic dermatitis, *etc.*), burns, Raynaud's phenomenon, lupus erythematosus, hyperpigmentation disorders (*e.g.*, melasma, *etc.*), hypopigmentation disorders (*e.g.*, vitiligo, *etc.*), and/or skin cancer (*e.g.*, squamous cell skin carcinoma, basal cell skin carcinoma, *etc.*).

[0007] In some embodiments, methods of treating conditions or disorders associated with dermal structures (*e.g.*, sweat glands, sebaceous glands, hair follicles, *etc.*) involve applying to a skin surface a composition containing a provided composition (*e.g.*, an empty nanoparticle composition such as an empty nanoemulsion, or another composition comprising one or more components of an empty nanoparticle composition). In some embodiments, a provided composition (*e.g.*, an empty nanoparticle composition such as an empty nanoemulsion, or another composition comprising one or more components of an

empty nanoparticle composition) is arranged and constructed such that it does not induce unwanted clinical effects inside and/or outside of the dermis.

[0008] In some embodiments, provided compositions may be formulated and/or delivered so that systemic delivery is achieved; in some embodiments, provided compositions may be formulated and/or delivered so that local, but not systemic, delivery is achieved.

[0009] According to the present invention, provided compositions are useful in various cosmetic and medical applications. In some embodiments, provided compositions are utilized to treat acne. In some embodiments, provided compositions are utilized to treat hyperhidrosis. In some embodiments, provided compositions are utilized to treat acne. In some embodiments, provided compositions are utilized to treat unwanted sweating. In some embodiments, provided compositions are utilized to treat bromhidrosis. In some embodiments, provided compositions are utilized to treat acne. In some embodiments, provided compositions are utilized to treat body odor. In some embodiments, provided compositions are utilized to treat chromhidrosis. In some embodiments, provided compositions are used to treat disorders or conditions associated with sweat glands. In some embodiments, provided compositions are used to treat disorders or conditions associated with sebaceous glands, such as excess sebum-producing disorders (*e.g.*, seborrhea, seborrheic dermatitis, *etc.*). In some embodiments, provided compositions are used to treat disorders or conditions associated with any component of the dermis that is present at around the same level of depth as sweat and sebaceous glands. In some embodiments, provided compositions are used to treat rosacea. In some embodiments, provided compositions are used to treat hair loss. In some embodiments, provided compositions are used to treat psoriasis. In some embodiments, provided compositions are used to treat dermal infections (*e.g.*, bacterial infections, viral infections, fungal infection, *etc.*). In some embodiments, provided compositions are used to treat actinic keratosis. In some embodiments, provided compositions are used to treat eczematous dermatitis (*e.g.*, atopic dermatitis, *etc.*). In some embodiments, provided compositions are used to treat excess sebum-producing disorders (*e.g.*, seborrhea, seborrheic dermatitis, *etc.*). In some embodiments, provided compositions are used to treat burns. In some embodiments, provided compositions are used to treat Raynaud's phenomenon. In some embodiments, provided compositions are used to treat lupus erythematosus. In some embodiments, provided compositions are used to treat hyperpigmentation disorders (*e.g.*, melasma, *etc.*). In some embodiments, provided compositions are used to treat hypopigmentation disorders (*e.g.*, vitiligo, *etc.*) or

hyperpigmentation disorders (e.g., melasma). In some embodiments, provided compositions are used to treat skin cancer (e.g., squamous cell skin carcinoma, basal cell skin carcinoma, *etc.*). As used herein, the term “treat” refers to partially or completely alleviating, ameliorating, relieving, inhibiting, delaying onset of, reducing severity of, and/or reducing incidence of one or more symptoms of a condition or disorder associated with dermal structures (e.g., sweat glands, sebaceous glands, hair follicles, *etc.*), including, but not limited to, those conditions or disorders described herein.

[00010] As described herein, the present inventors have found that particular provided compositions are surprisingly useful and/or effective in the treatment of certain conditions when applied to the dermis. In some embodiments, provided compositions formulated and used according to the present invention are administered via topical and/or transdermal (e.g., by lotions, creams, powders, ointments, liniments, gels, drops, *etc.*) administration.

[00011] Without wishing to be bound by any particular theory, Applicant appreciates that, particularly to the extent that the observed activity results at least in part from previously unappreciated biological activity of one or more components of provided compositions, and/or one or more structural features (e.g., nanoemulsion characteristics) of provided compositions, in at least some contexts, provided compositions may well be useful and/or effective when formulated for delivery by a route other than topical. For example, in some embodiments, provided compositions are formulated for delivery and/or are delivered by a route selected from the group consisting of oral (PO), intravenous (IV), intramuscular (IM), intra-arterial (IA), intramedullary, intrathecal, subcutaneous (SQ), intraventricular, interdermal, intradermal, rectal (PR), vaginal, intraperitoneal (IP), intragastric (IG), mucosal, intranasal, buccal, enteral, vitreal, sublingual; by intratracheal instillation, bronchial instillation, and/or inhalation; as an oral spray, nasal spray, and/or aerosol, and/or through a portal vein catheter; and/or combinations thereof.

[00012] Comparably, provided novel compositions may be used in accordance with the present invention for any purpose, including for example to achieve any therapeutic, diagnostic, or cosmetic result.

[00013] The inventors have discovered that, in some embodiments, provided compositions can be used for treatment of conditions or disorders associated with dermal structures (e.g., sweat glands, sebaceous glands, hair follicles, *etc.*) without changing or altering the structure of the skin. For example, abrasive agents or agents that erode or deteriorate the superficial layer of the skin are not required for provided compositions (e.g.,

empty nanoparticle compositions such as an empty nanoemulsions, or other compositions comprising one or more components of an empty nanoparticle composition) to be therapeutically useful. Thus, in many embodiments, treatment of conditions or disorders associated with dermal structures (*e.g.*, sweat glands, sebaceous glands, hair follicles, *etc.*) using provided compositions is accomplished without significant irritation of the skin.

[00014] In some embodiments, provided compositions for use in accordance with the present invention are prepared by exposure to high shear forces; in some embodiments, provided compositions are prepared by microfluidization; in some embodiments, provided compositions are prepared by high pressure homogenization.

[00015] According to the present invention, provided compositions may be used (*e.g.*, in the treatment of conditions or disorders associated with dermal structures (*e.g.*, sweat glands, sebaceous glands, hair follicles, *etc.*)) in any of a variety of formats. In some embodiments, a provided composition is incorporated within a cream, gel, powder, or lotion such that the provided composition is administered to a subject by application to the skin. In some embodiments, a provided composition is incorporated within an ointment and/or liniment such that the provided composition is administered to a subject by application to the skin. In some embodiments, a provided composition is incorporated within a suspension, microemulsion, nanoemulsion, and/or liposome such that the provided composition is administered to a subject by application to the skin. In some embodiments, a provided composition is incorporated within a transdermal patch such that the provided composition is administered to a subject from the patch.

[00016] In some embodiments, provided compositions are or include emulsions containing a population of particles having maximum and minimum diameters, wherein the difference between the maximum and minimum diameters does not exceed about 600 nanometers (nm), about 550 nm, about 500 nm, about 450 nm, about 400 nm, about 350 nm, about 300 nm, about 250 nm, about 200 nm, about 150 nm, about 100 nm, about 90 nm, about 80 nm, about 70 nm, about 60 nm, about 50 nm, or fewer than about 50 nm.

[00017] In some embodiments, particles within provided compositions used in accordance with the present invention have diameters that are smaller than about 600 nm, about 550 nm, about 500 nm, about 450 nm, about 400 nm, about 350 nm, about 300 nm, about 250 nm, about 200 nm, about 150 nm, about 130 nm, about 120 nm, about 115 nm, about 110 nm, about 100 nm, about 90 nm, about 80 nm, about 70 nm, about 60 nm, about 50 nm, about 40 nm, about 30 nm, about 20 nm, or less than about 20 nm.

[00018] In some embodiments, particles within provided compositions have diameters within the range of about 10 and about 600 nm. In some embodiments, particles within nanoparticle compositions have diameters within the range of about 10 nm and about 300 nm, about 10 nm and about 200 nm, about 10 nm and about 150 nm, about 10 nm and about 130 nm, about 10 nm and about 120 nm, about 10 nm and about 115 nm, about 10 nm and about 110 nm, about 10 nm and about 100 nm, or about 10 nm and about 90 nm.

[00019] In some embodiments, particles within provided compositions have an average particle size that is under about 600 nm, about 550 nm, about 500 nm, about 450 nm, about 400 nm, about 350 nm, about 300 nm, about 250 nm, about 200 nm, about 150 nm, about 130 nm, about 120 nm, about 115 nm, about 110 nm, about 100 nm, or about 90 nm. In some embodiments, the average particle size is within the range of about 10 nm and about 300 nm, about 50 nm and about 250 nm, about 60 nm and about 200 nm, about 65 nm and about 150 nm, or about 70 nm and about 130 nm. In some embodiments, the average particle size is about 80 nm and about 110 nm, about 70 nm and about 90 nm, about 60 nm and about 80 nm, about 50 nm and about 70 nm, or about 10 nm and about 50 nm. In some embodiments, the average particle size is about 90 nm and about 100 nm.

[00020] In some embodiments, a majority of the particles within provided compositions used in accordance with the invention have diameters below a specified size or within a specified range. In some embodiments, the majority is more than 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, 99.9% or more of the particles in the composition.

[00021] In some embodiments, provided compositions used in accordance with the present invention are substantially free of particles having diameters greater than about 600 nm, about 500 nm, about 400 nm, about 300 nm, about 200 nm, about 150 nm, and/or about 120 nm. In some embodiments, particles within provided compositions have diameters within the range of about 30 nm and about 115 nm. In some embodiments, most of the particles within the composition have diameters within this range; in some embodiments, such compositions are substantially free of particles having diameters larger than about 115 nm. In some embodiments, particles within provided compositions have diameters within the range of about 30 nm to about 70 nm or 40 nm to 90 nm. In some embodiments, most of the particles within such compositions have diameters within this range; in some embodiments the provided compositions are substantially free of particles with diameters larger than about 70 nm.

[00022] In some embodiments, provided compositions used in accordance with the present invention have at least two distinct populations of particles. For example, in some such embodiments, a majority of the particles in provided compositions have diameters within the range of about 30 nm and about 70 nm, while a second population of particles has diameters within the range of about 70 nm and about 120 nm. In some such embodiments, the composition is not contaminated with particles greater than 120 nm in diameter.

[00023] This application refers to various patent publications, all of which are incorporated herein by reference.

Definitions

[00024] *Abrasion:* The term “abrasion,” as used herein, refers to any means of altering, disrupting, removing, or destroying the top layer of the skin. In some embodiments, abrasion refers to a mechanical means of altering, disrupting, removing, or destroying the top layer of the skin. In some embodiments, abrasion refers to a chemical means of altering, disrupting, removing, or destroying the top layer of skin. To give but a few examples, agents such as exfoliants, fine particles (*e.g.*, magnesium or aluminum particles), acids (*e.g.*, alpha-hydroxy acids or beta-hydroxy acids), and/or alcohols may cause abrasion. In general, permeation enhancers such as those described, for example, by Donovan (see, *e.g.*, U.S. Patent Publications 2004/009180 and 2005/175636; and PCT Publication WO 04/06954; all of which are incorporated herein by reference), and Graham (see, *e.g.*, U.S. Patent 6,939,852 and U.S. Patent Publication 2006/093624; both of which are incorporated herein by reference), *etc.*, are expected to cause abrasion. Of course, those of ordinary skill in the art will appreciate that a particular agent may cause abrasion when present at one concentration, or in association with one or more other agents, but may not cause abrasion under different circumstances. Thus, whether or not a particular material is an “abrasive agent” depends on context. Abrasion can readily be assessed by those of ordinary skill in the art, for example by observation of redness or irritation of the skin and/or histologic examination of skin showing alteration, disruption, removal, or erosion of the stratum corneum.

[00025] *Administration:* The term “administration,” as used herein to refers to the administration of a provided composition (*e.g.*, an empty nanoparticle composition such as an empty nanoemulsion, or another composition comprising one or more components of an empty nanoparticle composition) to a subject, is not limited to any particular route but rather refers to any route accepted as appropriate by the medical community. For example, the

present invention contemplates routes of administering that include, but are not limited to, topical and/or transdermal. In some embodiments, the present invention contemplates routes of administering that include, but are not limited to, oral (PO), intravenous (IV), intramuscular (IM), intra-arterial, intramedullary, intrathecal, subcutaneous (SQ), intraventricular, transdermal, interdermal, intradermal, rectal (PR), vaginal, intraperitoneal (IP), intragastric (IG), topical and/or transdermal (*e.g.*, by lotions, creams, powders, ointments, liniments, gels, drops, *etc.*), mucosal, intranasal, buccal, enteral, vitreal, and/or sublingual administration; by intratracheal instillation, bronchial instillation, and/or inhalation; as an oral spray, nasal spray, and/or aerosol, and/or through a portal vein catheter; and/or combinations of any of the foregoing.

[00026] *Amino acid:* As used herein, term “amino acid,” in its broadest sense, refers to any compound and/or substance that can be incorporated into a polypeptide chain. In some embodiments, an amino acid has the general structure $\text{H}_2\text{N}-\text{C}(\text{H})(\text{R})-\text{COOH}$. In some embodiments, an amino acid is a naturally-occurring amino acid. In some embodiments, an amino acid is a synthetic amino acid; in some embodiments, an amino acid is a D-amino acid; in some embodiments, an amino acid is an L-amino acid. “Standard amino acid” refers to any of the twenty standard L-amino acids commonly found in naturally occurring peptides. “Nonstandard amino acid” refers to any amino acid, other than the standard amino acids, regardless of whether it is prepared synthetically or obtained from a natural source. Amino acids, including carboxy- and/or amino-terminal amino acids in peptides, can be modified by methylation, amidation, acetylation, and/or substitution with other chemical groups that can change the peptide's circulating half-life without adversely affecting their activity. Amino acids may participate in a disulfide bond. The term “amino acid” is used interchangeably with “amino acid residue,” and may refer to a free amino acid and/or to an amino acid residue of a peptide. It will be apparent from the context in which the term is used whether it refers to a free amino acid or a residue of a peptide.

[00027] *Animal:* As used herein, the term “animal” refers to any member of the animal kingdom. In some embodiments, “animal” refers to humans, at any stage of development. In some embodiments, “animal” refers to non-human animals, at any stage of development. In some embodiments, the non-human animal is a mammal (*e.g.*, a rodent, a mouse, a rat, a rabbit, a monkey, a dog, a cat, a sheep, cattle, a primate, and/or a pig). In some embodiments, animals include, but are not limited to, mammals, birds, reptiles, amphibians, fish, and/or worms. In some embodiments, an animal may be a transgenic

animal, genetically-engineered animal, and/or a clone.

[00028] *Approximately:* As used herein, the terms “approximately” or “about” in reference to a number are generally taken to include numbers that fall within a range of 5%, 10%, 15%, or 20% in either direction (greater than or less than) of the number unless otherwise stated or otherwise evident from the context (except where such number would be less than 0% or exceed 100% of a possible value).

[00029] *Biologically active agent:* As used herein, the phrase “biologically active agent” refers to any substance that has activity in a biological system and/or organism. For instance, a substance that, when administered to an organism, has a biological effect on that organism is considered to be biologically active. In some embodiments, where a substance (*e.g.*, a polypeptide, nucleic acid, antibody, *etc.*) is biologically active, a portion of that substance that shares at least one biological activity of the whole substance is typically referred to as a “biologically active” portion.

[00030] *Cosmetic formulation:* The term “cosmetic formulation” is used herein to refer to a topically applied composition that contains one or more agents having cosmetic properties. To give but a few examples, a cosmetic formulation may be a skin softener, nutrition lotion type emulsion, cleansing lotion, cleansing cream, skin milk, emollient lotion, massage cream, emollient cream, make-up base, lipstick, facial pack or facial gel, cleaner formulation such as shampoos, rinses, body cleanser, hair-tonics, or soaps, and/or a dermatological composition such as a lotion, ointment, gel, cream, patch, deodorant, and/or spray.

[00031] *Cream:* The term “cream” refers to a spreadable composition, typically formulated for application to the skin. Creams typically contain an oil and/or fatty acid based-matrix. Creams formulated according to the present invention may enhance and/or improve penetration and/or may be capable of substantially complete penetration (*e.g.*, of provided compositions) through the skin upon topical administration.

[00032] *Dispersion medium:* The term “dispersion medium” as used herein, refers to a liquid medium in which particles (*e.g.*, empty nanoparticles) are dispersed. In general, a dispersion is formed when at least two immiscible materials are combined. An “oil-in-water” dispersion is one in which oily particles are dispersed within an aqueous dispersion medium. A “water-in-oil” dispersion is one in which aqueous particles are dispersed within an oily dispersion medium. Those of ordinary skill in the art will appreciate that a dispersion can be formed from any two immiscible media and is not limited strictly to combinations of aqueous

and oily media. The term “dispersion medium” therefore applies broadly to *any* dispersion medium notwithstanding that it is common to refer to “aqueous” and “oily” categories.

[00033] *Encapsulated:* The term “encapsulated” (also “encapsulate” or “encapsulating”) is used herein to mean that the encapsulated entity is completely surrounded by another material. To give but one example, known therapeutic agents and/or independently active biologically active agents are not encapsulated within empty nanoparticles in an emulsion in accordance with the invention.

[00034] *Empty nanoparticle composition:* The term “empty nanoparticle composition,” as used herein, refers to a nanoparticle composition which does not include a known therapeutic agent and/or an independently active biologically active agent.

[00035] *In conjunction with:* As used herein, the phrase “administered in conjunction with” refers to the co-administration of two or more substances or agents. In particular, according to the present invention, the phrase is used herein in reference to simultaneous administration of a provided composition (*e.g.*, an empty nanoparticle composition such as an empty nanoemulsion, or another composition comprising one or more components of an empty nanoparticle composition) with another composition comprising a known therapeutic agent and/or independently active biologically active agent. In such embodiments, a known therapeutic agent and/or independently active biologically active agent is not part of the provided composition, but instead, is administered separately to the subject (*e.g.*, either as a separate composition, or having been admixed and/or formulated together with the provided composition. In some embodiments, a known therapeutic and/or independently active biologically active agent is not incorporated within nanoparticles of a nanoparticle composition; in some embodiments, a known therapeutic and/or independently active biologically active agent is not encapsulated within nanoparticles of a nanoparticle composition; in some embodiments, a known therapeutic and/or independently active biologically active agent is not otherwise in association with nanoparticles of a nanoparticle composition).

[00036] *Independently active biologically active agent:* The term “independently active biologically active agent” refers to an agent that shows biological activity whether or not the agent is present in a nanoparticle composition as described herein. In some embodiments, one or more particular biological activities of the agent is/are improved in a nanoparticle composition; in some embodiments, one or more biological activities of the agent is/are not improved in a nanoparticle composition.

[00037] *Isolated:* As used herein, the term “isolated” refers to a substance and/or entity that has been (1) separated from at least some of the components with which it was associated when initially produced (whether in nature and/or in an experimental setting), and/or (2) produced, prepared, and/or manufactured by the hand of man. Isolated substances and/or entities may be separated from at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or more of the other components with which they were initially associated. In some embodiments, isolated substances and/or entities are more than 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% pure.

[00038] *Known therapeutic agent:* As used herein, the term “known therapeutic agent” describes a biologically active agent known, prior to its incorporation in a nanoparticle composition, to have a particular biological effect *e.g.*, on a dermal structure (*e.g.*, for example, on sweat glands, sebaceous glands, hair follicles, *etc.*). In some embodiments, a known therapeutic agent describes a biologically active agent known prior to filing of the present application to have a particular biological effect, *e.g.*, on a dermal structure (*e.g.*, for example, on sweat glands, sebaceous glands, hair follicles, *etc.*). Exemplary known therapeutic agents known to have a particular biological effect on sweat glands include aluminum chloride, aluminum chlorohydrate, aluminum chlorohydrate compounds, aluminum dichlorohydrate, aluminum dichlorohydrate compounds, aluminum sesquichlorohydrate, aluminum sesquichlorohydrate compounds, aluminum zirconium tetrachlorohydrate gly, aluminum zirconium trichlorohydrate gly, ammonium alum, aluminum sulfate compounds, aluminum zirconium compounds, botulinum toxin, oral medication (*e.g.*, diphenhydramine hydrochloride, hydroxyzine, glycopyrrolate, *etc.*), anticholinergic drugs (*e.g.*, oxybutynin, glycopyrrolate, propantheline bromide, benztropine, *etc.*), beta-blockers, antidepressants, anxiolytics, talc, baby powder, and/or combinations thereof. Exemplary known therapeutic agents known to have a particular biological effect on sebaceous glands include botulinum toxin, cleansers or soaps, a topical bactericidal (*e.g.*, benzoyl peroxide, triclosan, and/or chlorhexidine gluconate), topical antibiotics (*e.g.*, externally-applied erythromycin, clindamycin, tetracycline, *etc.*), oral antibiotics (*e.g.*, erythromycin, tetracycline, oxytetracycline, doxycycline, minocycline, lymecycline, trimethoprim, *etc.*), hormonal treatments (*e.g.*, estrogen/progesterone oral contraceptives, low dose spironolactone, cortisone, *etc.*), a keratolytic (*i.e.*, a substance that dissolves keratin plugging pores), benzoyl peroxide, a topical retinoid (*e.g.*, tretinoin [RETIN-A[®]], adapalene [DIFFERIN[®]], and tazarotene [TAZORAC[®]], retinol, isotretinoin, *etc.*), oral retinoids (*e.g.*, isotretinoin

[ACUTANE[®], AMNESTEEM[™], SOTRET[™], CLARAVIS[™]]), retinoic acids, a natural product with anti-acne activity (*e.g.*, aloe vera, aruna, haldi [*i.e.*, turmeric], papaya, *etc.*), azelaic acid (brand names AZELEX[™], FINACEA[®], FINEVIN[®], SKINOREN, *etc.*), anti-inflammatory agents (*e.g.*, naproxen, ibuprofen, rofecoxib, *etc.*), nicotinamide (*i.e.*, vitamin B3), tea tree oil (melaleuca oil), aminolevulinic acid, azithromycin, methylaminolevuninate, nadifloxacin, PRK124, talarozole, zileuton, rofecoxib, zinc, an agent described in Krowchuk (2000, *Pediatric Dermatology*, 47:841-857; incorporated herein by reference) and/or in Johnson *et al.* (2000, *American Family Physician*, 62:1823-1830 and 1835-1836; incorporated herein by reference), and/or combinations thereof. Exemplary known therapeutic agents known to have a particular biological effect on hair follicles include minoxidil (ROGAINE[®]/REGAINE[®]), finasteride (PROPECIA[®]), dutasteride (AVODART[®]), an antiandrogen (*e.g.*, ketoconazole, fluconazole, spironolactone, *etc.*), saw palmetto, caffeine, copper peptides, nitroxide spin labels TEMPO and TEMPOL, unsaturated fatty acids (*e.g.*, gamma linolenic acid), hedgehog agonists, azelaic acid and zinc in combination, Chinese knotweed, pumpkin seed, tretinoin, zinc, stinging nettle, Tempol alcohol-based gel (*e.g.*, MTS-01, *etc.*), Aldara, alefacept, AS101, bimatoprost, capsaicin, efalizumab, FK506, GP11046, GP11511, hydroxychloroquine, latanoprost, MK0906, roxithromycin, Targretin Gel 1%, tetrapeptide aldehyde proteasome inhibitor (*e.g.*, NEOSH101, *etc.*), and/or combinations thereof.

[00039] *Microfluidized*: As used herein, the term “microfluidized” means exposed to high shear forces. In some embodiments, such exposure to high shear forces is accomplished by exposure to high pressure; in some embodiments such high pressure is within the range of about 15,000 psi to about 26,000 psi. In some embodiments, such exposure to high shear forces is accomplished by cavitation. In some embodiments, such exposure to high shear forces is accomplished by passing a sample through an instrument such as, for example, a Microfluidizer[®] (Microfluidics Corporation/MFIC Corporation) or other like device that may be useful in creating a uniform nanoparticle composition. In some embodiments, a sample is microfluidized through exposure to high shear forces for a period of time less than about 10 minutes. In some embodiments, the period of time is less than about 9, about 8, about 7, about 6, about 5, about 4, about 3, about 2, or about 1 minute(s). In some embodiments, the period of time is within the range of about 1 – about 2 minutes. In some embodiments, the period of time is about 30 seconds. In some embodiments, a sample is “microfluidized” through a single exposure to high shear forces; such embodiments are referred to as “single

pass” microfluidization.

[00040] *Nanoemulsion*: An emulsion is traditionally defined in the art “as a system ... consisting of a liquid dispersed with or without an emulsifier in an immiscible liquid usually in droplets of larger than colloidal size” *Medline Plus Online Medical Dictionary, Merriam Webster* (2005). The term “nanoemulsion,” as used herein, refers to an emulsion in which at least some of the droplets (or particles) have diameters in the nanometer size range. As will be understood by those of ordinary skill in the art, a nanoemulsion is characterized by droplets or particles one thousand fold smaller than microemulsion droplets or particles.

[00041] *Nanoparticle*: As used herein, the term “nanoparticle” refers to any particle having a diameter of less than 1000 nanometers (nm). In some embodiments, a nanoparticle has a diameter of less than 300 nm, as defined by the National Science Foundation. In some embodiments, a nanoparticle has a diameter of less than 100 nm as defined by the National Institutes of Health. In some embodiments, nanoparticles are micelles in that they comprise an enclosed compartment, separated from the bulk solution by a micellar membrane. A “micellar membrane” comprises amphiphilic entities which have aggregated to surround and enclose a space or compartment (*e.g.*, to define a lumen).

[00042] *Nanoparticle composition*: As used herein, the term “nanoparticle composition” refers to any substance that contains at least one nanoparticle. In some embodiments, a nanoparticle composition is a uniform collection of nanoparticles. In some embodiments, nanoparticle compositions are dispersions or emulsions. In general, a dispersion or emulsion is formed when at least two immiscible materials are combined. An “oil-in-water” dispersion is one in which oily particles (or hydrophobic or non-polar) are dispersed within an aqueous dispersion medium. A “water-in-oil” dispersion is one in which aqueous (or hydrophilic or polar) particles are dispersed within an oily dispersion medium. Those of ordinary skill in the art will appreciate that a dispersion can be formed from any two immiscible media and is not limited strictly to combinations of aqueous and oily media. The term “dispersion medium” therefore applies broadly to *any* dispersion medium notwithstanding that it is common to refer to “aqueous” and “oily” categories. In some embodiments, nanoparticle compositions are nanoemulsions. In some embodiments, nanoparticle compositions comprise micelles. In some embodiments, a nanoparticle composition comprises particles such as those described in U.S. patent number 7,763,663, issued on July 27, 2010, and entitled “POLYSACCHARIDE-CONTAINING BLOCK COPOLYMER PARTICLES AND USES THEREOF” (incorporated herein by reference). In

some embodiments, a nanoparticle composition comprises a nanoemulsion as described in PCT patent application number PCT/US06/026918, filed July 11, 2006, published as WO 08/010788 on January 24, 2008, and entitled “COMPOSITIONS AND METHODS FOR MAKING AND USING NANOEMULSIONS” (incorporated herein by reference). In some embodiments, a nanoparticle composition comprises a nanoemulsion as described in PCT patent application number PCT US06/46236, filed December 1, 2006, published as WO 08/045107 on April 17, 2008, and entitled “BOTULINUM NANOEMULSIONS” (incorporated herein by reference). In some embodiments, a nanoparticle composition comprises amphiphilic entity nanoparticles as described in PCT patent application number PCT/US07/86018, filed November 30, 2007, published as WO 08/070538 on June 12, 2008, and entitled “AMPHIPHILIC ENTITY NANOPARTICLES” (incorporated herein by reference). In some embodiments, a nanoparticle composition comprises particles as described in PCT application serial number PCT/US08/65329, filed May 30, 2008, published as PCT publication WO 08/151022 on December 11, 2008, and entitled “NUCLEIC ACID NANOPARTICLES AND USES THEREFOR” (incorporated herein by reference). In some embodiments, a nanoparticle composition comprises particles as described in PCT patent application number PCT/ US07/86040, filed November 30, 2007, published as PCT publication WO 08/140594 on November 20, 2008, and entitled “PEPTIDE NANOPARTICLES AND USES THEREFOR” (incorporated herein by reference). In some embodiments, a nanoparticle composition comprises particles as described in PCT patent application number PCT US09/48972, filed June 26, 2009, published as WO 09/158687 on December 30, 2009, and entitled “DERMAL DELIVERY” (incorporated herein by reference). In some embodiments, a nanoparticle composition is stable. In some embodiments, nanoparticle compositions are provided compositions. In accordance with the present invention, nanoparticle compositions do not contain any known therapeutic agents and/or independently active biologically active agents.

[00043] *Not contaminated with:* The phrase “not contaminated with,” when used herein to refer to a provided composition, is synonymous with “substantially free of” and describes a provided composition containing no more than about 50% of the recited material. For example, if a provided composition is said to be “substantially free of” particles whose diameter is outside of a stated range, then no more than about 50% of the particles in that composition have diameters outside of the range. In some embodiments, no more than 25% of the particles are outside of the range. In some embodiments, no more than 20%, 19%,

18%, 17%, 16%, 15%, 14%, 13%, 12%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5% or less of the particles have diameters outside of the stated range.

[00044] *Nucleic acid:* As used herein, the term “nucleic acid,” in its broadest sense, refers to any compound and/or substance that is or can be incorporated into an oligonucleotide chain. In some embodiments, a nucleic acid is a compound and/or substance that is or can be incorporated into an oligonucleotide chain via a phosphodiester linkage. In some embodiments, “nucleic acid” refers to individual nucleic acid residues (*e.g.*, nucleotides and/or nucleosides). In some embodiments, “nucleic acid” refers to an oligonucleotide chain comprising individual nucleic acid residues. As used herein, the terms “oligonucleotide” and “polynucleotide” can be used interchangeably. In some embodiments, “nucleic acid” encompasses RNA as well as single and/or double-stranded DNA and/or cDNA. Furthermore, the terms “nucleic acid,” “DNA,” “RNA,” and/or similar terms include nucleic acid analogs, *e.g.*, analogs having other than a phosphodiester backbone. For example, the so-called “peptide nucleic acids,” which are known in the art and have peptide bonds instead of phosphodiester bonds in the backbone, are considered within the scope of the present invention. The term “nucleotide sequence encoding an amino acid sequence” includes all nucleotide sequences that are degenerate versions of each other and/or encode the same amino acid sequence. Nucleotide sequences that encode proteins and/or RNA may include introns. Nucleic acids can be purified from natural sources, produced using recombinant expression systems and optionally purified, chemically synthesized, *etc.* Where appropriate, *e.g.*, in the case of chemically synthesized molecules, nucleic acids can comprise nucleoside analogs such as analogs having chemically modified bases or sugars, backbone modifications, *etc.* A nucleic acid sequence is presented in the 5' to 3' direction unless otherwise indicated. The term “nucleic acid segment” is used herein to refer to a nucleic acid sequence that is a portion of a longer nucleic acid sequence. In many embodiments, a nucleic acid segment comprises at least 3, 4, 5, 6, 7, 8, 9, 10, or more residues. In some embodiments, a nucleic acid is or comprises natural nucleosides (*e.g.*, adenosine, thymidine, guanosine, cytidine, uridine, deoxyadenosine, deoxythymidine, deoxyguanosine, and deoxycytidine); nucleoside analogs (*e.g.*, 2-aminoadenosine, 2-thiothymidine, inosine, pyrrolo-pyrimidine, 3-methyl adenosine, 5-methylcytidine, C-5 propynyl-cytidine, C-5 propynyl-uridine, 2-aminoadenosine, C5-bromouridine, C5-fluorouridine, C5-iodouridine, C5-propynyl-uridine, C5-propynyl-cytidine, C5-methylcytidine, 2-aminoadenosine, 7-deazaadenosine, 7-deazaguanosine, 8-oxoadenosine, 8-oxoguanosine, O(6)-methylguanine,

and 2-thiocytidine); chemically modified bases; biologically modified bases (*e.g.*, methylated bases); intercalated bases; modified sugars (*e.g.*, 2'-fluororibose, ribose, 2'-deoxyribose, arabinose, and hexose); and/or modified phosphate groups (*e.g.*, phosphorothioates and 5'-*N*-phosphoramidite linkages). In some embodiments, the present invention is specifically directed to "unmodified nucleic acids," meaning nucleic acids (*e.g.*, polynucleotides and residues, including nucleotides and/or nucleosides) that have not been chemically modified.

[00045] *Patient:* As used herein, the term "patient" or "subject" refers to any organism to which provided compositions can be administered, *e.g.*, for experimental, diagnostic, prophylactic, cosmetic, and/or therapeutic purposes. Typical patients include animals (*e.g.*, mammals such as mice, rats, rabbits, non-human primates, and humans). In some embodiments, a patient is a human.

[00046] *Pharmaceutically acceptable:* The term "pharmaceutically acceptable" as used herein, refers to agents that, within the scope of sound medical judgment, are suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00047] *Premix:* As used herein, the term "premix" refers to any combination of components that is subsequently used to generate a nanoparticle composition (*e.g.*, an empty nanoparticle composition, such as an empty nanoemulsion) according to the present invention. For example, a premix is any collection of ingredients that, when subjected to high shear forces, generates nanoparticles according to the present invention. In some embodiments, a premix contains two or more immiscible solvents. In some embodiments, a premix contains components that self-assemble into nanoparticles. In some embodiments, a premix contains components that self-assemble into micelles. In some embodiments, a premix contains one or more amphiphilic entities as described in co-pending PCT application serial number PCT US07/86018, filed November 30, 2007, published as WO 08/070538 on June 12, 2008, and entitled "AMPHIPHILIC ENTITY NANOPARTICLES". In accordance with the present invention, a premix does not contain any known therapeutic agents and/or independently active biologically active agents. In some embodiments, a premix is agitated, mixed, and/or stirred; in some embodiments, a premix is agitated, mixed, and/or stirred prior to being subjected to high shear force. In some embodiments, a premix comprises at least one solubilized component (*i.e.*, at least one component that is in solution); in some such embodiments, the premix is subjected to high shear force after such solubilization is

achieved.

[00048] *Provided Composition:* As used herein, a “provided composition” refers to any composition described herein, including, but not limited to, empty nanoparticle compositions (*e.g.*, empty nanoemulsions) and/or other compositions comprising one or more components of an empty nanoparticle composition as described herein.

[00049] *Pure:* As used herein, a substance and/or entity is “pure” if it is substantially free of other components. For example, a preparation that contains more than about 90% of a particular substance and/or entity is typically considered to be a pure preparation. In some embodiments, a substance and/or entity is at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% pure.

[00050] *Refractory:* The term “refractory” as used herein, refers to any subject that does not respond with an expected clinical efficacy following administration of provided compositions (*e.g.*, for treatment of conditions or disorders associated with dermal structures such as sweat glands, sebaceous glands, hair follicles, *etc.*) as normally observed by practicing medical personnel.

[00051] *Self-administration:* The term “self-administration,” as used herein, refers to the situation where a subject has the ability to administer a composition to him or herself without requiring medical supervision. In some embodiments, self-administration may be performed outside of a clinical setting. To give but one example, in some embodiments, a facial cosmetic cream may be administered by a subject in one’s own home.

[00052] *Shear force:* As used herein, the term “shear force” refers to a force that is parallel or tangential to the face of a material, as opposed to a force that is perpendicular to the face of a material. In some embodiments, a composition is exposed to high shear forces in order to produce a uniform nanoparticle composition (*e.g.*, uniform empty nanoparticle composition, nanoemulsion, *etc.*). Any method known in the art can be used to generate high shear forces. In some embodiments, cavitation is used to generate high shear forces. In some embodiments, high pressure homogenization is used to generate high shear forces.

Alternatively or additionally, high shear force may be administered by exposure to high pressure, for example about 15,000 psi. In some embodiments, such high pressure is within the range of about 18,000 psi to about 26,000 psi; in some embodiments, it is within the range of about 20,000 psi to about 25,000 psi. In some embodiments, and to give but one example, a Microfluidizer[®] Processor (Microfluidics Corporation/MFIC Corporation) or other like device is used to generate high shear force. Microfluidizer[®] Processors provide high pressure

and a resultant high shear rate by accelerating a composition through microchannels (typically having dimensions on the order of 75 microns) at a high velocity (typically in the range of 50 m/s – 300 m/s) for size reduction to the nanoscale range. As the fluid exits the microchannels it forms jets which collide with jets from opposing microchannels. In the channels the fluid experiences high shear (up to 10^7 1/s) which is orders of magnitude higher than that of conventional technologies. Jet collisions result in mixing at submicron levels. Therefore, in such devices, high shear and/or impact can achieve particle size reduction and mixing of multiphase. In some embodiments, a sample is exposed to high shear forces for a period of time less than about 10 minutes. In some embodiments, the period of time is less than about 9 minutes, about 8 minutes, about 7 minutes, about 6 minutes, about 5 minutes, about 4 minutes, about 3 minutes, about 2 minutes, or about 1 minute. In some embodiments, the period of time is within the range of about 1 minute to about 2 minutes; in some embodiments, the period of time is less than about 1 minute; in some embodiments, the period of time is about 30 seconds. In some embodiments, a sample is “microfluidized” through a single exposure to high shear forces; such embodiments are referred to herein as “single pass” microfluidization.

[00053] *Small Molecule:* In general, a “small molecule” is a molecule that is less than about 5 kilodaltons (kD) in size. In some embodiments, the small molecule is less than about 4 kD, 3 kD, about 2 kD, or about 1 kD. In some embodiments, the small molecule is less than about 800 daltons (D), about 600 D, about 500 D, about 400 D, about 300 D, about 200 D, or about 100 D. In some embodiments, a small molecule is less than about 2000 g/mol, less than about 1500 g/mol, less than about 1000 g/mol, less than about 800 g/mol, or less than about 500 g/mol. In some embodiments, small molecules are non-polymeric. In some embodiments, in accordance with the present invention, small molecules are not proteins, polypeptides, oligopeptides, peptides, polynucleotides, oligonucleotides, polysaccharides, glycoproteins, proteoglycans, *etc.*

[00054] *Stable:* The term “stable,” when applied to provided compositions herein, means that the compositions maintain one or more aspects of their physical structure (*e.g.*, size range and/or distribution of particles) over a period of time. In some embodiments, a stable nanoparticle composition (*e.g.*, empty nanoparticle composition, such as empty nanoemulsion) is one for which the average particle size, the maximum particle size, the range of particle sizes, and/or the distribution of particle sizes (*i.e.*, the percentage of particles above a designated size and/or outside a designated range of sizes) is maintained for a period

of time. In some embodiments, a stable provided composition (*e.g.*, an empty nanoparticle composition such as an empty nanoemulsion, or another composition comprising one or more components of an empty nanoparticle composition) is one for which a biologically relevant activity is maintained for a period of time. In some embodiments, the period of time is at least about one hour; in some embodiments the period of time is about 5 hours, about 10 hours, about one (1) day, about one (1) week, about two (2) weeks, about one (1) month, about two (2) months, about three (3) months, about four (4) months, about five (5) months, about six (6) months, about eight (8) months, about ten (10) months, about twelve (12) months, about twenty-four (24) months, about thirty-six (36) months, or longer. In some embodiments, the period of time is within the range of about one (1) day to about twenty-four (24) months, about two (2) weeks to about twelve (12) months, about two (2) months to about five (5) months, *etc.* For example, if a population of empty nanoparticles is subjected to prolonged storage, temperature changes, and/or pH changes, and a majority of the nanoparticles in the composition maintain a diameter within a stated range (for example, between approximately 10 nm and approximately 120 nm), the nanoparticle composition is stable. For some such populations, a majority is more than about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5%, about 99.6%, about 99.7%, about 99.8%, about 99.9% or more.

[00055] *Substantially*: As used herein, the term “substantially” refers to the qualitative condition of exhibiting total or near-total extent or degree of a characteristic or property of interest. One of ordinary skill in the biological arts will understand that biological and chemical phenomena rarely, if ever, go to completion and/or proceed to completeness or achieve or avoid an absolute result. The term “substantially” is therefore used herein to capture the potential lack of completeness inherent in many biological and chemical phenomena.

[00056] *Substantially free of*: A provided composition (*e.g.*, an empty nanoparticle composition such as an empty nanoemulsion, or another composition comprising one or more components of an empty nanoparticle composition) is said to be “substantially free of” particles whose diameter is outside of a stated range when no more than about 50% of the particles in that composition have diameters outside of the range. In some embodiments, no more than 25% of the particles are outside of the range. In some embodiments, no more than 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5% or less of the particles have diameters outside of the stated range.

[00057] *Suffering from:* An individual who is “suffering from” a disease, disorder, or condition (*e.g.*, any disease, disorder, or condition, including, but not limited to, any disease, disorder, or condition described herein) has been diagnosed with or exhibits symptoms of the disease, disorder, or condition. In some embodiments, exemplary diseases, disorders, or conditions include, but are not limited to, a condition associated with sweat glands or sebaceous glands, such as acne; hyperhidrosis; unwanted sweating; bromhidrosis; body odor; chromhidrosis; hair loss; psoriasis; actinic keratosis; dermal infection; eczematous dermatitis (*e.g.*, atopic dermatitis, *etc.*); excess sebum-producing disorder; burns; Raynaud’s phenomenon; lupus erythematosus; hyperpigmentation disorder; hypopigmentation disorder; skin cancer; *etc.*

[00058] *Susceptible to:* An individual who is “susceptible to” a disease, disorder, or condition (*e.g.*, any disease, disorder, or condition, including, but not limited to, any disease, disorder, or condition described herein) is at risk for developing the disease, disorder, or condition. In some embodiments, an individual who is susceptible to a disease, disorder, or condition does not display any symptoms of the disease, disorder, or condition. In some embodiments, an individual who is susceptible to a disease, disorder, or condition has not been diagnosed with the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, or condition is an individual who has been exposed to conditions associated with development of the disease, disorder, or condition (*e.g.*, the individual has been exposed to an infectious agent; the individual has been exposed to an environmental hazard thought to cause the disease, disorder, and/or condition; *etc.*). In some embodiments, a risk of developing a disease, disorder, and/or condition is a population-based risk (*e.g.*, an individual carries a gene and/or allele associated with the disease, disorder, and/or condition).

[00059] *Symptoms are reduced:* According to the present invention, “symptoms are reduced” when one or more symptoms of a particular disease, disorder or condition is reduced in magnitude (*e.g.*, intensity, severity, *etc.*) or frequency. For purposes of clarity, a delay in the onset of a particular symptom is considered one form of reducing the frequency of that symptom. To give but a few examples, where the condition in question is acne, symptoms of that condition are reduced when the size (*e.g.*, diameter, volume, *etc.*) and/or severity (*e.g.*, redness, inflammatory response, *etc.*) of one or more blemishes in the selected area is reduced, and/or when the number of total blemishes is reduced (*e.g.*, on a subject’s face, back, *etc.*). Where the condition in question is hyperhidrosis, symptoms are reduced

when the subject produces less sweat. It is not intended that the present invention be limited only to cases where the symptoms are eliminated. The present invention specifically contemplates treatment such that one or more symptoms is/are reduced (and the condition of the subject is thereby “improved”), albeit not completely eliminated.

[00060] *Therapeutically effective amount:* As used herein, the term “therapeutically effective amount” means an amount that is sufficient, when administered to a population suffering from or susceptible to a disease, disorder, and/or condition, to treat the disease, disorder, and/or condition. In some embodiments, a therapeutically effective amount is one that reduces the incidence and/or severity of, and/or delays onset of, one or more symptoms of the disease, disorder, and/or condition. Those of ordinary skill in the art will appreciate that the term “therapeutically effective amount” does not in fact require successful treatment be achieved in a particular individual. Rather, a therapeutically effective amount may be that amount that provides a particular desired pharmacological response in a significant number of subjects when administered to patients in need of such treatment. It is specifically understood that particular subjects may, in fact, be “refractory” to a “therapeutically effective amount.” To give but one example, a refractory subject may have a low bioavailability such that clinical efficacy is not obtainable. In some embodiments, reference to a therapeutically effective amount may be a reference to an amount as measured in one or more specific tissues. Those of ordinary skill in the art will appreciate that, in some embodiments, a therapeutically effective agent may be formulated and/or administered in a single dose. In some embodiments, a therapeutically effective agent may be formulated and/or administered in a plurality of doses, for example, as part of a dosing regimen.

[00061] *Therapeutic agent:* As used herein, the phrase “therapeutic agent” refers to any agent that has a therapeutic effect and/or elicits a desired biological and/or pharmacological effect, when administered to a subject.

[00062] *Toxic solvent:* As used herein, the term “toxic solvent” refers to any substance that may alter, disrupt, remove, or destroy an animal’s tissue. As would be understood by one of ordinary skill in the art, an animal’s tissue can include living cells, dead cells, extracellular matrix, cellular junctions, biological molecules, *etc.* To give but a few examples, toxic solvents include dimethyl sulfoxide, dimethyl acetimide, dimethyl formamide, chloroform, tetramethyl formamide, acetone, acetates, and alkanes.

[00063] *Treatment:* As used herein, the term “treatment” (also “treat” or “treating”) refers to any administration of a substance (*e.g.*, provided compositions) that partially or

completely alleviates, ameliorates, relieves, inhibits, delays onset of, reduces severity of, and/or reduces incidence of one or more symptoms, features, and/or causes of a particular disease, disorder, and/or condition. Such treatment may be of a subject who does not exhibit signs of the relevant disease, disorder and/or condition and/or of a subject who exhibits only early signs of the disease, disorder, and/or condition. Alternatively or additionally, such treatment may be of a subject who exhibits one or more established signs of the relevant disease, disorder and/or condition. In some embodiments, treatment may be of a subject who has been diagnosed as suffering from the relevant disease, disorder, and/or condition. In some embodiments, treatment may be of a subject known to have one or more susceptibility factors that are statistically correlated with increased risk of development of the relevant disease, disorder, and/or condition.

[00064] *Uniform:* The term “uniform,” when used herein in reference to a nanoparticle composition (*e.g.*, empty nanoparticle composition, such as an empty nanoemulsion), refers to a nanoparticle composition in which the individual nanoparticles have a specified range of particle diameter sizes. For example, in some embodiments, a uniform nanoparticle composition is one in which the difference between the minimum diameter and maximum diameter does not exceed about 600 nm, about 550 nm, about 500 nm, about 450 nm, about 400 nm, about 350 nm, about 300 nm, about 250 nm, about 200 nm, about 150 nm, about 100 nm, about 90 nm, about 80 nm, about 70 nm, about 60 nm, about 50 nm, or fewer nm. In some embodiments, particles within uniform provided compositions in accordance with the invention have diameters that are smaller than about 600 nm, about 550 nm, about 500 nm, about 450 nm, about 400 nm, about 350 nm, about 300 nm, about 250 nm, about 200 nm, about 150 nm, about 130 nm, about 120 nm, about 115 nm, about 110 nm, about 100 nm, about 90 nm, about 80 nm, or less. In some embodiments, particles within uniform provided compositions in accordance with the invention have diameters within the range of about 10 nm and about 600 nm. In some embodiments, particles within uniform provided compositions in accordance with the invention have diameters within the range of about 10 nm and about 300 nm, about 10 nm and about 200 nm, about 10 nm and about 150 nm, about 10 nm and about 130 nm, about 10 nm and about 120 nm, about 10 nm and about 115 nm, about 10 nm and about 110 nm, about 10 nm and about 100 nm, or about 10 nm and about 90 nm. In some embodiments, particles within provided compositions in accordance with the invention have an average particle size that is under about 300 nm, about 250 nm, about 200 nm, about 150 nm, about 130 nm, about 120 nm, about 115 nm, about 110 nm, about 100 nm,

or about 90 nm. In some embodiments, the average particle size is within the range of about 10 nm and about 300 nm, about 50 nm and about 250 nm, about 60 nm and about 200 nm, about 65 nm and about 150 nm, about 70 nm and about 130 nm. In some embodiments, the average particle size is between about 80 nm and about 110 nm. In some embodiments, the average particle size is about 90 nm to about 100 nm. In some embodiments, a majority of the particles within uniform provided compositions in accordance with the invention have diameters below a specified size or within a specified range. In some embodiments, the majority is more than 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, 99.9% or more of the particles in the composition. In some embodiments, a uniform nanoparticle composition is achieved by microfluidization of a sample. In some embodiments, a uniform nanoparticle composition is achieved by single-pass microfluidization of a sample. In some embodiments, a uniform nanoparticle composition is prepared by exposure to high shear force, *e.g.*, by microfluidization.

[00065] *Unwanted side effects:* As used herein, the term “unwanted side effects” refers to one or more effects and/or symptoms associated with administration of a substance to a patient that are not the desired and/or intended effects and/or are unpleasant to the patient. Exemplary unwanted side effects include pain; bruising; ecchymosis; hematoma; botulism poisoning; unwanted systemic effects; undesirable blood levels of the administered substance; damage to underlying nervous tissue (*e.g.*, neuronal paralysis); unwanted effects on muscles (*e.g.*, muscle paralysis); flu-like symptoms; morbidity; mortality; alteration in body weight; alteration in enzyme levels; pathological changes detected at the microscopic, macroscopic, and/or physiological levels; infection; hemorrhage; inflammation; scarring; loss of function; changes in local blood flow; fever; malaise; teratogenesis; pulmonary hypertension; stroke; heart disease; heart attack; neuropathy; nausea; vomiting; dizziness; diarrhea; headache; dermatitis; dry mouth; addiction; miscarriage; abortion; uterine hemorrhage; birth defects; bleeding; cardiovascular disease; deafness; kidney damage and/or failure; liver damage and/or failure; dementia; depression; diabetes; erectile dysfunction; glaucoma; hair loss; anaemia; insomnia; lactic acidosis; melasma; thrombosis; priapism; rhabdomyolysis; seizures; drowsiness; increase in appetite; decrease in appetite; increase in libido; decrease in libido; tardive dyskinesia; non-axillary sweating; injection site pain and hemorrhage; pharyngitis; neck pain; back pain; pruritus; anxiety; follicular obstruction; and/or combinations thereof.

Description of Certain Embodiments

[00066] The present invention relates to methods for treating disorders or conditions associated with dermal structures (*e.g.*, sweat glands, sebaceous glands, hair follicles, *etc.*) by administration of provided compositions (*e.g.*, provided compositions such as empty nanoemulsions, or other compositions comprising one or more components of an empty nanoparticle composition as described herein) to the skin of a subject. In some embodiments, the present invention provides treatments for unwanted sweating. In some embodiments, the present invention provides treatments for excessive sweating. In some embodiments, the present invention provides treatments for hyperhidrosis, bromhidrosis, and/or chromhidrosis. In some embodiments, the present invention provides treatments for body odor. In some embodiments, the present invention provides treatments for rosacea. In some embodiments, the present invention provides treatments for acne. In some embodiments, the present invention provides treatments for hair loss. In some embodiments, the present invention provides treatments for psoriasis. In some embodiments, the present invention provides treatments for dermal infection (*e.g.*, herpes simplex virus infection, human papillomavirus infection, fungal infection, *etc.*). In some embodiments, the present invention provides treatments for actinic keratosis. In some embodiments, the present invention provides treatments for eczematous dermatitis (*e.g.*, atopic dermatitis, *etc.*). In some embodiments, the present invention provides treatments for excess sebum-producing disorders (*e.g.*, seborrhea, seborrheic dermatitis, *etc.*). In some embodiments, the present invention provides treatments for burns. In some embodiments, the present invention provides treatments for Raynaud's phenomenon. In some embodiments, the present invention provides treatments for lupus erythematosus. In some embodiments, the present invention provides treatments for hyperpigmentation disorders (*e.g.*, melasma, *etc.*). In some embodiments, the present invention provides treatments for hypopigmentation disorders (*e.g.*, vitiligo, *etc.*). In some embodiments, the present invention provides treatments for skin cancer (*e.g.*, squamous cell skin carcinoma, basal cell skin carcinoma, *etc.*). In general, such treatments involve topical formulations and/or administration to a subject in need thereof of provided compositions (*e.g.*, empty nanoparticle compositions such as empty nanoemulsions, or other compositions comprising one or more components of an empty nanoparticle composition).

[00067] The present invention also provides novel compositions – specifically particular nanoemulsion compositions – that may be used in accordance with the present invention for any purpose, including in medicine or cosmetics. In some embodiments,

provided nanoparticle compositions (and particularly nanoemulsions) are substantially free of any known therapeutic agent. In some embodiments, provided nanoparticle compositions (and particularly nanoemulsions) are substantially free of any therapeutic agent known to be useful in the treatment of any particular disease, disorder, or condition for which the provided nanoparticle composition is to be employed.

[00068] In many embodiments, provided compositions are formulated for and/or administered to a subject via a topical route, and particular via application to a subject's skin. In some embodiments, provided compositions are formulated for and/or administered to a subject via a non-topical route. In some embodiments, provided compositions are formulated for delivery and/or are delivered by a route selected from the group consisting of oral (PO), intravenous (IV), intramuscular (IM), intra-arterial (IA), intramedullary, intrathecal, subcutaneous (SQ), intraventricular, interdermal, intradermal, rectal (PR), vaginal, intraperitoneal (IP), intragastric (IG), mucosal, intranasal, buccal, enteral, vitreal, and/or sublingual administration; by intratracheal instillation, bronchial instillation, and/or inhalation; as an oral spray, nasal spray, and/or aerosol, and/or through a portal vein catheter; and/or combinations thereof.

Nanoparticle Compositions

[00069] As described herein, the present invention provides, among other things, uses involving provided compositions (*e.g.*, empty nanoparticle compositions such as empty nanoemulsions, or other compositions comprising one or more components of an empty nanoparticle composition). In general, provided compositions do not contain any known therapeutic agents and/or independently active biologically active agents. The present invention provides novel uses for such provided compositions. In some embodiments, provided compositions comprise empty nanoparticle compositions, such as empty nanoemulsions. In some embodiments, provided compositions comprise other compositions comprising one or more components of an empty nanoparticle composition.

[00070] In general, an empty nanoparticle composition is any composition that includes at least one nanoparticle, wherein the nanoparticles do not contain a known therapeutic agent and/or an independently active biologically active agent. In some embodiments, provided compositions are empty nanoparticle compositions. In some embodiments, provided compositions are not empty nanoparticle compositions, but contain one or more components of an empty nanoparticle composition.

[00071] As described herein, the present invention provides, among other things, novel new and improved nanoparticle compositions. In some embodiments, provided nanoparticle compositions have particular components, and/or relative amounts of components, as described herein. In some embodiments, provided nanoparticle compositions have particular structural and/or functional attributes that distinguish and/or define them. In some embodiments, exemplary attributes (e.g., physical, structural, and/or functional attributes) that have been associated with nanoparticle compositions in general are described in the following paragraphs. In some embodiments, provided nanoparticle compositions have one or more of these attributes. In some embodiments, provided nanoparticle compositions do not have any of these attributes.

[00072] In some embodiments, provided compositions in accordance with the invention are stable. In some embodiments, provided compositions in accordance with the invention are uniform. For example, in some embodiments, the difference between the minimum diameter and maximum diameter of particles within provided compositions does not exceed approximately 600 nm, approximately 550 nm, approximately 500 nm, approximately 450 nm, approximately 400 nm, approximately 350 nm, approximately 300 nm, approximately 250 nm, approximately 200 nm, approximately 150 nm, or approximately 100 nm, approximately 90 nm, approximately 80 nm, approximately 70 nm, approximately 60 nm, approximately 50 nm, or fewer nm.

[00073] In some embodiments, particles within provided compositions have diameters (e.g., average and/or median diameters) that are smaller than about 1000 nm, about 600 nm, about 550 nm, about 500 nm, about 450 nm, about 400 nm, about 350 nm, about 300 nm, about 250 nm, about 200 nm, about 150 nm, about 130 nm, about 120 nm, about 115 nm, about 110 nm, about 100 nm, about 90 nm, about 80 nm, about 50 nm, or less.

[00074] In some embodiments, particles within provided compositions have diameters (e.g., average and/or median diameters) within the range of about 10 nm and about 600 nm. In some embodiments, particles within provided compositions have diameters (e.g., average and/or median diameters) within the range of about 10 nm to about 300 nm, about 10 nm to about 200 nm, about 10 nm to about 150 nm, about 10 nm to about 130 nm, about 10 nm to about 120 nm, about 10 nm to about 115 nm, about 10 nm to about 110 nm, about 10 nm to about 100 nm, or about 10 nm to about 90 nm. In some embodiments, particles within provided compositions have diameters (e.g., average and/or median diameters) within the range of about 1 nm to about 1000 nm, about 1 nm to about 600 nm, about 1 nm to about 500

nm, about 1 nm to about 400 nm, about 1 nm to about 300 nm, about 1 nm to about 200 nm, about 1 nm to about 150 nm, about 1 nm to about 120 nm, about 1 nm to about 100 nm, about 1 nm to about 75 nm, about 1 nm to about 50 nm, or about 1 nm to about 25 nm. In some embodiments, particles within provided compositions have diameters (*e.g.*, average and/or median diameters) of 1 nm to 15 nm, 15 nm to 200 nm, 25 nm to 200 nm, 50 nm to 200 nm, or 75 nm to 200 nm.

[00075] In some embodiments, the total particle distribution is encompassed within the specified range of particle diameter size. In some embodiments, less than 50%, 25%, 20%, 15%, 10%, 5%, 4%, 3%, 2%, or 1% of the total particle distribution is outside of the specified range of particle diameter sizes. In some embodiments, less than 1% of the total particle distribution is outside of the specified range of particle diameter sizes. In some embodiments, none of the total particle distribution is outside of the specified range of particle diameter sizes. In some embodiments, the empty nanoparticle composition is substantially free of particles having a diameter larger than about 600 nm, about 550 nm, about 500 nm, about 450 nm, about 400 nm, about 350 nm, about 300 nm, about 250 nm, about 200 nm, about 150 nm, about 120 nm, about 100 nm, about 75 nm, about 50 nm, or about 25 nm. In some embodiments, less than 50%, 25%, 20%, 15%, 10%, 5%, 4%, 3%, 2%, or 1% of the total particle distribution have diameters larger than about 600 nm, about 550 nm, about 500 nm, about 450 nm, about 400 nm, about 350 nm, about 300 nm, about 250 nm, about 200 nm, about 150 nm, about 120 nm, about 100 nm, about 75 nm, about 50 nm, or about 25 nm.

[00076] In some embodiments, particles within provided compositions have an average particle size that is under about 600 nm, about 550 nm, about 500 nm, about 450 nm, about 400 nm, about 350 nm, about 300 nm, about 250 nm, about 200 nm, about 150 nm, about 130 nm, about 120 nm, about 115 nm, about 110 nm, about 100 nm, about 90 nm, or about 50 nm. In some embodiments, the average particle size is within the range of about 10 nm and about 300 nm, about 50 nm and about 250, about 60 nm and about 200 nm, about 65 nm and about 150 nm, or about 70 nm and about 130 nm. In some embodiments, the average particle size is about 80 nm and about 110 nm. In some embodiments, the average particle size is about 90 nm and about 100 nm.

[00077] In some embodiments, a majority of the particles within provided compositions have diameters below a specified size or within a specified range. In some embodiments, the majority is more than 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 96%,

97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, 99.9% or more of the particles in the provided composition.

[00078] In some embodiments, provided compositions are substantially free of particles having a diameter in excess of 600 nm. Specifically, in some embodiments, fewer than 50% of the nanoparticles in provided compositions have a diameter in excess of 600 nm. In some embodiments, fewer than 25% of the particles have a diameter in excess of 600 nm. In some embodiments, fewer than 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5% or less of the particles have a diameter in excess of 600 nm. Furthermore, in some embodiments, the nanoparticles in provided compositions have diameters within the range of 10 nm and 600 nm.

[00079] In some embodiments, provided compositions are substantially free of particles having a diameter in excess of 500 nm. Specifically, in some embodiments, fewer than 50% of the nanoparticles in provided compositions have a diameter in excess of 500 nm. In some embodiments, fewer than 25% of the particles have a diameter in excess of 500 nm. In some embodiments, fewer than 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5% or less of the particles have a diameter in excess of 500 nm. Furthermore, in some embodiments, the nanoparticles in provided compositions have diameters within the range of 10 nm and 500 nm.

[00080] In some embodiments, provided compositions are substantially free of particles having a diameter in excess of 400 nm. Specifically, in some embodiments, fewer than 50% of the nanoparticles in provided compositions have a diameter in excess of 400 nm. In some embodiments, fewer than 25% of the particles have a diameter in excess of 400 nm. In some embodiments, fewer than 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5% or less of the particles have a diameter in excess of 400 nm. Furthermore, in some embodiments, the nanoparticles in provided compositions have diameters within the range of 10 nm and 400 nm.

[00081] In some embodiments, provided compositions are substantially free of particles having a diameter in excess of 300 nm. Specifically, in some embodiments, fewer than 50% of the nanoparticles in provided compositions have a diameter in excess of 300 nm. In some embodiments, fewer than 25% of the particles have a diameter in excess of 300 nm. In some embodiments, fewer than 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5% or less of the particles have a diameter in excess of 300 nm. Furthermore, in some embodiments, the nanoparticles in provided

compositions have diameters within the range of 10 nm and 300 nm.

[00082] In some embodiments, provided compositions are substantially free of particles having a diameter in excess of 200 nm. Specifically, in some embodiments, fewer than 50% of the nanoparticles in provided compositions have a diameter in excess of 200 nm. In some embodiments, fewer than 25% of the particles have a diameter in excess of 200 nm. In some embodiments, fewer than 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5% or less of the particles have a diameter in excess of 200 nm. Furthermore, in some embodiments, the nanoparticles in provided compositions have diameters within the range of 10 nm and 200 nm.

[00083] In some embodiments, provided compositions are substantially free of particles having a diameter in excess of 150 nm. Specifically, in some embodiments, fewer than 50% of the nanoparticles in provided compositions have a diameter in excess of 150 nm. In some embodiments, fewer than 25% of the particles have a diameter in excess of 150 nm. In some embodiments, fewer than 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5% or less of the particles have a diameter in excess of 150 nm. Furthermore, in some embodiments, the nanoparticles in provided compositions have diameters within the range of 10 nm and 150 nm.

[00084] In some embodiments, provided compositions are substantially free of particles having a diameter in excess of 120 nm. Specifically, in some embodiments, fewer than 50% of the nanoparticles in provided compositions have a diameter in excess of 120 nm. In some embodiments, fewer than 25% of the particles have a diameter in excess of 120 nm. In some embodiments, fewer than 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5% or less of the particles have a diameter in excess of 120 nm. Furthermore, in some embodiments, the nanoparticles in provided compositions have diameters within the range of 10 nm and 120 nm.

[0001] In some embodiments, a majority of particles in a provided composition have diameters (*e.g.*, average and/or median diameters) between 10 nm and 150 nm. In some embodiments, a majority of particles in a provided composition have diameters (*e.g.*, average and/or median diameters) between 10 nm and 120 nm. In some embodiments, a majority of particles in a provided composition have diameters (*e.g.*, average and/or median diameters) between 20 nm and 120 nm. In some embodiments, a majority of particles in a provided composition have diameters (*e.g.*, average and/or median diameters) between 20 nm and 110 nm. In some embodiments, a majority of particles in a provided composition have diameters

(*e.g.*, average and/or median diameters) between 20 nm and 100 nm. In some embodiments, a majority of particles in a provided composition have diameters (*e.g.*, average and/or median diameters) between 20 nm and 90 nm. In some embodiments, a majority of particles in a provided composition have diameters (*e.g.*, average and/or median diameters) between 20 nm and 80 nm. In some embodiments, a majority of particles in a provided composition have diameters (*e.g.*, average and/or median diameters) between 20 nm and 70 nm. In some embodiments, a majority of particles in a provided composition have diameters (*e.g.*, average and/or median diameters) between 20 nm and 60 nm. In some embodiments, a majority of particles in a provided composition have diameters (*e.g.*, average and/or median diameters) between 20 nm and 50 nm. In some embodiments, a majority of particles in a provided composition have diameters (*e.g.*, average and/or median diameters) between 20 nm and 40 nm. In some embodiments, a majority of particles in a provided composition have diameters (*e.g.*, average and/or median diameters) between 20 nm and 30 nm.

[00085] In some embodiments, a majority of nanoparticles in a nanoparticle composition have diameters (*e.g.*, average and/or median diameters) between 10 nm and 120 nm. In some embodiments, a majority of nanoparticles in a nanoparticle composition have diameters (*e.g.*, average and/or median diameters) between 20 nm and 120 nm. In some embodiments, a majority of nanoparticles in a nanoparticle composition have diameters (*e.g.*, average and/or median diameters) between 20 nm and 110 nm. In some embodiments, a majority of nanoparticles in a nanoparticle composition have diameters (*e.g.*, average and/or median diameters) between 20 nm and 100 nm. In some embodiments, a majority of nanoparticles in a nanoparticle composition have diameters between 20 nm and 90 nm. In some embodiments, a majority of nanoparticles in a nanoparticle composition have diameters (*e.g.*, average and/or median diameters) between 20 nm and 80 nm. In some embodiments, a majority of nanoparticles in a nanoparticle composition have diameters (*e.g.*, average and/or median diameters) between 20 nm and 70 nm. In some embodiments, a majority of nanoparticles in a nanoparticle composition have diameters (*e.g.*, average and/or median diameters) between 20 nm and 60 nm. In some embodiments, a majority of nanoparticles in a nanoparticle composition have diameters (*e.g.*, average and/or median diameters) between 20 nm and 50 nm. In some embodiments, a majority of nanoparticles in a nanoparticle composition have diameters (*e.g.*, average and/or median diameters) between 20 nm and 40 nm. In some embodiments, a majority of nanoparticles in a nanoparticle composition have diameters (*e.g.*, average and/or median diameters) between 20 nm and 30 nm.

[00086] In some embodiments, about 50% of particles in a provided composition have diameters (*e.g.*, average and/or median diameters) between 10 nm and 40 nm. In some embodiments, about 90% of particles in a provided composition have diameters (*e.g.*, average and/or median diameters) between 10 nm and 80 nm. In some embodiments, about 90% of particles in a provided composition have diameters (*e.g.*, average and/or median diameters) between 10 nm and 90 nm. In some embodiments, about 95% of particles in a provided composition have diameters (*e.g.*, average and/or median diameters) between 10 nm and 110 nm. In some embodiments, about 95% of particles in a provided composition have diameters (*e.g.*, average and/or median diameters) between 10 nm and 120 nm. In some embodiments, about 95% of particles in a provided composition have diameters (*e.g.*, average and/or median diameters) between 10 nm and 150 nm.

[00087] In some embodiments, about 50% of the aggregate volume of all particles in a provided composition comprises or consists of nanoparticles having diameters between 10 nm and 40 nm. In some embodiments, about 90% of the aggregate volume of all particles in a provided composition comprises or consists of nanoparticles having diameters between 10 nm and 80 nm. In some embodiments, about 95% of the aggregate volume of all particles in a provided composition comprises or consists of nanoparticles having diameters between 10 nm and 110 nm. In some embodiments, about 95% of the aggregate volume of all particles in a provided composition comprises or consists of nanoparticles having diameters between 10 nm and 120 nm. In some embodiments, about 95% of the aggregate volume of all particles in a provided composition comprises or consists of nanoparticles having diameters between 10 nm and 150 nm.

[00088] Zeta potential is a measurement of the electric potential at a shear plane. A shear plane is an imaginary surface separating a thin layer of liquid bound to a solid surface (*e.g.*, nanoparticle surface) and showing elastic behavior from the rest of liquid (*e.g.*, liquid dispersion medium) showing normal viscous behavior. In some embodiments, particles in a provided composition have a zeta potential ranging between -80 mV and +80 mV. In some embodiments, particles in a provided composition have a zeta potential ranging between -50 mV and +50 mV. In some embodiments, particles in a provided composition have a zeta potential ranging between -25 mV and +25 mV. In some embodiments empty, nanoparticles have a zeta potential ranging between -10 mV and +10 mV. In some embodiments, particles in a provided composition have a zeta potential of about -80 mV, about -70 mV, about -60 mV, about -50 mV, about -40 mV, about -30 mV, about -25 mV, about -20 mV,

about -15 mV, about -10 mV, or about -5 mV. In some embodiments, particles in a provided composition have a zeta potential of about +50 mV, about +40 mV, about +30 mV, about +25 mV, about +20 mV, about +15 mV, about +10 mV, or about +5 mV. In some embodiments, particles in a provided composition have a zeta potential that is about 0 mV.

[00089] In some embodiments, particles in a provided composition have a zeta potential that is about -5 mV to about -80 mV. In some embodiments, particles in a provided composition have a zeta potential that is about -5 mV to about -70 mV. In some embodiments, particles in a provided composition have a zeta potential that is about -5 mV to about -60 mV. In some embodiments, particles in a provided composition have a zeta potential that is about -5 mV to about -50 mV. In some embodiments, particles in a provided composition have a zeta potential that is about -5 mV to about -40 mV. In some embodiments, particles in a provided composition have a zeta potential that is about -5 mV to about -30 mV. In some embodiments, particles in a provided composition have a zeta potential that is about -5 mV to about -20 mV.

[00090] In some embodiments, particles in a provided composition have a zeta potential that is about -10 mV to about -15 mV. In some embodiments, particles in a provided composition have a zeta potential that is about -10 mV to about -80 mV. In some embodiments, particles in a provided composition have a zeta potential that is about -10 mV to about -70 mV. In some embodiments, particles in a provided composition have a zeta potential that is about -10 mV to about -60 mV. In some embodiments, particles in a provided composition have a zeta potential that is about -10 mV to about -50 mV. In some embodiments, particles in a provided composition have a zeta potential that is about -10 mV to about -40 mV. In some embodiments, particles in a provided composition have a zeta potential that is about -10 mV to about -30 mV. In some embodiments, particles in a provided composition have a zeta potential that is about -10 mV to about -20 mV.

[00091] In some embodiments, particles in a provided composition have a zeta potential that is about -80 mV to about -70 mV. In some embodiments, particles in a provided composition have a zeta potential that is about -70 mV to about -60 mV. In some embodiments, particles in a provided composition have a zeta potential that is about -60 mV to about -50 mV. In some embodiments, particles in a provided composition have a zeta potential that is about -50 mV to about -40 mV. In some embodiments, particles in a provided composition have a zeta potential that is about -40 mV to about -30 mV. In some embodiments, particles in a provided composition have a zeta potential that is about -30 mV

to about -20 mV. In some embodiments, particles in a provided composition have a zeta potential that is about -20 mV to about -10 mV. In some embodiments, particles in a provided composition have a zeta potential that is about -10 mV to about 0 mV.

[00092] In some embodiments, particles in a provided composition have a zeta potential that is about -15 mV to about -20 mV. In some embodiments, particles in a provided composition have a zeta potential that is about -5 mV, about -6 mV, about -7 mV, about -8 mV, about -9 mV, -10 mV, about -11 mV, about -12 mV, about -13 mV, about -14 mV, about -15 mV, about 16 mV, about -17 mV, about -18 mV, about -19 mV, or about -20 mV.

[00093] In some embodiments, provided compositions are emulsions or dispersions. In some embodiments, provided compositions are “oil-in-water” dispersions (*i.e.*, dispersions in which oily particles are dispersed within an aqueous dispersion medium); in some embodiments, provided compositions are “water-in-oil” dispersions (*i.e.*, dispersions in which aqueous particles are dispersed within an oily dispersion medium).

[00094] In some embodiments, provided compositions do not require toxic solvents. By contrast, many conventional strategies for inducing formation of nanoparticles in a composition utilize toxic (typically organic) solvents. In some embodiments, provided compositions do not require polymers. By contrast, many conventional strategies for preparing compositions that contain nanoparticle structures require polymers.

[00095] In some embodiments, provided compositions have better tissue absorption and/or better biocompatibility than other nanoparticle compositions. For example, in some embodiments, provided compositions have better tissue absorption and/or better biocompatibility than nanoparticle compositions that are not uniform, that utilize one or more toxic (*e.g.*, organic) solvents, and/or that utilize one or more polymers.

[00096] In some embodiments, provided compositions are stable. In some embodiments, a stable empty nanoparticle composition is one for which the average particle size, the maximum particle size, the range of particle sizes, and/or the distribution of particle sizes (*i.e.*, the percentage of particles above a designated size and/or outside a designated range of sizes) is maintained for a period of time. In some embodiments, the period of time is at least about one hour; in some embodiments the period of time is about 5 hours, about 10 hours, about one (1) day, about one (1) week, about two (2) weeks, about one (1) month, about two (2) months, about three (3) months, about four (4) months, about five (5) months, about six (6) months, about eight (8) months, about ten (10) months, about twelve (12)

months, about twenty-four (24) months, or longer. In some embodiments, the period of time is within the range of about one (1) day to about twenty-four (24) months, about two (2) weeks to about twelve (12) months, about two (2) months to about five (5) months, *etc.* For example, if a population of empty nanoemulsion particles is subjected to prolonged storage, temperature changes, and/or pH changes and a majority of the nanoparticles in the population maintain a diameter within a stated range (*i.e.*, for example, between approximately 10 nm and about 120 nm), the empty nanoparticle composition is stable. For some such populations, a majority is more than about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5%, about 99.6%, about 99.7%, about 99.8%, about 99.9%, or more than about 99.9% pure.

[00097] As described herein, provided compositions are useful in various cosmetic and/or medical applications. Such compositions may be administered to a subject by any available route, including, but not limited to, oral (PO), intravenous (IV), intramuscular (IM), intra-arterial, intramedullary, intrathecal, subcutaneous (SQ), intraventricular, transdermal, interdermal, intradermal, rectal (PR), vaginal, intraperitoneal (IP), intragastric (IG), topical and/or transdermal (*e.g.*, by lotions, creams, powders, ointments, liniments, gels, drops, *etc.*), mucosal, intranasal, buccal, enteral, vitreal, and/or sublingual administration; by intratracheal instillation, bronchial instillation, and/or inhalation; as an oral spray, nasal spray, and/or aerosol, and/or through a portal vein catheter; and/or combinations of any of the foregoing.

Methods of Making Nanoparticle Compositions

[00098] In general, provided compositions (*e.g.*, empty nanoparticle compositions such as an empty nanoemulsions, or other compositions comprising one or more components of an empty nanoparticle composition) for use in accordance with the present invention may be prepared by any available method. In some embodiments, provided compositions are prepared by chemical means. However, chemical means often require toxic (typically organic) solvents; in some embodiments, provided compositions are prepared in accordance with the present invention without utilizing such solvents.

[00099] To give but a few particular examples, exemplary methods known to be useful for preparing nanoparticle compositions are described below. In some embodiments, provided nanoparticle compositions are prepared using one or more of these methods. In some embodiments, provided nanoparticle compositions are not prepared using these methods.

High Shear Force

[000100] In some embodiments, provided compositions (*e.g.*, empty nanoparticle compositions such as empty nanoemulsions, or other compositions comprising one or more components of an empty nanoparticle composition) in accordance with the invention self-assemble from a collection of combined components. In some embodiments, provided compositions are prepared by subjecting a combination of components (*i.e.*, a “premix”) to high shear force. As used herein, the term “shear force” refers to a force that is parallel or tangential to the face of a material, as opposed to a force that is perpendicular to the face of a material. In some embodiments, high shear force is applied by high pressure, by cavitation, by homogenization, and/or by microfluidization. In some embodiments, combined nanoparticle-forming components are agitated, stirred, or otherwise mixed. In some such embodiments, the components are subjected to high shear force after having been mixed. In some specific embodiments, mixing may be performed for a period of time such as, for example, about 1 minute, about 3 minutes, about 5 minutes, about 10 minutes, about 15 minutes, about 30 minutes, about 45 minutes, about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, about 12 hours, about 13 hours, about 14 hours, or about 15 hours. In some specific embodiments, mixing may be performed for a period of time such as, for example, more than 15 minutes, more than 30 minutes, more than 45 minutes, more than 1 hour, more than 2 hours, more than 3 hours, more than 4 hours, more than 5 hours, more than 6 hours, more than 7 hours, more than 8 hours, more than 9 hours, more than 10 hours, more than 11 hours, more than 12 hours, more than 13 hours, more than 14 hours, or more than 15 hours. In some specific embodiments, mixing may be performed for a period of time such as, for example, less than 15 minutes, less than 30 minutes, less than 45 minutes, less than 1 hour, less than 2 hours, less than 3 hours, less than 4 hours, less than 5 hours, less than 6 hours, less than 7 hours, less than 8 hours, less than 9 hours, less than 10 hours, less than 11 hours, less than 12 hours, less than 13 hours, less than 14 hours, or less than 15 hours. In some embodiments, solubilization is achieved.

[000101] Any method known in the art can be used to generate high shear forces. In some embodiments, cavitation is used to generate high shear forces. According to the present invention, the use of mechanical energy (*i.e.*, high shear forces) can replace or minimize any requirement to use costly and/or toxic chemical solvents; can increase the speed at which

nanoparticles assemble, can increase the yield of nanoparticles generated in a particular mix of components, and/or can greatly reduce the overall cost of preparing nanoparticle compositions.

[000102] In some embodiments, high shear forces are achieved by exposure to high pressure, for example by continuous turbulent flow at high pressure, for example about 15,000 psi. In some embodiments, such high pressure is within the range of about 18,000 psi to about 26,000 psi; in some embodiments, it is within the range of about 20,000 psi to about 25,000 psi; in some embodiments, it is within the range of about 25,000 psi to about 30,000 psi; in some embodiments, it is within the range of about 30,000 psi to about 35,000 psi; in some embodiments, it is within the range of about 30,000 psi to about 40,000 psi; in some embodiments, it is within the range of about 40,000 psi to about 50,000 psi.

[000103] In some embodiments, high shear force or high pressure may be administered by cavitation or high pressure homogenization.

[000104] In some embodiments, high shear force may be administered by passage through an instrument such as, for example, a Microfluidizer[®] Processor (Microfluidics Corporation/MFIC Corporation) or other like device. Microfluidizer[®] Processors provide high pressure and a resultant high shear rate by accelerating the product through microchannels to a high velocity for size reduction to the nanoscale range. The fluid is split in two and is pushed through microchannels with typical dimensions in the order of 75 microns at high velocities (in the range of 50 m/s to 300 m/s). As the fluid exits the microchannels it forms jets which collide with jets from opposing microchannels. In the channels the fluid experiences high shear (up to 10^7 1/s) which is orders of magnitude higher than that of conventional technologies. Jet collisions result in mixing in submicron level. Therefore, high shear and impact are responsible for particle size reduction and mixing of multiphase fluids in the Microfluidizer[®] technology.

[000105] More generally, a microfluidizer may be any device that powers a single acting intensifier pump. The intensifier pump amplifies the hydraulic pressure to a selected level which, in turn, imparts that pressure to the product stream. As the pump travels through its pressure stroke, it drives the product at constant pressure through the interaction chamber. Within the interaction chamber are specially designed fixed-geometry microchannels through which the product stream will accelerate to high velocities, creating high shear and impact forces that can generate a uniform nanoparticle composition (*e.g.*, nanoemulsion) as the high velocity product stream impinges on itself and on wear-resistant surfaces.

[000106] As the intensifier pump completes its pressure stroke, it reverses direction and draws in a new volume of product. At the end of the intake stroke, it again reverses direction and drives the product at constant pressures, thereby repeating the process.

[000107] Upon exiting the interaction chamber, the product flows through an onboard heat exchanger which regulates the product to a desired temperature. At this point, the product may be recirculated through the system for further processing or directed externally to the next step in the process (U.S. Patents 4,533,254; and 4,908,154; both of which are incorporated herein by reference).

[000108] In some embodiments, a sample is “microfluidized” through exposure to high shear forces for a period of time less than about 10 minutes. In some embodiments, the period of time is less than about 9, about 8, about 7, about 6, about 5, about 4, about 3, about 2, or about 1 minute(s). In some embodiments, the period of time is within the range of about 1 to about 2 minutes or less; in some embodiments, the period of time is about 30 seconds.

[000109] In some embodiments, a sample is “microfluidized” through a single exposure to high shear forces; such embodiments are referred to herein as “single pass” microfluidization.

Premix Composition

[000110] The present invention encompasses the recognition that subjecting a premix to high shear forces can generate an empty nanoparticle composition, and in particular can generate a uniform empty nanoparticle composition.

[000111] In some embodiments, provided nanoparticle compositions are prepared by subjecting a premix to high shear forces. In some embodiments, provided nanoparticle compositions are not prepared by subjecting a premix to high shear forces.

[000112] In general, the premix from which provided compositions are prepared through the application of high shear force is expected to contain at least two immiscible materials, one of which will constitute the dispersion medium (*i.e.*, the liquid medium in which particles (*e.g.*, empty nanoparticles) are dispersed in the ultimate nanoparticle composition). An “oil-in-water” dispersion is one in which oily particles are dispersed within an aqueous dispersion medium. A “water-in-oil” dispersion is one in which aqueous particles are dispersed within an oily dispersion medium. Those of ordinary skill in the art will appreciate that a dispersion can be formed from any two immiscible media and is not limited strictly to combinations of aqueous and oily media. The term “dispersion medium” therefore

applies broadly to *any* dispersion medium notwithstanding that it is common to refer to “aqueous” and “oily” categories.

[000113] Thus, in some embodiments, a premix will contain an aqueous dispersion medium and an oily medium that becomes dispersed in nanoparticle form in the dispersion medium; in some embodiments, a premix contains an oily dispersion medium and an aqueous medium that becomes dispersed in nanoparticle form in the oily dispersion medium.

[0002] Those of ordinary skill in the art will be well aware of suitable aqueous media that can be used as dispersion media or as media to be dispersed in accordance with the present invention. Representative such aqueous media include, for example, water, saline solutions (including phosphate buffered saline), water for injection, short chain alcohols, 5% dextrose, Ringer’s solutions (lactated Ringer’s injection, lactated Ringer’s plus 5% dextrose injection, acylated Ringer’s injection), Normosol-M, Isolyte E, and the like, and combinations thereof.

[000114] In some embodiments, a premix comprises an aqueous dispersion medium that comprises an isotonic sodium chloride solution. In some embodiments, a premix comprises an aqueous dispersion medium that consists essentially of an isotonic sodium chloride solution. In some embodiments, a premix comprises an aqueous dispersion medium that consists of an isotonic sodium chloride solution. In some embodiments, a premix comprises an aqueous dispersion medium that comprises gelatin. In some embodiments, a premix comprises an aqueous dispersion medium that comprises sodium phosphate. In some embodiments, a premix comprises an aqueous dispersion medium that comprises purified water. In some embodiments, a premix comprises an aqueous dispersion medium that comprises hydrochloric acid. In some embodiments, a premix comprises an aqueous dispersion medium that comprises gelatin, sodium phosphate, purified water, and hydrochloric acid. In some embodiments, a premix comprises an aqueous dispersion medium that consists essentially of gelatin, sodium phosphate, purified water, and hydrochloric acid. In some embodiments, a premix comprises an aqueous dispersion medium that consists of gelatin, sodium phosphate, purified water, and hydrochloric acid.

[000115] Those of ordinary skill in the art will also be well aware of suitable oily media that can be used as dispersion media or as media to be dispersed in accordance with the present invention. In some embodiments, oils may comprise one or more fatty acid groups or salts thereof. In some embodiments, a fatty acid group may comprise digestible, substituted or unsubstituted hydrocarbons. In some embodiments, a fatty acid group may be a C₆-C₅₀ fatty acid or salt thereof. In some embodiments, a fatty acid group may be a C₆-C₂₀ fatty acid

or salt thereof. In some embodiments, a fatty acid group may be a C₆-C₁₆ fatty acid or salt thereof. In some embodiments, a fatty acid group may be a C₆-C₁₂ fatty acid or salt thereof. In some embodiments, a fatty acid group may be a C₆ fatty acid or salt thereof. In some embodiments, a fatty acid group may be a C₈ fatty acid or salt thereof. In some embodiments, a fatty acid group may be a C₁₀ fatty acid or salt thereof. In some embodiments, a fatty acid group may be a C₁₂ fatty acid or salt thereof. In some embodiments, a fatty acid group may be unsaturated. In some embodiments, a fatty acid group may be monounsaturated. In some embodiments, a fatty acid group may be polyunsaturated. In some embodiments, a double bond of an unsaturated fatty acid group may be in the *cis* conformation. In some embodiments, a double bond of an unsaturated fatty acid may be in the *trans* conformation. In some embodiments, a fatty acid group may be one or more of butyric, caproic, caprylic, capric, lauric, myristic, palmitic, stearic, arachidic, behenic, lignoceric acid, and/or combinations thereof. In some embodiments, a fatty acid group may be one or more of palmitoleic, oleic, vaccenic, linoleic, alpha-linolenic, gamma-linolenic, arachidonic, gadoleic, arachidonic, eicosapentaenoic, docosahexaenoic, erucic acid, and/or combinations thereof.

[000116] In some embodiments, an oil is a liquid triglyceride. In some embodiments, an oil is a medium chain triglyceride. In general, medium chain triglycerides are fatty acids containing 6–12 carbons atoms (*e.g.*, caprylic acid, caproic acid, octanoic acid, capric acid, decanoic acid, lauric acid, *etc.*) and may be obtained from coconut oil or palm kernel oil or camphor tree fruit extracts. In some embodiments 1349 oil is a medium-chain triglyceride that can be utilized in accordance with the invention. In some embodiments, exemplary medium-chain triglycerides include, but are not limited, to saturated, monounsaturated, and/or polyunsaturated soybean oil, coconut oil, canola oil, safflower oil, olive oil, corn oil, cottonseed oil, linseed oil, safflower oil, palm oil, peanut oil, flaxseed oil, sunflower oil, rice bran oil, sesame oil, rapeseed oil, cocoa butter, almond oil, cashew oil, hazelnut oil, mongongo nut oil, acai oil, borage seed oil, evening primrose oil, carob pod oil, amaranth oil, apple seed oil, artichoke oil, avocado oil, babassu oil, ben oil, borneo tallow nut oil, cocoa butter, cocklebur oil, cohune oil, dika oil, grape seed oil, hemp oil, kapok seed oil, kenaf seed oil, lallemantia oil, marula oil, meadowfoam seed oil, mustard oil, papaya seed oil, perilla seed oil, pequi oil, poppyseed oil, prune kernel oil, quinoa oil, tea seed oil, thistle oil, tigernut oil, tomato seed oil, wheat germ oil, Labrafac[™] Lipophile WL 1349 oil, a silicone oil, a mineral oil, a lauroyl macrogol-6 glyceride, a lauroyl polyoxyl-6 glyceride, an oleoyl

macrogol-6 glyceride, an oleoyl polyoxyl-6 glyceride, a linoleoyl macrogol-6 glyceride, a linoleoyl polyoxyl-6 glyceride, propylene glycol monocaprylate, propylene glycol monolaurate, propylene glycol monolaurate, polglyceryl-3 dioleate, propylene glycol dicaprylocaprate, diethylene glycol monethyl ether, a caprylocaproyl macrogol-8 glyceride, a caprylocaproyl polyoxyl-8 glyceride, and/or combinations thereof.

[000117] In some embodiments, an oil is or comprises saturated, monounsaturated, and/or polyunsaturated short-chain fatty acids, medium-chain fatty acids, long-chain fatty acids, very-long-chain fatty acids, and/or combinations thereof. In some embodiments, exemplary very-long-chain fatty acids include, but are not limited to, myristoleic acid, palmitoleic acid, sapienic acid, oleic acid, linoleic acid, alpha linolenic acid, arachidonic acid, eicosapentaenoic acid, erucic acid, docosahexaenoic acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, lignoceric acid, cerotic acid, and/or combinations thereof.

[000118] In some embodiments, an oil is selected from the group consisting of short-chain triglycerides, medium-chain triglycerides, long-chain triglycerides, and/or combinations thereof. In some embodiments, a short-chain triglyceride, a medium-chain triglyceride, and/or a long-chain triglyceride selected from the group consisting of saturated, monounsaturated, and/or polyunsaturated soybean oil, coconut oil, canola oil, safflower oil, olive oil, corn oil, cottonseed oil, linseed oil, safflower oil, palm oil, peanut oil, flaxseed oil, sunflower oil, rice bran oil, sesame oil, rapeseed oil, cocoa butter, almond oil, cashew oil, hazelnut oil, macadamia oil, mongongo nut oil, pecan oil, pine nut oil, pistachio oil, sachainchi oil, walnut oil, bottle gourd oil, buffalo gourd oil, butternut squash seed oil, pumpkin seed oil, watermelon seed oil, acai oil, blackcurrant seed oil, borage seed oil, evening primrose oil, carob pod oil, amaranth oil, apricot oil, apricot kernel oil, apple seed oil, argan oil, artichoke oil, avocado oil, babassu oil, ben oil, borneo tallow nut oil, cape chestnut oil, cassia oil, cocoa butter, cocklebur oil, cohune oil, coriander seed oil, dika oil, grape seed oil, hemp oil, kapok seed oil, kenaf seed oil, lallemantia oil, marula oil, meadowfoam seed oil, mustard oil, nutmeg butter, okra seed oil, papaya seed oil, perilla seed oil, pequi oil, poppyseed oil, prune kernel oil, quinoa oil, ramtil oil, royle oil, tea seed oil, thistle oil, tigernut oil, tomato seed oil, wheat germ oil, radish oil, salicornia oil, tung oil, algae oil, copaiba oil, honge oil, jatropha oil, petroleum nut oil, WL 1349 oil, a silicone oil, a mineral oil, a lauroyl macrogol-6 glyceride, a lauroyl polyoxyl-6 glyceride, an oleoyl macrogol-6 glyceride, an oleoyl polyoxyl-6 glyceride, a linoleoyl macrogol-6 glyceride, a

linoleoyl polyoxyl-6 glyceride, propylene glycol monocaprylate, propylene glycol monolaurate, propylene glycol monolaurate, polglyceryl-3 dioleate, propylene glycol dicaprylocaprate, diethylene glycol monethyl ether, a caprylocaproyl macrogol-8 glyceride, a caprylocaproyl polyoxyl-8 glyceride, and/or combinations thereof.

[000119] In some embodiments, an oil agent is or comprises saturated, monounsaturated, and/or polyunsaturated soybean oil, coconut oil, canola oil, safflower oil, olive oil, corn oil, cottonseed oil, linseed oil, safflower oil, palm oil, peanut oil, flaxseed oil, sunflower oil, rice bran oil, sesame oil, rapeseed oil, cocoa butter, almond oil, cashew oil, hazelnut oil, macadamia oil, mongongo nut oil, pecan oil, pine nut oil, pistachio oil, sachainchi oil, walnut oil, bottle gourd oil, buffalo gourd oil, butternut squash seed oil, pumpkin seed oil, watermelon seed oil, acai oil, blackcurrant seed oil, borage seed oil, evening primrose oil, carob pod oil, amaranth oil, apricot oil, apricot kernel oil, apple seed oil, argan oil, artichoke oil, avocado oil, babassu oil, ben oil, borneo tallow nut oil, cape chestnut oil, cassia oil, cocoa butter, cocklebur oil, cohune oil, coriander seed oil, dika oil, grape seed oil, hemp oil, kapok seed oil, kenaf seed oil, lallemantia oil, marula oil, meadowfoam seed oil, mustard oil, nutmeg butter, okra seed oil, papaya seed oil, perilla seed oil, pequi oil, poppyseed oil, prune kernel oil, quinoa oil, ramtil oil, royle oil, tea seed oil, thistle oil, tigernut oil, tomato seed oil, wheat germ oil, radish oil, salicornia oil, tung oil, algae oil, copaiba oil, honge oil, jatropha oil, petroleum nut oil, WL 1349 oil, a silicone oil, a mineral oil, a lauroyl macrogol-6 glyceride, a lauroyl polyoxyl-6 glyceride, an oleoyl macrogol-6 glyceride, an oleoyl polyoxyl-6 glyceride, a linoleoyl macrogol-6 glyceride, a linoleoyl polyoxyl-6 glyceride, propylene glycol monocaprylate, propylene glycol monolaurate, propylene glycol monolaurate, polglyceryl-3 dioleate, propylene glycol dicaprylocaprate, diethylene glycol monethyl ether, a caprylocaproyl macrogol-8 glyceride, a caprylocaproyl polyoxyl-8 glyceride, bergamot, cade, camomile, caraway, carnauba, castor, cinnamon, cod liver, coffee, emu, eucalyptus, fish, geraniol, hyssop, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, mallow, mango seed, mink, orange, orange roughy, palm kernel, peach kernel, rosemary, sandalwood, sasquana, savoury, sea buckthorn, shea butter, tea tree, tsubaki, vetiver, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, octyldodecanol, oleyl alcohol, and/or combinations thereof. In some embodiments, a premix comprises an oily dispersion medium that comprises 1349 oil. In some embodiments, a premix comprises an oily dispersion medium that consists essentially of 1349 oil. In some embodiments, a premix

comprises an oily dispersion medium that consists of 1349 oil.

[000120] In some embodiments, a premix comprises an oily dispersion medium that comprises soybean oil. In some embodiments, a premix comprises an oily dispersion medium that consists essentially of soybean oil. In some embodiments, a premix comprises an oily dispersion medium that consists of soybean oil.

[000121] In addition to the two immiscible media, a premix according to the present invention may include, for example, one or more surfactants or emulsifying agents. In some embodiments, a surfactant is or comprises an amphiphilic entity in that it contains a hydrophilic moiety and a hydrophobic moiety, typically at opposing ends of the entity. In some embodiments, an amphiphilic entity is said to have a hydrophilic head and a hydrophobic tail. In some embodiments, an amphiphilic entity has a charged (anionic, cationic, or zwitterionic) head group; in some embodiments, an amphiphilic entity has an uncharged head group.

[0003] Suitable such surfactants or emulsifying agents include, but are not limited to, pemulen; phosphoglycerides; phosphatidylcholines; dipalmitoyl phosphatidylcholine (DPPC); dioleoylphosphatidyl ethanolamine (DOPE); dioleoyloxypropyltriethylammonium (DOTMA); dioleoylphosphatidylcholine; cholesterol; cholesterol ester; diacylglycerol; diacylglycerolsuccinate; diphosphatidyl glycerol (DPPG); hexanodecanol; fatty alcohols such as polyethylene glycol (PEG); polyoxyethylene-9-lauryl ether; a surface active fatty acid, such as palmitic acid or oleic acid; fatty acids; fatty acid monoglycerides; fatty acid diglycerides; fatty acid amides; sorbitan trioleate (SPAN[®]85) glycocholate; sorbitan monolaurate (SPAN[®]20); polyoxyethylene monostearate; surfactin; a poloxomer; a sorbitan fatty acid ester such as sorbitan trioleate; lecithin; lysolecithin; phosphatidylserine; phosphatidylinositol; sphingomyelin; phosphatidylethanolamine (cephalin); cardiolipin; phosphatidic acid; cerebroside; dicetylphosphate; dipalmitoylphosphatidylglycerol; stearylamine; dodecylamine; hexadecyl-amine; acetyl palmitate; glycerol ricinoleate; hexadecyl stearate; isopropyl myristate; tyloxapol; poly(ethylene glycol)5000-phosphatidylethanolamine; poly(ethylene glycol)400-monostearate; phospholipids; synthetic and/or natural detergents having high surfactant properties; deoxycholates; cyclodextrins; chaotropic salts; ion pairing agents; sodium dodecyl sulfate; pemulen; an amphiphilic entity having a head group based on a polyoxyethylene glycol sorbitan alkyl ester (*e.g.*, as in a polysorbate (TWEEN[®]), a super-refined polysorbate (TWEEN[®]), and/or combination thereof; including, but not limited to, polysorbate 20 (TWEEN[®]20); polysorbate 60 (TWEEN[®]60);

polysorbate 65 (TWEEN[®]65); polysorbate 80 (TWEEN[®]80); polysorbate 85 (TWEEN[®]85); super-refined polysorbate 20 (SR TWEEN[®]20); super-refined polysorbate 60 (SR TWEEN[®]60); super-refined polysorbate 65 (SR TWEEN[®]65); super-refined polysorbate 80 (SR TWEEN[®]80); super-refined polysorbate 85 (SR TWEEN[®]85); and/or combinations thereof); an amphiphilic entity having a sulfate-based head group (*e.g.*, as in ammonium lauryl sulfate, sodium lauryl sulfate, sodium laureth sulfate, sodium myreth sulfate, *etc.*); an amphiphilic entity having a sulfonate-based head group (*e.g.*, as in dioctyl sodium sulfosuccinate, perfluorooctanesulfonate [PFOS], perfluorobutanesulfonate, alkyl benzene sulfonates, CHAPS (3-[(3-Cholamidopropyl)dimethylammonio]-1-propanesulfonate, cocamidopropyl hydroxysultaine, *etc.*); an amphiphilic entity having a phosphate-based head group (*e.g.*, as in alkyl aryl ether phosphate, alkyl ether phosphate, lecithin, *etc.*); an amphiphilic entity having a carboxylate-based head group (*e.g.*, as in fatty acids, sodium stearate, sodium lauroyl sarcosinate, carboxylate fluorosurfactants, perfluorononanoate, perfluorooctanoate [PFOA or PFO], amino acids, imino acids, cocamidopropyl betaine, *etc.*); an amphiphilic entity having an amine-based head group (*e.g.*, a primary, secondary, or tertiary amine, as in octenidine dihydrochloride); an amphiphilic entity having a head group comprising a quaternary ammonium ion (*e.g.*, as in cetyl trimethylammonium bromide [CTAB] a.k.a. hexadecyl trimethyl ammonium bromide, cetyl trimethylammonium chloride [CTAC], cetylpyridinium chloride [CPC], polyethoxylated tallow amine [POEA], benzalkonium chloride [BAC], Benzethonium chloride [BZT], 5-Bromo-5-nitro-1,3-dioxane, Dimethyldioctadecylammonium chloride, Dioctadecyldimethylammonium bromide [DODAB]); an amphiphilic entity having a head group based on a fatty alcohol (*e.g.*, as in cetyl alcohol, stearyl alcohol, cetostearyl alcohol, oleyl alcohol, *etc.*); an amphiphilic entity having a head group based on a polyoxyethylene glycol alkyl ether (*e.g.*, as in octaethylene glycol monododecyl ether, pentaethylene glycol monododecyl ether); an amphiphilic entity having a head group based on polyoxypropylene glycol alkyl ether; an amphiphilic entity having a head group based on a glucoside alkyl ether (*e.g.*, as in decyl glucoside, lauryl glucoside, octyl glucoside, *etc.*); an amphiphilic entity having a head group based on a polyoxyethylene glycol octylphenol ether (*e.g.*, as in Triton X-100); an amphiphilic entity having a head group based on a polyoxyethylene glycol alkylphenol ether (*e.g.*, as in nonosynol-9); an amphiphilic entity having a head group based on a glycerol alkyl ester (*e.g.*, as in glyceryl laurate); an amphiphilic entity having a head group based on a sorbitan alkyl ester (*e.g.*, spans); an amphiphilic entity that is or comprises cocamide MEA, cocamide

DEA< dodecyl dimethylamine oxide; a block copolymer of polyethylene glycol and polypropylene glycol (*i.e.*, a poloxamer); an amphiphilic entity having a tail group based on or containing a hydrocarbon chain; an amphiphilic entity having a tail group based on or containing an alkyl ether chain; an amphiphilic entity having a tail group based on or containing a polyethylene; an amphiphilic entity having a tail group based on or containing polypropylene oxide; an amphiphilic entity having a tail group based on or containing a fluorocarbon chain; an amphiphilic entity having a tail group based on or containing a siloxane chain; and/or combinations thereof.

[000122] In some embodiments, a premix comprises a surfactant that comprises a polysorbate (TWEEN[®]) substance. In some embodiments, a premix comprises a surfactant that comprises a super-refined polysorbate (SR TWEEN[®]) substance. In some embodiments, a premix comprises a surfactant that comprises a polysorbate selected from the group consisting of polysorbate 20 (TWEEN[®]20); polysorbate 60 (TWEEN[®]60); polysorbate 65 (TWEEN[®]65); polysorbate 80 (TWEEN[®]80); polysorbate 85 (TWEEN[®]85); super-refined polysorbate 20 (SR TWEEN[®]20); super-refined polysorbate 60 (SR TWEEN[®]60); super-refined polysorbate 65 (SR TWEEN[®]65); super-refined polysorbate 80 (SR TWEEN[®]80); super-refined polysorbate 85 (SR TWEEN[®]85); and combinations thereof. In some embodiments, a premix comprises a surfactant that comprises polysorbate 80 (TWEEN[®]80). In some embodiments, a premix comprises a surfactant that comprises super-refined polysorbate 80 (SR TWEEN[®]80). In some embodiments, a premix comprises a surfactant that consists essentially of a polysorbate (TWEEN[®]) substance. In some embodiments, a premix comprises a surfactant that consists essentially of a super-refined polysorbate (SR TWEEN[®]) substance. In some embodiments, a premix comprises a surfactant that consists essentially of a polysorbate selected from the group consisting of polysorbate 20 (TWEEN[®]20); polysorbate 60 (TWEEN[®]60); polysorbate 65 (TWEEN[®]65); polysorbate 80 (TWEEN[®]80); polysorbate 85 (TWEEN[®]85); super-refined polysorbate 20 (SR TWEEN[®]20); super-refined polysorbate 60 (SR TWEEN[®]60); super-refined polysorbate 65 (SR TWEEN[®]65); super-refined polysorbate 80 (SR TWEEN[®]80); super-refined polysorbate 85 (SR TWEEN[®]85); and combinations thereof. In some embodiments, a premix comprises a surfactant that consists essentially of polysorbate 80 (TWEEN[®]80). In some embodiments, a premix comprises a surfactant that consists essentially of super-refined polysorbate 80 (SR TWEEN[®]80). In some embodiments, a premix comprises a surfactant that consists of a polysorbate (TWEEN[®]) substance. In some embodiments, a premix comprises a surfactant

that consists of a super-refined polysorbate (SR TWEEN[®]) substance. In some embodiments, a premix comprises a surfactant that consists of a polysorbate selected from the group consisting of polysorbate 20 (TWEEN[®]20); polysorbate 60 (TWEEN[®]60); polysorbate 65 (TWEEN[®]65); polysorbate 80 (TWEEN[®]80); polysorbate 85 (TWEEN[®]85); super-refined polysorbate 20 (SR TWEEN[®]20); super-refined polysorbate 60 (SR TWEEN[®]60); super-refined polysorbate 65 (SR TWEEN[®]65); super-refined polysorbate 80 (SR TWEEN[®]80); super-refined polysorbate 85 (SR TWEEN[®]85); and combinations thereof. In some embodiments, a premix comprises a surfactant that consists of polysorbate 80 (TWEEN[®]80). In some embodiments, a premix comprises a surfactant that consists of super-refined polysorbate 80 (SR TWEEN[®]80). In some embodiments, a premix comprises a surfactant that comprises pemulen. In some embodiments, a premix comprises a surfactant that consists essentially of pemulen. In some embodiments, a premix comprises a surfactant that consists of pemulen.

[000123] In some embodiments, a surfactant is a mixture of different surfactants. Surfactants may be extracted and purified from a natural source or may be prepared synthetically in a laboratory. In some embodiments, surfactants are commercially available.

[000124] In some embodiments, a premix comprises a gelatin agent selected from the group consisting of a hydrolyzed collagen protein, including, but not limited to, gelatin agents selected from the group consisting of Gelatine, Gelfoam, Puragel, Galfoam, a substance corresponding to CAS number 9000-70-8, other forms of gelatin, and/or combinations thereof. In some embodiments, a premix is substantially or completely free of a gelating agent.

[000125] In light of the teachings provided herein, those of ordinary skill in the art will readily be able to identify alternative or additional gelatin agents. In general, as is known in the art, a gelatin is a protein substance that is produced by partial, typically irreversible hydrolysis of collagen extracted from the boiled bones, connective tissues, organs and some intestines of animals such as domesticated cattle, pigs, and horses.

[000126] One of ordinary skill in the art would readily appreciate that gelatin itself may not be the only agent with desirable attributes, such as those described herein, and could readily test a variety of agents, particularly peptide agents, to identify additional agents having similar attributes and/or functions. Exemplary peptide agents that could be tested for attributes and/or functions similar to those exhibited by gelatin include, but are not limited to, proteins derived from blood and/or plasma, including, but not limited to, albumin, fibrin,

thrombin, prothrombin, and/or combinations thereof.

[000127] In addition to the two immiscible media, and optionally a surfactant, a premix according to the present invention may include, for example, one or more excipients. In some embodiments, a premix comprises an excipient that comprises methylparaben. In some embodiments, a premix comprises an excipient that consists essentially of methylparaben. In some embodiments, a premix comprises an excipient that consists of methylparaben. In some embodiments, a premix comprises an excipient that comprises propylparaben. In some embodiments, a premix comprises an excipient that consists essentially of propylparaben. In some embodiments, a premix comprises an excipient that consists of propylparaben. In some embodiments, a premix comprises an excipient that comprises propylparaben and methylparaben. In some embodiments, a premix comprises an excipient that consists essentially of propylparaben and methylparaben. In some embodiments, a premix comprises an excipient that consists of propylparaben and methylparaben. In some embodiments, a premix is substantially or completely free of parabens.

[000128] In some embodiments, all components present in the final empty nanoparticle composition are present in the premix and are subjected to high shear force to produce an empty nanoparticle composition. In some embodiments, one or more components that are present in a final empty nanoparticle composition is/are missing from a premix or is/are present in the premix in a smaller amount than in the final empty nanoparticle composition. That is, in some embodiments, one or more materials are added to the empty nanoparticle composition after the premix is subjected to high shear force.

[000129] In some embodiments, the premix is prepared as a solution prior to application of high shear force.

[000130] In some embodiments, the premix components may assemble into particles before the application of high shear force. At least some of such particles may be microparticles or even nanoparticles. In some embodiments, an empty nanoparticle composition is prepared from a premix, wherein the premix is selected from the group comprising a suspension or a microemulsion. In some embodiments, however, particle structures do not form in the premix before application of high shear force.

[000131] In some embodiments, relative amount of premix components are selected or adjusted to generate nanoparticles having desired characteristics.

[000132] In some embodiments, the premix comprises oil and surfactant at a ratio ranging between 0.5 – 10. In some embodiments, the ratio of oil to surfactant is

approximately 0.5:1, approximately 1:1, approximately 2:1, approximately 3:1, approximately 4:1, approximately 5:1, approximately 6:1, approximately 7:1, approximately 8:1, approximately 9:1 or approximately 10:1. In some embodiments, the ratio of surfactant to oil is approximately 0.5:1, approximately 1:1, approximately 2:1, approximately 3:1, approximately 4:1, approximately 5:1, approximately 6:1, approximately 7:1, approximately 8:1, approximately 9:1 or approximately 10:1.

[000133] In some embodiments, oil and surfactant are utilized at a ratio ranging between 0.1 and 2. In some embodiments, the ratio of oil to surfactant is approximately 0.1:1. In some embodiments, the ratio of oil to surfactant is approximately 0.15:1. In some embodiments, the ratio of oil to surfactant is approximately 0.2:1. In some embodiments, the ratio of oil to surfactant is approximately 0.25:1. In some embodiments, the ratio of oil to surfactant is approximately 0.3:1. In some embodiments, the ratio of oil to surfactant is approximately 0.35:1. In some embodiments, the ratio of oil to surfactant is approximately 0.4:1. In some embodiments, the ratio of oil to surfactant is approximately 0.45:1. In some embodiments, the ratio of oil to surfactant is approximately 0.5:1. In some embodiments, the ratio of oil to surfactant is approximately 0.55:1. In some embodiments, the ratio of oil to surfactant is approximately 0.6:1. In some embodiments, the ratio of oil to surfactant is approximately 0.65:1. In some embodiments, the ratio of oil to surfactant is approximately 0.7:1. In some embodiments, the ratio of oil to surfactant is approximately 0.75:1. In some embodiments, the ratio of oil to surfactant is approximately 0.8:1. In some embodiments, the ratio of oil to surfactant is approximately 0.85:1. In some embodiments, the ratio of oil to surfactant is approximately 0.9:1. In some embodiments, the ratio of oil to surfactant is approximately 0.95:1. In some embodiments, the ratio of oil to surfactant is approximately 1:1. In some embodiments, the ratio of oil to surfactant is approximately 1:1.05. In some embodiments, the ratio of oil to surfactant is approximately 1:1.1. In some embodiments, the ratio of oil to surfactant is approximately 1:1.15. In some embodiments, the ratio of oil to surfactant is approximately 1:1.2. In some embodiments, the ratio of oil to surfactant is approximately 1:1.25. In some embodiments, the ratio of oil to surfactant is approximately 1:1.3. In some embodiments, the ratio of oil to surfactant is approximately 1:1.35. In some embodiments, the ratio of oil to surfactant is approximately 1:1.4. In some embodiments, the ratio of oil to surfactant is approximately 1:1.45. In some embodiments, the ratio of oil to surfactant is approximately 1:1.5. In some embodiments, the ratio of oil to surfactant is approximately 1:1.55. In some embodiments, the ratio of oil to surfactant is approximately

1:1.6. In some embodiments, the ratio of oil to surfactant is approximately 1:1.65. In some embodiments, the ratio of oil to surfactant is approximately 1:1.7. In some embodiments, the ratio of oil to surfactant is approximately 1:1.75. In some embodiments, the ratio of oil to surfactant is approximately 1:1.8. In some embodiments, the ratio of oil to surfactant is approximately 1:1.85. In some embodiments, the ratio of oil to surfactant is approximately 1:1.9. In some embodiments, the ratio of oil to surfactant is approximately 1:1.95. In some embodiments, the ratio of oil to surfactant is approximately 1:2. In some embodiments, the ratio of oil to surfactant is approximately 1:2.5. In some embodiments, the ratio of oil to surfactant is approximately 1:3. In some embodiments, the ratio of oil to surfactant is approximately 1:3.5. In some embodiments, the ratio of oil to surfactant is approximately 1:4. In some embodiments, the ratio of oil to surfactant is approximately 1:4.5. In some embodiments, the ratio of oil to surfactant is approximately 1:5.

[000134] In some embodiments, the premix comprises oil and surfactant at a ratio ranging between about 0.1:1 to about 2:1. In some embodiments, the premix comprises oil and surfactant at a ratio of about 0.1:1 to about 1:1. In some embodiments, the premix comprises oil and surfactant at a ratio of about 0.5:1 to about 1:1. In some embodiments, the premix comprises oil and surfactant at a ratio of about 0.1:1, about 0.15:1, about 0.2:1, about 0.25:1, about 0.3:1, about 0.35:1, about 0.4:1, about 0.45:1, about 0.5:1, about 0.5:1, about 0.55:1, about 0.6:1, about 0.65:1, about 0.7:1, about 0.75:1, about 0.8:1, about 0.85:1, about 0.9:1, about 0.95:1, or about 1:1. In some embodiments, the premix comprises oil and surfactant at a ratio of about 0.67:1.

[000135] In some embodiments, the aqueous dispersion medium (*e.g.*, water, buffer, salt solution, *etc.*) and surfactant are utilized at a ratio ranging between 0.01 and 20. In some embodiments, the aqueous dispersion medium (*e.g.*, water, buffer, salt solution, *etc.*) and surfactant are utilized at a ratio ranging between 0.1 and 20. In some embodiments, the aqueous dispersion medium (*e.g.*, water, buffer, salt solution, *etc.*) and surfactant are utilized at a ratio ranging between 0.5 and 10. In some embodiments, the aqueous dispersion medium (*e.g.*, water, buffer, salt solution, *etc.*) and surfactant are utilized at a ratio ranging between 0.5 and 1. In some embodiments, the ratio of aqueous dispersion medium (*e.g.*, water, buffer, salt solution, *etc.*) to surfactant is approximately 0.01:1, approximately 0.02:1, approximately 0.03:1, approximately 0.04:1, approximately 0.05:1, approximately 0.06:1, approximately 0.07:1, approximately 0.08:1, approximately 0.0:1, approximately 0.1:1, approximately 0.2:1, approximately 0.3:1, approximately 0.4:1, approximately 0.5:1, approximately 1:1,

approximately 2:1, approximately 3:1, approximately 4:1, approximately 5:1, approximately 6:1, approximately 7:1, approximately 8:1, approximately 9:1 or approximately 10:1. In some embodiments, the ratio of surfactant to water is approximately 0.5:1, approximately 1:1, approximately 2:1, approximately 3:1, approximately 4:1, approximately 5:1, approximately 6:1, approximately 7:1, approximately 8:1, approximately 9:1, approximately 10:1, approximately 11:1, approximately 12:1, approximately 13:1, approximately 14:1, approximately 15:1, approximately 16:1, approximately 17:1, approximately 18:1, approximately 19:1, or approximately 20:1. In some embodiments, aqueous dispersion medium (*e.g.*, water, buffer, salt solution, *etc.*) and surfactant are utilized at a ratio ranging between 0.5 and 2. In some embodiments, the ratio of aqueous dispersion medium (*e.g.*, water, buffer, salt solution, *etc.*) to surfactant is approximately 0.5:1, approximately 1:1, or approximately 2:1. In some embodiments, the ratio of surfactant to aqueous dispersion medium (*e.g.*, water, buffer, salt solution, *etc.*) is approximately 0.5:1, approximately 1:1, or approximately 2:1. In some embodiments, the ratio of aqueous dispersion medium (*e.g.*, water, buffer, salt solution, *etc.*) to surfactant is approximately 1:1. In some embodiments, compositions utilizing such ratios of aqueous dispersion medium (*e.g.*, water, buffer, salt solution, *etc.*) to surfactant comprise water-in-oil emulsions.

[000136] In some embodiments, aqueous dispersion media and surfactant are utilized at a ratio ranging between about 8:1 and about 9:1. In some embodiments, aqueous dispersion media and surfactant are utilized at a ratio of about 8:1, about 8.1:1, about 8.2:1, about 8.3:1, about 8.4:1, about 8.5:1, about 8.6:1, about 8.7:1, about 8.8:1, about 8.9:1, about 9:1, etc. In some embodiments, aqueous dispersion media and surfactant are utilized at a ratio of about 8.7:1. In some embodiments, aqueous dispersion media and surfactant are utilized at a ratio of about 8.8:1.

[000137] In some embodiments, aqueous dispersion media and oil are utilized at a ratio ranging between about 12:1 and about 14:1. In some embodiments, aqueous dispersion media and surfactant are utilized at a ratio of about 12:1, about 12.1:1, about 12.2:1, about 12.3:1, about 12.4:1, about 12.5:1, about 12.6:1, about 12.7:1, about 12.8:1, about 12.9:1, about 13:1, about 13.1:1, about 13.2:1, about 13.3:1, about 13.4:1, about 13.5:1, about 13.6:1, about 13.7:1, about 13.8:1, about 13.9:1, about 14:1, etc. In some embodiments, aqueous dispersion media and surfactant are utilized at a ratio of about 13.1:1.

[000138] In some embodiments, the percent of oil in the premix ranges between 0% and 50%. In some embodiments, the percent of oil in the premix ranges between 0% and 40%.

In some embodiments, the percent of oil in the premix ranges between 0% and 30%. In some embodiments, the percent of oil in the premix ranges between 0% and 20%. In some embodiments, the percent of oil in the premix ranges between 0% and 10%. In some embodiments, the percent of oil in the premix ranges between 0% and 5%. In some embodiments, the percent of oil in the premix ranges between 5% and 10%, between 10% and 15%, between 15% and 20%, between 20% and 25%, between 25% and 30%, between 35% and 40%, or between 45% and 50%. In some embodiments, the percent of oil in the premix ranges between 10% and 20%, between 10% and 30%, between 10% and 40%, or between 10% and 50%. In some embodiments, the percent of oil in the premix ranges between 20% and 30%, between 20% and 40%, between 20% and 50%. In some embodiments, the percent of oil in the premix ranges between 30% and 40% or between 30% and 50%. In some embodiments, the percent of oil in the premix ranges between 40% and 50%.

[000139] In some embodiments the percent of oil in the premix is approximately 1%, approximately 2%, approximately 3%, approximately 4%, approximately 5%, approximately 6%, approximately 7%, approximately 9%, approximately 10%, approximately 11%, approximately 12%, approximately 13%, approximately 14%, approximately 15%, approximately 16%, approximately 17%, approximately 18%, approximately 19%, approximately 20%, approximately 21%, approximately 22%, approximately 23%, approximately 24%, approximately 25%, approximately 26%, approximately 27%, approximately 28%, approximately 29%, approximately 30%, approximately 31%, approximately 32%, approximately 33%, approximately 34%, approximately 35%, approximately 36%, approximately 37%, approximately 38%, approximately 39%, approximately 40%, approximately 41%, approximately 42%, approximately 43%, approximately 44%, approximately 45%, approximately 46%, approximately 47%, approximately 48%, approximately 49%, or approximately 50%. In some embodiments the percent of oil is approximately 10%. In some embodiments the percent of oil is approximately 9%. In some embodiments the percent of oil is approximately 8%. In some embodiments the percent of oil is approximately 7%. In some embodiments the percent of oil is approximately 6%. In some embodiments the percent of oil is approximately 5%. In some embodiments the percent of oil is approximately 4%. In some embodiments the percent of oil is approximately 3%. In some embodiments the percent of oil is approximately 2%. In some embodiments the percent of oil is approximately 1%.

[000140] In some embodiments, the percent of oil in the premix ranges between about 5% and about 8%. In some embodiments, the percent of oil in the premix is about 5%, about 5.1%, about 5.2%, about 5.3%, about 5.4%, about 5.5%, about 5.6%, about 5.7%, about 5.8%, about 5.9%, about 6%, about 6.1%, about 6.2%, about 6.3%, about 6.4%, about 6.5%, about 6.6%, about 6.7%, about 6.8%, about 6.9%, about 7%, about 7.1%, about 7.2%, about 7.3%, about 7.4%, about 7.5%, about 7.6%, about 7.7%, about 7.8%, about 7.9%, or about 8%. In some embodiments, the percent of oil in the premix is about 6.3%. In some embodiments, the percent of oil in the premix is about 6.4%. The percent of aqueous dispersion medium (*e.g.*, water, buffer, salt solution, *etc.*) in the premix can range from 0% to 99%, from 10% to 99%, from 25% to 99%, from 50% to 99%, or from 75% to 99%. In some embodiments, the percent of aqueous dispersion medium (*e.g.*, water, buffer, salt solution, *etc.*) in the premix can range from 0% to 75%, from 0% to 50%, from 0% to 25%, or from 0% to 10%. In some embodiments, the percent of aqueous dispersion medium (*e.g.*, water, buffer, salt solution, *etc.*) in the premix ranges between 0% and 30%. In some embodiments the percent of aqueous dispersion medium (*e.g.*, water, buffer, salt solution, *etc.*) is approximately 1%, approximately 2%, approximately 3%, approximately 4%, approximately 5%, approximately 6%, approximately 7%, approximately 9%, approximately 10%, approximately 11%, approximately 12%, approximately 13%, approximately 14%, approximately 15%, approximately 16%, approximately 17%, approximately 18%, approximately 19%, approximately 20%, approximately 21%, approximately 22%, approximately 23%, approximately 24%, approximately 25%, approximately 26%, approximately 27%, approximately 28%, approximately 29%, approximately 30%, approximately 35%, approximately 40%, approximately 45%, approximately 50%, approximately 55%, approximately 60%, approximately 65%, approximately 70%, approximately 71%, approximately 72%, approximately 73%, approximately 74%, approximately 75%, approximately 76%, approximately 77%, approximately 78%, approximately 79%, approximately 80%, approximately 81%, approximately 82%, approximately 83%, approximately 84%, approximately 85%, approximately 86%, approximately 87%, approximately 88%, approximately 89%, approximately 90%, approximately 91%, approximately 92%, approximately 93%, approximately 94%, approximately 95%, approximately 96%, approximately 97%, approximately 98%, or approximately 99%,. In some embodiments the percent of water is approximately 83%. In some embodiments the percent of water is approximately 9%. In some embodiments the

percent of water is approximately 5%.

[000141] In some embodiments, the percent of aqueous dispersion medium in the premix ranges between about 80% and about 85%. In some embodiments, the percent of aqueous dispersion medium in the premix is about 80, about 80.5%, about 81%, about 81.5%, about 82%, about 82.5%, about 83%, about 83.5%, about 84%, about 84.5%, or about 85%. In some embodiments, the percent of aqueous dispersion medium in the premix is about 83.5%. In some embodiments, the percent of oil in the premix is about 84%.

[000142] In some embodiments, the percent of surfactant in the premix ranges between 0% –30%. In some embodiments the percent of surfactant in the premix is approximately 1%, approximately 2%, approximately 3%, approximately 4%, approximately 5%, approximately 6%, approximately 7%, approximately 9%, approximately 10%, approximately 11%, approximately 12%, approximately 13%, approximately 14%, approximately 15%, approximately 16%, approximately 17%, approximately 18%, approximately 19%, approximately 20%, approximately 21%, approximately 22%, approximately 23%, approximately 24%, approximately 25%, approximately 26%, approximately 27%, approximately 28%, approximately 29%, approximately 30%, approximately 31%, approximately 32%, approximately 33%, approximately 34%, approximately 35%, approximately 36%, approximately 37%, approximately 38%, approximately 39%, approximately 40%, approximately 41%, approximately 42%, approximately 43%, approximately 44%, approximately 45%, approximately 46%, approximately 47%, approximately 48%, approximately 49%, or approximately 50%. In some embodiments the percent of surfactant is approximately 10%. In some embodiments the percent of surfactant is approximately 9%. In some embodiments the percent of surfactant is approximately 8%. In some embodiments the percent of surfactant is approximately 7%. In some embodiments the percent of surfactant is approximately 6%. In some embodiments the percent of surfactant is approximately 5%.

[0004] In some embodiments, the percent of surfactant in the premix ranges between about 8% and about 11%. In some embodiments, the percent of surfactant in the premix is about 8%, about 8.1%, about 8.2%, about 8.3%, about 8.4%, about 8.5%, about 8.6%, about 8.7%, about 8.8%, about 8.9%, about 9%, about 9.1%, about 9.2%, about 9.3%, about 9.4%, about 9.5%, about 9.6%, about 9.7%, about 9.8%, about 9.9%, about 10%, about 10.1%, about 10.2%, about 10.3%, about 10.4%, about 10.5%, about 10.6%, about 10.7%, about

10.8%, about 10.9%, or about 11%. In some embodiments, the percent of oil in the premix is about 9.5%. In some embodiments, the percent of surfactant in the premix is about 9.6%.

[0005] In some embodiments, the percent of excipient in the premix ranges between about 0.1% and about 1%. In some embodiments, the percent of excipient in the premix is about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, or about 1%. In some embodiments, the percent of excipient in the premix is about 0.4%.

[0006] In some embodiments, a premix consists essentially of the following proportions of ingredients:

Table 4. Exemplary Premix

% w/w	Ingredient
6.375	1349 Oil
9.562	Polysorbate 80
0.199	Propylparaben
63.75	Isotonic Sodium Chloride Solution
0.199	Methylparaben
19.92	Buffer Solution*
xx	If applicable, known therapeutic agent and/or independently active biologically active agent diluted in Buffer Solution
100	TOTAL

* Buffer Solution contains (w/w) 0.199% gelatin, 0.398% sodium phosphate dibasic, 99.4% purified water, pH adjusted to 6.0 ± 0.2 with hydrochloric acid.

[000143] In some embodiments, a provided composition does not contain more than one oil. In some embodiments, a provided composition may comprise two or more oils (*e.g.*, 2, 3, 4, 5, or more oils). In some embodiments, a provided composition does not contain more than one surfactant. In some embodiments, a provided composition may comprise two or more surfactants (*e.g.*, 2, 3, 4, 5, or more surfactants).

[000144] In some embodiments, a provided composition consists essentially of an aqueous dispersion medium (*e.g.*, water, buffer, salt solution, *etc.*), an oil, and a surfactant. In some embodiments, a provided composition consists essentially of an aqueous dispersion

medium (*e.g.*, water, buffer, salt solution, *etc.*), an oil, and a surfactant, and at least one substance used to produce and/or preserve the composition (*e.g.*, proteins, salts, *etc.*).

[000145] In some embodiments, a provided composition consists of an aqueous dispersion medium (*e.g.*, water, buffer, salt solution, *etc.*), an oil, and a surfactant. In some embodiments, a provided composition consists of an aqueous dispersion medium (*e.g.*, water, buffer, salt solution, *etc.*), an oil, a surfactant, and at least one substance used to produce and/or preserve the composition (*e.g.*, proteins, salts, *etc.*). In some embodiments, a provided composition consists of an aqueous dispersion medium (*e.g.*, water, buffer, salt solution, *etc.*), one or more oils, and one or more surfactants. In some embodiments, a provided composition consists of an aqueous dispersion medium (*e.g.*, water, buffer, salt solution, *etc.*), one or more oils, one or more surfactants, and at least one substance used to produce and/or preserve the composition (*e.g.*, proteins, salts, *etc.*). In some embodiments, a provided composition does not contain an added preservative. In some embodiments, a provided composition does not contain parabens, such as methyparaben and propylparaben.

Identification and/or Characterization of Biologically Active Components

[000146] As described herein, the present invention encompasses the finding that certain nanoparticle compositions, not containing any agent previously known to have relevant biological activity, nonetheless can achieve biological effects. The present invention further encompasses the recognition that such effects may result from and/or require nanoparticle structure, and in particular may result from and/or require certain embodiments of nanoparticle structure described herein. Alternatively or additionally, the present invention encompasses the recognition that one or more components of described nanoparticle compositions may contribute to or provide the biological effects observed with the empty nanoparticle composition, partially or wholly independent of nanoparticle structure.

[000147] The present invention therefore provides systems for identifying and/or characterizing biologically active agents by assaying individual components, or combinations of components, of provided compositions as described herein. According to certain embodiments of the present invention, one or more such components, alone or in combination with others, may have biological activity independent of nanoparticle structure (*e.g.*, in the context of a composition that is not a nanoparticle composition, and particularly is not a nanoemulsion, or a uniform nanoparticle composition, as described herein). Such

embodiments of the present invention provide both (i) the identification/characterization of such components, and (ii) compositions containing such components, in amounts appropriate to achieve the relevant biological effects when administered as part of a dosing regimen, *e.g.*, as described herein. Such component-containing compositions are “provided compositions” herein, whether or not they contain nanoparticle structure. The present invention also provides uses for such provided compositions, as described herein.

Dermatologic Conditions

[000148] The present invention provides methods and compositions for the treatment and/or prevention of any of a variety of dermatologic conditions. In some embodiments, the present invention provides methods and compositions for the treatment and/or prevention of diseases, disorders, or conditions associated with activity of sweat and/or sebaceous glands. In some embodiments, the present invention provides methods and compositions for the treatment and/or prevention of diseases, disorders or conditions associated with the epidermal and/or dermal level of the skin.

[000149] In some embodiments, the present invention provides methods and compositions for the treatment and/or prevention of one or more of acne, unwanted sweating, body odor, hyperhidrosis, bromhidrosis, chromhidrosis, rosacea, hair loss, psoriasis, actinic keratosis, eczematous dermatitis (*e.g.*, atopic dermatitis, *etc.*), excess sebum-producing disorders (*e.g.*, seborrhea, seborrheic dermatitis, *etc.*), burns, Raynaud’s phenomenon, lupus erythematosus, hyperpigmentation disorders (*e.g.*, melasma, *etc.*), hypopigmentation disorders (*e.g.*, vitiligo, *etc.*), skin cancer (*e.g.*, squamous cell skin carcinoma, basal cell skin carcinoma, *etc.*), dermal infection (*e.g.*, bacterial infection, viral infection, fungal infection, *etc.*), facial wrinkles, (*e.g.*, wrinkles involving the forehead, glabellar, rhytids and/or periorbital regions), headache, unsightly facial expressions (*e.g.*, due to overactivity of underlying facial musculature), neck lines, hyperfunctional facial lines, hyperkinetic facial lines, platysma bands, neuromuscular disorders and conditions involving muscular spasm and/or contracture (including various forms of facial palsy, cerebral palsy, blepharospasm, facial contracture), dystonia, prostate hyperplasia, strabismus, hemifacial spasm, tremor, spasticity such as that resulting from multiple sclerosis, retroorbital muscle, various ophthalmologic conditions, and/or combinations thereof.

[000150] In some embodiments, the present invention involves administration of at least one provided composition according to a dosing regimen sufficient to achieve a reduction in

the degree and/or prevalence of a relevant dermatologic condition of at least about 20%; in some embodiments according to a dosing regimen sufficient to achieve a of at least about 25%; in some embodiments according to a dosing regimen sufficient to achieve a reduction of at least about 30%; in some embodiments according to a dosing regimen sufficient to achieve a reduction of at least about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, or more.

[000151] In some embodiments, the present invention involves administration of at least one provided composition according to a dosing regimen sufficient to achieve a reduction in the degree and/or prevalence of a relevant dermatologic condition of at least about 20% in a specified percentage of a population of patients to which the composition was administered; in some embodiments according to a dosing regimen sufficient to achieve a of at least about 25% in a specified percentage of a population of patients to which the composition was administered; in some embodiments according to a dosing regimen sufficient to achieve a reduction of at least about 30% in a specified percentage of a population of patients to which the composition was administered; in some embodiments according to a dosing regimen sufficient to achieve a reduction of at least about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90% or more in a specified percentage of a population of patients to which the composition was administered. In some embodiments, the specified percentage of population of patients to which the composition was administered is at least

about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%. To give but a few illustrative examples, in some embodiments, the present invention involves administration of at least one provided composition according to a dosing regimen sufficient to achieve a reduction in the degree and/or prevalence of a relevant dermatologic condition of at least about 20% in at least about 50% of the population of patients to which the composition was administered. In some embodiments, the present invention involves administration of at least one provided composition according to a dosing regimen sufficient to achieve a reduction in the degree and/or prevalence of a relevant dermatologic condition of at least about 30% in at least about 50% of the population of patients to which the composition was administered.

[000152] The present invention provides methods of treating and/or preventing a dermatologic condition comprising administration of a provided composition to a subject suffering from, susceptible to, and/or displaying symptoms the dermatologic condition. In some embodiments, provided compositions for treatment of a dermatologic condition as described herein are formulated for any route of administration described herein. In some embodiments, provided compositions are formulated for topical administration. In some embodiments, provided compositions are formulated into a cream, liniment, lotion, gel, shampoo, conditioner, sunscreen, deodorant, and/or antiperspirant (*e.g.*, as a roll-on, solid stick, gel, cream, aerosol, *etc.*), *etc.*, as appropriate to the condition being treated.

[000153] In some embodiments, provided compositions are formulated for injection, *e.g.*, into an affected site. In some embodiments, provided compositions are formulated for systemic delivery.

[000154] In some embodiments, such a provided composition is administered locally to an affected site (*e.g.*, axillae, hands, feet, scalp, hair follicle, face, neck, back, arms, chest, *etc.*, as appropriate to the particular condition being treated). In some embodiments, local administration is achieved by topical administration and/or by injection. In some embodiments, a provided composition is administered systemically (*e.g.*, orally, topically, via injection, *etc.*).

[000155] Further considerations for formulation and administration are described in further detail in the sections entitled “Compositions and Formulations” and “Administration.”

[000156] More detailed discussion of certain of these conditions and their treatment and/or prevention in accordance with the present invention is provided below.

Unwanted Sweating

[000157] In some embodiments, provided compositions are useful for treating and/or preventing unwanted sweating (or perspiration). In some embodiments, unwanted sweating is a symptom of a clinically diagnosed condition such as hyperhidrosis. In some embodiments, unwanted sweating is not associated with a clinical diagnosis such as hyperhidrosis, but is simply any sweating (perspiration) which is unwanted by the patient. In some embodiments, sweating which is unwanted by the patient includes all sweating.

[000158] In some embodiments, administration of a provided composition according to a dosing regimen sufficient to achieve sweat reduction upon administration of provided compositions to individuals who are not suffering from a clinical sweating condition, but nonetheless desire sweat reduction. As a further discovery, in some embodiments, the present invention achieves such levels to individuals who suffer from a sweat-related clinical disorder, for example hyperhidrosis, chromhidrosis, bromhidrosis, *etc.*

[000159] In some embodiments, provided compositions for treatment and/or prevention of unwanted sweating are formulated into a cream, liniment, lotion, gel, sunscreen, deodorant, and/or antiperspirant (*e.g.*, as a roll-on, solid stick, gel, cream, aerosol, *etc.*), *etc.*

[000160] In some embodiments, provided compositions for treatment and/or prevention of unwanted sweating are administered locally to an affected site (*e.g.*, axillae, hands, feet, *etc.*).

[000161] Current therapies useful in the treatment of unwanted sweating include, but are not limited to, botulinum toxin; antiperspirants (*e.g.*, aluminum chloride, aluminum chlorohydrate, aluminum-zirconium compounds, aluminum zirconium tetrachlorohydrate gly, aluminum zirconium trichlorohydrate gly, ammonium alum, *etc.*); aluminum chlorohydrate compounds; aluminum dichlorohydrate; aluminum dichlorohydrate compounds; aluminum sesquichlorohydrate; aluminum sesquichlorohydrate compounds; oral medication (*e.g.*, diphenhydramine hydrochloride, hydroxyzine, glycopyrrolate, *etc.*); anticholinergic drugs (*e.g.*, oxybutynin, glycopyrrolate, propantheline bromide, benztropine, *etc.*); beta-blockers; antidepressants; anxiolytics; talc and/or baby powder; and/or combinations thereof.

[000162] Alternative or additional current treatments for unwanted sweating include, but are not limited to, surgery (*e.g.*, endoscopic thoracic sympathectomy, lumbar sympathectomy, sweat gland suction, percutaneous sympathectomy, *etc.*); iontophoresis; weight loss; relaxation and/or meditation; hypnosis; use of shoe inserts; and/or combinations thereof.

Hyperhidrosis

[000163] In some embodiments, provided compositions are useful for treating hyperhidrosis. Hyperhidrosis is a medical condition in which a person sweats excessively and unpredictably. People with hyperhidrosis can sweat even when the temperature is cool, and when they are at rest. Sweating helps the body stay cool and is perfectly natural. People sweat more in warm temperatures, when they exercise, or in response to situations that make them nervous, angry, embarrassed, or afraid. Uncontrollable sweating can lead to significant discomfort, both physical and emotional.

[000164] Hyperhidrosis occurs without normal sweat triggers, and refers to the condition characterized by perspiration in excess of that required for regulation of body temperature. Those with hyperhidrosis appear to have overactive sweat glands. Hyperhidrosis can either be generalized or localized to specific parts of the body. Hands, feet, axillae, forehead, and the groin area are among the most active regions of perspiration due to the relatively high concentration of sweat glands; however, any part of the body may be affected. Excessive sweating that affects hands, feet, and armpits and has no other identifiable cause is referred to as “primary” or “focal hyperhidrosis.” Primary hyperhidrosis affects 2% – 3% of the population, yet less than 40% of patients with this condition seek medical advice. There may be a genetic component involved in primary hyperhidrosis. One theory is that hyperhidrosis results from an overactive sympathetic nervous system. Primary hyperhidrosis is found to start during adolescence or even before.

[000165] If sweating occurs as a result of another medical condition, it is called secondary hyperhidrosis. Sweating may be all over one’s body, or it may be localized to one area. Secondary hyperhidrosis can start at any point in life. For some, it can seem to come on unexpectedly. Conditions that cause secondary hyperhidrosis include but are not limited to, acromegaly, hyperthyroidism, glucose control disorders (including diabetes), pheochromocytoma, carcinoid syndrome, cancer, tuberculosis, infections, menopause, spinal cord injury, stroke, thyroid gland disorder, pituitary gland disorder, gout, mercury poisoning, Parkinson’s disease, heart disease, lung disease, certain medications, substance abuse, or anxiety conditions.

[000166] Hyperhidrosis can be categorized as “palmar” (*i.e.*, excessive sweating of the hands), “axillary” (*i.e.*, excessive sweating of the armpits), “plantar” (*i.e.*, excessive sweating of the feet), “facial” (*i.e.*, excessive sweating of the face), “cranial” (*i.e.*, excessive sweating

of the head, especially noted around the hairline), or “general” (*i.e.*, overall excessive sweating).

[000167] In some embodiments, provided compositions for treatment and/or prevention of hyperhidrosis are formulated into a cream, liniment, lotion, gel, sunscreen, deodorant, and/or antiperspirant (*e.g.*, as a roll-on, solid stick, gel, cream, aerosol, *etc.*), *etc.*.

[000168] In some embodiments, provided compositions for treatment and/or prevention of hyperhidrosis are administered locally to an affected site (*e.g.*, axillae, hands, feet, *etc.*).

[000169] Current therapies for the treatment of hyperhidrosis include, but are not limited to, botulinum toxin, antiperspirants (*e.g.*, aluminum chloride, aluminum chlorohydrate, aluminum-zirconium compounds, aluminum zirconium tetrachlorohydrate gly, aluminum zirconium trichlorohydrate gly, ammonium alum, *etc.*); oral medication (*e.g.*, diphenhydramine hydrochloride, hydroxyzine, glycopyrrolate, *etc.*); anticholinergic drugs (*e.g.*, oxybutynin, glycopyrrolate, propantheline bromide, benztropine, *etc.*); beta-blockers; antidepressants; anxiolytics; talc and/or baby powder; and/or combinations thereof.

[000170] Alternative or additional current therapies for the treatment of hyperhidrosis include, but are not limited to, surgery (*e.g.*, endoscopic thoracic sympathectomy [ETS], lumbar sympathectomy, sweat gland suction, percutaneous sympathectomy, *etc.*); iontophoresis; weight loss; relaxation and/or meditation; hypnosis; use of shoe inserts; and/or combinations thereof.

[000171] In ETS procedures, select sympathetic nerves or nerve ganglia in the chest are either excised, cut, burned, or clamped. The procedure causes relief of excessive hand sweating in about 85% – 95% of patients. However, compensatory sweating is seen in about 20% to 80% of patients. While ETS can be helpful to treat axillary hyperhidrosis, palmar hyperhidrosis patients frequently have better results.

[000172] Lumbar sympathectomy can be useful for patients for whom endoscopic thoracic sympathectomy did not relieve their excessive plantar sweating. With this procedure, the sympathetic chain in the lumbar region is being clipped or divided in order to relieve the severe or excessive feet sweating. The success rate is about 90%.

[000173] Sweat gland suction is a technique adapted and modified from liposuction (Bieniek *et al.*, 2005, *Acta dermatovenerologica Croatica: ADC / Hrvatsko dermatolosko društvo*, 13:212-8; incorporated herein by reference). Approximately 30% of the sweat glands are removed with a proportionate reduction in sweat.

[000174] Iontophoresis was originally described in the 1950s, and its exact mode of

action remains elusive to date (Kreyden, 2004, *J. Cosmetic Dermatol.*, 3:211-4; incorporated herein by reference). An affected area is placed in a device that has two pails of water with a conductor in each one. The hand or foot acts like a conductor between the positively- and negatively-charged pails. As the low current passes through the area, the minerals in the water clog the sweat glands, limiting the amount of sweat released. The device is usually used for the hands and feet, but there has been a device created for the axillae area and for the stump region of amputees.

[000175] Percutaneous sympathectomy is a minimally invasive procedure in which nerves are blocked by injection of phenol (Wang *et al.*, 2001, *Neurosurgery*, 49:628-34; incorporated herein by reference).

[000176] In some subjects, weight loss can help alleviate one or more symptoms of hyperhidrosis, as hyperhidrosis can be aggravated by obesity.

[000177] Relaxation, meditation, and/or hypnosis therapies are sometimes utilized in the treatment and/or prevention of hyperhidrosis. For example, hypnosis has been used with some success in improving the process of administering injections for the treatment of hyperhidrosis (Maillard *et al.*, 2007, *Annales de dermatologie et de vénéréologie*, 134:653-4; incorporated herein by reference).

Body Odor

[000178] In some embodiments, provided compositions are useful for treating and/or preventing body odor. In some embodiments, body odor is a symptom of a clinically diagnosed condition such as bromhidrosis. In some embodiments, body odor is not associated with a clinical diagnosis such as bromhidrosis, but is simply any body odor (*e.g.*, unwanted body odor) of a subject. In some embodiments, therapies effective for treating unwanted sweating and/or hyperhidrosis are also effective for treating body odor.

[000179] In some embodiments, provided compositions for treatment and/or prevention of body odor are formulated into a cream, liniment, lotion, gel, sunscreen, deodorant, and/or antiperspirant (*e.g.*, as a roll-on, solid stick, gel, cream, aerosol, *etc.*), *etc.*

[000180] In some embodiments, provided compositions for treatment and/or prevention of body odor are administered locally to an affected site (*e.g.*, axillae, hands, feet, *etc.*).

Bromhidrosis

[000181] In some embodiments, provided compositions may be useful for treating bromhidrosis (also called osmidrosis, ozochrotia, body odor, and B.O.) is the smell of bacteria growing on a body. Bacteria multiply rapidly in the presence of sweat, but sweat itself is almost completely odorless. Body odor is associated with the hair, feet, groin, anus, skin in general, armpits, genitals, pubic hair, and mouth.

[000182] Apocrine bromhidrosis is the most prevalent form, whereas eccrine bromhidrosis is less common. Several factors contribute to the pathogenesis of apocrine bromhidrosis. Bacterial decomposition of apocrine secretion yields ammonia and short-chain fatty acids, with their characteristic strong odors. The most abundant of these acids is (E)-3-methyl-2-hexanoic acid (E-3M2H), which is brought to the skin surface bound by two apocrine secretion odor-binding proteins (ASOB1 and ASOB2). One of these binding proteins, ASOB2, has been identified as apolipoprotein D (apoD), a known member of the lipocalin family of carrier proteins.

[000183] Axillary bacterial flora have been shown to produce the distinctive axillary odor by transforming nonodiferous precursors in sweat to more odiferous volatile acids. The most common of these are E-3M2H and (RS)-3-hydroxy-3-methylhexanoic acid (HMHA), which are released through the action of a specific zinc-dependent *N*-alpha-acyl-glutamine aminoacylase (*N*-AGA) from *Corynebacterium* species. This aminoacylase has recently been demonstrated to also release other odiferous acids from glutamine conjugates in sweat, which may be the basis of individual body odor.

[000184] In certain circumstances, eccrine secretion, which is typically odorless, assumes an offensive aroma and causes eccrine bromhidrosis. When eccrine sweat softens keratin, bacterial degradation of the keratin yields a foul smell. Ingestion of some foods, including garlic, onion, curry, alcohol, certain drugs (*e.g.*, penicillin, bromides), and toxins may cause eccrine bromhidrosis. Eccrine bromhidrosis may result from underlying metabolic or endogenous causes.

[000185] The role of excessive eccrine secretion, or hyperhidrosis, in the pathogenesis of bromhidrosis is unclear. Hyperhidrosis may promote the spread of apocrine sweat and contribute further to bromhidrosis by creating a moist environment, one ripe for bacterial overgrowth. Conversely, eccrine hyperhidrosis may cause a decrease in odor because the eccrine sweat flushes away the more odiferous apocrine sweat.

[000186] In some embodiments, therapies effective for treating unwanted sweating

and/or hyperhidrosis are also effective for treating bromhidrosis.

[000187] In some embodiments, provided compositions for treatment and/or prevention of bromhidrosis are formulated into a cream, liniment, lotion, gel, sunscreen, deodorant, and/or antiperspirant (*e.g.*, as a roll-on, solid stick, gel, cream, aerosol, *etc.*), *etc.*.

[000188] In some embodiments, provided compositions for treatment and/or prevention of bromhidrosis are administered locally to an affected site (*e.g.*, axillae, hands, feet, *etc.*).

Chromhidrosis

[000189] In some embodiments, provided compositions are useful for treating and/or preventing chromhidrosis, a rare condition characterized by the secretion of colored sweat. Chromhidrosis is caused by the deposition of lipofuscin in the sweat glands. Approximately 10% of people without the disease have colored sweat that is regarded as acceptable and within the normal range. Usually chromhidrosis affects the apocrine glands, mainly on the face and underarms. Lipofuscin pigment is produced in the apocrine gland, and its various oxidative states account for the characteristic yellow, green, blue, or black secretions observed in apocrine chromhidrosis. Chromhidrosis of the eccrine glands is rare, occurring mainly after the ingestion of certain dyes or drugs. Pseudochromhidrosis occurs when clear eccrine sweat becomes colored on the surface of the skin as a result of extrinsic dyes, paints, or chromogenic bacteria.

[000190] In some embodiments, therapies effective for treating unwanted sweating and/or hyperhidrosis are also effective for treating chromhidrosis.

[000191] In some embodiments, provided compositions for treatment and/or prevention of chromhidrosis are formulated into a cream, liniment, lotion, gel, sunscreen, deodorant, and/or antiperspirant (*e.g.*, as a roll-on, solid stick, gel, cream, aerosol, *etc.*).

[000192] In some embodiments, provided compositions for treatment and/or prevention of chromhidrosis are administered locally to an affected site (*e.g.*, axillae, hands, feet, *etc.*).

Rosacea

[000193] In some embodiments, provided compositions may be useful for treating and/or preventing rosacea, a condition that is estimated to affect over 45 million people worldwide. Rosacea affects both sexes, but is almost three times more common in women, and has a peak age of onset between 30 and 60. It begins as erythema (*i.e.*, flushing and redness) on the central face and across the cheeks, nose, and/or forehead but can also less

commonly affect the neck and chest. As rosacea progresses, other symptoms can develop such as one or more of semi-permanent erythema, telangiectasia (*i.e.*, dilation of superficial blood vessels on the face), red domed papules and pustules, red gritty eyes, burning and stinging sensations, and/or rhinophyma (*i.e.*, a red lobulated nose).

[000194] There are four main subtypes of rosacea. “Erythematotelangiectatic rosacea” is characterized by permanent redness with a tendency to flush and blush easily. It is also common to have small blood vessels visible near the surface of the skin (*i.e.*, telangiectasias) and/or burning or itching sensations. “Papulopustular rosacea” is characterized by some permanent redness with papules and/or pustules, which typically last 1 to 4 days. This subtype is commonly confused with acne. “Phymatous rosacea” is most commonly associated with rhinophyma, an enlargement of the nose. Symptoms include thickening skin, irregular surface nodularities, and enlargement. Phymatous rosacea can also affect the chin (gnatophyma), forehead (metophyma), cheeks, eyelids (blepharophyma), and/or ears (otophyma) (see, *e.g.*, Jansen and Plewig, 1998, *Facial Plast. Surg.*, 14:241; incorporated herein by reference). Small blood vessels visible near the surface of the skin (*i.e.*, telangiectasias) may be present. “Ocular rosacea” is characterized by red, dry, irritated eyes and/or eyelids. Other symptoms may include foreign body sensations, itching, and/or burning.

[000195] Rosacea can be triggered by any of a variety of stimuli. Triggers that cause episodes of flushing and blushing play a part in the development of rosacea, such as exposure to temperature extremes, strenuous exercise, heat from sunlight, severe sunburn, stress, anxiety, cold wind, and/or moving to a warm or hot environment from a cold one. Some foods and drinks can trigger flushing, such as alcohol, foods and beverages containing caffeine (*e.g.*, hot tea, coffee), foods high in histamines, and spicy foods. Certain medications and topical irritants can quickly progress rosacea (*e.g.*, steroids, benzoyl peroxide, isotretinoin, *etc.*).

[000196] In some embodiments of the present invention, different subtypes of rosacea are treated differently from other subtypes of rosacea (Cohen and Tiemstra, 2002, *J. Am. Board Fam. Pract.*, 15:214; incorporated herein by reference). In some embodiments, different subtypes of rosacea are not treated differently from other subtypes of rosacea.

[000197] Current therapies utilized in the treatment of rosacea include, for example, botulinum toxin, oral antibiotics (*e.g.*, tetracycline, doxycycline, minocycline, metronidazole, macrolide antibiotics, *etc.*), and/or combinations thereof. In some embodiments, oral

antibiotics may be administered at anti-inflammatory doses (*e.g.*, about 40 mg/day) or at higher doses. In some embodiments, such agents include oral isotretinoin. In some embodiments, such agents include topical antibiotics (*e.g.*, metronidazole, clindamycin, erythromycin, *etc.*); topical azelaic acid (*e.g.*, FINACEA™, AZELEX™, FINEVIN®, SKINOREN, *etc.*); topical sulfacetamide; topical sulfur; topical calcineurin inhibitor (*e.g.*, tacrolimus, pimecrolimus, *etc.*); topical benzoyl peroxide; topical permethrin; a combination of plant-sourced methylsulfonylmethane (MSM) and Silymarin; and/or combinations thereof.

[000198] Alternative or additional current therapies for the treatment of rosacea include, but are not limited to, use of a gentle skin cleansing regimen using non-irritating cleansers; protecting skin from the sun by covering skin with clothing; applying sunscreen to exposed skin; dermatological vascular laser (single wavelength); intense pulsed light (broad spectrum); carbon dioxide lasers; low level light therapies; and/or combinations thereof.

[000199] Rosacea may be treated via dermatological vascular laser (single wavelength) and/or intense pulsed light (broad spectrum) (Angermeier, 1999, *J. Cutan. Laser Ther.*, 1:95; incorporated herein by reference). These methods use light to penetrate the epidermis to target the capillaries in the dermis. Light is absorbed by oxy-hemoglobin, thereby causing capillary walls to heat up to 70 °C, damaging them, which causes them to be absorbed by the body's natural defense mechanism. These methods may be successful for eliminating redness altogether, though additional periodic treatments might be necessary to remove newly-formed capillaries. Alternatively or additionally, a 595 nm long pulse-duration pulsed-dye laser may be useful for the treatment of rosacea (Kligman and Bernstein, 2008, *Lasers Surg. Med.*, 40:233; incorporated herein by reference).

[000200] Alternatively or additionally, carbon dioxide lasers can be used to remove excess tissue, for example, caused by phymatous rosacea. Carbon dioxide lasers emit a wavelength that is absorbed directly by the skin. The laser beam can be focused into a thin beam and used as a scalpel or defocused and used to vaporize tissue.

[000201] In some embodiments, rosacea can be treated using low level light therapies.

[000202] In some embodiments, provided compositions for treatment and/or prevention of rosacea are formulated into a cream, liniment, lotion, gel, sunscreen, deodorant, and/or antiperspirant (*e.g.*, as a roll-on, solid stick, gel, cream, aerosol, *etc.*), *etc.*.

[000203] In some embodiments, provided compositions for treatment and/or prevention of rosacea are administered locally to an affected site (*e.g.*, axillae, hands, feet, scalp, face, neck, back, arms, chest, *etc.*).

Hair Loss

[000204] In some embodiments, provided compositions are useful for treating and/or preventing hair loss. Baldness involves the state of lacking hair where it often grows, especially on the head. The most common form of baldness is a progressive hair thinning condition called androgenic alopecia or “male pattern baldness” that occurs in adult male humans and other species. The amount and patterns of baldness can vary greatly; it ranges from male and female “pattern alopecia” (androgenic alopecia, also called androgenetic alopecia or alopecia androgenetica); “alopecia areata,” which involves the loss of some of the hair from the head; “alopecia totalis,” which involves the loss of all head hair; to the most extreme form, “alopecia universalis,” which involves the loss of all hair from the head and the body.

[000205] Current therapies used in the treatment of hair loss include, but are not limited to, botulinum toxin, aza-steroids, such as finasteride (PROPECIA[®]; PROSCAR[®]; *etc.*) or dutasteride (AVODART[®]); topically applied minoxidil, a vasodilator (ROGAINE[®]); antiandrogens (*e.g.*, ketoconazole, fluconazole, spironolactone, *etc.*); saw palmetto; caffeine; copper peptides; nitroxide spin labels TEMPO and TEMPOL; unsaturated fatty acids (*e.g.*, gamma linolenic acid); hedgehog agonists; azelaic acid and zinc in combination; Chinese knotweed; pumpkin seed; spironolactone; tretinoin; zinc; stinging nettle; and/or combinations thereof.

[000206] In some embodiments, provided compositions for treatment and/or prevention of hair loss are formulated into a cream, liniment, lotion, gel, shampoo, conditioner, *etc.*

[000207] In some embodiments, provided compositions for treatment and/or prevention of hair loss are administered locally to an affected site (*e.g.*, scalp, hair follicle, face, neck, back, arms, chest, *etc.*).

Acne

[000208] In some embodiments, provided compositions are useful for treating and/or preventing acne vulgaris (commonly referred to as “acne”), a skin disease caused by changes in the pilosebaceous units (*i.e.*, skin structures comprising a hair follicle and its associated sebaceous gland). In some embodiments, acne is inflammatory. In some embodiments, acne is noninflammatory. While not life-threatening, acne vulgaris can cause significant problems for affected individuals. Depending on its severity and other factors, recalcitrant acne can be psychologically debilitating, and can impose significant financial and emotional costs on

those whom it afflicts. Despite some recent successes in acne therapy, treatment failures are still common, especially in adult women. While many adults “outgrow” this disease, there are some who continue to be afflicted during much of adulthood, despite continued medical advances. Unfortunately, the most potent acne medication in current use is administered systemically via a treatment that is teratogenic, an important issue for many women. There is an unfilled need for a more localized and effective treatment for acne, one with minimal side effects.

[000209] In general, acne develops as a result of blockages in follicles. The pathology centers on the pilosebaceous units, comprising a sebaceous gland, a follicle (*i.e.*, pore), and a vellus hair. Among the first events leading to acne are hyperkeratinization and formation of a plug of keratin and sebum (a “microcomedo”), obstructing the upper region of a follicle. Enlargement of sebaceous glands and an increase in sebum production occur with increased androgen production at adrenarche. A microcomedo may enlarge to form an open comedo (a “blackhead”) or closed comedo (a “whitehead”). In these conditions the naturally occurring largely commensal bacteria *Propionibacterium acnes* can cause inflammation, leading to inflammatory lesions (papules, infected pustules, or nodules) in the dermis around the microcomedo or comedo, which results in redness and may result in scarring or hyperpigmentation.

[000210] Adolescence is marked by an increase in levels of circulating androgens, particularly dehydroepiandrosterone sulfate (DHEAS). Increased androgen levels are thought to cause sebaceous glands to enlarge and to increase sebum production. While most acne patients have normal hormone levels, there are reasons to conclude that increased sebum production plays a role in acne. For example, there may be a correlation between the rate of sebum production and the severity of acne. In addition, acne patients typically produce sebum that is deficient in linoleic acid, which is a potential cause of abnormal keratinization and follicular obstruction.

[000211] In response to increased sebum levels, *Propionibacterium acnes*, a relatively slow growing, typically aerotolerant anaerobic gram positive, diphtheroid bacterium, often colonizes the sebaceous follicles. *P. acnes* exacerbates acne by acting as a chemo-attractant for neutrophils. Neutrophils ingest *P. acnes*, and in doing so release various hydrolytic enzymes that damage the follicular wall. Released follicular contents then invade the dermis and cause an inflammatory reaction, manifesting as pustules, erythematous papules, or nodules. In a separate route, *P. acnes* can hydrolyze triglycerides to free fatty acids, which

also increase inflammation and follicular obstruction. *P. acnes* may also activate the complement components of the immune system, which can also lead to follicular obstruction.

[000212] Follicles are lined with squamous epithelium, a layer of cells that is contiguous with the skin surface. In an acne-prone individual, the shedding of cells from this lining is often impeded, perhaps due to an increased level of intercellular adhesion that promotes the retention of cells. Retained cells can obstruct follicles, resulting in comedones. Such inhibited shedding may be related to abnormalities in epidermal differentiation and/or to abnormal sebum composition (*e.g.*, a deficiency in linoleic acid). It has also been demonstrated that increased sebum levels can irritate keratinocytes, causing the release of interleukin-1, which in turn can cause follicular hyperkeratinization. In general, each of these acne-causing routes, which are not mutually exclusive, is associated with follicular obstruction.

[000213] Several factors are known to be linked to acne, including, but not limited to, family and/or genetic history (see, *e.g.*, Ballanger *et al.*, 2006, *Dermatology*, 212:145-149; incorporated herein by reference); hormonal activity (*e.g.*, menstrual cycles, puberty, *etc.*); stress (*e.g.*, through increased output of hormones from the adrenal glands); hyperactive sebaceous glands; accumulation of dead skin cells; bacteria in the pores (*e.g.*, *P. acnes*); skin irritation or scratching; use of anabolic steroids; use of medications containing halogens (*e.g.*, iodides, chlorides, bromides), lithium, barbiturates, or androgens; exposure to certain chemical compounds (*e.g.*, dioxins such as chlorinated dioxins); exposure to testosterone, dihydrotestosterone (DHT), dehydroepiandrosterone sulfate (DHEAS), and/or insulin-like growth factor 1 (IGF-I); diet including milk and/or high levels of carbohydrate; low levels of vitamins A and/or E; poor hygiene; or any combinations thereof.

[000214] In some embodiments, acne treatments work via one or more of the following mechanisms: (1) normalizing shedding into the pore to prevent blockage; (2) killing *P. acnes*; (3) having antiinflammatory activity; and/or (4) manipulating hormone levels.

[000215] The present invention provides methods of treating and/or preventing acne comprising administration of a provided composition to a subject suffering from, susceptible to, and/or displaying symptoms of acne. In some embodiments, such a provided composition is administered locally to an affected site (*e.g.*, face, neck, back, arms, chest, *etc.*).

[000216] In some embodiments, provided compositions for treatment of acne are formulated into a cream, liniment, lotion, gel, sunscreen, *etc.*

[000217] Exemplary current treatments for acne include, but are not limited to,

botulinum toxin, cleansers or soaps; topical bactericidals (*e.g.*, benzoyl peroxide, triclosan, chlorhexidine gluconate, *etc.*); topical antibiotics (*e.g.*, externally-applied erythromycin, clindamycin, tetracycline, *etc.*); oral antibiotics (*e.g.*, erythromycin, tetracycline, oxytetracycline, doxycycline, minocycline, lymecycline, trimethoprim, *etc.*); hormonal treatments (*e.g.*, estrogen/progestogen oral contraceptives, low dose spironolactone, cortisone, *etc.*); topical retinoids (*e.g.*, tretinoin [RETIN-A[®]], adapalene [DIFFERIN[®]], tazarotene [TAZORAC[®]], retinol, isotretinoin, *etc.*); oral retinoids (*e.g.*, isotretinoin [ACUTANE[®]], AMNESTEEM[™], SOTRET[™], CLARAVIS[™]]); herbs (*e.g.*, aloe vera; aruna, haldi [turmeric], papaya, *etc.*); azelaic acid; anti-inflammatory agents (*e.g.*, naproxen, ibuprofen, rofecoxib [Tehrani and Dharmalingam, 2004, *Indian J. Dermatol. Venereol. Leprol.*, 70:345-348; incorporated herein by reference], *etc.*); nicotinamide [vitamin B3]; tea tree oil [melaleuca oil]; rofecoxib; zinc (Dreno *et al.*, 1989, *Acta Derm. Venereol.*, 69:541-3; and Dreno *et al.*, 2001, *Dermatology*, 203:135-40; both of which are incorporated herein by reference); and/or combinations thereof.

[000218] Alternative or additional current therapies for the treatment and/or prevention of acne include, but are not limited to, phototherapy (*e.g.*, alternating blue and red light); photodynamic therapy (*e.g.*, intense blue/violet light); laser treatment (*e.g.*, to burn away the follicle sac from which the hair grows; to burn away the sebaceous gland which produces the oil; and/or to induce formation of oxygen in the bacteria, killing them); local heating; and/or combinations thereof.

[000219] It is known in the art that short-term improvement of acne can be achieved with sunlight, but studies have shown that sunlight worsens acne long-term. More recently, visible light has been successfully employed to treat acne (*i.e.*, “phototherapy”) – in particular, intense violet light (405 nm – 420 nm) generated by purpose-built fluorescent lighting, dichroic bulbs, LEDs, and/or lasers. Used twice weekly, this has been shown to reduce the number of acne lesions by about 64% (Kawada *et al.*, 2002, *J. Dermatol. Sci.*, 30:129-35; incorporated herein by reference) and is even more effective when applied daily. Without wishing to be bound by any one theory, a porphyrin (Coproporphyrin III) produced within *P. acnes* generates free radicals when irradiated by 420 nm and shorter wavelengths of light (Kjeldstad, 1984, *Z. Naturforsch [C]*, 39:300-2; incorporated herein by reference). Particularly when applied over several days, these free radicals ultimately kill bacteria (Ashkenazi *et al.*, 2003, *FEMS Immunol. Med. Microbiol.*, 35:17-24; incorporated herein by reference). Since porphyrins are not otherwise present in skin, and no ultraviolet (UV) light

is employed, it appears to be safe, and has been licensed by the U.S. FDA. The treatment apparently works even better if used with red visible light (about 660 nm), resulting in a 76% reduction of lesions after 3 months of daily treatment for 80% of the patients (Papageorgiou *et al.*, 2000, *Br. J. Dermatol.*, 142:973-8; incorporated herein by reference). Unlike most of other treatments, few negative side effects are typically experienced, and development of bacterial resistance to the treatment seems very unlikely. After treatment, clearance can be longer lived than is typical with topical or oral antibiotic treatments (*e.g.*, may be up to several months).

[000220] There is some evidence that photodynamic therapy (*e.g.*, therapy with intense blue/violet light (405 nm – 425 nm)) can decrease the number of inflammatory acne lesion by 60% – 70% in 4 weeks of therapy, particularly when *P. acnes* is pretreated with delta-aminolevulinic acid (ALA), which increases the production of porphyrins.

[000221] Laser surgery has been in use for some time to reduce the scars left behind by acne, but research has been done on lasers for prevention of acne formation itself. In general, laser is used to burn away the follicle sac from which the hair grows, to burn away the sebaceous gland which produces the oil, and/or to induce formation of oxygen in the bacteria, thereby killing them.

[000222] Local heating therapies are sometimes used, for example, to kill bacteria in a developing pimple, thereby expediting healing.

[000223] In some embodiments, provided compositions for treatment and/or prevention of acne are formulated into a cream, liniment, lotion, gel, sunscreen, *etc.*

[000224] In some embodiments, provided compositions for treatment and/or prevention of acne are administered locally to an affected site (*e.g.*, axillae, hands, feet, face, neck, back, arms, chest, *etc.*).

Psoriasis

[000225] In some embodiments, provided compositions are useful for treating psoriasis and/or preventing, a disorder which affects the skin and joints. Psoriasis commonly causes red scaly patches to appear on the skin. The scaly patches caused by psoriasis, called “psoriatic plaques,” are areas of inflammation and excessive skin production. Skin rapidly accumulates at these sites and takes a silvery-white appearance. Plaques frequently occur on the skin of the elbows and knees, but can affect any area including the scalp and genitals. Psoriasis is hypothesized to be immune-mediated and is not contagious.

[000226] Psoriasis is a chronic recurring condition which varies in severity from minor localized patches to complete body coverage. Fingernails and toenails are frequently affected (“psoriatic nail dystrophy”). Psoriasis can also cause inflammation of the joints, which is known as “psoriatic arthritis.” Ten to fifteen percent of people with psoriasis have psoriatic arthritis.

[000227] The cause of psoriasis is not known, but it is believed to have a genetic component. Several factors are thought to aggravate psoriasis, including stress, excessive alcohol consumption, and smoking. Individuals with psoriasis may suffer from depression and loss of self-esteem. As such, quality of life is an important factor in evaluating the severity of the disease.

[000228] Current therapies utilized in the treatment and/or prevention of psoriasis include, but are not limited to, botulinum toxin, coal tar; dithranol (anthralin); a corticosteroid such as desoximetasone (TOPICORT®); a vitamin D3 analog (*e.g.*, calcipotriol); a retinoid; argan oil; topical administration of psoralen with exposure to ultraviolet A light (PUVA); milk thistle; methotrexate; cyclosporine; the antimetabolite tioguanine; hydroxyurea; sulfasalazine; mycophenolate mofetil; azathioprine; tacrolimus; and/or antibody-based therapeutics (*e.g.*, alefacept [AMEVIEVE®], etanercept [EMBREL®], infliximab [REMICADE®], efalizumab [RAPTIVA®] *etc.*).

[000229] In some embodiments, provided compositions for treatment and/or prevention of psoriasis are formulated into a cream, liniment, lotion, gel, sunscreen, *etc.*

[000230] In some embodiments, provided compositions for treatment and/or prevention of psoriasis are administered locally to an affected site (*e.g.*, axillae, hands, feet, scalp, face, neck, back, arms, chest, *etc.*).

Dermal Infections

[000231] In some embodiments, provided compositions are useful for treating and/or preventing dermal infections (*e.g.*, bacterial, viral, and/or fungal infections).

[000232] In some embodiments, diseases, disorders, or conditions associated with infection of the dermis are associated with bacterial infection, for example caused by or correlated with infection by one or more of *Staphylococcus aureus*, *Streptococcus pyogenes*, group B and C streptococci, anaerobic bacteria (*e.g.*, *Clostridium* species), *Corynebacterium* species (*e.g.*, *Corynebacterium minutissimum*, *Corynebacterium tenuis*, *etc.*), *Dermatophilus congolensis*, and/or combinations thereof. Diseases, disorders, or conditions associated with

bacterial infection of the dermis, include, but are not limited to, impetigo, folliculitis, furunculosis, carbunculosis, hidradenitis suppurativa (*i.e.*, bacterial infection of sweat glands and/or hair follicles), skin abscesses, cat scratch disease, cellulitis, erysipelas, ecthyma, necrotizing fasciitis, erythrasma, pitted keratolysis, trichomycosis axillaris, staphylococcal scalded skin syndrome, acute paronychia, and/or combinations thereof.

[000233] In some embodiments, diseases, disorders, or conditions associated with infection of the dermis are associated with viral infection, for example caused by or correlated with infection by one or more of herpes simplex virus (*e.g.*, type 1 and/or type 2), varicella-zoster virus, human papillomavirus, poxvirus, *etc.* Diseases, disorders, or conditions associated with viral infection of the dermis include, but are not limited to, herpes labialis, genital herpes, shingles, molluscum contagiosum, warts, and/or combinations thereof.

[000234] In some embodiments, diseases, disorders, or conditions associated with infection of the dermis are associated with fungal infection, for example caused by or correlated with infection by one or more of *Trichophyton* species (*e.g.*, *Trichophyton rubrum*), *Microsporum* species, *Epidermophyton* species, *Candida* species (*e.g.*, *Candida albicans*), *Pityrosporum ovale*, and/or combinations thereof. Diseases, disorders, or conditions associated with fungal infection of the dermis, include, but are not limited to, dermatophytosis, tinea pedis (“athlete’s foot”), candidal intertrigo, thrush, paronychia, angular cheilitis, candidal vulvovaginitis, balanitis, tinea versicolor, chronic paronychia, and/or combinations thereof.

[000235] Current therapies for treatment and/or prevention of bacterial infection of the dermis include, but are not limited to, botulinum toxin, antibiotics (*e.g.*, penicillin, dicloxacillin, cephalexin, erythromycin, clindamycin, gentamicin, *etc.*), topical antibiotics (*e.g.* clindamycin, erythromycin, mupirocin *etc.*), topical mixture of bacitracin and polymyxin (*e.g.*, NEOSPORIN[®], POLYSPORIN[®]), topical fusidic acid cream, and combinations thereof.

[000236] Current therapies for treatment and/or prevention of diseases, disorders, or conditions associated with viral infection of the dermis include, but are not limited to, botulinum toxin, antiviral therapeutics (*e.g.*, acyclovir, famciclovir, valacyclovir, *etc.*), topical treatments (*e.g.*, trichloroacetic acid, salicylic acid, podophyllin, canthacur, imiquimod cream, *etc.*), and/or combinations thereof.

[000237] Current therapies for treatment and/or prevention of diseases, disorders, or conditions associated with fungal infection of the dermis include, but are not limited to,

botulinum toxin, topical therapeutics (*e.g.*, terbinafine [LAMISIL[®]], clotrimazole [LOTRIMIN[®], MYCELEX[®]], or econazole [SPECTAZOLE[®]], selenium sulfide shampoo, ketoconazole shampoo, *etc.*), oral therapeutics (*e.g.*, itraconazole [SPORANOX[®]], terbinafine, *etc.*), and/or combinations thereof.

[000238] Alternative or additional current therapies utilized in the treatment and/or prevention of one or more symptoms and/or causes of dermal infection include, but are not limited to, surgical removal of affected skin, amputation, *etc.*

[000239] In some embodiments, provided compositions for treatment and/or prevention of dermal infections are formulated into a cream, liniment, lotion, gel, shampoo, conditioner, sunscreen, deodorant, and/or antiperspirant (*e.g.*, as a roll-on, solid stick, gel, cream, aerosol, *etc.*), *etc.*.

[000240] In some embodiments, provided compositions for treatment and/or prevention of dermal infections are administered locally to an affected site (*e.g.*, on axillae, hands, feet, scalp, hair follicle, face, neck, back, arms, chest, *etc.*).

Actinic Keratosis

[000241] In some embodiments, provided compositions may be useful for treating and/or preventing actinic keratosis. Actinic keratosis (also called “solar keratosis,” or “AK”) is a premalignant condition of thick, scaly, or crusty patches of skin. Actinic keratosis is most common in fair-skinned people who are frequently exposed to the sun. When skin is exposed to the sun constantly, thick, scaly, or crusty bumps appear. The scaly or crusty part of the bump is dry and rough. A growth starts out as flat scaly areas, and later grows into a tough, wart-like area.

[000242] An actinic keratosis site commonly ranges between 2 mm and 6 mm in size, and can be dark or light, tan, pink, red, a combination of all these, or have the same pigment as the surrounding skin. It may appear on any sun-exposed area, such as the face, ears, neck, scalp, chest, backs of hands, forearms, or lips.

[000243] Current therapies utilized for treatment and/or prevention of diseases, disorders, or conditions associated with actinic keratosis include, but are not limited to, botulinum toxin, 5-fluorouracil, imiquimod, diclofenac, crocodile oil, and/or combinations thereof.

[000244] Alternative or additional current therapies utilized to treat and/or prevent one or more symptoms and/or causes of actinic keratosis include, but are not limited to,

cryosurgery, photodynamic therapy, laser treatment, electrocautery, surgery, *etc.*

[000245] In some embodiments, provided compositions for treatment and/or prevention of actinic keratosis are formulated into a cream, liniment, lotion, gel, shampoo, conditioner, sunscreen, deodorant, and/or antiperspirant (*e.g.*, as a roll-on, solid stick, gel, cream, aerosol, *etc.*), *etc.*.

[000246] In some embodiments, provided compositions for treatment and/or prevention of actinic keratosis are administered locally to an affected site (*e.g.*, on axillae, hands, feet, scalp, hair follicle, face, neck, back, arms, chest, *etc.*).

Eczematous Dermatitis

[000247] In some embodiments, provided compositions are useful for treating and/or preventing eczematous dermatitis, a skin condition characterized by local inflammatory reactions that are erythematous with indistinct margins. In the acute phase, lesions may exhibit edema, vesiculation, oozing, and in some cases bullae. Most chronic lesions are dry and scaly and may exhibit secondary lichenification. These lesions frequently get secondary bacterial infections, which may also cause crusting. These lesions are frequently pruritic. Sometimes, this condition may be secondary to exposure to an allergen.

[000248] Atopic dermatitis is a more generalized form of eczematous dermatitis which typically involves many areas of the skin and intense pruritis. This condition is often associated with a personal or family history of asthma, hay fever, or other allergies. Lesions are frequently distributed on the antecubital and popliteal fossae, and on the wrist and neck. Eczematous dermatitis and atopic dermatitis are also known in the art as “eczema.”

[000249] Current therapies utilized for treating and/or preventing one or more symptoms and/or causes of eczematous dermatitis include botulinum toxin, glucocorticosteroids, coal tar, calcineurin inhibitors (*e.g.*, tacrolimus, pimecrolimus, *etc.*), antihistamines (*e.g.*, diphenhydramine, *etc.*), cyclosporine, interferon, omalizumab, rituximab, mycophenolate mofetil, AMG 157, JNJ-26113100, CD 2027, SUN13834, S-777469, GW842470X, TS022, roflumilast, calcipotriol, pitrakinra, and/or combinations thereof.

[000250] In some embodiments, provided compositions for treatment and/or prevention of eczematous dermatitis are formulated into a cream, liniment, lotion, gel, shampoo, conditioner, sunscreen, deodorant, and/or antiperspirant (*e.g.*, as a roll-on, solid stick, gel, cream, aerosol, *etc.*), *etc.*

[000251] In some embodiments, provided compositions for treatment and/or prevention of eczematous dermatitis are administered locally to an affected site (*e.g.*, on axillae, hands, feet, scalp, face, neck, back, arms, chest, *etc.*).

Excess Sebum-Producing Disorders

[000252] In some embodiments, provided compositions are useful for treating and/or preventing excess sebum-producing disorders (*e.g.*, seborrhea, seborrheic dermatitis, *etc.*), disorders affecting the areas of the skin that are rich in sebum glands, which typically include the scalp, face, and/or trunk. Patients with these conditions typically have scaly, flaky, erythematous, and often pruritic skin. Involvement of the scalp can result in hair loss. In some cases, the skin is also oily.

[000253] Current therapies utilized for treating and/or preventing one or more symptoms and/or causes of excess sebum-producing disorders include botulinum toxin, salicylic acid, azelaic acid, selenium sulfide, imidazoles (*e.g.*, ketoconazole, miconazole, fluconazole, econazole, bifonazole, climazole, ciclopirox, ciclopiroxolamine, *etc.*), itraconazole, terbinafine, zinc pyrithione, benzoyl peroxide, coal tar, juniper tar, glucocorticosteroids (*e.g.*, hydrocortisone, *etc.*), metronidazole, lithium, calcineurin inhibitors (*e.g.*, tacrolimus, pimecrolimus, *etc.*), Vitamin D3, isotretinoin, and/or combinations thereof.

[000254] In some embodiments, provided compositions for treatment and/or prevention of one or more excess sebum-producing disorders are formulated into a cream, liniment, lotion, gel, sunscreen, deodorant, and/or antiperspirant (*e.g.*, as a roll-on, solid stick, gel, cream, aerosol, *etc.*), *etc.*

[000255] In some embodiments, provided compositions for treatment and/or prevention of one or more excess sebum-producing disorders are administered locally to an affected site (*e.g.*, on axillae, hands, feet, scalp, face, neck, back, arms, chest, *etc.*).

Burns

[000256] In some embodiments, provided compositions are useful for treating burns, a type of injury to flesh caused by heat, electricity, chemicals, light, radiation or friction. Many burns affect only the skin, but sometimes burns can injure deeper tissues, such as muscle, bone, and blood vessels. Burns can be classified as either first-degree, second-degree, third-degree, or fourth-degree.

[000257] First-degree burns are usually limited to redness (erythema), a white plaque

and minor pain at the site of injury. These burns generally involve only the epidermis. Most sunburns can be included as first-degree burns.

[000258] Second-degree burns manifest as erythema with superficial blistering of the skin, and can involve more or less pain depending on the level of nerve involvement. Second-degree burns typically involve the superficial (papillary) dermis and may also involve the deep (reticular) dermis layer. Burns that require more than three weeks to heal are often excised and skin grafted for best result.

[000259] Third-degree burns occur when the epidermis is lost with damage to the subcutaneous tissue. Burn victims will typically exhibit charring and extreme damage of the epidermis, and sometimes hard eschar will be present. Third-degree burns result in scarring and victims will also exhibit the loss of hair shafts and keratin. These burns may require grafting. These burns are not painful, as all the nerves have been damaged by the burn and are not sending pain signals; however, all third-degree burns are surrounded by first and second-degree burns, which are painful.

[000260] Fourth-degree burns involve muscle, tendon, and bone. When extremities are involved, this often leads to amputation or significant functional impairment.

[000261] Current therapies utilized for treating and/or preventing one or more symptoms and/or causes of burns include botulinum toxin, antibiotics, analgesics, and/or combinations thereof.

[000262] In some embodiments, provided compositions for treatment and/or prevention of burns are formulated into a cream, liniment, lotion, gel, sunscreen, *etc.*

[000263] In some embodiments, provided compositions for treatment of burns are administered locally to an affected site (*e.g.*, on axillae, hands, feet, scalp, face, neck, back, arms, chest, *etc.*).

Raynaud's Phenomenon

[000264] In some embodiments, provided compositions are for treating and/or preventing Raynaud's phenomenon, a vasospastic condition of the fingers and toes. Typically in response to cold or emotional stress, the skin of the fingers become discolored (white, blue, and/or red, often in this sequence) and painful. Severe Raynaud's can result in necrosis of the skin and ultimately the fingers and/or toes, resulting in "auto-amputation." Nails of Raynaud's patients may become brittle. This condition is frequently associated with connective tissue diseases such as scleroderma and/or rheumatoid arthritis.

[000265] Current therapies for treatment and/or prevention of one or more symptoms and/or causes of Raynaud's phenomenon include botulinum toxin, calcium channel blockers (*e.g.*, nifedipine, *etc.*), alpha blockers (*e.g.*, hydralazine, *etc.*), nitroglycerin, angiotensin II receptor antagonists (*e.g.*, losartan, *etc.*), selective serotonin reuptake inhibitors (*e.g.*, fluoxetine, *etc.*), glyceryl trinitrate, tadalafil, *Ginkgo biloba* extract, SLx-2101, St. John's Wort, fasudil, cilostazol, iloprost, relaxin, treprostinil diethanolamine, sildenafil, atorvastatin, imatinib mesylate, treprostinil diethanolamine, and/or combinations thereof.

[000266] In some embodiments, provided compositions for treatment and/or prevention of Raynaud's phenomenon are formulated into a cream, liniment, lotion, gel, sunscreen, *etc.*

[000267] In some embodiments, provided compositions for treatment and/or prevention of Raynaud's phenomenon are administered locally to an affected site (*e.g.*, on axillae, hands, feet, *etc.*).

Lupus Erythematosus

[000268] In some embodiments, provided compositions are useful for treating and/or preventing lupus erythematosus, an autoimmune condition that may involve the skin as well as disease of multiple organ systems, including the brain and nervous system, kidneys, liver, and/or blood vessels. A lupus rash often involves the malar region of the face and is described as a "butterfly rash". Some patients exhibit thick, red, scaly patches of skin referred to as discoid lupus. Hair loss can also be a manifestation of the disease. Mouth, nasal and vaginal ulcers are also possible.

[000269] Current therapies for the treatment and/or prevention of one or more symptoms and/or causes of lupus erythematosus include botulinum toxin, nonsteroidal anti-inflammatory medications (*e.g.*, ibuprofen, *etc.*), aspirin, antimalarial drugs (*e.g.*, chloroquine, hydroxychloroquine, *etc.*), corticosteroids (*e.g.*, hydrocortisone, *etc.*), immunosuppressive medications (*e.g.*, azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil, methotrexate, therapeutic antibodies, *etc.*), and/or combinations thereof.

[000270] In some embodiments, provided compositions for treatment and/or prevention of lupus erythematosus are formulated into a cream, liniment, lotion, gel, sunscreen, *etc.*

[000271] In some embodiments, provided compositions for treatment and/or prevention of lupus erythematosus are administered locally to an affected site (*e.g.*, on axillae, hands, feet, scalp, face, neck, back, arms, chest, *etc.*).

Hyperpigmentation Disorders

[000272] In some embodiments, provided compositions are useful for treating and/or preventing one or more hyperpigmentation disorders (*e.g.*, melasma, *etc.*), that result in focal or generalized abnormal darkening of the skin. Hyperpigmentation is often due to skin damage due to sun exposure, medications, and/or inflammation (including inflammation due to acne vulgaris). Melasma is a condition of dark, irregular patches of skin found most usually on the upper cheek, nose, lips, upper lip, and/or forehead. Melasma is often associated with pregnancy.

[000273] Current therapies utilized for the treatment and/or prevention of one or more symptoms and/or causes of hyperpigmentation disorders include botulinum toxin, phenols (*e.g.*, hydroxyquinone, mequinol, *etc.*), retinoids (*e.g.*, tretinoin, isotretinoin, *etc.*), alpha-hydroxy acids (*e.g.*, glycolic acid, salicylic acid, azelaic acid, *etc.*) and/or combinations thereof.

[000274] In some embodiments, provided compositions for treatment and/or prevention of one or more hyperpigmentation disorders are formulated into a cream, liniment, lotion, gel, sunscreen, *etc.*

[000275] In some embodiments, provided compositions for treatment and/or prevention of one or more hyperpigmentation disorders are administered locally to an affected site (*e.g.*, on axillae, hands, feet, scalp, hair follicle, face, neck, back, arms, chest, *etc.*).

Hypopigmentation Disorders

[000276] In some embodiments, provided compositions may be for treating and/or preventing one or more hypopigmentation disorders (*e.g.*, vitiligo, *etc.*), which are characterized by focal and/or generalized abnormal lightening of the skin. Vitiligo is characterized by a chronic focal loss of skin pigment and hence lightening of the skin. When skin lesions occur, they are most prominent on the face, hands and wrists. Depigmentation is particularly noticeable around body orifices, such as the mouth, eyes, nostrils, genitalia, and/or umbilicus.

[000277] Current therapies utilized for the treatment and/or prevention of one or more symptoms and/or causes of hypopigmentation disorders include botulinum toxin, corticosteroids, calcineurin inhibitors (*e.g.*, tacrolimus, pimecrolimus, *etc.*), calcipotriol, psoralen, and/or combinations thereof.

[000278] In some embodiments, provided compositions for treatment and/or prevention of one or more hypopigmentation disorders are formulated into a cream, liniment, lotion, gel, sunscreen, *etc.*

[000279] In some embodiments, provided compositions for treatment and/or prevention of one or more hypopigmentation disorders are administered locally to an affected site (*e.g.*, on axillae, hands, feet, scalp, face, neck, back, arms, chest, *etc.*).

Skin Cancer

[000280] In some embodiments, provided compositions are useful for treating and/or preventing skin cancer (*e.g.*, squamous cell skin carcinoma, basal cell skin carcinoma, *etc.*), a malignant growth of skin tissue, often resulting in a visible tumor. Skin cancer may exhibit skin growths, changes in the skin that do not heal, ulceration of the skin, discolored skin, and/or changes to existing moles, such as the appearance of irregular edges to the mole and/or an enlargement of the mole. Basal cell carcinoma usually looks like a raised, smooth, pearly bump on the sun-exposed skin of the head, neck, and/or shoulders. Occasionally, small blood vessels can be seen within these tumors. Crusting and bleeding in the center of these tumors are frequently exhibited. Squamous cell carcinoma is commonly a red, scaling, thickened patch on sun-exposed skin. Ulceration and bleeding may be exhibited and when untreated, this form of skin cancer may develop into a large mass.

[000281] Current therapies utilized for treatment and/or prevention of squamous cell skin carcinoma include botulinum toxin, 5-aminolevulinic acid, 5-fluorouracil, acitretin, afamelanotide, API 31510, API 31510, cetuximab, dasatinib, eflornithine, erlotinib, GDC-0449, efitinib, HPPH, imiquinod, methyl aminolevulinate, PEG-interferon alfa-2a, PEP005, silicon phthalocyanine 4, tazarotene, tretinoin, verteporfin, and/or combinations thereof.

[000282] Current therapies utilized for treatment and/or prevention of basal cell skin carcinoma include botulinum toxin, 5-aminolevulinic acid, 5-fluorouracil, acitretin, afamelanotide, API 31510, API 31510, cetuximab, dasatinib, eflornithine, erlotinib, GDC-0449, gefitinib, HPPH, imiquinod, methyl aminolevulinate, PEG-interferon alfa-2a, PEP005, silicon phthalocyanine 4, tazarotene, Tretinoin, verteporfin, and/or combinations thereof.

[000283] In some embodiments, provided compositions for treatment and/or prevention of skin cancer are formulated into a cream, liniment, lotion, gel, sunscreen, deodorant, and/or antiperspirant (*e.g.*, as a roll-on, solid stick, gel, cream, aerosol, *etc.*), *etc.*

[000284] In some embodiments, provided compositions for treatment and/or prevention

of skin cancer are administered locally to an affected site (*e.g.*, on axillae, hands, feet, scalp, face, neck, back, arms, chest, *etc.*).

Treatment of Wrinkles

[000285] In some embodiments, provided compositions are useful for treating and/or preventing wrinkles (*e.g.*, facial wrinkles). Facial wrinkles involving the forehead, glabellar, rhytids and/or periorbital regions are a common aesthetic problem and are believed related to overactivity of the underlying facial musculature. For instance, the development of glabellar wrinkles is related, at least in part, to the dynamics of the underlying procerus, corrugator supercilii, and orbicularis oculi muscles. Facial lines are considered problematic because they produce the appearance of aging. In some cases, they can also be misinterpreted as manifestations of negative emotions (*e.g.*, anger, anxiety, sadness, *etc.*), fatigue, or stress.

[000286] Current therapies utilized in the treatment and/or prevention of wrinkles include, but are not limited to, botulinum toxin; tretinoin (RETIN-A[®]); epidermal growth factor; and/or glycosaminoglycans.

[000287] In recent years, injections of botulinum toxin solutions have become one of the most popular therapies for the treatment of hyperfunctional facial lines. After injection, the toxin acts to paralyze or weaken facial mimetic muscles. This apparently reduces or eliminates the appearance of wrinkles. Sadick, 2004, *Clin. Dermatol.* 22:29-33 (incorporated herein by reference).

[000288] The initial cosmetic use of a botulinum toxin solution was for treatment of forehead frown lines (Carruthers *et al.*, 1992, *J. Dermatol. Surg Oncol.*, 18:17; incorporated herein by reference). It has also been noted that injection of botulinum toxin solution into the platysma produces an uplift of the mouth (Brandt *et al.*, 1998, *Dermatol. Surg.*, 24:1232; incorporated herein by reference). Injection of botulinum toxin solution into the point of the chin has also been done for treatment of prominent mental crease (Carruthers *et al.*, "Cosmetic Uses of Botulinum A Exotoxin," pp. 325-48, *Advances in Dermatology*, James, *et al.*, eds., Mosby-Yearbook, Chicago, 1997; incorporated herein by reference).

[000289] It has been recently been suggested that the onset of facial wrinkles and/or lines can be delayed by the long-term use of botulinum type A toxin treatment via repeated injections (Binder, 2006, *Arch. Facial Plast. Surg.*, 8:426). However, repeated injections are painful to the patient, and there is a risk of injecting unintended muscle groups, potentially causing adverse side-effects (*e.g.* ptosis).

[000290] Recent development of nanoparticle (*e.g.*, nanoemulsion) compositions comprising botulinum toxin (for example as described in PCT application serial number PCT/US06/46236, filed on December 1, 2006, and published on April 17, 2008, as PCT publication number WO 08/045107, entitled “BOTULINUM NANOEMULSIONS”; incorporated herein by reference) provides a promising therapeutic approach to the treatment of wrinkles. In some embodiments, a botulinum nanoemulsion is applied to the face and/or neck over an extended period of time to delay the onset of facial (or neck) lines or wrinkles. In some embodiments, a botulinum nanoemulsion is applied at regular intervals to the face and/or neck over an extended period of time to delay the onset of facial lines or wrinkles. In some embodiments, a botulinum toxin is applied at regular intervals to the face and/or neck over a period of time greater than 6 months to delay the onset of facial lines or wrinkles. In some embodiments, a botulinum toxin is applied at regular intervals to the face and/or neck over a period of time greater than 1 year to delay the onset of facial lines or wrinkles. In some embodiments, a botulinum toxin is applied at regular intervals to the face and/or neck over a period of time greater than 5 years to delay the onset of facial lines or wrinkles. In some embodiments, a botulinum toxin is applied at regular intervals to the face and/or neck over a period of time greater than 10 years to delay the onset of facial lines or wrinkles.

[000291] In some embodiments, provided compositions for treatment and/or prevention of wrinkles are formulated into a cream, liniment, lotion, gel, sunscreen, *etc.*

[000292] In some embodiments, provided compositions for treatment and/or prevention of wrinkles are administered locally to an affected site (*e.g.*, face, neck, *etc.*).

Headache

[000293] In some embodiments, provided compositions are useful for treating and/or preventing headache. In some embodiments, headache includes, but is not limited to, migraine headache, essential headache, cervicogenic headache, and/or tension headache.

[000294] Current therapies utilized for treatment and/or prevention of headache include botulinum toxin, analgesics (*e.g.*, paracetamol, acetaminophen, non-steroidal anti-inflammatory drugs, such as aspirin, ibuprofen, diclofenac, naproxen), amitriptyline, fluoxetine, gabapentin, tizanidine, topiramate, anti-epileptics (*e.g.*, valproate), muscle relaxants such as any of those described herein, opiates (*e.g.*, morphine, codeine, thebaine, papaverine, oxycodone, hydrocodone, *etc.*), and/or combinations thereof.

[000295] In some embodiments, provided compositions for treatment and/or prevention of headache are formulated into a cream, liniment, lotion, gel, sunscreen, *etc.*

[000296] In some embodiments, provided compositions for treatment and/or prevention of headache are administered locally to an affected site (*e.g.*, face, neck, *etc.*).

Other Uses

[000297] It will be appreciated by those skilled in the art that provided novel compositions may be utilized in accordance with the present invention for any purpose, including any use in medicine, or any cosmetic use. In general, provided novel compositions may be administered to a subject by any route, and in particular by topical routes such as application to the subject's skin.

[000298] In some embodiments, a subject is a candidate for a therapy using provided compositions in accordance with the present invention where the subject is suffering from or is susceptible to developing any of the variety of diseases, disorders, conditions in addition to or alternatively to the diseases, disorders, and conditions associated with dermal structures, as described herein. Examples of such other diseases, disorders and conditions include but are not limited to: Raynaud's phenomenon, lupus erythematosus, arthritis, osteoarthritis, bruxism, cervical neck pain, dry eyes, gastrointestinal disorders, achalasia, esophageal spasm, gastroparesis, spasm of the sphincter of oddi, anal fissure, anismus, lateral epicondylitis, back pain, lower back pain, upper back pain, masseter muscle hypertrophy, facial nerve disorders, neuromuscular disorders and conditions involving muscular spasm or contracture, facial palsy such as hemi facial spasm, cerebral palsy, spasticity due to stroke, blepharospasm, facial contracture, dystonia, cervical dystonia, laryngeal dystonia, oromandibular dystonia, writer's cramp, neuralgias, trigeminal neuralgia, neuropathic pain, Parkinson's disease, plantar fasciitis pain, prostate hyperplasia, headache, migraine, essential headache, cervicogenic headache, tension headache, prostatic disorders, prostatic pain, prostatic hypertrophy, restless leg syndrome, rhinitis, allergic rhinitis, sialorrhea, strabismus, temporomandibular joint ("TMJ") syndrome, tics, Tourette's syndrome, hemifacial spasm, tremor, essential tremor, urinary bladder dysfunction, detrusor sphincter dysnergia, painful bladder, bladder spasticity, overactive bladder, vaginismus, spasticity such as that resulting from multiple sclerosis, retroorbital muscle, various ophthalmologic conditions and any combination thereof.

Compositions and Formulations

[000299] As noted herein, the present invention provides compositions comprising one or more empty nanoparticle compositions and/or individual components thereof. Provided compositions may be formulated for an appropriate route of delivery.

[000300] In some embodiments, the present invention provides pharmaceutical and/or compositions comprising at least one provided composition. Such a composition may be formulated for any route of delivery, including, but not limited to, oral (PO), intravenous (IV), intramuscular (IM), intra-arterial (IA), intramedullary, intrathecal, subcutaneous (SQ), intraventricular, transdermal, interdermal, intradermal, rectal (PR), vaginal, intraperitoneal (IP), intragastric (IG), topical and/or transdermal (*e.g.*, by lotions, creams, liniments, ointments, powders, gels, drops, *etc.*), mucosal, intranasal, buccal, enteral, vitreal, sublingual; by intratracheal instillation, bronchial instillation, and/or inhalation; as an oral spray, nasal spray, and/or aerosol, and/or through a portal vein catheter; and/or combinations thereof.

[000301] Formulations of provided compositions may be prepared by any appropriate method, for example as known or hereafter developed in the art of pharmacology. In general, such preparatory methods include the step of bringing an provided composition into association with one or more excipients, and then, if necessary and/or desirable, shaping and/or packaging the product into an appropriate form for administration, for example as or in a single- or multi-dose unit.

[000302] In some embodiments, compositions may be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a “unit dose” is a discrete amount of the pharmaceutical composition comprising a predetermined amount of the provided composition. The amount of the provided composition is generally equal to the dosage of the provided composition which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

[000303] Appropriate excipients for use in compositions (*e.g.*, pharmaceutically and/or cosmetically acceptable compositions) may, for example, include one or more excipients such as solvents, dispersion media, granulating media, diluents, or other liquid vehicles, dispersion or suspension aids, surface active agents and/or emulsifiers, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants, disintegrating agents, binding agents, preservatives, buffering agents and the like, as suited to the particular dosage form desired. Alternatively or additionally, excipients such as cocoa butter and/or

suppository waxes, coloring agents, coating agents, sweetening, flavoring, and/or perfuming agents can be utilized. Remington's *The Science and Practice of Pharmacy*, 21st Edition, A. R. Gennaro (Lippincott, Williams & Wilkins, Baltimore, MD, 2005; incorporated herein by reference) discloses various excipients used in formulating pharmaceutical compositions and known techniques for the preparation thereof.

[000304] In some embodiments, an appropriate excipient (*e.g.*, a pharmaceutically and/or cosmetically acceptable excipient) is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% pure. In some embodiments, an excipient is approved by United States Food and Drug Administration. In some embodiments, an excipient is pharmaceutical grade. In some embodiments, an excipient meets the standards of the United States Pharmacopoeia (USP), the European Pharmacopoeia (EP), the British Pharmacopoeia, and/or other International Pharmacopoeia.

[000305] In some embodiments, provided compositions are formulated as a cream, liniment, ointment, oil, foam, spray, lotion, liquid, powder, thickening lotion, or gel (*e.g.*, formulated for transdermal delivery as described herein). Particular exemplary such formulations may be prepared, for example, as cosmetic formulation products such as skin softeners, nutritional lotion type emulsions, cleansing lotions, cleansing creams, skin milks, emollient lotions, massage creams, emollient creams, make-up bases, lipsticks, facial packs or facial gels, cleaner formulations such as shampoos, rinses, body cleansers, hair-tonics, or soaps, or dermatological compositions such as lotions, ointments, gels, creams, liniments, patches, deodorants, or sprays.

[000306] In some embodiments, provided compositions (*e.g.*, provided compositions formulated for topical, and particularly for dermal/transdermal administration) are formulated with cosmetically acceptable components. For example, in some embodiments, provided compositions are formulated with water and also any cosmetically acceptable solvent, in particular, monoalcohols, such as alkanols having 1 to 8 carbon atoms (like ethanol, isopropanol, benzyl alcohol and phenylethyl alcohol), polyalcohols, such as alkylene glycols (like glycerine, ethylene glycol and propylene glycol), and glycol ethers, such as mono-, di-, and tri-ethylene glycol monoalkyl ethers, for example, ethylene glycol monomethyl ether and diethylene glycol monomethyl ether, used singly or in a mixture. Such components can be present, for example, in proportions of up to as much as 60%, 70%, 80%, or 90% by weight, relative to the weight of the total composition.

[000307] In some embodiments, provided compositions for topical administration

include one or more cosmetically acceptable components that impart appearance attributes desirable or appropriate to the subject to which the composition is to be applied (*e.g.*, a matte appearance, which may be particularly desirable or appropriate for administration to subjects having greasy skin).

[000308] In some embodiments, provided compositions are formulated with at least one cosmetically acceptable filler material, for example, in order to obtain a matte product, which may be especially desired for individuals with greasy skin.

[000309] Those of ordinary skill in the art will appreciate that provided compositions may be incorporated into a device such as, for example, a patch. A variety of transdermal patch structures are known in the art; those of ordinary skill will appreciate that provided compositions may readily be incorporated into any of a variety of such structures. In some embodiments, a transdermal patch may further comprise a plurality of needles extending from one side of the patch that is applied to the skin, wherein needles extend from the patch to project through the stratum corneum of the skin. In some embodiments, needles do not rupture a blood vessel.

[000310] In some embodiments, a transdermal patch includes an adhesive. Some examples of adhesive patches are well known (for example, see U.S. Design Patent 296,006; and U.S. Patents 6,010,715; 5,591,767; 5,008,110; 5,683,712; 5,948,433; and 5,965,154; all of which are incorporated herein by reference). Adhesive patches are generally characterized as having an adhesive layer, which will be applied to a patient's skin, a depot or reservoir for holding a provided composition, and an exterior surface that prevents leakage of the provided composition from the depot. The exterior surface of a patch is typically non-adhesive.

[000311] In accordance with the present invention, a provided composition is incorporated into the patch so that it remains stable for extended periods of time. For example, a provided composition may be incorporated into a polymeric matrix that stabilizes the agent, and permits the agent to diffuse from the matrix and the patch. A provided composition may also be incorporated into the adhesive layer of the patch so that once the patch is applied to the skin, the provided composition may diffuse through the skin. In some embodiments, an adhesive layer may be heat-activated where temperatures of about 37 °C cause the adhesive to slowly liquefy so that the agent diffuses through the skin. The adhesive may remain tacky when stored at less than 37 °C, and once applied to the skin, the adhesive loses its tackiness as it liquefies.

[000312] In some embodiments, a provided composition can be provided in a depot in

the patch so that pressure applied to the patch causes the provided composition to be directed out of the patch (optionally through needles) and through the stratum corneum.

[000313] Suitable devices for use in administering provided compositions intradermally include short needle devices such as those described in U.S. Patents 4,886,499; 5,190,521; 5,328,483; 5,527,288; 4,270,537; 5,015,235; 5,141,496; and 5,417,662. Intradermal compositions may be administered by devices which limit the effective penetration length of a needle into the skin, such as those described in PCT publication WO 99/34850 and functional equivalents thereof. Jet injection devices which deliver provided compositions to the dermis via a liquid jet injector and/or via a needle which pierces the stratum corneum and produces a jet which reaches the dermis are suitable. Jet injection devices are described, for example, in U.S. Patents 5,480,381; 5,599,302; 5,334,144; 5,993,412; 5,649,912; 5,569,189; 5,704,911; 5,383,851; 5,893,397; 5,466,220; 5,339,163; 5,312,335; 5,503,627; 5,064,413; 5,520,639; 4,596,556; 4,790,824; 4,941,880; 4,940,460; and PCT publications WO 97/37705 and WO 97/13537. Ballistic powder/particle delivery devices which use compressed gas to accelerate provided compositions in powder form through the outer layers of the skin to the dermis are suitable. Alternatively or additionally, conventional syringes may be used in the classical mantoux method of intradermal administration.

[000314] Liquid dosage forms for oral and/or parenteral administration include, but are not limited to, emulsions, microemulsions, solutions, suspensions, syrups, and/or elixirs. In addition to provided compositions, liquid dosage forms may comprise inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, oral compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and/or perfuming agents. In certain embodiments for parenteral administration, compositions are mixed with solubilizing agents such as CREMOPHOR[®], alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and/or combinations thereof.

[000315] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing agents, wetting agents, and/or suspending agents. Sterile injectable preparations may be sterile

injectable solutions, suspensions, and/or emulsions in nontoxic parenterally acceptable diluents and/or solvents, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P., and isotonic sodium chloride solution. Sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. Fatty acids such as oleic acid can be used in the preparation of injectables.

[000316] Injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, and/or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[000317] In order to prolong the effect of a provided composition, it may be desirable to slow the absorption of the provided composition from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the provided composition then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered provided composition form is accomplished by dissolving or suspending the provided composition in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the provided composition in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of provided composition to polymer and the nature of the particular polymer employed, the rate of provided composition release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are prepared by entrapping the provided composition in liposomes or microemulsions which are compatible with body tissues.

[000318] Compositions for rectal or vaginal administration are typically suppositories which can be prepared by mixing compositions with suitable non-irritating excipients such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the provided composition.

[000319] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the provided composition is mixed with at least one inert, pharmaceutically acceptable excipient such as sodium citrate or dicalcium

phosphate and/or fillers or extenders (*e.g.*, starches, lactose, sucrose, glucose, mannitol, and silicic acid), binders (*e.g.*, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia), humectants (*e.g.*, glycerol), disintegrating agents (*e.g.*, agar, calcium carbonate, potato starch, tapioca starch, alginic acid, certain silicates, and sodium carbonate), solution retarding agents (*e.g.*, paraffin), absorption accelerators (*e.g.*, quaternary ammonium compounds), wetting agents (*e.g.*, cetyl alcohol and glycerol monostearate), absorbents (*e.g.*, kaolin and bentonite clay), and lubricants (*e.g.*, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate), and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may comprise buffering agents.

[000320] Solid compositions of a similar type may be employed as fillers in soft and/or hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally comprise opacifying agents and can be of a composition that they release the provided composition(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. Solid compositions of a similar type may be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[000321] In some embodiments, compositions (*e.g.*, pharmaceutical compositions) may be prepared, packaged, and/or sold in a formulation suitable for pulmonary administration via the buccal cavity. Such a formulation may comprise dry particles which comprise the provided composition and which have a diameter in the range from about 0.5 nm to about 7 nm or from about 1 nm to about 6 nm. Such compositions are conveniently in the form of dry powders for administration using a device comprising a dry powder reservoir to which a stream of propellant may be directed to disperse the powder and/or using a self propelling solvent/powder dispensing container such as a device comprising the provided composition dissolved and/or suspended in a low-boiling propellant in a sealed container. Such powders comprise particles wherein at least 98% of the particles by weight have a diameter greater than 0.5 nm and at least 95% of the particles by number have a diameter less than 7 nm. Alternatively, at least 95% of the particles by weight have a diameter greater than 1 nm and at least 90% of the particles by number have a diameter less than 6 nm. Dry powder

compositions may include a solid fine powder diluent such as sugar and are conveniently provided in a unit dose form.

[000322] Low boiling propellants generally include liquid propellants having a boiling point of below 65 °F at atmospheric pressure. Generally the propellant may constitute 50% to 99.9% (w/w) of the composition, and the provided composition may constitute 0.1% to 20% (w/w) of the composition. The propellant may further comprise additional ingredients such as a liquid non-ionic and/or solid anionic surfactant and/or a solid diluent (which may have a particle size of the same order as particles comprising the provided composition).

[000323] In some embodiments, compositions (e.g., pharmaceutical compositions) formulated for pulmonary delivery may provide the provided composition in the form of droplets of a solution and/or suspension. Such formulations may be prepared, packaged, and/or sold as aqueous and/or dilute alcoholic solutions and/or suspensions, optionally sterile, comprising the provided composition, and may conveniently be administered using any nebulization and/or atomization device. Such formulations may further comprise one or more additional ingredients including, but not limited to, a flavoring agent such as saccharin sodium, a volatile oil, a buffering agent, a surface-active agent, and/or a preservative such as methylhydroxybenzoate. The droplets provided by this route of administration may have an average diameter in the range from about 0.1 nm to about 200 nm.

[000324] Formulations described herein as being useful for pulmonary delivery may be useful for intranasal delivery of a pharmaceutical composition. Another formulation suitable for intranasal administration is a coarse powder comprising the provided composition and having an average particle from about 0.2 μm to 500 μm . Such a formulation can be administered in the manner in which snuff is taken, *i.e.*, by rapid inhalation through the nasal passage from a container of the powder held close to the nose.

[000325] Formulations suitable for nasal administration may, for example, comprise from about as little as 0.1% (w/w) and as much as 100% (w/w) of the provided composition, and may comprise one or more of the additional ingredients described herein. In some embodiments, pharmaceutical compositions may be prepared, packaged, and/or sold in a formulation suitable for buccal administration. Such formulations may, for example, be in the form of tablets and/or lozenges made using conventional methods, and may, for example, 0.1% to 20% (w/w) provided composition, the balance comprising an orally dissolvable and/or degradable composition and, optionally, one or more of the additional ingredients described herein. Alternately, formulations suitable for buccal administration may comprise

a powder and/or an aerosolized and/or atomized solution and/or suspension comprising the provided composition. Such powdered, aerosolized, and/or aerosolized formulations, when dispersed, may have an average particle and/or droplet size in the range from about 0.1 nm to about 200 nm, and may further comprise one or more of the additional ingredients described herein.

[000326] In some embodiments, provided compositions may be prepared, packaged, and/or sold in a formulation suitable for ophthalmic administration. Such formulations may, for example, be in the form of eye drops including, for example, a 0.1/1.0% (w/w) solution and/or suspension of the provided composition in an aqueous or oily liquid excipient. Such drops may further comprise buffering agents, salts, and/or one or more other of the additional ingredients described herein. Other ophthalmically-administrable formulations which are useful include those which comprise the provided composition in microcrystalline form and/or in a liposomal preparation. Ear drops and/or eye drops are contemplated as being within the scope of this invention.

Administration

[000327] As described herein, the present invention provides methods of administering provided compositions to a subject for various applications including, for example, cosmetic and/or medical applications. In some embodiments, the present invention provides methods of treating and/or preventing diseases, disorders, and/or conditions associated with activity of epidermal and/or dermal structures (*e.g.*, sweat glands, sebaceous glands, hair follicles, *etc.*) by administering provided compositions to a subject in need thereof.

[000328] In some embodiments, the present invention provides methods of administration of provided compositions via any route of delivery, including, but not limited to, oral (PO), intravenous (IV), intramuscular (IM), intra-arterial, intramedullary, intrathecal, subcutaneous (SQ), intraventricular, transdermal, interdermal, intradermal, rectal (PR), vaginal, intraperitoneal (IP), intragastric (IG), topical and/or transdermal (*e.g.*, by lotions, creams, liniments, ointments, powders, gels, drops, *etc.*), mucosal, intranasal, buccal, enteral, vitreal, and/or sublingual administration; by intratracheal instillation, bronchial instillation, and/or inhalation; as an oral spray, nasal spray, and/or aerosol, and/or through a portal vein catheter; and/or combinations thereof.

[000329] In some embodiments, provided methods involve topical, transdermal, or intradermal administration of provided compositions to the skin of a subject. In some

embodiments, such routes achieve local delivery.

Transdermal Administration

[000330] Human skin comprises the dermis and the epidermis. The epidermis has several layers of tissue, namely, stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale (identified in order from the outer surface of the skin inward).

[000331] The stratum corneum presents the most significant hurdle in traditional methods of transdermal delivery of medications. The stratum corneum is typically about 10 μm – 15 μm thick, and it comprises flattened, keratised cells (corneocytes) arranged in several layers. The intercellular space between the corneocytes is filled with lipidic structures, and may play a role in the permeation of substances through skin (Bauerova *et al.*, 2001, *Eur. J. Drug Metabolism Pharmacokinetics*, 26:85; incorporated herein by reference).

[000332] The rest of the epidermis below the stratum corneum is approximately 150 μm thick. The dermis is about 1 mm – 2 mm thick and is located below the epidermis. The dermis is supported by various tissues, such as connective tissue, capillaries neuronal processes, *etc.*

[000333] Transdermal administration of pharmaceuticals generally has been the subject of research in an attempt to provide an alternative route of administration of medications without undesirable consequences associated with injections and oral delivery. For example, needles often cause localized pain, bleeding and bruising, and potentially expose patients to transmissible diseases; oral administration can suffer from poor bioavailability of medications due to the extremely acidic environment of the patient's stomach. In some embodiments, transdermal delivery has a more even, regular, and/or consistent pharmacokinetic profile as compared with other routes of administration.

[000334] Efforts have been made to develop transdermal administration delivery systems for certain pharmaceuticals. It is generally desirable with transdermal administration to minimize damage to a patient's skin. Among other beneficial features, transdermal administration of medication may reduce or eliminate pain associated with injections and/or reduce the likelihood of infection.

[000335] Traditionally, attempts at transdermal administration of medication have been focused on increasing the permeability of the stratum corneum. Some attempts have included using chemical penetration enhancing agents that increase the permeability of molecules

through the skin. Some attempts have included using mechanical apparatus to bypass or ablate portions of the stratum corneum. In addition, attempts have included use of ultrasound or iontophoresis to facilitate the permeation of pharmaceuticals through the skin. In some instances, the goal has been to deliver a pharmaceutical agent, typically a small molecule, through the skin, for example so that an agent may pass to the capillary bed in the dermis where the agent may be systemically incorporated into the subject to achieve a therapeutic effect. In some instances, the goal has been to achieve local and/or non-systemic effects.

[000336] In some embodiments, the present invention achieves transdermal delivery with provided compositions without use of abrasive or other disrupting agents (whether chemical, mechanical, electrical, magnetic, *etc.*). In some embodiments, the present invention achieves transdermal delivery of provided compositions without affirmative steps to permeabilize or disrupt the stratum corneum.

[000337] In some embodiments, the present invention contemplates transdermal delivery of provided compositions to achieve systemic delivery and/or effects. In some embodiments, the present invention contemplates transdermal delivery of provided compositions to achieve local delivery and/or effects, for example without achieving systemic delivery and/or effects.

[000338] In some embodiments, a provided composition is applied directly to the skin. In some embodiments, an applied composition is absorbed through the epidermal layers. In some embodiments, a provided composition can penetrate the top layer of the skin, including the stratum corneum, dermal pores, and/or dermal glands, without the use of chemical or mechanical skin permeation enhancers or other agents that cause abrasion.

[000339] In some embodiments, the present invention provides methods and compositions for specific delivery of provided compositions to epidermal and/or dermal structures. In some embodiments, provided compositions are specifically delivered to epidermal and/or dermal structures without significant delivery to subdermal structures. In some embodiments, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 85%, greater than about 90%, greater than about 95%, greater than about 96%, greater than about 97%, greater than about 98%, greater than about 99%, greater than about 99.5%, or about 100% of a provided composition administered to the skin of a subject is delivered specifically to the epidermis and/or dermis. In some embodiments, less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 10%, less than about 5%, less than about 4%, less than about 3%, less

than about 2%, less than about 1%, less than about 0.5%, or less than about 0.1% of a provided composition administered to the skin of a subject is delivered to subdermal structures.

[000340] In some embodiments, specific delivery to epidermal and/or dermal structures is achieved through application of a dose of provided composition that is lower than a dose per area used to achieve delivery to subdermal structures. For example, in some embodiments, a volume of provided composition is applied to a larger surface area; in some embodiments, a provided composition containing a reduced amount of provided composition per unit volume of composition is utilized than would be utilized to achieve delivery to subdermal structures; in some embodiments, penetration of provided composition into the skin is reduced (*e.g.*, through combination with penetration inhibitors and/or adjustment of provided composition characteristics such as component ratios, component identity, *etc.*, and combinations thereof). In some embodiments, such a lower dose is at least about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 10-fold, about 20-fold, about 30-fold, about 40-fold, about 50-fold, about 100-fold, or greater than about 100-fold lower than a dose per area used to achieve delivery to subdermal structures.

Combination Therapy

[000341] In some embodiments, when provided compositions are administered to a subject, compositions comprising known therapeutic agents and/or independently active biologically active agents may also be administered to the subject so the subject is simultaneously exposed to both the provided composition and the known therapeutic agent and/or independently active biologically active agent.

[000342] In some embodiments, a provided composition is found in a pharmaceutical formulation that is separate from and distinct from the pharmaceutical formulation containing a therapeutic agent and/or independently active biologically active agent. In some embodiments, a provided composition is admixed with the composition comprising a therapeutic agent and/or independently active biologically active agent. In other words, a provided composition is produced individually, and the final provided composition product is simply mixed with another composition comprising a therapeutic agent and/or independently active biologically active agent. In some such embodiments, where the provided composition is a nanoemulsion composition, it will be appreciated that the nanoparticle composition itself is indeed an *empty* nanoparticle composition; it does not contain a therapeutic agent and/or

independently active biologically active agent. Indeed, in some embodiments, no a therapeutic agent and/or independently active biologically active agent is included in the premix that is used to produce the resulting empty nanoparticle composition.

[000343] The particular combination of therapies (substances and/or procedures) to employ in a combination regimen will take into account compatibility of the desired substances and/or procedures and the desired therapeutic effect to be achieved. In some embodiments, provided compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutic agents and/or independently active biologically active agents.

[000344] It will be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an empty nanoparticle composition useful for treating acne may be administered concurrently with a therapeutic agent and/or independently active biologically active agent that is also useful for treating acne), or they may achieve different effects (for example, an empty nanoparticle composition that is useful for treating acne may be administered concurrently with a therapeutic agent and/or independently active biologically active agent that is useful for alleviating adverse side effects, for instance, swelling). In some embodiments, provided compositions in accordance with the invention are administered with a second therapeutic agent that is approved by the U.S. Food and Drug Administration (FDA).

[000345] By “in combination with” or “in conjunction with,” it is not intended to imply that the substances and/or procedures must be administered at the same time and/or formulated for administration together, although these methods of administration are within the scope of the invention. Provided compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutic agents and/or independently active biologically active agents and/or procedures. In general, each substance will be administered at a dose and/or on a time schedule determined for that agent.

[000346] In some embodiments, provided compositions include or are administered in combination with one or more other active agents useful for the treatment of the relevant dermatologic or other disease, disorder and/or condition, for example as discussed herein in context of the relevant disease, disorder, and/or condition. In some embodiments, exemplary biologically active agents that can be administered in combination with provided compositions in accordance with the invention include, but are not limited to, nucleic acids (*e.g.*, DNA, RNA, DNA-RNA hybrids, siRNAs, shRNAs, miRNAs, RNAi-inducing entities,

aptamers, *etc.*), polypeptides, proteins, peptides, antibodies, glycoproteins, small molecules, carbohydrates, lipids, fragments thereof, and/or combinations thereof.

Kits

[000347] In some embodiments, the present invention provides pharmaceutical packs or kits including provided compositions to be used in treatment methods according to the present invention. In some embodiments, pharmaceutical packs or kits include preparations or pharmaceutical compositions containing provided compositions (*e.g.*, an empty nanoparticle composition such as an empty nanoemulsion, or another composition comprising one or more components of an empty nanoparticle composition) in one or more containers filled with optionally one or more additional ingredients of pharmaceutical compositions in accordance with the invention. In some embodiments, the pharmaceutical pack or kit includes an additional approved therapeutic agent (*e.g.*, benzoyl peroxide for treatment of acne; aluminum compounds for treatment of hyperhidrosis; *etc.*) for use in combination therapies, as described herein. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceutical products, which notice reflects approval by the agency of manufacture, use, or sale for human administration.

[000348] Kits are provided that include provided compositions and instructions for use. Pharmaceutical doses or instructions therefor may be provided in a kit for administration to an individual suffering from or at risk for conditions or disorders associated with the dermal level of the skin, including, but not limited to, acne, hyperhidrosis, unwanted sweating, bromhidrosis, body odor, chromhidrosis, rosacea, hair loss, actinic keratosis, psoriasis, eczematous dermatitis (*e.g.*, atopic dermatitis, *etc.*), excess sebum-producing disorders (*e.g.*, seborrhea, seborrheic dermatitis, *etc.*), burns, Raynaud's phenomenon, lupus erythematosus, hyperpigmentation disorders (*e.g.*, melasma, *etc.*), hypopigmentation disorders (*e.g.*, vitiligo, *etc.*), skin cancer (*e.g.*, squamous cell skin carcinoma, basal cell skin carcinoma, *etc.*) and/or dermal infection (*e.g.*, fungal infection, herpes simplex virus infection, human papillomavirus infection, *etc.*).

[000349] In some embodiments, a kit may comprise (i) an empty nanoparticle composition; and (ii) at least one pharmaceutically acceptable excipient; and optionally (iii) at least one syringe, spatula, swab for administration to skin; and (iv) instructions for use.

Exemplification

[000350] The representative examples that follow are intended to help illustrate the invention, and are not intended to, nor should they be construed to, limit the scope of the invention. Indeed, various modifications of the invention and many further embodiments thereof, in addition to those shown and described herein, will become apparent to those skilled in the art from the full contents of this document, including the examples which follow and the references to the scientific and patent literature cited herein. The following examples contain information, exemplification and guidance, which can be adapted to the practice of this invention in its various embodiments and the equivalents thereof.

[000351] Examples 1-3 describe methods involving use of provided compositions, such as any of those described in U.S. patent number 7,763,663, issued on July 27, 2010, and entitled "POLYSACCHARIDE-CONTAINING BLOCK COPOLYMER PARTICLES AND USES THEREOF"; PCT patent application number PCT/US06/026918, filed July 11, 2006, published as WO 08/010788 on January 24, 2008, and entitled "COMPOSITIONS AND METHODS FOR MAKING AND USING NANOEMULSIONS"; PCT patent application number PCT US06/46236, filed December 1, 2006, published as WO 08/045107 on April 17, 2008, and entitled "BOTULINUM NANOEMULSIONS; in PCT patent application number PCT US07/86018, filed November 30, 2007, published as WO 08/070538 on June 12, 2008, and entitled "AMPHIPHILIC ENTITY NANOPARTICLES"; PCT patent application number PCT/ US07/86040, filed November 30, 2007, published as PCT publication WO 08/140594 on November 20, 2008, and entitled "PEPTIDE NANOPARTICLES AND USES THEREFOR"; PCT application serial number PCT/US08/65329, filed May 30, 2008, published as PCT publication WO 08/151022 on December 11, 2008, and entitled "NUCLEIC ACID NANOPARTICLES AND USES THEREFOR"; and/or in PCT patent application number PCT US09/48972, filed June 26, 2009, published as WO 09/158687 on December 30, 2009, and entitled "DERMAL DELIVERY"; all of which are incorporated herein by reference.

Example 1: Exemplary Provided Compositions for Treatment of Hyperhidrosis

[000352] The primary objective of the study was to determine whether there is a difference between the baseline level of subject's axillary sweating and the level of sweating at 4 weeks after treatment as measured by Gravimetric Sweat Production (GSP).

Materials and Methods

Treatment Composition

[000353] The treatment consisted of a novel composition described in Table 1.

Table 1: Treatment Composition

Component	% (by wt.)
1349 Oil	3.20
Tween-80	4.80
Methylparaben	0.20
Propylparaben	0.20
Sodium Chloride	0.63
Sodium Phosphate Dibasic	0.04
Gelatin	0.02
Mineral Oil	0.63
Isopropyl Myristate	0.62
White Petrolatum	0.25
Emulsifying Wax	1.87
Purified Water	87.76
Total	100.00

[000354] An “empty nanoparticle” composition was created by passing several of the components of this composition (*e.g.*, 1394 oil, Tween-80, methylparaben, propylparaben, sodium chloride, sodium phosphate dibasic, gelatin, and water) once through a microfluidizer at 22,000 PSI. The empty nanoparticle composition was approximately 80 nm in size. The empty nanoparticle composition was then combined with the remaining ingredients listed in Table 1 to formulate the treatment composition.

Administration

[000355] 0.3 cc of the treatment was rubbed into each axillary vault of the subject until none of the treatment was visible on the skin. Only a single application of the treatment to each axillary vault was given to the subject.

Secondary Objectives

[000356] The secondary objectives of the study were to determine:

- Change from Baseline in Hyperhidrosis Disease Severity Scale (HDSS) score at Week 4; changes from Baseline in HDSS score at all other observed time points.
- Change from Baseline in gravimetrically measured sweat production at all office

visits.

- The incidence of adverse events potentially related to the treatment.

Study Design

[000357] The study was a multicenter, out-patient clinical trial during which the subjects were assessed for the level sweating by objective (GSP) and subjective (HDSS) measures over a 12 week period, during which they were observed at baseline and again at Weeks 2, 4 and 12 after treatment.

Study Subjects

[000358] The subject has to meet the following enrollment criteria:

Inclusion Criteria

- able to understand and give written informed consent
- ages 18 - 70 years of age
- HDSS score of ≥ 3
- ≥ 50 mg of sweat production/axilla in 5 minutes as measured gravimetrically
- willingness to use only over-the-counter deodorants during the course of the study
- patients should be in good general health as determined by the investigator and free of any
- disease that may interfere with study evaluations or the Investigational Product

Exclusion Criteria

- diagnosis of secondary hyperhidrosis (that is, hyperhidrosis due to another medical condition such as hyperthyroidism, cancer, tuberculosis, malaria, or other infection)
- signs of infection in the axilla
- skin affliction in the axilla requiring medical treatment
- application of topical medication to the treatment area within 14 days prior to treatment
- use of antiperspirants, deodorants, powders or lotions in the 2 days prior to the baseline office visit
- history of surgery for axillary hyperhidrosis
- participation in another investigational drug trial or receiving any investigational

treatment(s) within 30 days of Baseline

Results

[000359] Twelve subjects were enrolled in the study. At 4 weeks, study subjects had an average 62% reduction in GSP; an average 97.9 mg reduction in GSP; and an average 1.9 point reduction in HDSS. At 4 weeks, the percent reduction in GSP was statistically significant ($p < .0001$), as were the reductions in GSP by absolute weight ($p < .001$) and in HDSS ($p < .02$). At 12 weeks, study subjects had an average 64% reduction in GSP; an average 73.5 mg reduction in GSP; and an average 1.8 point reduction in HDSS.

[000360] No subject had an adverse reaction to the treatment.

Conclusion

[000361] The treatment reduces sweat production and the subjective perspective of excessive sweating in a clinically and statistically significant way. The treatment had a favorable safety profile.

Example 2: Exemplary Provided Compositions for Treatment of Acne

Materials and Methods

Selection of Subjects

[000362] Inclusion criteria include a diagnosis of acne.

Experimental Design

[000363] A pre-determined number of subjects (*e.g.*, 2, 4, 8, 10, 12, 14, 16, 18, 20, or more) receives a single 0.3 cc topical treatment containing an “empty nanoemulsion” (*e.g.*, the nanoemulsion described in Example 1). If no significant adverse events are observed with a single treatment at a pre-determined endpoint (*e.g.*, 4, 6, 8, 10, 12, or more than 12 weeks after treatment), a second group of different subjects of a similar size to the first group receives two 0.3 cc topical treatment of empty nanoemulsion as described in Example 1. The second treatment is administered two weeks after the first. If no significant adverse events are observed with the second group of subjects, a third group of subjects of similar size is treated with three sequential treatments of 0.3 cc of empty nanoemulsion, each two weeks apart.

Treatment Procedure

[000364] The clinical investigator wipes a region affected by acne with an alcohol wipe and then wipe dry with cotton gauze. Using a latex-gloved finger, the investigator massages the topical treatment into the skin. This procedure is completed when there is no topical treatment visible on the surface of the skin. Subjects are evaluated prior to treatment (Week 0) and 2, 4, 8, 12, and 16 weeks after the initial treatment.

Study Visits

[000365] During the first office visit and the follow-up office visits, the study investigator evaluates the treatment region for number of open comedones, closed comedones, raised lesions, papules, pustules, lesion with erythema, and cysts.

Results

[000366] The study shows that the area of treatment is significantly improved on at least one of the follow-up office observation visits when compared to pre-treatment levels for at least some of the number of open comedones, closed comedones, raised lesions, papules, pustules, lesion with erythema, and cysts for treatment with at least one of the dose levels selected for study.

[000367] Based on these results, the investigator concludes that topical treatment using empty nanoemulsions in accordance with the invention is effective in treating acne.

Example 3: Exemplary Provided Compositions for Treatment of Rosacea**Materials and Methods***Selection of Subjects*

[000368] Inclusion criteria include a diagnosis of rosacea.

Experimental Design

[000369] A pre-determined number of subjects (*e.g.*, 2, 4, 8, 10, 12, 14, 16, 18, 20, or more) receives a single 0.3 cc topical treatment containing an “empty nanoemulsion” (*i.e.*, the nanoemulsion described in Example 1). If no significant adverse events are observed with a single treatment at a pre-determined endpoint (*e.g.*, 4, 6, 8, 10, 12, or more than 12 weeks after treatment), a second group of different subjects of a similar size to the first group

receives two 0.3 cc topical treatment of empty nanoemulsion as described in Example 1. The second treatment is administered two weeks after the first. If no significant adverse events are observed with the second group of subjects, a third group of subjects of similar size is treated with three sequential treatments of 0.3 cc of empty nanoemulsion, each two weeks apart.

Treatment Procedure

[000370] The clinical investigator wipes the surface of the affected skin area with an alcohol wipe and then wipes it dry with cotton gauze. Using a latex-gloved finger, the investigator massages the topical treatment into the skin. This procedure is completed when there is no topical treatment visible on the surface of the skin. Subjects are evaluated prior to treatment (Week 0) and 2, 4, 8, 12, and 16 weeks after the initial treatment.

Study Visits

[000371] During the first office visit and the four week follow-up office visit, the study investigator evaluates the treatment region in terms of Investigator Global Assessment (using, for example, a seven point scale with 0 = clear, 1 = minimal, 2 = mild to moderate, 4 = moderate, 5 = moderate to severe, and 6 = severe); Subject Global Self-Assessment (using, for example, a nine point scale from 100% worse to no change to 100% improved as measured in 25% increments); and erythema intensity and teleangiectasis intensity (each using, for example, a four point scale from 1 = none, 2 = mild, 3 = moderate, and 4 = severe).

Results

[000372] The study shows that the area of treatment is significantly improved on at least one of the follow-up office observation visits when compared to pre-treatment levels for at least some of the number of Investigator Global Assessment, Subject Global Self-Assessment, erythema intensity or teleangiectasis intensity for treatment with one or more applications of the empty nanoemulsion.

[000373] Based on these results, the investigator concludes that topical treatment using empty nanoemulsions in accordance with the invention is effective in treating rosacea.

Example 4: Clinical Study to Examine the Potential Effect Chemical Compounds that May Reduce Axillary Sweating

[000374] The primary objective of the study is to determine whether specific individual compounds when applied to a subject's axilla can produce a reduction from the baseline level of subject's axillary sweating and the level of sweating at 2 and 4 weeks after treatment as measured by Gravimetric Sweat Production (GSP). These individual components had been combined together previously and tested in a similar manner and had been found to reduce sweat production as well as the subjective perspective of excessive sweating in a clinically and statistically significant way (see *e.g.*, Example 3).

Materials and Methods

Treatment Composition

[000375] Each compound to be tested is listed in Table 2.

Table 2: Treatment Composition

Component	% (by wt.)
1349 Oil	3.20
Tween-80	4.80
Methylparaben	0.20
Propylparaben	0.20
Sodium Chloride	0.63
Sodium Phosphate Dibasic	0.04
Gelatin	0.02
Mineral Oil	0.63
Isopropyl Myristate	0.62
White Petrolatum	0.25
Emulsifying Wax	1.87
Purified Water	87.76
Total	100.00

[000376] Each treatment consists of a solution comprised of water and one of these compounds mixed into water such that the compound comprises the percent of the final treatment listed in Table 2, with the balance of the treatment being comprised of water. The volume of treatment per axilla is 0.3cc.

Administration

[000377] 0.3 cc of the treatment are rubbed into each axillary vault of the subject until none of the treatment is visible on the skin. Only a single application of the treatment to each axillary vault is given to the subject.

Secondary Objectives

[000378] The secondary objectives of the study are to determine:

- Change from Baseline in Hyperhidrosis Disease Severity Scale (HDSS) score at Week 2 and 4;
- Change from Baseline in gravimetrically measured sweat production at all office visits.

Study Design

[000379] The study is a multicenter, out-patient clinical trial during which the subjects are assessed for the level sweating by objective (GSP) and subjective (HDSS) measures, during which they are observed at baseline and again at Weeks 2 and 4 after treatment. Five or more subjects are be enrolled for each treatment. The data are analyzed for each treatment group to determine if there is a statistically and/or clinical significant difference between the baseline level of sweating and sweating at Weeks 2 and 4. The data are analyzed for each treatment group to determine if there is a statistically and/or clinical significant difference between the baseline level of HDSS and HDSS at Weeks 2 and 4.

Study Subjects

[000380] The subject meet the following enrollment criteria:

Inclusion Criteria

- able to understand and give written informed consent
- ages 18 - 70 years of age
- HDSS score of ≥ 3
- ≥ 50 mg of sweat production/axilla in 5 minutes as measured gravimetrically
- willingness to use only over-the-counter deodorants during the course of the study
- patients should be in good general health as determined by the investigator and free of any
- disease that may interfere with study evaluations or the Investigational Product

Exclusion Criteria

- diagnosis of secondary hyperhidrosis (that is, hyperhidrosis due to another medical condition such as hyperthyroidism, cancer, tuberculosis, malaria, or other

infection)

- signs of infection in the axilla
- skin affliction in the axilla requiring medical treatment
- application of topical medication to the treatment area within 14 days prior to treatment
- use of antiperspirants, deodorants, powders or lotions in the 2 days prior to the baseline office visit
- history of surgery for axillary hyperhidrosis
- participation in another investigational drug trial or receiving any investigational treatment(s) within 30 days of Baseline

Example 5: Clinical Study to Evaluate Effect of Empty Nanoemulsion Formulation (“Composition H”) on Axillary Sweating

Study Design Summary

[000381] The purpose of the study was to determine if Emulsion H is biologically active in reducing sweating. Subjects were selected who believed they sweated excessively and who demonstrated excessive sweating by gravimetric sweat measurement. Some subjects received treatment with the potentially biologically active formulation and some subjects received treatment with a placebo, i.e. water. Neither the subject nor the investigator knew which treatment the subject was receiving.

[000382] Two weeks after a single treatment, subjects were re-assessed by gravimetric sweat measurement to determine the degree of sweat reduction. A comparison of post-treatment sweat production between the treatment groups was made to determine the degree of sweat reduction by the potentially biologically active formulation.

Study Subject Inclusion / Exclusion Criteria

[000383] The study used the following criteria to enroll subjects:

Inclusion Criteria

- able to understand and give written informed consent
- ages 18 - 70 years of age
- diagnosis of moderate to severe primary axillary hyperhidrosis

- Hyperhidrosis Disease Severity Scale score of ≥ 3 (the HDSS scale is described below)
- ≥ 50 mg of sweat production/axilla in 5 minutes as measured gravimetrically
- willingness to use only over-the-counter deodorants during the course of the study
- willingness to shave underarms prior to each study visit
- female subjects must have a negative urine pregnancy test and be non-lactating at the initial (“Baseline”) study site visit
- patients should be in good general health as determined by the investigator and free of any disease that may interfere with study evaluations

Exclusion Criteria

- diagnosis of secondary hyperhidrosis (that is, hyperhidrosis due to another medical condition such as hyperthyroidism, cancer, tuberculosis, malaria, or other infection)
- signs of infection in the axilla
- skin affliction in the axilla requiring medical treatment
- application of topical medication to the treatment area within 14 days prior to treatment
- 20% aluminum hydrochloride, e.g. Drysol[®], in 2 weeks prior of Baseline
- oral anticholinergic treatment (e.g., Benadryl, Atarax, Chlortrimeton, and Robinul) in prior 2 weeks
- use of antiperspirants, deodorants, powders or lotions in the 2 days prior to Baseline
- botulinum toxin treatment in prior 9 months
- history of surgery for axillary hyperhidrosis
- participation in another investigational drug trial or receiving any investigational treatment(s) within 30 days of Baseline
- alcohol or drug abuse within the past 3 years
- female subjects who are pregnant or are nursing a child
- psychiatric disease interfering with the patient’s ability to give informed consent
- use of axillary depilatories, e.g. Nair[®], Veet[®]
- use of axillary epilation (waxing, laser, electrolysis) within 1 week of Baseline
- refusal or inability to comply with the requirements of the protocol for any reason

Treatment and Assessment Methods

Clinical Visits

[000384] Prior to scheduling an initial visit to the investigator's study site, potential participants were queried with regards to their use of anti-perspirants, topical medications, or depilatory products in the axilla. Subjects who met Exclusion Criteria were not scheduled. Potential participants were instructed not to use such products and to shave his or her underarms prior to the Baseline study visit.

[000385] At the Baseline study visit, prior to participating in any aspect of the study, each subject was fully informed, both verbally and in writing, of the conduct and consequences of the study. Each subject signed the written Informed Consent Form prior to the conduct of the screening evaluation to determine whether the subject was potentially eligible for the study. A verbal screening evaluation and gravimetric sweat measurement were performed to determine if the subject met the Inclusion Criteria but did not meet the Exclusion Criteria.

The Hyperhidrosis Disease Severity Scale

[000386] The subject was asked to rate the perceived severity of the subject's disease by selecting the one sentence that best describes the current level to which subject's underarm sweating interferes with the subject's life:

- [000387] 0 = My underarm sweating is not noticeable and never interferes with my daily activities.
- [000388] 1 = My underarm sweating is noticeable but rarely interferes with my daily activities.
- [000389] 2 = My underarm sweating is tolerable but sometimes interferes with my daily activities.
- [000390] 3 = My underarm sweating is barely tolerable and frequently interferes with my daily activities.
- [000391] 4 = My underarm sweating is barely tolerable and always interferes with my daily activities.
- [000392] 5 = My underarm sweating is intolerable and always interferes with my daily activities.

Gravimetric Sweat Measurement Method

[000393] The sweat production of the subject is measured gravimetrically by the following procedure:

- The subject was placed in a room with relatively constant temperature and humidity for at least 30 min.
- The subject was placed in a semi-reclining position with the axilla fully exposed and the arm resting comfortably above the head.
- The subject's axilla was dried gently with a cotton gauze pad.
- The investigator used a forceps to place one filter paper (90 mm diameter) on a balance sensitive to 0.1 mg and recorded its weight.
- The investigator used a forceps to place the measured filter paper on the axilla, covered it with plastic and taped the edges of the bag against the subject's skin with hypoallergenic tape to form a seal around the plastic bag.
- After 5 minutes, the investigator gently removed the tape and plastic from the subject's axilla and then, using forceps, immediately placed the filter paper onto the scale to record its weight. The scale was then dried and zero balanced.
- This measurement was then repeated as described above with the other axilla.

Treatment application

[000394] If the subject was eligible for treatment on this basis, the subject was then treated. For treatment, one of the study preparations (0.3 mL/axilla) was applied topically with a gloved finger by the investigator to the subject's skin of the axilla. Emulsion H contained 19.2 mg Labrafac Lipophile WL 1349 and 28.8 mg Polysorbate 80, NF, in addition to 0.9% Sodium Chloride Irrigation, USP, and Gelatin Phosphate Buffer. The average diameter (e.g., particle size) of nanoparticles contained in the Emulsion H empty nanoparticle composition was approximately 80.1 nm. The preparation was administered in small increments to avoid run-off. The liquid was rubbed-in until vanished.

[000395] Following treatment, the subject was instructed to shower on the day of treatment immediately prior to going to bed and, in so doing, wash the axilla with soap and water. The subject was instructed not to use any of the following medications:

- Botulinum Toxin containing products applied to the axilla for the course of the study
- Aluminum hydrochloride topical, e.g. Drysol[®] for the course of the study
- Oral anticholinergic treatment (e.g., Benadryl, Atarax, Chlortrimeton, and Robinul) for the course of the study
- Use of antiperspirants, deodorants, powders, or lotions in the 2 days prior to the Baseline visit and 2 days prior to the office visit two weeks following treatment when gravimetric sweat measurement would be conducted.
- Use of antiperspirants, deodorants, powders or lotions for 1 day after the treatment
- Topical medications applied to the treatment area for 5 days following treatment
- Investigational Medications or treatments within 30 days of Baseline and during the course of the study.

[000396] The subject was scheduled for a follow-up office visit two weeks after the treatment. At the follow-up office visit, the subject was questioned as to their compliance with the instructions regarding which medications not to use between treatment and the two week follow-up office visit. If the subject was non-compliant, the subject was disqualified from the study. If the subject was compliant, the subject was re-assessed using the gravimetric sweat measurement procedure.

Treatment Results and Conclusion

[000397] The study was conducted at multiple study sites and conducted in compliance with Good Clinical Practice standards. Ten subjects were treated with Emulsion H. Two weeks after the treatment, each subject was re-assessed by gravimetric sweat measurement.

[000398] On average, subjects in the Emulsion H group had a reduction in sweat production of 151 mg two weeks after treatment as measured by gravimetric sweat measurement. In contrast, subjects treated with the placebo had a 53 mg reduction in sweat production as measured by gravimetric sweat measurement. Therefore, subjects treated with Emulsion H had a 286% greater reduction in sweat production than the subjects in the control group.

[000399] It was also determined what percent of study subjects receiving either Emulsion H or placebo experienced at least a 30% reduction in sweat production when compared to levels measured at the Baseline visit. It was found that 60% of subjects treated with Emulsion H had at least a 30% reduction in sweat production when compared to levels at the Baseline visit. This contrasts with only 29% of subjects in the control group that had at least a 30% reduction in sweat production when compared to levels at the Baseline visit. Therefore, by this assessment subjects treated with Emulsion H had a 210% greater effectiveness in reducing sweat production than those subjects treated with placebo.

[000400] Given these data, it is concluded that Emulsion H is (i) biologically active in reducing sweat production, (ii) is an anti-perspirant formulation, and (iii) may be used effectively in treating hyperhidrosis.

Example 6: Clinical Study to Evaluate Effect of “Emulsion V” Nanoparticle Composition on Axillary Sweating

Study Design Summary

[000401] The purpose of the study was to determine if Emulsion V is biologically active in reducing sweating. Subjects were selected who believed they sweated excessively and who demonstrated excessive sweating by gravimetric sweat measurement. Some subjects received treatment with the potentially biologically active formulation and some subjects received treatment with a placebo, i.e. water. Neither the subject nor the investigator knew which treatment the subject was receiving.

[000402] Two weeks after a single treatment, subjects were re-assessed by gravimetric sweat measurement to determine the degree of sweat reduction. A comparison of post-treatment sweat production between the treatment groups was made to determine the degree of sweat reduction by the potentially biologically active formulation.

Study Subject Inclusion / Exclusion Criteria

[000403] The study used the following criteria to enroll subjects:

Inclusion Criteria

- able to understand and give written informed consent
- ages 18 - 70 years of age
- diagnosis of moderate to severe primary axillary hyperhidrosis
- Hyperhidrosis Disease Severity Scale score of ≥ 3 (the HDSS scale is described below)
- ≥ 50 mg of sweat production/axilla in 5 minutes as measured gravimetrically
- willingness to use only over-the-counter deodorants during the course of the study
- willingness to shave underarms prior to each study visit
- female subjects must have a negative urine pregnancy test and be non-lactating at the initial ("Baseline") study site visit
- patients should be in good general health as determined by the investigator and free of any disease that may interfere with study evaluations

Exclusion Criteria

- diagnosis of secondary hyperhidrosis (that is, hyperhidrosis due to another medical condition such as hyperthyroidism, cancer, tuberculosis, malaria, or other infection)
- signs of infection in the axilla
- skin affliction in the axilla requiring medical treatment
- application of topical medication to the treatment area within 14 days prior to treatment
- 20% aluminum hydrochloride, e.g. Drysol[®], in 2 weeks prior of Baseline
- oral anticholinergic treatment (e.g., Benadryl, Atarax, Chlortrimeton, and Robinul) in prior 2 weeks
- use of antiperspirants, deodorants, powders or lotions in the 2 days prior to Baseline

- botulinum toxin treatment in prior 9 months
- history of surgery for axillary hyperhidrosis
- participation in another investigational drug trial or receiving any investigational treatment(s) within 30 days of Baseline
- alcohol or drug abuse within the past 3 years
- female subjects who are pregnant or are nursing a child
- psychiatric disease interfering with the patient's ability to give informed consent
- use of axillary depilatories, e.g Nair[®], Veet[®]
- use of axillary epilation (waxing, laser, electrolysis) within 1 week of Baseline
- refusal or inability to comply with the requirements of the protocol for any reason

Treatment and Assessment Methods

Clinical Visits

[000404] Prior to scheduling an initial visit to the investigator's study site, potential participants were queried with regards to their use of anti-perspirants, topical medications, or depilatory products in the axilla. Subjects who met Exclusion Criteria were not scheduled. Potential participants were instructed not to use such products and to shave his or her underarms prior to the Baseline study visit.

[000405] At the Baseline study visit, prior to participating in any aspect of the study, each subject was fully informed, both verbally and in writing, of the conduct and consequences of the study. Each subject signed the written Informed Consent Form prior to the conduct of the screening evaluation to determine whether the subject was potentially eligible for the study. A verbal screening evaluation and gravimetric sweat measurement were performed to determine if the subject met the Inclusion Criteria but did not meet the Exclusion Criteria.

The Hyperhidrosis Disease Severity Scale

[000406] The subject was asked to rate the perceived severity of the subject's disease by selecting the one sentence that best describes the current level to which subject's underarm sweating interferes with the subject's life:

[000407] 0 = My underarm sweating is not noticeable and never interferes with my daily activities.

[000408] 1 = My underarm sweating is noticeable but rarely interferes with my daily activities.

[000409] 2 = My underarm sweating is tolerable but sometimes interferes with my daily activities.

[000410] 3 = My underarm sweating is barely tolerable and frequently interferes with my daily activities.

[000411] 4 = My underarm sweating is barely tolerable and always interferes with my daily activities.

[000412] 5 = My underarm sweating is intolerable and always interferes with my daily activities.

Gravimetric Sweat Measurement Method

[000413] The sweat production of the subject is measured gravimetrically by the following procedure:

- The subject was placed in a room with relatively constant temperature and humidity for at least 30 min.
- The subject was placed in a semi-reclining position with the axilla fully exposed and the arm resting comfortably above the head.
- The subject's axilla was dried gently with a cotton gauze pad.
- The investigator used a forceps to place one filter paper (90 mm diameter) on a balance sensitive to 0.1 mg and recorded its weight.
- The investigator used a forceps to place the measured filter paper on the axilla, covered it with plastic and taped the edges of the bag against the subject's skin with hypoallergenic tape to form a seal around the plastic bag.
- After 5 minutes, the investigator gently removed the tape and plastic from the subject's axilla and then, using forceps, immediately placed the filter paper onto the scale to record its weight. The scale was then dried and zero balanced.
- This measurement was then repeated as described above with the other axilla.

Treatment application

[000414] If the subject was eligible for treatment on this basis, the subject was then treated. For treatment, one of the study preparations (0.3 mL/axilla) was applied topically with a gloved finger by the investigator to the subject's skin of the axilla. Emulsion V

contained Emulsifying Wax, Gelatin Phosphate Buffer Solution, Isopropyl Myristate, Labrafac Lipophile, Methylparaben, Mineral Oil Heavy Viscosity Range, Polysorbate 80, Propylparaben, Purified Water, Sodium Chloride Injection, and White Petrolatum. All ingredients are either NF or USP grade. The average diameter (e.g., particle size) of nanoparticles contained in the Emulsion V empty nanoparticle composition was approximately 77.1 nm. The preparation was administered in small increments to avoid run-off. The liquid was rubbed-in until vanished.

[000415] Following treatment, the subject was instructed to shower on the day of treatment immediately prior to going to bed and, in so doing, wash the axilla with soap and water. The subject was instructed not to use any of the following medications:

- Botulinum Toxin containing products applied to the axilla for the course of the study
- Aluminum hydrochloride topical, e.g. Drysol[®] for the course of the study
- Oral anticholinergic treatment (e.g., Benadryl, Atarax, Chlortrimeton, and Robinul) for the course of the study
- Use of antiperspirants, deodorants, powders, or lotions in the 2 days prior to the Baseline visit and 2 days prior to the office visit two weeks following treatment when gravimetric sweat measurement would be conducted.
- Use of antiperspirants, deodorants, powders or lotions for 1 day after the treatment
- Topical medications applied to the treatment area for 5 days following treatment
- Investigational Medications or treatments within 30 days of Baseline and during the course of the study.

[000416] The subject was scheduled for a follow-up office visit two weeks after the treatment. At the follow-up office visit, the subject was questioned as to their compliance with the instructions regarding which medications not to use between treatment and the two week follow-up office visit. If the subject was non-compliant, the subject was disqualified from the study. If the subject was compliant, the subject was re-assessed using the gravimetric sweat measurement procedure.

Treatment Results and Conclusion

[000417] The study was conducted at multiple study sites and conducted in compliance with Good Clinical Practice standards. Ten subjects were treated with Emulsion V. Two weeks after the treatment, each subject was re-assessed by gravimetric sweat measurement.

[000418] On average, subjects in the Emulsion V group had a reduction in sweat production of 151 mg two weeks after treatment as measured by gravimetric sweat measurement. In contrast, subjects treated with the placebo had a 53 mg reduction in sweat production as measured by gravimetric sweat measurement. Therefore, subjects treated with Emulsion V had a 286% greater reduction in sweat production than the subjects in the control group.

[000419] It was also determined what percent of study subjects receiving either Emulsion V or placebo experienced at least a 30% reduction in sweat production when compared to levels measured at the Baseline visit. It was found that 60% of subjects treated with Emulsion V had at least a 30% reduction in sweat production when compared to levels at the Baseline visit. This contrasts with only 29% of subjects in the control group that had at least a 30% reduction in sweat production when compared to levels at the Baseline visit. Therefore, by this assessment subjects treated with Emulsion V had a 210% greater effectiveness in reducing sweat production than those subjects treated with placebo.

[000420] Given these data, it is concluded that Emulsion V is (i) biologically active in reducing sweat production, (ii) is an anti-perspirant formulation, and (iii) may be used effectively in treating hyperhidrosis.

Example 7: Clinical Study to Evaluate Effect of Polysorbate 80 on Axillary Sweating

Study Design Summary

[000421] The purpose of the study was to determine if Polysorbate 80 is biologically active in reducing sweating. Subjects were selected who believed they sweated excessively and who demonstrated excessive sweating by gravimetric sweat measurement. Some subjects received treatment with the potentially biologically active substance and some subjects received treatment with a placebo, i.e. water. Neither the subject nor the investigator knew which treatment the subject was receiving.

[000422] Two weeks after a single treatment, subjects were re-assessed by gravimetric sweat measurement to determine the degree of sweat reduction. A comparison of post-treatment sweat production between the treatment groups was made to determine the degree of sweat reduction by the potentially biologically active substance.

Study Subject Inclusion / Exclusion Criteria

[000423] The study used the following criteria to enroll subjects:

Inclusion Criteria

- able to understand and give written informed consent
- ages 18 - 70 years of age
- diagnosis of moderate to severe primary axillary hyperhidrosis
- Hyperhidrosis Disease Severity Scale score of ≥ 3 (the HDSS scale is described below)
- ≥ 50 mg of sweat production/axilla in 5 minutes as measured gravimetrically
- willingness to use only over-the-counter deodorants during the course of the study
- willingness to shave underarms prior to each study visit
- female subjects must have a negative urine pregnancy test and be non-lactating at the initial ("Baseline") study site visit
- patients should be in good general health as determined by the investigator and free of any disease that may interfere with study evaluations

Exclusion Criteria

- diagnosis of secondary hyperhidrosis (that is, hyperhidrosis due to another medical condition such as hyperthyroidism, cancer, tuberculosis, malaria, or other infection)
- signs of infection in the axilla
- skin affliction in the axilla requiring medical treatment
- application of topical medication to the treatment area within 14 days prior to treatment
- 20% aluminum hydrochloride, e.g. Drysol[®], in 2 weeks prior of Baseline
- oral anticholinergic treatment (e.g., Benadryl, Atarax, Chlortrimeton, and Robinul) in prior 2 weeks
- use of antiperspirants, deodorants, powders or lotions in the 2 days prior to Baseline
- botulinum toxin treatment in prior 9 months
- history of surgery for axillary hyperhidrosis

- participation in another investigational drug trial or receiving any investigational treatment(s) within 30 days of Baseline
- alcohol or drug abuse within the past 3 years
- female subjects who are pregnant or are nursing a child
- psychiatric disease interfering with the patient's ability to give informed consent
- use of axillary depilatories, e.g Nair[®], Veet[®]
- use of axillary epilation (waxing, laser, electrolysis) within 1 week of Baseline
- refusal or inability to comply with the requirements of the protocol for any reason

Treatment and Assessment Methods

Clinical Visits

[000424] Prior to scheduling an initial visit to the investigator's study site, potential participants were queried with regards to their use of anti-perspirants, topical medications, or depilatory products in the axilla. Subjects who met Exclusion Criteria were not scheduled. Potential participants were instructed not to use such products and to shave his or her underarms prior to the Baseline study visit.

[000425] At the Baseline study visit, prior to participating in any aspect of the study, each subject was fully informed, both verbally and in writing, of the conduct and consequences of the study. Each subject signed the written Informed Consent Form prior to the conduct of the screening evaluation to determine whether the subject was potentially eligible for the study. A verbal screening evaluation and gravimetric sweat measurement were performed to determine if the subject met the Inclusion Criteria but did not meet the Exclusion Criteria.

The Hyperhidrosis Disease Severity Scale

[000426] The subject was asked to rate the perceived severity of the subject's disease by selecting the one sentence that best describes the current level to which subject's underarm sweating interferes with the subject's life:

- [000427] 0 = My underarm sweating is not noticeable and never interferes with my daily activities.
- [000428] 1 = My underarm sweating is noticeable but rarely interferes with my daily activities.
- [000429] 2 = My underarm sweating is tolerable but sometimes interferes with my daily activities.
- [000430] 3 = My underarm sweating is barely tolerable and frequently interferes with my daily activities.
- [000431] 4 = My underarm sweating is barely tolerable and always interferes with my daily activities.
- [000432] 5 = My underarm sweating is intolerable and always interferes with my daily activities.

Gravimetric Sweat Measurement Method

[000433] The sweat production of the subject is measured gravimetrically by the following procedure:

- The subject was placed in a room with relatively constant temperature and humidity for at least 30 min.
- The subject was placed in a semi-reclining position with the axilla fully exposed and the arm resting comfortably above the head.
- The subject's axilla was dried gently with a cotton gauze pad.
- The investigator used a forceps to place one filter paper (90 mm diameter) on a balance sensitive to 0.1 mg and recorded its weight.
- The investigator used a forceps to place the measured filter paper on the axilla, covered it with plastic and taped the edges of the bag against the subject's skin with hypoallergenic tape to form a seal around the plastic bag.
- After 5 minutes, the investigator gently removed the tape and plastic from the subject's axilla and then, using forceps, immediately placed the filter paper onto the scale to record its weight. The scale was then dried and zero balanced.
- This measurement was then repeated as described above with the other axilla.

Treatment application

[000434] If the subject was eligible for treatment on this basis, the subject was then treated. For treatment, one of the study preparations (0.3 mL/axilla) was applied topically with a gloved finger by the investigator to the subject's skin of the axilla. The preparation was administered in small increments to avoid run-off. The liquid was rubbed-in until vanished. Each subject who was selected to have a treatment with the potentially biologically active substance had 14.34 mg of Polysorbate 80 applied to each axilla.

[000435] Following treatment, the subject was instructed to shower on the day of treatment immediately prior to going to bed and, in so doing, wash the axilla with soap and water. The subject was instructed not to use any of the following medications:

- Botulinum Toxin containing products applied to the axilla for the course of the study
- Aluminum hydrochloride topical, e.g. Drysol[®] for the course of the study
- Oral anticholinergic treatment (e.g., Benadryl, Atarax, Chlortrimeton, and Robinul) for the course of the study
- Use of antiperspirants, deodorants, powders, or lotions in the 2 days prior to the Baseline visit and 2 days prior to the office visit two weeks following treatment when gravimetric sweat measurement would be conducted.
- Use of antiperspirants, deodorants, powders or lotions for 1 day after the treatment
- Topical medications applied to the treatment area for 5 days following treatment
- Investigational Medications or treatments within 30 days of Baseline and during the course of the study.

[000436] The subject was scheduled for a follow-up office visit two weeks after the treatment. At the follow-up office visit, the subject was questioned as to their compliance with the instructions regarding which medications not to use between treatment and the two week follow-up office visit. If the subject was non-compliant, the subject was disqualified from the study. If the subject was compliant, the subject was re-assessed using the gravimetric sweat measurement procedure.

Treatment Results and Conclusion

[000437] The study was conducted at multiple study sites and conducted in compliance with Good Clinical Practice standards. Ten subjects were treated with Polysorbate 80. Two weeks after the treatment, each subject was re-assessed by gravimetric sweat measurement.

[000438] On average, subjects in the Polysorbate 80 group had a reduction in sweat production of 159 mg two weeks after treatment as measured by gravimetric sweat measurement. In contrast, subjects treated with the placebo had a 53 mg reduction in sweat production as measured by gravimetric sweat measurement. Therefore, subjects treated with Polysorbate 80 had a 300% greater reduction in sweat production than the subjects in the control group.

[000439] It was also determined what percent of study subjects receiving either Polysorbate 80 or placebo experienced at least a 30% reduction in sweat production when compared to levels measured at the Baseline visit. It was found that 80% of subjects treated with Polysorbate 80 had at least a 30% reduction in sweat production when compared to levels at the Baseline visit. This contrasts with only 29% of subjects in the control group that had at least a 30% reduction in sweat production when compared to levels at the Baseline visit. Therefore, by this assessment subjects treated with Polysorbate 80 had a 280% greater effectiveness in reducing sweat production than those subjects treated with placebo.

[000440] Given these data, it is concluded that Polysorbate 80 is (i) biologically active in reducing sweat production, (ii) is an anti-perspirant substance, and (iii) may be used effectively in treating hyperhidrosis.

Example 8: Clinical Study to Evaluate Effect of Labrafac® Lipophile WL 1349 on Axillary Sweating

Study Design Summary

[000441] The purpose of the study was to determine if Labrafac Lipophile WL 1349 is biologically active in reducing sweating. Subjects were selected who believed they sweated excessively and who demonstrated excessive sweating by gravimetric sweat measurement. Some subjects received treatment with the potentially biologically active substance and some subjects received treatment with a placebo, i.e. water. Neither the subject nor the investigator knew which treatment the subject was receiving.

[000442] Two weeks after a single treatment, subjects were re-assessed by gravimetric sweat measurement to determine the degree of sweat reduction. A comparison of post-treatment sweat production between the treatment groups was made to determine the degree of sweat reduction by the potentially biologically active substance.

Study Subject Inclusion / Exclusion Criteria

[000443] The following criteria were used to enroll subject:

Inclusion Criteria

- able to understand and give written informed consent
- ages 18 - 70 years of age
- diagnosis of moderate to severe primary axillary hyperhidrosis
- Hyperhidrosis Disease Severity Scale score of ≥ 3 (the HDSS scale is described below)
- ≥ 50 mg of sweat production/axilla in 5 minutes as measured gravimetrically
- willingness to use only over-the-counter deodorants during the course of the study
- willingness to shave underarms prior to each study visit
- female subjects must have a negative urine pregnancy test and be non-lactating at the initial ("Baseline") study site visit
- patients should be in good general health as determined by the investigator and free of any disease that may interfere with study evaluations

Exclusion Criteria

- diagnosis of secondary hyperhidrosis (that is, hyperhidrosis due to another medical condition such as hyperthyroidism, cancer, tuberculosis, malaria, or other infection)
- signs of infection in the axilla
- skin affliction in the axilla requiring medical treatment
- application of topical medication to the treatment area within 14 days prior to treatment
- 20% aluminum hydrochloride, e.g. Drysol[®], in 2 weeks prior of Baseline
- oral anticholinergic treatment (e.g., Benadryl, Atarax, Chlortrimeton, and Robinul) in prior 2 weeks
- use of antiperspirants, deodorants, powders or lotions in the 2 days prior to Baseline

- botulinum toxin treatment in prior 9 months
- history of surgery for axillary hyperhidrosis
- participation in another investigational drug trial or receiving any investigational treatment(s) within 30 days of Baseline
- alcohol or drug abuse within the past 3 years
- female subjects who are pregnant or are nursing a child
- psychiatric disease interfering with the patient's ability to give informed consent
- use of axillary depilatories, e.g Nair[®], Veet[®]
- use of axillary epilation (waxing, laser, electrolysis) within 1 week of Baseline
- refusal or inability to comply with the requirements of the protocol for any reason

Treatment and Assessment Methods

Clinical Visits

[000444] Prior to scheduling an initial visit to the investigator's study site, potential participants were queried with regards to their use of anti-perspirants, topical medications, or depilatory products in the axilla. Subjects who met Exclusion Criteria were not scheduled. Potential participants were instructed not to use such products and to shave his or her underarms prior to the Baseline study visit.

[000445] At the Baseline study visit, prior to participating in any aspect of the study, each subject was fully informed, both verbally and in writing, of the conduct and consequences of the study. Each subject signed the written Informed Consent Form prior to the conduct of the screening evaluation to determine whether the subject was potentially eligible for the study. A verbal screening evaluation and gravimetric sweat measurement were performed to determine if the subject met the Inclusion Criteria but did not meet the Exclusion Criteria.

The Hyperhidrosis Disease Severity Scale

[000446] The subject was asked to rate the perceived severity of the subject's disease by selecting the one sentence that best describes the current level to which subject's underarm sweating interferes with the subject's life:

[000447] 0 = My underarm sweating is not noticeable and never interferes with my daily activities.

[000448] 1 = My underarm sweating is noticeable but rarely interferes with my daily

activities.

[000449] 2 = My underarm sweating is tolerable but sometimes interferes with my daily activities.

[000450] 3 = My underarm sweating is barely tolerable and frequently interferes with my daily activities.

[000451] 4 = My underarm sweating is barely tolerable and always interferes with my daily activities.

[000452] 5 = My underarm sweating is intolerable and always interferes with my daily activities.

Gravimetric Sweat Measurement Method

[000453] The sweat production of the subject is measured gravimetrically by the following procedure:

- The subject was placed in a room with relatively constant temperature and humidity for at least 30 min.
- The subject was placed in a semi-reclining position with the axilla fully exposed and the arm resting comfortably above the head.
- The subject's axilla was dried gently with a cotton gauze pad.
- The investigator used a forceps to place one filter paper (90 mm diameter) on a balance sensitive to 0.1 mg and recorded its weight.
- The investigator used a forceps to place the measured filter paper on the axilla, covered it with plastic and taped the edges of the bag against the subject's skin with hypoallergenic tape to form a seal around the plastic bag.
- After 5 minutes, the investigator gently removed the tape and plastic from the subject's axilla and then, using forceps, immediately placed the filter paper onto the scale to record its weight. The scale was then dried and zero balanced.
- This measurement was then repeated as described above with the other axilla.

Treatment application

[000454] If the subject was eligible for treatment on this basis, the subject was then treated. For treatment, one of the study preparations (0.3 mL/axilla) was applied topically with a gloved finger by the investigator to the subject's skin of the axilla. The preparation was administered in small increments to avoid run-off. The liquid was rubbed-in until

vanished. Each subject who was selected to have a treatment with the potentially biologically active substance had 9.57 mg of Labrafac Lipophile WL 1349 applied to each axilla.

[000455] Following treatment, the subject was instructed to shower on the day of treatment immediately prior to going to bed and, in so doing, wash the axilla with soap and water. The subject was instructed not to use any of the following medications:

- Botulinum Toxin containing products applied to the axilla for the course of the study
- Aluminum hydrochloride topical, e.g. Drysol[®] for the course of the study
- Oral anticholinergic treatment (e.g., Benadryl, Atarax, Chlortrimeton, and Robinul) for the course of the study
- Use of antiperspirants, deodorants, powders, or lotions in the 2 days prior to the Baseline visit and 2 days prior to the office visit two weeks following treatment when gravimetric sweat measurement would be conducted.
- Use of antiperspirants, deodorants, powders or lotions for 1 day after the treatment
- Topical medications applied to the treatment area for 5 days following treatment
- Investigational Medications or treatments within 30 days of Baseline and during the course of the study.

[000456] The subject was scheduled for a follow-up office visit two weeks after the treatment. At the follow-up office visit, the subject was questioned as to their compliance with the instructions regarding which medications not to use between treatment and the two week follow-up office visit. If the subject was non-compliant, the subject was disqualified from the study. If the subject was compliant, the subject was re-assessed using the gravimetric sweat measurement procedure.

Treatment Results and Conclusion

[000457] The study was conducted at multiple study sites and conducted in compliance with Good Clinical Practice standards. Ten subjects were treated with Labrafac Lipophile WL 1349. Two weeks after the treatment, each subject was re-assessed by gravimetric sweat measurement.

[000458] On average, subjects in the Labrafac Lipophile WL 1349 group had a reduction in sweat production of 165 mg two weeks after treatment as measured by gravimetric sweat measurement. In contrast, subjects treated with the placebo had a 53 mg reduction in sweat production as measured by gravimetric sweat measurement. Therefore, subjects treated with Labrafac Lipophile WL 1349 had a 313% greater reduction in sweat

production than the subjects in the control group.

[000459] It was also determined what percent of study subjects receiving either Labrafac Lipophile WL 1349 or placebo experienced at least a 30% reduction in sweat production when compared to levels measured at the Baseline visit. It was found that 80% of subjects treated with Labrafac Lipophile WL 1349 had at least a 30% reduction in sweat production when compared to levels at the Baseline visit. This contrasts with only 29% of subjects in the control group that had at least a 30% reduction in sweat production when compared to levels at the Baseline visit. Therefore, by this assessment subjects treated with Labrafac Lipophile WL 1349 had a 280% greater effectiveness in reducing sweat production than those subjects treated with placebo.

[000460] Given these data, it is concluded that Labrafac Lipophile WL 1349 is (i) biologically active in reducing sweat production, (ii) is an anti-perspirant substance, and (iii) may be used effectively in treating hyperhidrosis.

Example 9: Clinical Study to Evaluate Effect of Isopropyl Myristate on Axillary Sweating

Study Design Summary

[000461] The purpose of the study was to determine if Isopropyl Myristate is biologically active in reducing sweating. Subjects were selected who believed they sweated excessively and who demonstrated excessive sweating by gravimetric sweat measurement. Some subjects received treatment with the potentially biologically active substance and some subjects received treatment with a placebo, i.e. water. Neither the subject nor the investigator knew which treatment the subject was receiving.

[000462] Two weeks after a single treatment, subjects were re-assessed by gravimetric sweat measurement to determine the degree of sweat reduction. A comparison of post-treatment sweat production between the treatment groups was made to determine the degree of sweat reduction by the potentially biologically active substance.

Study Subject Inclusion / Exclusion Criteria

[000463] The following criteria were used to enroll subjects:

Inclusion Criteria

- able to understand and give written informed consent
- ages 18 - 70 years of age

- diagnosis of moderate to severe primary axillary hyperhidrosis
- Hyperhidrosis Disease Severity Scale score of ≥ 3 (the HDSS scale is described below)
- ≥ 50 mg of sweat production/axilla in 5 minutes as measured gravimetrically
- willingness to use only over-the-counter deodorants during the course of the study
- willingness to shave underarms prior to each study visit
- female subjects must have a negative urine pregnancy test and be non-lactating at the initial (“Baseline”) study site visit
- patients should be in good general health as determined by the investigator and free of any disease that may interfere with study evaluations

Exclusion Criteria

- diagnosis of secondary hyperhidrosis (that is, hyperhidrosis due to another medical condition such as hyperthyroidism, cancer, tuberculosis, malaria, or other infection)
- signs of infection in the axilla
- skin affliction in the axilla requiring medical treatment
- application of topical medication to the treatment area within 14 days prior to treatment
- 20% aluminum hydrochloride, e.g. Drysol[®], in 2 weeks prior of Baseline
- oral anticholinergic treatment (e.g., Benadryl, Atarax, Chlortrimeton, and Robinul) in prior 2 weeks
- use of antiperspirants, deodorants, powders or lotions in the 2 days prior to Baseline
- botulinum toxin treatment in prior 9 months
- history of surgery for axillary hyperhidrosis
- participation in another investigational drug trial or receiving any investigational treatment(s) within 30 days of Baseline
- alcohol or drug abuse within the past 3 years
- female subjects who are pregnant or are nursing a child
- psychiatric disease interfering with the patient’s ability to give informed consent
- use of axillary depilatories, e.g. Nair[®], Veet[®]
- use of axillary epilation (waxing, laser, electrolysis) within 1 week of Baseline
- refusal or inability to comply with the requirements of the protocol for any reason

Treatment and Assessment Methods

Clinical Visits

[000464] Prior to scheduling an initial visit to the investigator's study site, potential participants were queried with regards to their use of anti-perspirants, topical medications, or depilatory products in the axilla. Subjects who met Exclusion Criteria were not scheduled. Potential participants were instructed not to use such products and to shave his or her underarms prior to the Baseline study visit.

[000465] At the Baseline study visit, prior to participating in any aspect of the study, each subject was fully informed, both verbally and in writing, of the conduct and consequences of the study. Each subject signed the written Informed Consent Form prior to the conduct of the screening evaluation to determine whether the subject was potentially eligible for the study. A verbal screening evaluation and gravimetric sweat measurement were performed to determine if the subject met the Inclusion Criteria but did not meet the Exclusion Criteria.

The Hyperhidrosis Disease Severity Scale

[000466] The subject was asked to rate the perceived severity of the subject's disease by selecting the one sentence that best describes the current level to which subject's underarm sweating interferes with the subject's life:

[000467] 0 = My underarm sweating is not noticeable and never interferes with my daily activities.

[000468] 1 = My underarm sweating is noticeable but rarely interferes with my daily activities.

[000469] 2 = My underarm sweating is tolerable but sometimes interferes with my daily activities.

[000470] 3 = My underarm sweating is barely tolerable and frequently interferes with my daily activities.

[000471] 4 = My underarm sweating is barely tolerable and always interferes with my daily activities.

[000472] 5 = My underarm sweating is intolerable and always interferes with my daily activities.

Gravimetric Sweat Measurement Method

[000473] The sweat production of the subject is measured gravimetrically by the following procedure:

- The subject was placed in a room with relatively constant temperature and humidity for at least 30 min.
- The subject was placed in a semi-reclining position with the axilla fully exposed and the arm resting comfortably above the head.
- The subject's axilla was dried gently with a cotton gauze pad.
- The investigator used a forceps to place one filter paper (90 mm diameter) on a balance sensitive to 0.1 mg and recorded its weight.
- The investigator used a forceps to place the measured filter paper on the axilla, covered it with plastic and taped the edges of the bag against the subject's skin with hypoallergenic tape to form a seal around the plastic bag.
- After 5 minutes, the investigator gently removed the tape and plastic from the subject's axilla and then, using forceps, immediately placed the filter paper onto the scale to record its weight. The scale was then dried and zero balanced.
- This measurement was then repeated as described above with the other axilla.

Treatment application

[000474] If the subject was eligible for treatment on this basis, the subject was then treated. For treatment, one of the study preparations (0.3 mL/axilla) was applied topically with a gloved finger by the investigator to the subject's skin of the axilla. The preparation was administered in small increments to avoid run-off. The liquid was rubbed-in until vanished. Each subject who was selected to have a treatment with the potentially biologically active substance had 1.89 mg of Isopropyl Myristate applied to each axilla.

[000475] Following treatment, the subject was instructed to shower on the day of treatment immediately prior to going to bed and, in so doing, wash the axilla with soap and water. The subject was instructed not to use any of the following medications:

- Botulinum Toxin containing products applied to the axilla for the course of the study
- Aluminum hydrochloride topical, e.g. Drysol[®] for the course of the study
- Oral anticholinergic treatment (e.g., Benadryl, Atarax, Chlortrimeton, and Robinul) for the course of the study
- Use of antiperspirants, deodorants, powders, or lotions in the 2 days prior to the

Baseline visit and 2 days prior to the office visit two weeks following treatment when gravimetric sweat measurement would be conducted.

- Use of antiperspirants, deodorants, powders or lotions for 1 day after the treatment
- Topical medications applied to the treatment area for 5 days following treatment
- Investigational Medications or treatments within 30 days of Baseline and during the course of the study.

[000476] The subject was scheduled for a follow-up office visit two weeks after the treatment. At the follow-up office visit, the subject was questioned as to their compliance with the instructions regarding which medications not to use between treatment and the two week follow-up office visit. If the subject was non-compliant, the subject was disqualified from the study. If the subject was compliant, the subject was re-assessed using the gravimetric sweat measurement procedure.

Treatment Results and Conclusion

[000477] The study was conducted at multiple study sites and conducted in compliance with Good Clinical Practice standards. Ten subjects were treated with Isopropyl Myristate. Two weeks after the treatment, each subject was re-assessed by gravimetric sweat measurement.

[000478] On average, subjects in the Isopropyl Myristate group had a reduction in sweat production of 103 mg two weeks after treatment as measured by gravimetric sweat measurement. In contrast, subjects treated with the placebo had a 53 mg reduction in sweat production as measured by gravimetric sweat measurement. Therefore, subjects treated with Isopropyl Myristate had a 195% greater reduction in sweat production than the subjects in the control group.

[000479] It was also determined what percent of study subjects receiving either Isopropyl Myristate or placebo experienced at least a 30% reduction in sweat production when compared to levels measured at the Baseline visit. It was found that 55% of subjects treated with Isopropyl Myristate had at least a 30% reduction in sweat production when compared to levels at the Baseline visit. This contrasts with only 29% of subjects in the control group that had at least a 30% reduction in sweat production when compared to levels at the Baseline visit. Therefore, by this assessment subjects treated with Isopropyl Myristate had a 191% greater effectiveness in reducing sweat production than those subjects treated

with placebo.

[000480] Given these data, it is concluded that Isopropyl Myristate is (i) biologically active in reducing sweat production, (ii) is an anti-perspirant substance, and (iii) may be used effectively in treating hyperhidrosis.

Example 10: Clinical Study to Evaluate Effect of Propylparaben on Axillary Sweating

Study Design Summary

[000481] The purpose of the study was to determine if Propylparaben is biologically active in reducing sweating. Subjects were selected who believed they sweated excessively and who demonstrated excessive sweating by gravimetric sweat measurement. Some subjects received treatment with the potentially biologically active substance and some subjects received treatment with a placebo, i.e. water. Neither the subject nor the investigator knew which treatment the subject was receiving.

[000482] Two weeks after a single treatment, subjects were re-assessed by gravimetric sweat measurement to determine the degree of sweat reduction. A comparison of post-treatment sweat production between the treatment groups was made to determine the degree of sweat reduction by the potentially biologically active substance.

Study Subject Inclusion / Exclusion Criteria

[000483] The study enrolled subjects based on the following criteria:

Inclusion Criteria

- able to understand and give written informed consent
- ages 18 - 70 years of age
- diagnosis of moderate to severe primary axillary hyperhidrosis
- Hyperhidrosis Disease Severity Scale score of ≥ 3 (the HDSS scale is described below)
- ≥ 50 mg of sweat production/axilla in 5 minutes as measured gravimetrically
- willingness to use only over-the-counter deodorants during the course of the study
- willingness to shave underarms prior to each study visit
- female subjects must have a negative urine pregnancy test and be non-lactating at the initial ("Baseline") study site visit
- patients should be in good general health as determined by the investigator and free of

any disease that may interfere with study evaluations

Exclusion Criteria

- diagnosis of secondary hyperhidrosis (that is, hyperhidrosis due to another medical condition such as hyperthyroidism, cancer, tuberculosis, malaria, or other infection)
- signs of infection in the axilla
- skin affliction in the axilla requiring medical treatment
- application of topical medication to the treatment area within 14 days prior to treatment
- 20% aluminum hydrochloride, e.g. Drysol[®], in 2 weeks prior of Baseline
- oral anticholinergic treatment (e.g., Benadryl, Atarax, Chlortrimeton, and Robinul) in prior 2 weeks
- use of antiperspirants, deodorants, powders or lotions in the 2 days prior to Baseline
- botulinum toxin treatment in prior 9 months
- history of surgery for axillary hyperhidrosis
- participation in another investigational drug trial or receiving any investigational treatment(s) within 30 days of Baseline
- alcohol or drug abuse within the past 3 years
- female subjects who are pregnant or are nursing a child
- psychiatric disease interfering with the patient's ability to give informed consent
- use of axillary depilatories, e.g Nair[®], Veet[®]
- use of axillary epilation (waxing, laser, electrolysis) within 1 week of Baseline
- refusal or inability to comply with the requirements of the protocol for any reason

Treatment and Assessment Methods

Clinical Visits

[000484] Prior to scheduling an initial visit to the investigator's study site, potential participants were queried with regards to their use of anti-perspirants, topical medications, or depilatory products in the axilla. Subjects who met Exclusion Criteria were not scheduled. Potential participants were instructed not to use such products and to shave his or her underarms prior to the Baseline study visit.

[000485] At the Baseline study visit, prior to participating in any aspect of the study, each subject was fully informed, both verbally and in writing, of the conduct and

consequences of the study. Each subject signed the written Informed Consent Form prior to the conduct of the screening evaluation to determine whether the subject was potentially eligible for the study. A verbal screening evaluation and gravimetric sweat measurement were performed to determine if the subject met the Inclusion Criteria but did not meet the Exclusion Criteria.

The Hyperhidrosis Disease Severity Scale

[000486] The subject was asked to rate the perceived severity of the subject's disease by selecting the one sentence that best describes the current level to which subject's underarm sweating interferes with the subject's life:

[000487] 0 = My underarm sweating is not noticeable and never interferes with my daily activities.

[000488] 1 = My underarm sweating is noticeable but rarely interferes with my daily activities.

[000489] 2 = My underarm sweating is tolerable but sometimes interferes with my daily activities.

[000490] 3 = My underarm sweating is barely tolerable and frequently interferes with my daily activities.

[000491] 4 = My underarm sweating is barely tolerable and always interferes with my daily activities.

[000492] 5 = My underarm sweating is intolerable and always interferes with my daily activities.

Gravimetric Sweat Measurement Method

[000493] The sweat production of the subject is measured gravimetrically by the following procedure:

- The subject was placed in a room with relatively constant temperature and humidity for at least 30 min.
- The subject was placed in a semi-reclining position with the axilla fully exposed and the arm resting comfortably above the head.
- The subject's axilla was dried gently with a cotton gauze pad.
- The investigator used a forceps to place one filter paper (90 mm diameter) on a balance sensitive to 0.1 mg and recorded its weight.

- The investigator used a forceps to place the measured filter paper on the axilla, covered it with plastic and taped the edges of the bag against the subject's skin with hypoallergenic tape to form a seal around the plastic bag.
- After 5 minutes, the investigator gently removed the tape and plastic from the subject's axilla and then, using forceps, immediately placed the filter paper onto the scale to record its weight. The scale was then dried and zero balanced.
- This measurement was then repeated as described above with the other axilla.

Treatment application

[000494] If the subject was eligible for treatment on this basis, the subject was then treated. For treatment, one of the study preparations (0.3 mL/axilla) was applied topically with a gloved finger by the investigator to the subject's skin of the axilla. The preparation was administered in small increments to avoid run-off. The liquid was rubbed-in until vanished. Each subject who was selected to have a treatment with the potentially biologically active substance had 0.20 mg of Propylparaben applied to each axilla.

[000495] Following treatment, the subject was instructed to shower on the day of treatment immediately prior to going to bed and, in so doing, wash the axilla with soap and water. The subject was instructed not to use any of the following medications:

- Botulinum Toxin containing products applied to the axilla for the course of the study
- Aluminum hydrochloride topical, e.g. Drysol[®] for the course of the study
- Oral anticholinergic treatment (e.g., Benadryl, Atarax, Chlortrimeton, and Robinul) for the course of the study
- Use of antiperspirants, deodorants, powders, or lotions in the 2 days prior to the Baseline visit and 2 days prior to the office visit two weeks following treatment when gravimetric sweat measurement would be conducted.
- Use of antiperspirants, deodorants, powders or lotions for 1 day after the treatment
- Topical medications applied to the treatment area for 5 days following treatment
- Investigational Medications or treatments within 30 days of Baseline and during the course of the study.

[000496] The subject was scheduled for a follow-up office visit two weeks after the treatment. At the follow-up office visit, the subject was questioned as to their compliance with the instructions regarding which medications not to use between treatment and the two

week follow-up office visit. If the subject was non-compliant, the subject was disqualified from the study. If the subject was compliant, the subject was re-assessed using the gravimetric sweat measurement procedure.

Treatment Results and Conclusion

[000497] The study was conducted at multiple study sites and conducted in compliance with Good Clinical Practice standards. Ten subjects were treated with Propylparaben. Two weeks after the treatment, each subject was re-assessed by gravimetric sweat measurement.

[000498] On average, subjects in the Propylparaben group had a reduction in sweat production of 177 mg two weeks after treatment as measured by gravimetric sweat measurement. In contrast, subjects treated with the placebo had a 53 mg reduction in sweat production as measured by gravimetric sweat measurement. Therefore, subjects treated with Propylparaben had a 337% greater reduction in sweat production than the subjects in the control group.

[000499] It was also determined what percent of study subjects receiving either Propylparaben or placebo experienced at least a 30% reduction in sweat production when compared to levels measured at the Baseline visit. It was found that 70% of subjects treated with Propylparaben had at least a 30% reduction in sweat production when compared to levels at the Baseline visit. This contrasts with only 29% of subjects in the control group that had at least a 30% reduction in sweat production when compared to levels at the Baseline visit. Therefore, by this assessment subjects treated with Propylparaben had a 245% greater effectiveness in reducing sweat production than those subjects treated with placebo.

[000500] Given these data, it is concluded that Propylparaben is (i) biologically active in reducing sweat production, (ii) is an anti-perspirant substance, and (iii) may be used effectively in treating hyperhidrosis.

Example 11: Anti-wrinkle effects of “Emulsion V” Nanoparticle Composition

Study Design Summary

[000501] The purpose of the study was to determine if Emulsion V is biologically active in reducing Lateral Canthal Lines (Crow’s Feet Wrinkles). Subjects were selected who demonstrated moderate to severe Lateral Canthal Lines on contraction (i.e., while smiling) as assessed by the investigator. All subjects received treatment with the potentially biologically

active formulation.

[000502] After a single treatment at Baseline subjects were re-assessed by the investigator using an Investigator's Global Assessment ("IGA") score to determine the severity of the subject's Crows Feet at Week 1, 2, 4, 8, and Week 12, respectively. A comparison of post-treatment wrinkle severity to the Baseline score was made to determine the degree of wrinkle reduction by the potentially biologically active formulation.

Study Subject Inclusion / Exclusion Criteria

[000503] The study enrolled adult male and female subjects diagnosed with moderate to severe Crow's Feet wrinkles on contraction based on the following criteria:

Inclusion Criteria

- able to understand and give written informed consent
- 30 - 70 years of age
- mild to moderate Crow's Feet wrinkles (IGA 2-3) at rest
- moderate to severe Crow's Feet (IGA 3-4) on contraction
- willingness to refrain from the use of facial fillers, retinoids, injectible botulinum products, laser treatments, or any product affecting skin remodeling or that might cause an active dermal response during the course of the study
- subjects should be in good general health as determined by the investigator and free of any disease that may interfere with study evaluations or the Investigational Product

Exclusion Criteria

- botulinum toxin treatment in the prior 6 months
- history of peri-ocular surgery, brow lift or related procedures
- soft tissue augmentation or any procedures affecting the lateral canthal region in the prior 12 months
- dermabrasion or laser treatment in the periocular region in the last 6 months
- topical prescription-strength retinoids in the prior 3 months
- application of any topical prescription medication to the treatment area within 14 days prior to treatment
- subjects on clinically significant, concomitant drug therapy
- present or history of neuromuscular disease, eyelid ptosis, muscle weakness or paralysis

- systemic aminoglycoside use in the week prior to treatment application
- participation in another investigational drug trial or receiving any investigational treatment(s) within 30 days of Baseline
- alcohol or drug abuse within the past 3 years
- female subjects who are pregnant or are nursing a child
- psychiatric disease interfering with the subject's ability to give informed consent
- refusal or inability to comply with the requirements of the protocol for any reason

Treatment and Assessment Methods

Clinical Visits

[000504] Prior to participating in any aspect of the study, each subject was fully informed, both verbally and in writing, of the conduct and consequences of the study. Each subject signed the written Informed Consent Form prior to the conduct of the screening evaluation to determine whether the subject was potentially eligible for the study. The investigator recorded the right and left Investigator's Global Assessment score of Crow's Feet, both, "at rest" and "on contraction". Prior to scheduling an initial visit to the investigator's study site, potential participants were queried with regards to their use of topical medications or prior cosmetic procedures to the treatment area. Subjects who met Exclusion Criteria were not enrolled.

The Investigator's Global Assessment Score

[000505] The subject was asked to make an expressionless face for the "at rest" assessment.

[000506] The subject was asked to produce a maximally exaggerated smile for the "on contraction" assessment.

Table 3: IGA Score Standard

Score	Grade	Description
0	Absent	No visible wrinkles
1	Minimal	Very fine wrinkles (that are barely visible)
2	Mild	Fine wrinkles (that are shallow)
3	Moderate	Moderate wrinkles (that are moderately deep)
4	Severe	Severe wrinkles (that are severely deep)

Treatment application

[000507] If the subject was eligible for treatment on this basis, the subject was then treated. Emulsion V contained Emulsifying Wax, Gelatin Phosphate Buffer Solution, Isopropyl Myristate, Labrafac Lipophile, Methylparaben, Mineral Oil Heavy Viscosity Range, Polysorbate 80, Propylparaben, Purified Water, Sodium Chloride Injection, and White Petrolatum. All ingredients are either NF or USP grade. The average diameter (e.g., particle size) of nanoparticles contained in the Emulsion V empty nanoparticle composition was approximately 77.1 nm.

[000508] For treatment, the subject was instructed to close his/her eyes which were then covered with an absorbent paper or cloth. The clinical investigator then applied the study medication using a latex-gloved finger to the skin of the periorbital region in the distribution of the muscles responsible for the Crow's Feet wrinkles. The preparation was administered in small increments to avoid run-off. The liquid was rubbed-in until vanished.

[000509] The subject was scheduled for follow-up office visits 1, 2, 4, 8, and 12 weeks after the treatment. At the follow-up office visits, the subject was questioned as to their compliance with the instructions regarding medications and procedures not to use after treatment that might interfere with the wrinkle assessment. If the subject was non-compliant, the subject was disqualified from the study. If the subject was compliant, the subject was re-assessed using the Investigators Global Assessment score.

Treatment Results and Conclusion

[000510] The study was conducted at multiple study sites and conducted in compliance with Good Clinical Practice standards. 31 subjects were treated with Emulsion V. After treatment, each subject was re-assessed by the Investigators Global Assessment score at Week 1, 2, 4, 8, and Week 12.

[000511] On average, subjects treated with Emulsion V had a reduction in their wrinkle score as shown in the table below.

Table 4: Percentage Wrinkle Reduction

	Wk 01	Wk 02	Wk 04	Wk 08	Wk 12
At Rest	-10%	-15%	-10%	-14%	-15%
On Contraction	-12%	-19%	-18%	-25%	-24%

[000512] As can be seen, patients treated with Emulsion V experienced an improvement of up to 15% when assessed "at rest". The improvement was evident as early as Week 2. In addition, participants showed an even greater improvement of up to 25% in their wrinkle assessment "on contraction".

[000513] Given these data, it is concluded that Emulsion V is (i) biologically active in reducing Lateral Canthal Lines, (ii) is an anti-wrinkle formulation, and (iii) may be used effectively in treating Crow's Feet.

Equivalents

[000514] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. The scope of the present invention is not intended to be limited to the above Description, but rather is as set forth in the following claims:

Claims

We claim:

1. A method comprising steps of:
administering to a subject an empty nanoparticle composition, wherein the empty nanoparticle composition does not contain a therapeutically effective amount of any known therapeutic agents or independently active biologically active agents.
2. The method of claim 1, wherein the step of administering comprises administering topically.
3. The method of claim 2, wherein the step of administering comprises applying to the subject's skin.
4. The method of claim 2, wherein the step of administering comprises applying to surfaces of the subject's skin.
5. The method of claim 1, wherein the subject is a patient susceptible to or suffering from a disease, disorder or condition.
6. The method of claim 1, wherein the subject is a patient susceptible to or suffering from a condition or disorder associated with a dermal structure.
7. The method of claim 5 or 6, wherein the subject is human.
8. The method of claim 6, wherein the condition or disorder associated with a dermal structure is a condition or disorder associated with sebaceous glands.
9. The method of claim 8, wherein the condition or disorder of the sebaceous glands is acne.
10. The method of claim 9, wherein the step of administering comprises administering the

empty nanoparticle composition so that acne is reduced or onset is delayed.

11. The method of claim 6, wherein the condition or disorder associated with a dermal structure is a condition or disorder associated with sweat glands.
12. The method of claim 11, wherein the condition or disorder associated with a dermal structure is a unwanted sweating.
13. The method of claim 12, wherein the step of administering comprises administering the empty nanoparticle composition as an anti-perspirant.
14. The method of claim 12, wherein the step of administering comprises administering the empty nanoparticle composition as a deodorant.
15. The method of claim 12, wherein the step of administering comprises administering the empty nanoparticle composition so that sweating is reduced or onset is delayed.
16. The method of claim 11 wherein the condition or disorder associated with a dermal structure is a excessive sweating.
17. The method of claim 16, wherein the step of administering comprises administering the empty nanoparticle composition as an anti-perspirant.
18. The method of claim 16 wherein the step of administering comprises administering the empty nanoparticle composition as a deodorant.
19. The method of claim 16, wherein the step of administering comprises administering the empty nanoparticle composition so that sweating is reduced or onset is delayed.
20. The method of claim 11, wherein the condition or disorder associated with the sweat glands is hyperhidrosis.
21. The method of claim 20, wherein the step of administering comprises administering

the empty nanoparticle composition as an anti-perspirant.

22. The method of claim 20, wherein the step of administering comprises administering the empty nanoparticle composition as a deodorant.
23. The method of claim 20, wherein the step of administering comprises administering the empty nanoparticle composition so that sweating is reduced or onset is delayed.
24. The method of claim 11, wherein the condition or disorder associated with the sweat glands is bromhidrosis.
25. The method of claim 24, wherein the step of administering comprises administering the empty nanoparticle composition as an anti-perspirant.
26. The method of claim 25, wherein the step of administering comprises administering the empty nanoparticle composition as a deodorant.
27. The method of claim 25, wherein the step of administering comprises administering the empty nanoparticle composition so that sweating is reduced or onset is delayed.
28. The method of claim 6, wherein the condition or disorder associated with a dermal structure is a condition or disorder is unwanted body odor.
29. The method of claim 28, wherein the step of administering comprises administering the empty nanoparticle composition as an anti-perspirant.
30. The method of claim 28, wherein the step of administering comprises administering the empty nanoparticle composition as a deodorant.
31. The method of claim 6, wherein the condition or disorder associated with a dermal structure is a condition or disorder associated with hair follicles.
32. The method of claim 31, wherein the condition or disorder associated with hair

follicles is hair loss.

33. The method of claim 32, wherein the step of administering comprises administering the empty nanoparticle composition so that hair loss is reduced or onset is delayed.
34. The method of claim 5, wherein the condition or disorder associated with a dermal structure is selected from the group consisting of acne, hyperhidrosis, unwanted sweating, bromhidrosis, body odor, chromhidrosis, excess sebum-producing disorders, seborrhea, seborrheic dermatitis, rosacea, hair loss, psoriasis, dermal infections, viral infection, bacterial infection, fungal infection, actinic keratosis, eczematous dermatitis, atopic dermatitis, burns, Raynaud's phenomenon, lupus erythematosus, hyperpigmentation disorders, melasma, hypopigmentation disorders, vitiligo, skin cancer, squamous cell skin carcinoma, basal cell skin carcinoma, arthritis, osteoarthritis, bruxism, cervical neck pain, dry eyes, gastrointestinal disorders, achalasia, esophageal spasm, gastroparesis, spasm of the sphincter of oddi, anal fissure, anismus, lateral epicondylitis, back pain, lower back pain, upper back pain, masseter muscle hypertrophy, facial nerve disorders, facial wrinkles, wrinkles involving the forehead, glabellar, rhytids and/or periorbital regions, unsightly facial expressions, neck lines, hyperfunctional facial lines, hyperkinetic facial lines, platysma bands, neuromuscular disorders and conditions involving muscular spasm or contracture, facial palsy such as hemi facial spasm, cerebral palsy, spasticity due to stroke, blepharospasm, facial contracture, dystonia, cervical dystonia, laryngeal dystonia, oromandibular dystonia, writer's cramp, neuralgias, trigeminal neuralgia, neuropathic pain, Parkinson's disease, plantar fasciitis pain, prostate hyperplasia, headache, migraine, essential headache, cervicogenic headache, tension headache, prostatic disorders, prostatic pain, prostatic hypertrophy, restless leg syndrome, rhinitis, allergic rhinitis, sialorrhea, skin pruritis, strabismus, temporomandibular joint ("TMJ") syndrome, tics, Tourette's syndrome, hemifacial spasm, tremor, essential tremor, urinary bladder dysfunction, detrusor sphincter dysnergia, painful bladder, bladder spasticity, overactive bladder, vaginismus, spasticity such as that resulting from multiple sclerosis, retroorbital muscle, various ophthalmologic conditions, and/or combinations thereof.

35. The method of claim 6, wherein the condition or disorder associated with a dermal structure is selected from the group consisting of acne, hyperhidrosis, unwanted sweating, bromhidrosis, body odor, chromhidrosis, excess sebum-producing disorders, seborrhea, seborrheic dermatitis, rosacea, hair loss, psoriasis, dermal infections, viral infection, bacterial infection, fungal infection, actinic keratosis, eczematous dermatitis, atopic dermatitis, burns, hyperpigmentation disorders, melasma, hypopigmentation disorders, vitiligo, skin cancer, squamous cell skin carcinoma, basal cell skin carcinoma, skin pruritis, and any combinations thereof.
36. The method of claim 6, wherein the condition or disorder associated with a dermal structure is selected from the group consisting of facial wrinkles, wrinkles involving the forehead, glabellar, rhytids and/or periorbital regions, unsightly facial expressions, neck lines, hyperfunctional facial lines, hyperkinetic facial lines, platysma bands and any combination thereof.
37. The method of claim 6, wherein the empty nanoparticle composition is administered to the skin of the patient.
38. The method of claim 1, wherein the empty nanoparticle composition comprises a population of particles, wherein the majority of particles have diameters between approximately 10 and approximately 300 nanometers.
39. The method of claim 1, wherein the empty nanoparticle composition comprises a population of particles, wherein the majority of particles have diameters between approximately 60 and approximately 120 nanometers.
40. The method of claim 1, wherein the empty nanoparticle composition comprises a population of particles, wherein the majority of particles have diameters between approximately 70 and approximately 100 nanometers.
41. The method of claim 1, wherein the empty nanoparticle composition comprises at least one aqueous dispersion medium, at least one oil, and at least one surfactant.

42. The method of claim 41, wherein the ratio of oil to surfactant ranges between 0.1:1 to 2:1.
43. The method of claim 41, wherein the ratio of oil to surfactant ranges between 0.1:1 to 1:1.
44. The method of claim 41, wherein the ratio of oil to surfactant ranges between 0.5:1 to 1:1.
45. The method of claim 41, wherein the oil is selected from the group consisting of almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macadamia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, wheat germ oils, 1349 oil and combinations thereof.
46. The method of claim 41, wherein the oil is 1349 oil.
47. The method of claim 41, wherein the oil is a medium chain triglyceride.
48. The method of claim 47, wherein the medium chain triglyceride is an acid containing 6–12 carbons atoms.
49. The method of claim 48, wherein the acid is selected from caprylic acid, octanoic acid, capric acid, decanoic acid, and lauric acid.
50. The method of claim 41, wherein the surfactant is selected from the group consisting of: pemulen; phosphoglycerides; phosphatidylcholines; dipalmitoyl

phosphatidylcholine (DPPC); dioleoylphosphatidyl ethanolamine (DOPE); dioleoyloxypropyltriethylammonium (DOTMA); dioleoylphosphatidylcholine; cholesterol; cholesterol ester; diacylglycerol; diacylglycerolsuccinate; diphosphatidyl glycerol (DPPG); hexanedecanol; fatty alcohols such as polyethylene glycol (PEG); polyoxyethylene-9-lauryl ether; a surface active fatty acid, such as palmitic acid or oleic acid; fatty acids; fatty acid monoglycerides; fatty acid diglycerides; fatty acid amides; sorbitan trioleate (SPAN[®]85) glycocholate; sorbitan monolaurate (SPAN[®]20); polysorbate 20 (TWEEN[®]20); polysorbate 60 (TWEEN[®]60); polysorbate 65 (TWEEN[®]65); polysorbate 80 (TWEEN[®]80); polysorbate 85 (TWEEN[®]85); super-refined polysorbate 20 (SR TWEEN[®]20); super-refined polysorbate 60 (SR TWEEN[®]60); super-refined polysorbate 65 (SR TWEEN[®]65); super-refined polysorbate 80 (SR TWEEN[®]80); super-refined polysorbate 85 (SR TWEEN[®]85); polyoxyethylene monostearate; surfactin; a poloxomer; a sorbitan fatty acid ester such as sorbitan trioleate; lecithin; lysolecithin; phosphatidylserine; phosphatidylinositol; sphingomyelin; phosphatidylethanolamine (cephalin); cardiolipin; phosphatidic acid; cerebrosides; dicetylphosphate; dipalmitoylphosphatidylglycerol; stearylamine; dodecylamine; hexadecyl-amine; acetyl palmitate; glycerol ricinoleate; hexadecyl stearate; isopropyl myristate; tyloxapol; poly(ethylene glycol)5000-phosphatidylethanolamine; poly(ethylene glycol)400-monostearate; phospholipids; synthetic and/or natural detergents having high surfactant properties; deoxycholates; cyclodextrins; chaotropic salts; ion pairing agents; and combinations thereof.

51. The method of claim 41, wherein the surfactant is Tween-80.

52. The method of claim 41, S.R. Tween-80.

53. The method of claim 1, wherein the step of administration does not require a step of altering or changing the skin.

54. The method of claim 1, wherein the step of administration does not require use of skin permeation enhancers or abrasives.

55. The method of claim 1, wherein the empty nanoparticle composition is formulated as a cream.
56. The method of claim 55, wherein the cream formulation is prepared by admixing the empty nanoparticle composition with a cream composition.
57. The method of claim 1, wherein the empty nanoparticle composition is formulated as a lotion.
58. The method of claim 57, wherein the lotion formulation is prepared by admixing the empty nanoparticle composition with a lotion composition.
59. The method of claim 1, wherein the empty nanoparticle composition is formulated as a composition selected from the group consisting of a gel, powder, ointment, liniment, paste, deodorant, sunscreen, and combinations thereof.
60. The method of claim 1, wherein the empty nanoparticle composition is admixed with a known therapeutic agent for treatment of the condition or disorder associated with a dermal structure.
61. A method comprising steps of:
 providing a patient susceptible to or suffering from unwanted sweating;
 administering to the patient an empty nanoparticle composition, wherein the empty nanoparticle composition does not contain any known therapeutic agents or independently active biologically active agents.
62. The method of claim 61, wherein the step of administering comprises administering the empty nanoparticle composition as an anti-perspirant.
63. The method of claim 61, wherein the step of administering comprises administering the empty nanoparticle composition as a deodorant.
64. The method of claim 61, wherein the step of administering comprises administering

the empty nanoparticle composition so that sweating is reduced or onset is delayed.

65. A method comprising steps of:

providing a patient susceptible to or suffering from body odor;

administering to the patient an empty nanoparticle composition, wherein the empty nanoparticle composition does not contain any known therapeutic agents or independently active biologically active agents.

66. The method of claim 65, wherein the step of administering comprises administering the empty nanoparticle composition as an anti-perspirant.

67. The method of claim 65, wherein the step of administering comprises administering the empty nanoparticle composition as a deodorant.

68. The method of claim 65, wherein the step of administering comprises administering the empty nanoparticle composition so that body odor is reduced or onset is delayed.

69. A method comprising steps of:

administering to a test system for sweat production a component of an empty nanoparticle composition that is not known to have biological activity associated with sweating;

detecting in the test system an effect on sweating such that levels of hyperhidrosis sweating are not more than 80% of levels observed under otherwise identical conditions absent the component.

70. The method of claim 69, wherein the step of detecting comprises detecting in the test system an effect on hyperhidrosis such that levels of hyperhidrosis are not more than 70% of levels observed under otherwise identical conditions absent the component.

71. The method of claim 69, wherein the step of detecting comprises detecting in the test system an effect on hyperhidrosis such that levels of hyperhidrosis are not more than 60% of levels observed under otherwise identical conditions absent the component.

72. The method of claim 69, wherein the step of detecting comprises detecting in the test system an effect on hyperhidrosis such that levels of hyperhidrosis are not more than 50% of levels observed under otherwise identical conditions absent the component.
73. The method of claim 69, wherein the step of administering comprises administering the component in a composition that substantially lacks nanoparticle structure.
74. The method of claim 69, wherein the step of administering comprises administering the component in a composition that is not an emulsion.
75. A method comprising steps of:
- providing a patient susceptible to or suffering from a condition or disorder associated with a dermal structure;
 - administering to the patient at least one isolated component of an empty nanoparticle composition, wherein the empty nanoparticle composition does not contain any known therapeutic agents or independently active biologically active agents;
 - such that the incidence or severity of one or more symptoms of the condition or disorder associated with a dermal structure is reduced or onset is delayed.
76. The method of claim 75, wherein the condition or disorder associated with a dermal structure is a condition or disorder associated with sebaceous glands.
77. The method of claim 76, wherein the condition or disorder of the sebaceous glands is acne.
78. The method of claim 77, wherein the step of administering comprises administering the at least one isolated component of an empty nanoparticle composition so that acne is reduced or onset is delayed.
79. The method of claim 75, wherein the condition or disorder associated with a dermal structure is a condition or disorder associated with sweat glands.

80. The method of claim 78, wherein the condition or disorder associated with the sweat glands is hyperhidrosis.
81. The method of claim 80, wherein the step of administering comprises administering the at least one isolated component of an empty nanoparticle composition as an anti-perspirant.
82. The method of claim 80, wherein the step of administering comprises administering the at least one isolated component of an empty nanoparticle composition as a deodorant.
83. The method of claim 80, wherein the step of administering comprises administering the at least one isolated component of an empty nanoparticle composition so that sweating is reduced or onset is delayed.
84. The method of claim 79, wherein the condition or disorder associated with the sweat glands is bromhidrosis.
85. The method of claim 84, wherein the step of administering comprises administering the at least one isolated component of an empty nanoparticle composition as an anti-perspirant.
86. The method of claim 84, wherein the step of administering comprises administering the at least one isolated component of an empty nanoparticle composition as a deodorant.
87. The method of claim 84, wherein the step of administering comprises administering the at least one isolated component of an empty nanoparticle composition so that sweating is reduced or onset is delayed.
88. The method of claim 75, wherein the condition or disorder associated with a dermal structure is a condition or disorder associated with hair follicles.

89. The method of claim 88, wherein the condition or disorder associated with hair follicles is hair loss.
90. The method of claim 89, wherein the step of administering comprises administering the at least one isolated component of an empty nanoparticle composition so that hair loss is reduced or onset is delayed.
91. The method of claim 75, wherein the at least one isolated component of an empty nanoparticle composition is admixed with a known therapeutic agent for treatment of the condition or disorder associated with a dermal structure.
92. A method comprising steps of:
- providing a patient susceptible to or suffering from unwanted sweating;
 - administering to the patient at least one isolated component of an empty nanoparticle composition, wherein the empty nanoparticle composition does not contain any known therapeutic agents or independently active biologically active agents;
 - such that the incidence or severity of the unwanted sweating is reduced or onset is delayed.
93. The method of claim 92, wherein the step of administering comprises administering the empty nanoparticle composition as an anti-perspirant.
94. The method of claim 92, wherein the step of administering comprises administering the empty nanoparticle composition as a deodorant.
95. A method comprising steps of:
- providing a patient susceptible to or suffering from body odor;
 - administering to the patient at least one isolated component of an empty nanoparticle composition, wherein the empty nanoparticle composition does not contain any known therapeutic agents or independently active biologically active agents;
 - such that the incidence or severity of the body odor is reduced or onset is

delayed.

96. The method of claim 95, wherein the step of administering comprises administering the empty nanoparticle composition as an anti-perspirant.

97. The method of claim 95, wherein the step of administering comprises administering the empty nanoparticle composition as a deodorant.

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2012/022277

A. CLASSIFICATION OF SUBJECT MATTER
 INV. A61K9/51
 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

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, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/149868 A2 (UNIV CALIFORNIA [US]; KIM JENNY [US]; FRIEDMAN ADAM [US]; MODLIN ROBER) 27 December 2007 (2007-12-27) paragraphs [0012], [0013], [0064], [0065] -----	1-9, 34, 35, 37-45, 47-60, 73, 74, 76-78
X	WO 2010/087964 A2 (NANOBIO CORP [US]; SUTCLIFFE JOYCE A [US]; CIOTTI SUSAN M [US]; BAKER) 5 August 2010 (2010-08-05) page 7, lines 4-10; claim 1 ----- -/-	1-9, 34, 35, 37-45, 47-60, 73, 74, 76-78



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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

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"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

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2012/022277

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/158687 A1 (ANTERIOS INC [US]; EDELSON JONATHAN [US]; KOTYLA TIMOTHY [US]; ZHANG B) 30 December 2009 (2009-12-30) claim 151	1-97
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2012/022277

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