Title: COMPOSITIONS COMPRISING A RETINOID AND A LINCOSAMIDE ANTIBIOTIC FOR USE IN TREATING ROSACEA

Abstract: The invention provides compositions containing a retinoid and a lincosamide antibiotic for the treatment or amelioration of rosacea. The invention also provides methods for treating or ameliorating rosacea using compositions containing a retinoid and a lincosamide antibiotic.
COMPOSITIONS COMPRISING A RETINOID AND A LINCOSAMIDE ANTIBIOTIC FOR USE IN TREATING ROSACEA

FIELD OF THE INVENTION

The invention relates to compositions containing a retinoid and a lincosamide antibiotic for the treatment or amelioration of rosacea. The invention also relates to methods for treating or ameliorating rosacea using compositions containing a retinoid and a lincosamide antibiotic.

BACKGROUND OF THE INVENTION

Rosacea is a common chronic skin disease affecting up to 10% of fair-skinned individuals (Wolff et al., Fitzpatrick’s Color Atlas and Synopsis of Clinical Dermatology 8 (2005)). The disease is characterized by inflammation and vascular abnormalities of the cheeks, nose, chin, forehead, or eyelids, and can encompass various combinations of cutaneous signs including flushing, erythema, telangiectasia (dilation of superficial blood vessels on the face), papules, pustules, edema, ocular lesions, and rhinophyma (a red lobulated nose). The exact etiology of cutaneous rosacea is unknown, but is thought to be characterized by persistent vasodilatation, increased vascular permeability, and vascular hyper-reactivity of the microcirculation of the central part of the face. In fact, dermal inflammation, elastin and collagen degeneration, and alteration of the cutaneous vasculature are important findings in the histopathology of the disease (Pelle et al., 2004, J. Am. Acad. Dermatol. 51(4): 499-512).

The National Rosacea Society Expert Committee has proposed a classification and staging system for the disease, which defines four subtypes: erythematotelangiectatic, papulopustular, phymatous, and ocular (Wilkin et al., 2002, J. Am. Acad. Dermatol. 46(4): 584-87).

The erythematotelangiectatic subtype of rosacea is primarily characterized by flushing and persistent central facial erythema (redness of the skin). The appearance of telangiectases (small dilated blood vessels near the surface of the skin or mucous membranes that measure between about 0.5 to 1 mm in diameter) is common but not essential for a diagnosis of this rosacea subtype. Patients may also experience central facial edema (abnormal accumulation of fluid beneath the skin), stinging, and burning
sensations, as well as roughness or scaling. A history of flushing alone is common among patients with this subtype of rosacea.

The papulopustular subtype of rosacea is characterized by persistent central facial erythema with transient papules or pustules or both, the latter of which may or may not have a central facial distribution. This subtype of rosacea is often associated with the erythematotelangiectatic subtype.

The phymatous subtype of rosacea is characterized by thickening skin, irregular surface nodularities, and enlargement of the nose. This subtype of rosacea is often seen in combination with the erythematotelangiectatic and papulopustular subtypes, with the presence of persistent erythema and telangiectases.

The ocular subtype of rosacea is characterized by interpalpebral hyperemia and conjunctival, burning, stinging, light sensitivity, dryness, telangiectases of the conjunctiva and lid margin, and periocular erythema.

Although evidence demonstrates the lack of a clear infectious origin, oral and topical antibiotics (such as tetracyclines, macrolides, and metronidazole) may be effective in treating the papulopustular subtype of rosacea. In humans and animal models, chronic therapy with topical tretinoin promotes remodeling of the collagen in the papillary and reticular dermis and decreases dermal inflammation (Kligman et al., 1996, Arch. Dermatol. Res. 288(10): 615-20; Voorhees et al., 1990, J. Int. Med. Res. 18(Suppl. 3):26C-28C). Retinoids also produce inhibitory effects on vascular endothelial growth factor production by cultured human skin keratinocytes (Diaz et al., 2000, J. Biol. Chem. 27(1): 642-50). The clinical response to topical retinoids is typically delayed, with symptom abatement beginning 1-2 months after the commencement of therapy.

Despite the availability of reportedly efficacious treatment options for the papulopustular rosacea subtype, the need for efficacious and well tolerated pharmaceutical products for the treatment of rosacea remains.

SUMMARY OF THE INVENTION

The invention provides a method for treating or ameliorating the topical symptoms associated with rosacea comprising topically administering to a patient in need
thereof a therapeutically effective amount of a composition comprising a retinoid and a lincosamide antibiotic.

The invention also provides the use of a composition comprising a retinoid and a lincosamide antibiotic for the manufacture of a medicament for treating or ameliorating rosacea.

The invention further provides a composition comprising a retinoid and a lincosamide antibiotic for the treatment or amelioration of rosacea.

In some embodiments, the present disclosure provides a method for treating or ameliorating the topical symptoms associated with rosacea comprising topically administering to a patient in need thereof a therapeutically effective amount of a composition comprising a retinoid and a lincosamide antibiotic.

In certain embodiments, the lincosamide antibiotic is selected from the group consisting of clindamycin, clindamycin phosphate, and pharmaceutically acceptable salts thereof.

In certain embodiments, the lincosamide antibiotic is clindamycin phosphate.

In some embodiments, the retinoid is tretinoin or a pharmaceutically acceptable salt thereof.

In some embodiments, the composition comprises about 0.02 to about 0.03 weight percent of retinoid and about 1.0 to about 1.5 weight percent of lincosamide antibiotic. In particular embodiments, the composition comprises about 0.025 weight percent tretinoin and about 1.2 weight percent clindamycin or clindamycin phosphate.

In some embodiments, the composition further comprises a topically acceptable pharmaceutical carrier.

In certain embodiments, the composition is topically applied to an area of the skin of the patient where the symptoms are manifested.

In some embodiments, the composition is topically applied at least once a day for at least twelve weeks.

In some embodiments, the rosacea is the erythematotelangiectatic subtype.

In some embodiments, the treatment results in a reduction in erythema. In some embodiments, the treatment results in a reduction in telangiectasias.

In some embodiments, the composition is in the form of a gel, liquid suspension,
emulsion cream, ointment, or powder.

In some embodiments, the composition suitable use for any of the methods described herein comprises:

(a) about 0.025 weight percent tretinoin;

(b) about 1.2 weight percent clindamycin or clindamycin phosphate;

(c) a hydrophilic pharmaceutically acceptable lightly cross-linked polyacrylic acid polymer compatible with the compounds of (a) and (b);

(d) a pharmaceutically acceptable base to adjust pH;

(e) optionally a water miscible solvent; and

(f) optionally a preservative; and

wherein the composition has a pH of about 3 to about 9 and a viscosity of less than about 15,000 cP.

In some embodiments, the present disclosure provides for the use of a composition comprising a retinoid and a lincosamide antibiotic for the manufacture of a medicament for treating or ameliorating rosacea.

In some embodiments, the lincosamide antibiotic is selected from the group consisting of clindamycin, clindamycin phosphate, and pharmaceutically acceptable salts thereof.

In some embodiments, the lincosamide antibiotic is clindamycin phosphate.

In some embodiments, the retinoid is tretinoin or a pharmaceutically acceptable salt thereof.

In some embodiments, the composition comprises about 0.02 to about 0.03 weight percent of retinoid and about 1.0 to about 1.5 weight percent of lincosamide antibiotic. In other embodiments, the composition comprises about 0.025 weight percent tretinoin and about 1.2 weight percent clindamycin or clindamycin phosphate.

In some embodiments, the composition further comprises a topically acceptable pharmaceutical carrier.

In some embodiments, the composition is topically applied to an area of the skin of the patient where the symptoms are manifested.

In certain embodiments, the composition is topically applied at least once a day for at least twelve weeks.
In some embodiments, the rosacea is the erythematotelangiectatic subtype.
In certain embodiments, the treatment results in a reduction in erythema.
In some embodiments, the treatment results in a reduction in telangiectasias.
In some embodiments, the composition is in the form of a gel, liquid suspension, emulsion cream, ointment, or powder.

In some embodiments, the present disclosure provides a composition comprising a retinoid and a lincosamide antibiotic for the treatment or amelioration of the symptoms of rosacea.

In some embodiments, the lincosamide antibiotic is selected from the group consisting of clindamycin, clindamycin phosphate, and therapeutically acceptable salts thereof. In particular embodiments, the lincosamide antibiotic is clindamycin phosphate.

In some embodiments, the retinoid is tretinoin or a pharmaceutically acceptable salt thereof.

In some embodiments, the composition comprises about 0.02 to about 0.03 weight percent of retinoid and about 1.0 to about 1.5 weight percent of lincosamide antibiotic. In particular embodiments, composition comprises about 0.025 weight percent tretinoin and about 1.2 weight percent clindamycin or clindamycin phosphate.

In a further embodiment, the composition further comprises a topically acceptable pharmaceutical carrier.

In a further embodiments, the composition is topically applied to an area of the skin of the patient where the symptoms are manifested.

In a particular embodiment, the composition is topically applied at least once a day for at least twelve weeks.

In a certain embodiments, the rosacea is the erythematotelangiectatic subtype.

In another embodiments, the treatment results in a reduction in erythema.

In some embodiments, the treatment results in a reduction in telangiectasias.

In other embodiments, the composition is in the form of a gel, liquid suspension, emulsion cream, ointment, or powder.

Specific embodiments of the invention will become evident from the following more detailed description of certain embodiments and the claims.
BRIEF DESCRIPTION OF THE DRAWINGS

A better understanding of the invention may be obtained in light of the following drawings which are set forth for illustrative purposes, and should not be construed as limiting the invention in any way.

Figure 1 illustrates a summary of a study designed to assess the efficacy and safety of a clindamycin and tretinoin gel (ZIANA®) for the treatment of papulopustular rosacea.

DETAILED DESCRIPTION OF THE INVENTION

Because acne vulgaris and rosacea share similarities in that both diseases exhibit follicle based inflammation clinically and histologically, clindamycin and tretinoin gel would be expected to be useful for treating the papulopustular subtype of rosacea. In order to test this hypothesis, the efficacy and safety of a combination gel comprising 1.2% clindamycin phosphate and 0.025% tretinoin (ZIANA®, Medicis Pharmaceutical Corporation) was assessed in a double-blind, placebo-controlled two site study of 83 subjects with moderate to severe papulopustular rosacea. Surprisingly, treatment with clindamycin and tretinoin gel produced no significant change in the papulopustule count of study subjects, but showed improvement in physicians' assessment of the erythematotelangiectatic subtype of rosacea and showed nearly significant improvement in the reduction of telangiectases.

1. General Definitions

As utilized in accordance with the present disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings. Unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular.

The term "patient" as used herein refers to a human subject.

A "disease" or "disorder" is any condition that would benefit from treatment using the methods or compositions of the invention. "Disease," "disorder," and "condition" are
used interchangeably herein and include chronic and acute disorders or diseases.

The compositions and methods of the invention can be used to treat or ameliorate the topical symptoms of rosacea. In a preferred method, use, or composition of the invention, the subtype of rosacea being treated or ameliorated is the erythematotelangiectactic subtype of rosacea.

In one method, use, or composition of the invention, the treatment results in a reduction in erythema. In another method, use, or composition of the invention, the treatment results in a reduction in telangiectases.

The term "treat" as used herein refers to both therapeutic treatment and prophylactic or preventative measures. The term "treatment" as used herein refers to the alleviation of symptoms of a disease. Those in need of treatment include those having the disorder as well as those prone to have the disorder or those in which the disorder is to be prevented.

The terms "composition," "topical composition," "therapeutic composition," or "pharmaceutical composition" as used herein refer to a compound or composition capable of inducing a desired therapeutic effect when properly administered to a patient.

The terms "therapeutically acceptable" or "topically acceptable" as used herein refer to one or more formulation materials suitable for accomplishing or enhancing the delivery of a composition of the invention.

The term "pharmaceutically acceptable salt" as used herein refers to a salt of an active compound of the compositions of the invention that possesses essentially the same pharmacological activity as the active compound and which is neither biologically nor otherwise undesirable. A pharmaceutically acceptable salt of a compound is one that, upon administration of a composition of the invention to a subject, is capable of providing the compound or an active metabolite or residue thereof. As known to those of skill in the art, "salts" of the compounds of the compositions of the invention may be derived from inorganic or organic acids and bases.

Examples of acids include, but are not limited to, 4-acetamidobenzoic acid, acetic acid, adipic acid, alginic acid, L-ascorbie acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, butyric acid, (±)-camphoric acid, (±)-camphor-10-sulfonic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, cyclopentanepropionic acid, decanoic acid,
2,2-dichloroacetic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, D-glucoheptonic acid, D-gluconic acid, D-glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycolic acid, heptanoic acid, hexanoic acid, hippuric acid, hydrobromic acid, hydrochloric acid, hydroiodic acid, 2-hydroxyethanesulfonic acid, isethionic, isobutyric acid, DL-lactic acid, lactobionic acid, lauric acid, maleic acid, (−)-L-malic acid, malonic acid, DL-mandelic acid, methanesulfonic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, octanoic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, pantothenic acid, pectic acid, perchloric acid, phenylpropionic acid, phosphoric acid, picric acid, pivalic acid, propionic acid, (−)-L-pyroglutamic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tartaric acid, (+)-L-tartaric acid, thiocyanic acid, toluenesulfonic acid, p-toluene sulfonic acid, and undecylenic acid. Examples of such bases include, but are not limited to, alkali metals (e.g., sodium) hydroxides, alkaline earth metals (e.g., magnesium), hydroxides, ammonia, and compounds of formula NW₄⁺, wherein W is C₁₋₄ alkyl, and the like. For therapeutic use, salts of a compound of the compositions of the invention are contemplated as being pharmaceutically acceptable. However, salts of acids and bases that are non-pharmaceutically acceptable may also be used, for example, in the preparation or purification of a pharmaceutically acceptable compound.

Examples of pharmaceutically acceptable acids suitable for the preparation of pharmaceutically acceptable salts of an active compound include, but are not limited to, acetic acid, adipic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, citric acid, (+)-camphoric acid, (+)-camphor-10-sulfonic acid, dodecylsulfuric acid, D-gluconic acid, D-glucuronic acid, ethanesulfonic acid, fumaric acid, D-glucoheptonic acid, glycerophosphoric acid, hexanoic acid, hydrobromic acid, hydrochloric acid, 2-hydroxyethanesulfonic acid, isobutyric acid, DL-lactic acid, maleic acid, methanesulfonic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, oxalic acid, palmitic acid, propionic acid, succinic acid, sulfuric acid, (+)-L-tartaric acid, thiocyanic acid, p-toluene sulfonic acid, undecylenic acid.
acid, and the like. Other examples of salts include anions of an active compound combined with a suitable cation such as Na\(^+\), NH\(_4\)\(^+\), and NW\(_4\)\(^-\) (wherein W is a C\(_{1-4}\) alkyl group), and the like.

The terms "effective amount" and "therapeutically effective amount" when used in reference to a composition of the invention refer to an amount or dosage sufficient to produce a desired therapeutic result. More specifically, a therapeutically effective amount is an amount of the composition sufficient to inhibit, for some period of time, one or more of the clinically defined pathological processes associated with the condition being treated. The effective amount may vary depending on the specific composition that is being used, and also depends on a variety of factors and conditions related to the patient being treated and the severity of the disorder. The determination of an effective amount or therapeutically effective amount of a given composition is well within the ability of those skilled in the art.

The term "retinoid" as used herein refers to a class of compounds that are chemically related to vitamin A (retinol), and which includes, but is not limited to, retinal (retinaldehyde or vitamin A aldehyde), tretinoin (retinoic acid or vitamin A acid), isotretinoin, tazarotene, adapalene, beclomethasone, alitretinoin, retinyl acetate, and retinyl palmitate (vitamin A palmitate or retinol palmitate). In one method, use, or composition of the invention, the retinoid is tretinoin or a pharmaceutically acceptable salt thereof. In other embodiments of the invention, the retinoid is tazarotene or adapalene. In another embodiment of the invention, the retinoid is any known retinoid with the exception of adapalene.

The term "lincosamide antibiotic" as used herein refers to a class of antibiotics that includes, but is not limited to, lincomycin, clindamycin, clindamycin phosphate, and pirlimycin as well as pharmaceutically acceptable salts thereof. Without wishing to be bound by any particular theory, it is believed that lincosamide antibiotics kill bacteria by binding to bacterial ribosomes and causing premature dissociation of peptidyl-tRNA from the ribosome. In one method, use, or composition of the invention, the lincosamide antibiotic is clindamycin or a pharmaceutically acceptable salt thereof. In another method, use, or composition of the invention, the lincosamide antibiotic is clindamycin hydrochloride. In yet another method, use, or composition of the invention, the
2. **Topical Compositions and Administration Thereof**

Topical or therapeutic compositions comprising a retinoid (such as tretinoin) and a lincosamide antibiotic (such as clindamycin or clindamycin phosphate) are within the scope of the invention. Such topical or therapeutic compositions can comprise a therapeutically effective amount of a retinoid (such as tretinoin) and a lincosamide antibiotic (such as clindamycin or clindamycin phosphate), in admixture with one or more therapeutically or physiologically acceptable formulation agents selected for suitability with the mode of administration. Acceptable formulation materials preferably are nontoxic to recipients at the dosages and concentrations employed.

Topical or therapeutic compositions can contain formulation materials for modifying, maintaining, or preserving, for example, the pH, osmolarity, viscosity, clarity, color, isotonicity, odor, sterility, stability, adsorption, or penetration of the composition.

Suitable formulation materials include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine, or lysine), antimicrobials, antioxidants (such as ascorbic acid, sodium sulfite, or sodium hydrogen-sulfite), buffers (such as borate, bicarbonate, Tris-HCl, citrates, phosphates, or other organic acids), bulking agents (such as mannitol or glycine), chelating agents (such as ethylenediamine tetraacetic acid (EDTA)), complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin, or hydroxypropyl-beta-cyclodextrin), fillers, monosaccharides, disaccharides, and other carbohydrates (such as glucose, mannose, or dextrans), proteins (such as serum albumin, gelatin, or immunoglobulins), coloring and diluting agents, emulsifying agents, hydrophilic polymers (such as polyvinylpyrrolidone), low molecular weight polypeptides, salt-forming counterions (such as sodium), preservatives (such as benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid, or hydrogen peroxide), solvents (such as glycerin, propylene glycol, or polyethylene glycol), sugar alcohols (such as mannitol or sorbitol), suspending agents, surfactants or wetting agents (such as pluronic; PEG; sorbitan esters; polysorbates such as polysorbate 20 or polysorbate 80; triton; tromethamine; lecithin; cholesterol or tyloxapol), stability enhancing agents (such as
sucrose or sorbitol), tonicity enhancing agents (such as alkali metal halides — preferably sodium or potassium chloride — or mannitol sorbitol), delivery vehicles, diluents, excipients and/or pharmaceutical adjuvants (see, e.g., REMINGTON'S PHARMACEUTICAL SCIENCES (18th Ed., A.R. Gennaro, ed., Mack Publishing Company 1990), and subsequent editions of the same, incorporated herein by reference for any purpose). In one embodiment of the invention, the composition comprises a topically acceptable pharmaceutical carrier.

The optimal topical composition will be determined by a skilled artisan depending upon, for example, the delivery format and desired dosage. Such compositions can influence the physical state, stability, rate of in vivo release, and rate of in vivo clearance of a retinoid (such as tretinoin) and a linicosamide antibiotic (such as clindamycin or clindamycin phosphate). In some embodiments of the invention, the composition is in the form of a gel, liquid suspension, emulsion cream, ointment, or powder. In a preferred embodiment of the invention, the composition is in the form of a gel.

In a particular embodiment, a gel comprising a linicosamide antibiotic (such as clindamycin or clindamycin phosphate) and a retinoid (such as tretinoin) can be formulated using components described in U.S. Patent No. 6,387,383, the entirety of which is incorporated herein by reference. Such components include a hydrophilic pharmaceutically acceptable lightly cross-linked polyacrylic acid polymer compatible with the linicosamide antibiotic and retinoid, an optional water miscible solvent, an optional preservative, and an optional oil phase and surfactant. In some embodiments of the invention, the composition has a pH of about 3.0 to about 9.0 and a viscosity of less than about 15,000 centipoise (cP).

In particular embodiments of the invention, the linicosamide antibiotic and retinoid are formulated with a hydrophilic lightly cross-linked polyacrylic acid polymeric material that is present in an amount sufficient to bring the viscosity of the composition to a level of not more than about 15,000 cP, preferably between about 100 and about 12,000 cP, and more preferably between about 300 and about 10,000 cP. The polymers that are particularly useful in the composition of the invention are lightly cross-linked polyacrylic acid polymers that are marketed under the tradename CARBOPOL®. Such polymers are generically referred to as carboxomers. The CARBOPOL® polymers are
hydrophilic polymers based on a polyacrylic acid structure. For use in the compositions of the invention, the hydrophilic lightly cross-linked polyacrylic acid polymers include CARBOPOL® 910, 941, 971, and 981, and CARBOPOL® ETD 2050.

In certain methods, uses, and compositions of the invention, the hydrophilic lightly cross-linked polyacrylic acid polymer is present in the composition in an amount of about 0.05 to about 3 weight percent, and preferably about 0.05 to about 1 weight percent based on the total weight of the composition. In a more preferred embodiment of the invention, the hydrophilic lightly cross-linked polyacrylic acid polymer is present in the composition in an amount of about 0.1 to about 0.5 weight percent.

In some embodiments of the invention, the composition optionally includes a water miscible solvent and a preservative. The water miscible solvent (i.e., a cosolvent) may be present to assist in dissolving the active agent. The cosolvent may be a single component or a mixture. Examples include those that are miscible with water such as ethanol, propylene glycol, glycerin, polyethylene glycol 400, and the like. Certain water miscible solvents, such as glycerin or propylene glycol, also add beneficial humectant properties to the composition. Drug delivery and penetration into the skin can be modified by the water miscible cosolvent composition.

In certain methods, uses, and compositions of the invention, the water miscible solvent is present in the composition in an amount of 0 to about 70 weight percent, and preferably 0 to about 40 weight percent based on the total weight of the composition. In a more preferred embodiment of the invention, the water miscible solvent is present in the composition in an amount of 0 to about 25 weight percent.

The preservative may be useful for ensuring a stable composition and preventing growth of bacteria. Thus, a preservative may be one or more of an antioxidant, a chelator, an antibacterial, or the like. Suitable preservatives include methylparaben, butylparaben, propylparaben, benzyl alcohol, sorbic acid, imidurea, thimerisal, propyl gallate, BHA, BHT, citric acid, disodium edetate, and the like.

In certain methods, uses, and compositions of the invention, the preservative is present in the composition in an amount of 0 to about 3 weight percent, and preferably about 0.01 to about 1 weight percent based on the total weight of the composition. In a more preferred embodiment of the invention, the preservative is present in the
composition in an amount of about 0.05 to about 0.25 weight percent.

A preferred composition, particularly for the treatment of rosacea, will exhibit a pH of about 3 to 9, preferably about 4 to 7, and most preferably at about 5 to 6. Thus, the composition may also include a pH-adjusting agent as needed at a level to adjust the pH to the desired range. Such agents include many pharmaceutically acceptable organic or inorganic bases, e.g., sodium hydroxide and tromethamine. The pH chosen for a composition of the invention will depend in part on the pH tolerance of the lincomamide antibiotic and retinoid chosen for the composition.

Another aspect of this invention is an emollient embodiment, i.e., a fluid emulsion or lotion. This aspect of the invention is a composition having an internal oil phase dispersed with the aid of at least one surfactant, e.g., an emulsifier, in water. Suitable surfactants are well known in the art and include those referred to as anionic and nonionic agents. Representative surfactants include polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, sorbitan laurate, sorbitan oleate, sorbitan stearate, polyoxyethylene stearate, sodium laureth sulfate, and laureth-10. Oil phase components include those that are commonly used in the art such as mineral oil, petrolatum, stearyl alcohol, cetyl alcohol, isopropyl myristate, diisopropyl adipate, stearic acid, white wax, and the like.

In certain methods, uses, and compositions of the invention, the surfactant is present in the composition in an amount of 0 to about 8 weight percent, and preferably 0 to about 5 weight percent based on the total weight of the composition. In a more preferred embodiment of the invention, the surfactant is present in the composition in an amount of 0 to about 3.5 weight percent. In certain methods, uses, and compositions of the invention, the oil phase component is present in the composition in an amount of 0 to about 50 weight percent, and preferably 0 to about 25 weight percent based on the total weight of the composition. In a more preferred embodiment of the invention, the oil phase component is present in the composition in an amount of 0 to about 15 weight percent.

Further suitable formulations for the compositions of the invention are described in U.S. Patent No. RE41,134, the entirety of which is hereby incorporated by reference.

In the methods, uses, and compositions of the invention, a retinoid (such as tretinoin) is present in the composition in an amount of about 0.01 to about 0.5 weight...
percent, preferably about 0.01 to about 0.25 weight percent, and more preferably about 0.01 to about 0.1 weight percent based on the total weight of the composition. In certain embodiments of the invention, the retinoid is present in the composition in an amount of about 0.025, about 0.05, or about 0.1 weight percent. In one method, use, or composition of the invention, the retinoid is present in the composition in an amount of about 0.025 weight percent. In a preferred embodiment of the invention, the composition comprises about 0.025 weight percent of the retinoid tretinoin.

In the methods, uses, and compositions of the invention, a linicosamide antibiotic (such as clindamycin or clindamycin phosphate) is present in the composition in an amount of about 0.1 to about 5 weight percent, and preferably about 0.5 to about 2 weight percent based on the total weight of the composition. In one method, use, or composition of the invention, the linicosamide antibiotic is present in the composition in an amount of about 1.2 weight percent. In a preferred embodiment of the invention, the composition comprises about 1.2 weight percent of the linicosamide antibiotic clindamycin or clindamycin phosphate.

In certain embodiments of the invention, the composition comprises about 0.02 to about 0.03 weight percent of retinoid and about 1.0 to about 1.5 weight percent of linicosamide antibiotic. In one method, use, or composition of the invention, the retinoid is tretinoin and the linicosamide antibiotic is clindamycin or clindamycin phosphate. In a preferred embodiment, the composition comprises about 0.025 weight percent of tretinoin and about 1.2 weight percent of clindamycin or clindamycin phosphate.

Topical compositions for use in the invention will typically be applied directly to the sites of rosacea lesions, including areas of redness and pustules, as well as surrounding unaffected areas on the face and neck of a patient. The compositions of the invention are generally topically applied to the affected skin once or twice daily. However, since the compositions of the invention are typically used under a physician's care, the precise treatment regimen in each case will be determined by the physician based upon the exact diagnosis, severity of the condition, concurrent use of other therapeutic agents, responsiveness to treatment, tolerance of treatment, and other related medical considerations. In a preferred embodiment of the invention, the composition is topically applied at least once a day for at least twelve weeks to an area of the skin of the
patient where the symptoms are manifested.

Topical application of the compositions of the invention can be accomplished by using a carrier, particularly one in which the composition's ingredients are soluble or are effectively solubilized (e.g., as an emulsion or microemulsion). Where employed, the carrier is inert in that it does not bring about a deactivation or oxidation of the active ingredients, and does not cause any adverse effect on the skin areas to which the composition is applied. In one embodiment of the invention, the active ingredients are applied in admixture with a topically acceptable carrier or vehicle (e.g., as a lotion, cream, or ointment) so as to facilitate topical application and, in some cases, provide additional therapeutic effects, such as moisturizing the affected skin areas. While the carrier for dermatological compositions can consist of a relatively simple solvent or dispersant such as water, it is generally preferred that the carrier comprise a composition more conducive to topical application, and particularly one that will form a film or layer on the skin to which the composition is applied so as to localize the application and provide some resistance to washing off by immersion in water or by perspiration and aid in the percutaneous delivery of the active ingredients. Many preparations are known in the art, and include lotions containing oils or alcohols and emollients, vegetable oils, hydrocarbon oils and waxes, silicone oils, animal or marine fats or oils, glyceride derivatives, fatty acids or fatty acid esters or alcohols or alcohol ethers, lecithin, lanolin and derivatives, polyhydric alcohols or esters, wax esters, sterols, phospholipids and the like, and generally also emulsifiers (nonionic, cationic, or anionic), although some of the emollients inherently possess emulsifying properties. These same general ingredients can be formulated into a cream rather than a lotion, or into gels, by utilization of different proportions of the ingredients and by inclusion of thickening agents such as gums or other forms of hydrophilic colloids.

Topical compositions of the invention can comprise additional ingredients commonly found in skin care compositions, such as tinting agents, emollients, skin conditioning agents, emulsifying agents, humectants, preservatives, antioxidants, perfumes, and chelating agents, provided that they are physically and chemically compatible with the active ingredients and other components of the composition. Buffering agents may also be employed in the compositions of the invention. Preferably,
buffering agents are chemically and physically stable agents commonly found in skin care compositions, and can include compounds that are also adjunct ingredients such as citric acid, malic acid, and glycolic acid buffers.

3. **Examples**

The Examples that follow are illustrative of specific embodiments of the invention, and various uses thereof. They are set forth for explanatory purposes only, and should not be construed as limiting the scope of the invention in any way.

10 **Example 1. Selection of Study Population**

To assess the efficacy and safety of a clindamycin and tretinoin gel for the treatment of papulopustular rosacea, a double-blind, placebo-controlled two site study was conducted. A summary of the study design is shown in Figure 1. The study was conducted according to Declaration of Helsinki principles and was registered on www.clinicaltrials.gov website. Following Institutional Review Board approval at both clinical sites (Massachusetts General Hospital and Stanford Hospital and Clinics), study subjects were recruited from advertisements published in local newspapers, posters, and online. Potential study subjects were contacted by telephone and then subjected to a preliminary eligibility screen. Following the preliminary screen, potential study subjects were subjected to a formal screening appointment at the dermatology clinics, at which time the study protocol was explained in detail and informed consent was obtained. During the screening visit, the medical history for potential study subjects, including information about concomitant medications, was collected, and subjects were given a physical examination.

Upon completion of the general screening activities, subjects who appeared to be good candidates for the study were randomized (using a computerized random number generator) into two nearly equal populations and selected to receive either ZIANA® clindamycin phosphate (1.2 weight percent) and tretinoin (0.025 weight percent) gel ("CT") or placebo gel. The research staff member who randomized the study population was not involved with any study assessments. The CT and placebo gels were unlabeled except for tube number. Study subjects were instructed to apply the gel once daily for 12
weeks, and were given diaries to record usage and side effects. The weights of the gel tubes given to study subjects were taken at each visit to confirm compliance and usage of the CT and placebo gels.

Study subjects were selected based on the following inclusion criteria: were 18 years of age or older and had a clinical diagnosis of papulopustular facial rosacea with a minimum of four but not more than 50 facial inflammatory lesions (papules plus pustules). For purposes of the study, the following exclusion criteria were used:

- Acne conglobata, acne fulminans, secondary acne (e.g., chloracne, drug-induced acne), or severe acne requiring systemic treatment;
- A history or presence of regional enteritis or inflammatory bowel disease (e.g., ulcerative colitis, pseudomembranous colitis, chronic diarrhea, or a history of antibiotic-associated colitis, bloody diarrhea) or similar symptoms;
- Use a topical rosacea treatment within two weeks of enrollment;
- Use systemic antibiotics within four weeks of enrollment;
- Use systemic retinoids within three months of enrollment;
- Use laser or light-based rosacea treatments within two months of enrollment;
- Concomitant use of medications reported to exacerbate rosacea, such as topical and systemic steroids;
- Current drug or alcohol abuse;
- Other dermatologic conditions that required the use of interfering topical or systemic therapy or that might interfere with study assessments such as, but not limited to, atopic dermatitis, perioral dermatitis, or acne vulgaris;
- Pregnancy or planning a pregnancy;
- Use of any investigational therapy within four weeks of enrollment; or
- Known hypersensitivity or previous allergic reaction to clindamycin or retinoids.

The size of the study population was determined based on prior studies in the medical literature, with study subjects having a baseline papule count of between 15-17 lesions. For the purposes of the study, it was assumed that the treatment group would experience a 50% improvement and that the placebo group would show a 35% improvement. With a standard deviation of 3.5 lesions, a power of 80% and a 2-tailed alpha of 0.5, it was estimated that a sample size of 35 patients per group would be needed.
to achieve statistical significance. In order to allow for a 20% drop out rate, a study population of 43 subjects in both the treatment and placebo groups was a sought. Once it became clear that the drop out rate was substantially lower than expected, a final study population of 83 was achieved.

5

**Example 2. Study Procedure**

In addition to the screening visit, study subjects participated in four study visits: baseline (day 1), interim assessments (at weeks 2 and 6), and final assessments (at week 12). Subjects that did not require a washout before treatment were enrolled and participated in their baseline visit assessments on the same day. Subjects who required a washout period (wherein the washout period depended on the agent being used by the subject) were asked to return for their baseline visit once the washout period had been observed.

During baseline visits, disease assessments of study subjects were made as a final confirmation of eligibility prior to treatment. Once study eligibility was confirmed, subjects were randomized into either the CT or placebo gel group, and physician rosacea assessments and patient rosacea assessments were performed. During interim assessment visits at 2 and 6 weeks following the baseline visit, the medical history, adverse events, and concomitant medications for study subjects was reviewed, and physician rosacea assessments and patient rosacea assessments were performed. During the final assessment visit at 12 weeks following the baseline visit, the medical history, adverse events, and concomitant medications for study subjects was reviewed, and physician rosacea assessments and patient rosacea assessments were performed.

Primary endpoints in the study included a statistically significant decrease in absolute papule and pustule count on a study subject's face at week 12 as compared with baseline, as well as a percent decrease in papule and pustule count on a study subject's face at week 12 as compared with baseline. Secondary endpoints in the study included a statistically significant decrease in the clinical features of rosacea at week 12 as compared with baseline. These clinical features, which were based on the classification and staging system proposed by the National Rosacea Society Expert Committee, include: flushing, erythema, papules and pustules, telangiectasia, burning or stinging,
plaques, dry appearance, edema, ocular symptoms, peripheral location, and phymatous changes. Additional secondary endpoints included physician global assessments regarding the following rosacea subtypes: erythematoclangiectatic, papulopustular, and phymatous; subject self-assessments; and statistically significant differences in the nature and severity of adverse events between the treated and placebo groups at week 12.

Physician assessments were performed using a validated instrument for assessing the severity of rosacea (Wilkin et al., 2004, J. Am. Acad. Dermatol. 50(6): 907-12), and all items included answer choices ranging from 0=absent, 1=mild, 2=moderate, and 3=severe. Subject self-assessments were performed using a validated quality of life instrument for rosacea (Nicholson et al., 2007, J. Am. Acad. Dermatol. 57(2): 213-21), and all items included the following answer choices: 0=never, 1=rarely, 2=sometimes, 3=often, and 4=all the time.

Example 3. Analysis of Study Groups

Eighty-three subjects were enrolled in the study, with 43 subjects allocated to the treatment group and 40 allocated to the placebo group (Figure 1). The average age of the study subjects was in the early 50’s and about two-thirds of the subjects were female. As indicated in Table 1, there were no statistically significant differences at baseline between the treated and placebo groups with regard to age and sex distribution. Similarly, there was no difference in rosacea disease severity as measured by papule/pustule count at baseline, although the placebo group was somewhat more severe.

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>CT gel n=41</th>
<th>Placebo gel n=39</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – mean (SD) in years</td>
<td>53.2 (13.6)</td>
<td>51.2 (14.0)</td>
<td>0.524</td>
</tr>
<tr>
<td>Male – n (%)</td>
<td>14 (36.8%)</td>
<td>9 (23.7%)</td>
<td>0.318</td>
</tr>
<tr>
<td>Number of papules and pustules – mean (SD)</td>
<td>14.3 (8.5)</td>
<td>18.7 (13.7)</td>
<td>0.095</td>
</tr>
</tbody>
</table>

* Derived from Fisher Exact test for discrete variables and t-test for continuous variables (two-tail probability).

Of the 83 study subjects enrolled, 73 subjects completed all study visits. In the treated group, there was one early termination due to intolerance of the study medication (i.e., irritation) and one due to worsening rosacea. One subject in the placebo group
withdrew participation because of irritant dermatitis. One subject in the treated group was lost to follow-up, while two subjects in the placebo group were lost to follow-up, for unknown reasons. Three subjects were excluded from the modified intention-to-treat analysis because they did not complete at least one follow-up visit.

As indicated in Table 2, the percentage of study subjects with decreased papule and pustule counts was higher in the treated group (50.0%) than the placebo group (46.7%) group, but this difference was not statistically significant.

Table 2. Papule and Pustule Counts at Baseline and Week 12

<table>
<thead>
<tr>
<th></th>
<th>Baseline*</th>
<th>Week 12</th>
<th>Mean difference in count**</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT gel – mean (SD)</td>
<td>14.3 (9.5)</td>
<td>14.4 (13.2)</td>
<td>0.83 (10.84)</td>
<td>0.63</td>
</tr>
<tr>
<td>Placebo – mean (SD)</td>
<td>18.7 (14.1)</td>
<td>15.9 (11.6)</td>
<td>-3.13 (13.28)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

* Includes all study subjects.

** Mean difference in papule and pustule count between baseline and week 12, excluding subjects in modified intention-to-treat analysis.

<table>
<thead>
<tr>
<th>Week 12 across group comparisons</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean difference in count - CT vs. Placebo gel at week 12</td>
<td>0.151</td>
</tr>
<tr>
<td>Mean % improvement - CT vs. Placebo gel at week 12</td>
<td>0.197</td>
</tr>
</tbody>
</table>

The percentage of study subjects with decreased papule and pustule count was not statistically significant between the treated and placebo groups at week 12 (p=0.197). At 12 weeks, there was also no significant improvement within each group separately (paired t-test); the p values for CT and placebo were 0.63 and 0.14, respectively (Table 2).

Of the clinical features for rosacea listed in Table 3 (based on the National Rosacea Society Expert Committee scoring system), there was a trend towards significant and consistent improvement at 12 weeks in telangiectasia (p=0.06) and the erythematotelangiectatic subtype of rosacea (p=0.05) in the CT group as compared with the placebo group.

Table 3. Study Subject Improvement at 12 Weeks

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>CT</th>
<th>Placebo</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flushing</td>
<td>10 (26%)</td>
<td>11 (28%)</td>
<td>0.80</td>
</tr>
<tr>
<td>Erythema</td>
<td>11 (28%)</td>
<td>6 (15%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Papules and pustules</td>
<td>7 (18%)</td>
<td>6 (15%)</td>
<td>0.77</td>
</tr>
</tbody>
</table>
Neither telangiectasia severity nor erythematotelangiectasia severity was significantly different at baseline between the CT and placebo groups. For baseline erythema severity, the placebo group yielded the following scores: 6% =1, 36% =2, 50% =3, and 8% =4; and the CT group yielded the following scores: 0% =1, 33% =2, 59% =3, and 8% =4. For baseline erythematotelangiectasia rosacea subtype severity, the placebo group yielded the following scores: 32% =1, 18% =2, 42% =3, and 8% =4; and the CT group yielded the following scores: 8% =1, 28% =2, 56% =3, and 8% =4.

One unexpected finding was that a significant difference was observed between the placebo and CT groups in the number of subjects that showed improvement with respect to edema (p=0.03). However, the numbers of study subjects in the placebo group showing improvement with respect to this clinical feature was small. None of the other clinical features of rosacea reached statistical significance.

In addition, no difference was detected between the CT and placebo groups with respect to improvement in mean score for overall physician global assessment at week 12. There was also no reduction in transient erythema (flushing) or telangiectasia at week 12 in the CT group as compared to the placebo group.

Table 4 shows the results of subject self-assessment of rosacea severity.

**Table 4. Study Subject Self-Assessment Improvement at 12 Weeks**

<table>
<thead>
<tr>
<th>Survey Item</th>
<th>CT (n=41)</th>
<th>Placebo (n=39)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Telangiectasia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burning or stinging</td>
<td>13 (33%)</td>
<td>5 (13%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Plaques</td>
<td>10 (27%)</td>
<td>17 (49%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Dry appearance</td>
<td>3 (8%)</td>
<td>3 (8%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Edema</td>
<td>10 (25%)</td>
<td>14 (36%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Ocular</td>
<td>0 (0)</td>
<td>6 (16%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Peripheral location</td>
<td>2 (6%)</td>
<td>3 (9%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Phymatous changes</td>
<td>1 (3%)</td>
<td>6 (15%)</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Erythematotelangiectatic</strong></td>
<td>12 (30%)</td>
<td>4 (10%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Papulopustular</td>
<td>8 (20%)</td>
<td>8 (21%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Phymatous</td>
<td>6 (15%)</td>
<td>7 (18%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Ocular</td>
<td>6 (15%)</td>
<td>5 (13%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Physician Global Assessment</td>
<td>10 (25%)</td>
<td>7 (19%)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

* Fisher Exact test (two-tail probability).
<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I worry that my rosacea may be serious.</td>
<td>16 (39%)</td>
<td>13 (33%)</td>
<td>0.65</td>
</tr>
<tr>
<td>2. My rosacea burns or stings</td>
<td>9 (22%)</td>
<td>11 (28%)</td>
<td>0.61</td>
</tr>
<tr>
<td>3. I worry about getting scars from my rosacea</td>
<td>19 (46%)</td>
<td>14 (36%)</td>
<td>0.37</td>
</tr>
<tr>
<td>4. I worry that my rosacea may get worse</td>
<td>18 (43%)</td>
<td>14 (36%)</td>
<td>0.65</td>
</tr>
<tr>
<td>5. I worry about side effects from rosacea medications</td>
<td>12 (29%)</td>
<td>13 (33%)</td>
<td>0.81</td>
</tr>
<tr>
<td>6. My rosacea is irritated.</td>
<td>16 (39%)</td>
<td>13 (33%)</td>
<td>0.66</td>
</tr>
<tr>
<td>7. I am embarrassed by my rosacea.</td>
<td>18 (44%)</td>
<td>14 (36%)</td>
<td>0.5</td>
</tr>
<tr>
<td>8. I am frustrated by my rosacea.</td>
<td>22 (54%)</td>
<td>13 (33%)</td>
<td>0.08</td>
</tr>
<tr>
<td>9. My rosacea makes my skin sensitive.</td>
<td>14 (34%)</td>
<td>11 (28%)</td>
<td>0.63</td>
</tr>
<tr>
<td>10. I am annoyed by my rosacea.</td>
<td>15 (38%)</td>
<td>13 (33%)</td>
<td>0.81</td>
</tr>
<tr>
<td>11. I am bothered by the appearance of my skin (redness, blotchiness)</td>
<td>18 (44%)</td>
<td>12 (31%)</td>
<td>0.255</td>
</tr>
<tr>
<td>12. My rosacea makes me feel self-conscious.</td>
<td>12 (29%)</td>
<td>11 (28%)</td>
<td>1.0</td>
</tr>
<tr>
<td>13. I try to cover up my rosacea (with make-up).</td>
<td>10 (24%)</td>
<td>7 (18%)</td>
<td>0.59</td>
</tr>
<tr>
<td>14. I am bothered by persistence/reoccurrence of my rosacea.</td>
<td>19 (46%)</td>
<td>12 (31%)</td>
<td>0.17</td>
</tr>
<tr>
<td>15. I avoid certain foods or drinks because of my rosacea.</td>
<td>11 (27%)</td>
<td>7 (18%)</td>
<td>0.43</td>
</tr>
<tr>
<td>16. My skin feels bumpy (uneven, not smooth, irregular).</td>
<td>18 (44%)</td>
<td>16 (41%)</td>
<td>0.82</td>
</tr>
<tr>
<td>17. My skin flushes.</td>
<td>20 (49%)</td>
<td>14 (36%)</td>
<td>0.27</td>
</tr>
<tr>
<td>18. My skin gets irritated easily (cosmetics, aftershaves, cleansers).</td>
<td>15 (37%)</td>
<td>15 (38%)</td>
<td>1.00</td>
</tr>
<tr>
<td>19. My eyes bother me (feel dry or gritty).</td>
<td>14 (34%)</td>
<td>12 (31%)</td>
<td>0.81</td>
</tr>
<tr>
<td>20. I think about my rosacea.</td>
<td>14 (34%)</td>
<td>10 (26%)</td>
<td>0.47</td>
</tr>
<tr>
<td>21. I avoid certain environments (heat, humidity, cold) because of my rosacea.</td>
<td>13 (32%)</td>
<td>9 (23%)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

* Fisher Exact test (two-tail probability).

In particular, this table indicates that the CT group showed more improvement at 12 weeks on almost all parameters as compared with the placebo group. However, none of the individual survey items reached statistical significance in the CT group as compared with the placebo group.

As indicated in Tables 5-7, which show physicians' ratings (blinded rating) of
tolerability parameters, the CT gel was well tolerated by subjects in the treatment group. For subjects who did not complete the study, but completed at least one baseline visit, their last completed visit was carried over. If there was missing data within that visit, it was not carried over from the previous visit, but considered missing.

### Table 5. Tolerability – Scaling

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>11 (29%)</td>
<td>16 (43%)</td>
</tr>
<tr>
<td>P-value*</td>
<td>0.234</td>
<td></td>
</tr>
<tr>
<td>Worsened</td>
<td>10 (26%)</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>P-value*</td>
<td>0.137</td>
<td></td>
</tr>
</tbody>
</table>

* Fisher Exact test (two-tail probability).

### Table 6. Tolerability – Dryness

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>14 (37%)</td>
<td>11 (30%)</td>
</tr>
<tr>
<td>P-value*</td>
<td>0.626</td>
<td></td>
</tr>
<tr>
<td>Worsened</td>
<td>8 (21%)</td>
<td>5 (14%)</td>
</tr>
<tr>
<td>P-value*</td>
<td>0.544</td>
<td></td>
</tr>
</tbody>
</table>

* Fisher Exact test (two-tail probability).

### Table 7. Tolerability – Erythema

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>15 (38%)</td>
<td>12 (32%)</td>
</tr>
<tr>
<td>P-value*</td>
<td>0.635</td>
<td></td>
</tr>
<tr>
<td>Worsened</td>
<td>10 (26%)</td>
<td>7 (18%)</td>
</tr>
<tr>
<td>P-value*</td>
<td>0.584</td>
<td></td>
</tr>
</tbody>
</table>

* Fisher Exact test (two-tail probability).

In particular, Tables 5-7 show that scaling, dryness, and erythema were not significantly increased in the treatment group as compared with the placebo group at week 12. Scaling, dryness, and erythema were assessed using the following scale: 0 = None to normal, 1 = Trace to mild and localized, 2 = Mild to mild and diffuse, 3 = Moderate to moderate and diffuse, 4 = Marked to moderate and dense, 5 = Severe to prominent and
dense. These results suggest that physicians were truly blinded to the intervention, as no significant difference was observed in clinical side effects.

Table 8 shows adverse events that were observed more than once in the CT and placebo groups.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>CT</th>
<th>Placebo</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsening rosacea</td>
<td>17.5% (7)</td>
<td>25.0% (4)</td>
<td>0.35</td>
</tr>
<tr>
<td>Facial scaling</td>
<td>15% (6)</td>
<td>0% (0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Dry skin on face</td>
<td>22.7% (5)</td>
<td>12.5% (2)</td>
<td>0.26</td>
</tr>
<tr>
<td>Redness on facial skin</td>
<td>18.1% (4)</td>
<td>12.5% (2)</td>
<td>0.43</td>
</tr>
<tr>
<td>Facial burning</td>
<td>9% (2)</td>
<td>0% (0)</td>
<td>0.24</td>
</tr>
<tr>
<td>Itching facial skin</td>
<td>7.5% (3)</td>
<td>12.5% (2)</td>
<td>0.67</td>
</tr>
<tr>
<td>Increased blood pressure</td>
<td>9% (2)</td>
<td>0% (0)</td>
<td>0.24</td>
</tr>
<tr>
<td>Irritated Facial Skin</td>
<td>5% (2)</td>
<td>2.5% (1)</td>
<td>0.62</td>
</tr>
</tbody>
</table>

* Fisher Exact test (two-tail probability)

There were no serious adverse events in either the treatment or placebo groups. Facial scaling in the treatment group was significantly higher than in the placebo group, as would be expected, given the active ingredients included tretinoin. All of the other adverse events listed in Table 8 were not significantly different between the CT and placebo groups. In general, CT gel was well tolerated in the treatment group, especially considering that patients with rosacea typically have sensitivity to agents such as tretinoin, which may promote scaling, dryness and erythema.

Although a statistically significant difference could not be detected for the primary endpoint of decreased papule and pustule count between the CT and placebo groups, an improvement in telangiectasia and the erythematotelangiectatic subtype of rosacea was detected in the CT group based on physician assessment. The findings based on physician assessment were consistent with subject self-assessments (see, e.g., survey item 11 in Table 4), even though none of the subject self-assessments reached statistical significance.

The significance of the present invention is even more relevant in light of the paucity of treatments available to reduce erythema and telangiectasias. For example, according to a recent review of topical interventions for rosacea, only topical
metronidazole and azelaic acid appear to be effective for reduction of erythema (Van Auuren et al., 2005, Cochrane Database Syst. Rev. 20(3): CD003262). Similarly, only one study documents improvements in telangiectasia in a randomized placebo-controlled trial (Tan et al., 2002, J. Cutan. Med. Surg. 6(6): 529-34). In that study, subjects used 1% metronidazole cream together with sunscreen SPF15.

While it is as yet unclear, it seems likely that the improvement in the erythematotelangiectatic subtype of rosacea observed in the current study is due to a reduction in telangiectasias. This possibility is supported by the finding that physician-assessed erythema symptoms in the CT group did not improve at 12 weeks.

Surprisingly, while the CT group showed a reduction in telangiectasias and improvement in the erythematotelangiectatic subtype of rosacea, an improvement was not observed in the papulopustular subtype of rosacea. This is particularly surprising given the presence of clindamycin in the study drug because clindamycin has been used to eradicate pustules in acne vulgaris. It was anecdotally observed during the study that as the erythrotelangiectatic subtype of rosacea for some subjects improved, their papules could be more readily ascertained, which may be one possible explanation for this result.

While the invention has been described in terms of various embodiments, it is understood that variations and modifications will occur to those skilled in the art.

Therefore, it is intended that the appended claims cover all such equivalent variations that come within the scope of the invention as claimed. In addition, the section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

All references cited in this application are expressly incorporated by reference herein.
WHAT IS CLAIMED IS:

1. A method for treating or ameliorating the topical symptoms associated with rosacea comprising topically administering to a patient in need thereof a therapeutically effective amount of a composition comprising a retinoid and a lincosamide antibiotic.

2. The method of claim 1, wherein the lincosamide antibiotic is selected from the group consisting of clindamycin, clindamycin phosphate, and pharmaceutically acceptable salts thereof.

3. The method of claim 2, wherein the lincosamide antibiotic is clindamycin phosphate.

4. The method of claim 1, wherein the retinoid is tretinoin or a pharmaceutically acceptable salt thereof.

5. The method of claim 1, wherein the composition comprises about 0.02 to about 0.03 weight percent of retinoid and about 1.0 to about 1.5 weight percent of lincosamide antibiotic.

6. The method of claim 5, wherein the composition comprises about 0.025 weight percent tretinoin and about 1.2 weight percent clindamycin or clindamycin phosphate.

7. The method of claim 1, wherein the composition further comprises a topically acceptable pharmaceutical carrier.

8. The method of claim 1, wherein the composition is topically applied to an area of the skin of the patient where the symptoms are manifested.

9. The method of claim 1, wherein the composition is topically applied at least once a day for at least twelve weeks.
10. The method of claim 1, wherein the rosacea is the erythematotelangiectatic subtype.

11. The method of claim 1, wherein the treatment results in a reduction in erythema.

12. The method of claim 1, wherein the treatment results in a reduction in telangiectasias.

13. The method of claim 1, wherein the composition is in the form of a gel, liquid suspension, emulsion cream, ointment, or powder.

14. The method of claim 1, wherein the composition comprises:
   (a) about 0.025 weight percent tretinoin;
   (b) about 1.2 weight percent clindamycin or clindamycin phosphate;
   (c) a hydrophilic pharmaceutically acceptable lightly cross-linked polyacrylic acid polymer compatible with the compounds of (a) and (b);
   (d) a pharmaceutically acceptable base to adjust pH;
   (e) optionally a water miscible solvent; and
   (f) optionally a preservative; and
wherein the composition has a pH of about 3 to about 9 and a viscosity of less than about 15,000 cP.

15. The use of a composition comprising a retinoid and a lincosamide antibiotic for the manufacture of a medicament for treating or ameliorating rosacea.

16. The use of claim 15, wherein the lincosamide antibiotic is selected from the group consisting of clindamycin, clindamycin phosphate, and pharmaceutically acceptable salts thereof.

17. The use of claim 16, wherein the lincosamide antibiotic is clindamycin phosphate.
18. The use of claim 15, wherein the retinoid is tretinoin or a pharmaceutically acceptable salt thereof.

19. The use of claim 15, wherein the composition comprises about 0.02 to about 0.03 weight percent of retinoid and about 1.0 to about 1.5 weight percent of lincomamide antibiotic.

20. The use of claim 19, wherein the composition comprises about 0.025 weight percent tretinoin and about 1.2 weight percent clindamycin or clindamycin phosphate.

21. The use of claim 15, wherein the composition further comprises a topically acceptable pharmaceutical carrier.

22. The use of claim 15, wherein the composition is topically applied to an area of the skin of the patient where the symptoms are manifested.

23. The use of claim 15, wherein the composition is topically applied at least once a day for at least twelve weeks.

24. The use of claim 15, wherein the rosacea is the erythematotelangiectatic subtype.

25. The use of claim 15, wherein the treatment results in a reduction in erythema.

26. The use of claim 15, wherein the treatment results in a reduction in telangiectasias.

27. The use of claim 15, wherein the composition is in the form of a gel, liquid suspension, emulsion cream, ointment, or powder.
28. A composition comprising a retinoid and a lincosamide antibiotic for the treatment or amelioration of the symptoms of rosacea.

29. The composition of claim 28, wherein the lincosamide antibiotic is selected from the group consisting of clindamycin, clindamycin phosphate, and therapeutically acceptable salts thereof.

30. The composition of claim 29, wherein the lincosamide antibiotic is clindamycin phosphate.

31. The composition of claim 28, wherein the retinoid is tretinoin or a pharmaceutically acceptable salt thereof.

32. The composition of claim 28, wherein the composition comprises about 0.02 to about 0.03 weight percent of retinoid and about 1.0 to about 1.5 weight percent of lincosamide antibiotic.

33. The composition of claim 32, wherein the composition comprises about 0.025 weight percent tretinoin and about 1.2 weight percent clindamycin or clindamycin phosphate.

34. The composition of claim 28, wherein the composition further comprises a topically acceptable pharmaceutical carrier.

35. The composition of claim 28, wherein the composition is topically applied to an area of the skin of the patient where the symptoms are manifested.

36. The composition of claim 28, wherein the composition is topically applied at least once a day for at least twelve weeks.
37. The composition of claim 28, wherein the rosacea is the erythematotelangiectatic subtype.

38. The composition of claim 28, wherein the treatment results in a reduction in erythema.

39. The composition of claim 28, wherein the treatment results in a reduction in telangiectasias.

40. The composition of claim 28, wherein the composition is in the form of a gel, liquid suspension, emulsion cream, ointment, or powder.
FIG. 1

Randomized (n=83)

Allocated to ZIANA (n=43)
Received allocated intervention (n=43)

Lost to follow-up (n=2)
Reasons unknown
Discontinued intervention (n=2)
  Irritant contact dermatitis
  Rosacea too severe

Analyzed (n=41)
Excluded from analysis (n=2)
  Only baseline visit completed

Allocated to placebo (n=40)
Received allocated intervention (n=40)

Lost to follow-up (n=3)
Reasons unknown
Discontinued intervention (n=1)
  Irritant contact dermatitis

Analyzed (n=39)
Excluded from analysis (n=1)
  Only baseline visit completed
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K45/06 A61P17/00 A61K31/203 A61K31/7056
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 A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Relevant to claim No.</th>
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Date of the actual completion of the international search
30 August 2012

Date of mailing of the international search report
05/09/2012

Name and mailing address of the ISA/
European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer
Baumgärtner, Heike

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