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(54) Title: METHOD FOR TREATMENT OF ROSACEA INCLUDING PATIENT REPORTED OUTCOMES THEREOF

(57) Abstract: A regimen is described for the therapeutic treatment of rosacea including topically applying to the skin of a subject in need of the treatment a pharmaceutical composition. The pharmaceutical composition includes about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient. The benzoyl peroxide is the only active ingredient in said pharmaceutical composition, and the pharmaceutical composition is applied once daily for a period of at least about 2 weeks, about 4 weeks, about 8 weeks or about 12 weeks. A decrease in Patient Assessment of Papulopustular Rosacea Signs and Symptoms (PAPSS) is at least about 40% after treatment with the pharmaceutical composition for about 4 weeks, and a decrease in Patient Assessment of Papulopustular Rosacea Impacts (PAPI) is from about 60% to about 70% after treatment with the pharmaceutical composition for at least about 8 weeks.

METHOD FOR TREATMENT OF ROSACEA INCLUDING PATIENT REPORTED OUTCOMES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority under 35 U.S.C. § 119(e) from U.S. Provisional Application No. 62/977,974, filed February 18, 2020, U.S. Provisional Application No. 62/977,952, filed February 18, 2020, U.S. Provisional Application No. 62/972,896, filed February 11, 2020, U.S. Provisional Application No. 62/972,310, filed February 10, 2020, U.S. Provisional Application No. 62/960,384, filed January 13, 2020, U.S. Provisional Application No. 62/925,258, filed October 24, 2019, U.S. Provisional 62/871,286, filed July 8, 2019, U.S. Provisional 62/871,283, filed July 8, 2019, U.S. Provisional 62/807,356, filed February 19, 2019, and U.S. Provisional 62/807,368, filed February 19, 2019, the contents of which are incorporated in their entirety as if fully set forth herein.

TECHNICAL FIELD

This application relates to methods for providing therapeutic treatment of skin conditions and afflictions, such as rosacea and symptoms and considerations associated therewith, including topically applying to the skin of a subject in need of said treatment a pharmaceutical composition comprising benzoyl peroxide.

BACKGROUND

Rosacea is a chronic disease of inflammatory dermatitis that mainly affects the median part of the face and the eyelids of certain adults. It is characterized by telangiectatic erythema, dryness of the skin, papules and pustules. Conventionally, rosacea develops in adults from the ages of 30 to 50, and more frequently affects women, although the condition is generally more severe in men.

Rosacea is a primitively vascular condition whose inflammatory stage lacks the cysts and comedones characteristic of common acne.

Factors that have been described as possibly contributing towards the development of rosacea include for example: the presence of parasites such as the *Demodex folliculorum,* the presence of bacteria such as *Helicobacter pylori* (a bacterium associated with gastrointestinal disorders), hormonal factors (such as endocrine factors), climatic and immunological factors, and so forth.

Rosacea develops in four stages over several years, in spasms aggravated by variations in temperature, alcohol, spices, exposure to sunlight and stress. The various stages of the disease are:

Stage 1 (stage of erythema episodes): the patients have erythrosis spasms due to the sudden dilation of the arterioles of the face, which then take on a congestive, red appearance. These spasms are caused by emotions, meals and temperature changes.

Stage 2 (stage of couperosis, i.e., of permanent erythema with telangiectasia): certain patients also have oedema on the cheeks and the forehead.

Stage 3 (inflammatory stage, papulopustular rosacea): patients exhibit appearance of inflammatory papules and pustules, but without affecting the sebaceous follicles, and thus, with absence of cysts and comedones.

Stage 4 (rhinophyma stage): this late phase essentially affects men. The patients have a bumpy, voluminous red nose with sebaceous hyperplasia and fibrous reordering of the connective tissue.

Typical treatment of rosacea includes oral or topical administration of antibiotics such as tetracyclines, salicylic acid, anti-fungal agents, steroids, metronidazole (an anti-bacterial agent) and isotretinoin, or even with anti-infectious agents such as azelaic acid.

SUMMARY

An exemplary embodiment of this application is a regimen for the therapeutic treatment of rosacea, the regimen comprising topically applying to the skin of a subject in need of said treatment a pharmaceutical composition, the pharmaceutical composition comprising about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, wherein said pharmaceutical composition is applied once daily for a period of at least about 2 weeks, about 4 weeks, about 8 weeks or about 12 weeks, wherein a decrease in Patient Assessment of Papulopustular Rosacea Signs and Symptoms (PAPSS) is at least about 32% after treatment with said pharmaceutical composition for about 2 weeks, and about 40% after treatment with said pharmaceutical composition for about 4 weeks.

In another exemplary embodiment, the decrease in PAPSS is less than about 40% after treatment with vehicle alone for about 4 weeks.

Another exemplary embodiment of this application is a regimen for the therapeutic treatment of rosacea, the regimen comprising topically applying to the skin of a subject in need of said treatment a pharmaceutical composition, the pharmaceutical composition comprising about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, wherein said pharmaceutical composition is applied once daily for a period of at least about 2 weeks, about 4 weeks, about 8 weeks or about 12 weeks, wherein a decrease in PAPSS is from about 50% to about 65% after treatment with said pharmaceutical composition for at least about 8 weeks.

In another exemplary embodiment, the decrease in PAPSS is from about 25% to about 40% after treatment with vehicle alone for at least about 8 weeks.

In another exemplary embodiment, the papulopustular rosacea signs and symptoms are selected from burning, itching, redness, bumps, and combinations thereof, on the skin of a subject.

Another exemplary embodiment of this application is a regimen for the therapeutic treatment of rosacea, the regimen comprising topically applying to the skin of a subject in need of said treatment a pharmaceutical composition, the pharmaceutical composition comprising about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, wherein said pharmaceutical composition is applied once daily for a period of at least about 2 weeks, about 4 weeks, about 8 weeks or about 12 weeks, wherein a decrease in Patient Assessment of Papulopustular Rosacea Impacts (PAPI) is at least about 35%, preferably 40%, after treatment with said pharmaceutical composition for about 2 weeks.

In another exemplary embodiment, the decrease in PAPI is about 23%, preferably 25%, after treatment with vehicle alone for about 2 weeks.

Another exemplary embodiment of this application is a regimen for the therapeutic treatment of rosacea, the regimen comprising topically applying to the skin of a subject in need of said treatment a pharmaceutical composition, the pharmaceutical composition comprising about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, wherein said pharmaceutical composition is applied once daily for a period of at least about 2 weeks, about 4 weeks, about 8 weeks or about 12 weeks, wherein a decrease in PAPI is from about 60% to about 70% after treatment with said pharmaceutical composition for at least about 8 weeks.

In another exemplary embodiments, the decrease in patient assessment of papulopustular rosacea impacts is about 35%, preferably 40%, more preferably 45%, after treatment with vehicle alone for at least about 8 weeks.

In another exemplary embodiment, an average decrease in the patient assessment of papulopustular rosacea impacts after treatment with said pharmaceutical composition for at least about 8 weeks is approximately about 1.2 times to two times, preferably 1.5 times to two times, more preferably 1.6 times, an average decrease in the PAPI after treatment with vehicle alone.

In another exemplary embodiment, the papulopustular rosacea impact is selected from embarrassment, self-consciousness and frustration.

Another exemplary embodiment of this application is a pharmaceutical composition for use as a medicament for the therapeutic treatment of rosacea, the pharmaceutical composition comprising from about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, wherein said pharmaceutical composition is applied once daily for a period of at least about 2 weeks, about 4 weeks, about 8 weeks or about 12 weeks, wherein a decrease in Patient Assessment of Papulopustular Rosacea Signs and Symptoms (PAPSS) is at least about 32% after treatment with said pharmaceutical composition for about 2 weeks, and about 40% after treatment with said pharmaceutical composition for about 4 weeks.

In another exemplary embodiment, the decrease in PAPSS is less than about 40% after treatment with vehicle alone for about 4 weeks.

Another exemplary embodiment of this application is a pharmaceutical composition for use as a medicament for the therapeutic treatment of rosacea, the pharmaceutical composition comprising from about 1% w/w to about 10% w/w benzoyl peroxide as an active

ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, wherein said pharmaceutical composition is applied once daily for a period of at least about 2 weeks, about 4 weeks, about 8 weeks or about 12 weeks, wherein a decrease in Patient Assessment of Papulopustular Rosacea Impacts (PAPI) is from about 60% to about 70% after treatment with said pharmaceutical composition for at least about 8 weeks.

In another exemplary embodiment, the decrease in PAPI is about 35% after treatment with vehicle alone for at least about 8 weeks. In certain embodiments the decrease in PAPI is about 40%, preferably 45% after treatment with vehicle alone for at least about 8 weeks.

Another exemplary embodiment of this application is the use of a pharmaceutical composition for the treatment of rosacea, the pharmaceutical composition comprising from about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, wherein said pharmaceutical composition is applied once daily for a period of at least about 2 weeks, about 4 weeks, about 8 weeks or about 12 weeks, wherein a decrease in Patient Assessment of Papulopustular Rosacea Signs and Symptoms (PAPSS) is from about 50% to about 65% after treatment with said pharmaceutical composition for at least about 8 weeks.

In another exemplary embodiment, the decrease in PAPSS is from about 25% to about 40% after treatment with vehicle alone for at least about 8 weeks.

Another exemplary embodiment of this application is the use of a pharmaceutical composition for the treatment of rosacea, the pharmaceutical composition comprising from about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, wherein said pharmaceutical

composition is applied once daily for a period of at least about 2 weeks, about 4 weeks, about 8 weeks or about 12 weeks, wherein a decrease in Patient Assessment of Papulopustular Rosacea Impacts (PAPI) is from about 60% to about 70% after treatment with said pharmaceutical composition for at least about 8 weeks.

In another exemplary embodiment, the decrease in PAPI is about 35%, preferably about 40%, more preferably 45%, after treatment with vehicle alone for at least about 8 weeks.

In other exemplary embodiments, the benzoyl peroxide is the sole active ingredient administered to the subject in need of said treatment during the duration of the regimen; the pharmaceutical composition comprises about 2.5% w/w to about 10% w/w of benzoyl peroxide, preferably about 5% w/w of benzoyl peroxide; the benzoyl peroxide is in a form selected from solid, solution or suspension; the rosacea is any of erythematotelengietatic, papulopustular, phymatous or ocular rosacea; the pharmaceutical composition is a cream or an emulsion; the pharmaceutical composition is an extended release formulation; and/or the extended-release effect is obtained by encapsulation, microencapsulation, microspheres or coating, preferably the benzoyl peroxide is encapsulated and/or microencapsulated and/or the benzoyl peroxide is included in a microsphere and/or a coating.

Details of other exemplary embodiments of the present disclosure will be included in the following detailed description and the accompanying drawings. It is appreciated that certain features of the exemplary embodiments described in this application, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment.

BRIEF DESCRIPTION OF THE DRAWINGS

In order to understand the disclosure and to see how it can be carried out in practice, embodiments will now be described, by way of non-limiting examples only, with reference to the accompanying drawings, in which:

FIGURES 1A to 1D are graph presenting each of the Patient Assessment of Papulopustular Rosacea Signs and Symptoms (PAPSS) of burning, itching, redness and bumps after treatment with BPO composition as compared with vehicle alone over a period of about 2 weeks (FIG. 1A), about 4 weeks (FIG. 1B), about 8 weeks (FIG. 1C) and about 12 weeks (FIG. 1D).

FIGURE 2 is a graph presenting the total of all Patient Assessment of Papulopustular Rosacea Signs and Symptoms (PAPSS) after treatment with BPO composition as compared with vehicle alone over a period of about 2 weeks, about 4 weeks, about 8 weeks and about 12 weeks.

FIGURES 3A to 3D are graph presenting each of the Patient Assessment of Papulopustular Rosacea Impacts (PAPI) of embarrassment, self-consciousness and frustration after treatment with BPO composition as compared with vehicle alone over a period of about 2 weeks (FIG. 2A), about 4 weeks (FIG. 2B), about 8 weeks (FIG. 2C) and about 12 weeks (FIG. 2D).

FIGURE 4 is a graph presenting the total of all Patient Assessment of Patient Assessment of Papulopustular Rosacea Impacts (PAPI) after treatment with BPO composition as compared with vehicle alone over a period of about 2 weeks, about 4 weeks, about 8 weeks and about 12 weeks.

DETAILED DESCRIPTION

Multiple studies have been directed to the treatment of rosacea using a pharmaceutical or dermatological active agent such as metronidazole, azelaic acid, sulfacetamide, brimonidine,

ivermectin, permethrin and clindamycin, and with doxycycline, which is identified as the only FDA-approved treatment for rosacea (Oge et al., "Rosacea: Diagnosis and Treatment," *American Family Physician*, v. 92(3), pp. 187-198 (2015); Gul et al., "A case of granulomatous rosacea successfully treated with pimecrolimus cream," *J. Derm. Treatment*, 19, 313-315 (2008)).

Benzoyl peroxide (BPO) is generally identified as an anti-acne agent, used alone (U.S. Patent No. 9,439,857; Wester et al., "Controlled release of benzoyl peroxide from a porous microsphere polymeric system can reduce topical irritancy," *J. Am. Acad. Derma.* 24, 720-726 (1991); Sawleshwarkar, "Multicenter study to evaluate efficacy and irritation potential of benzoyl peroxide 4% cream in hydrophase base (Brevoxyl) in acne vulgaris," *Ind. J. Derm. Vener. Lepro.*, 69(1), 19-22 (2003)) or in combination with a primary active such as avermectin (U.S. 2011/0052515).

One such study includes a therapeutic regimen involving treatment of acne rosacea in a group of patients in need of such treatment with 5% BPO-acetone gel for four weeks, followed by treatment of the same group of patients with 10% BPO-acetone gel for an additional four weeks. (Montes et al., "Topical Treatment of Acne Rosacea with Benzoyl Peroxide Acetone Gel," *Therapeutics for the Clinician: New Reports on Treatment Modalities of Possible Interest to Patient-Caring Physicians*, 32, 185-190 (1983)). The *Montes* study showed a significantly better response during the five to eight weeks of treatment with 10% BPO-acetone gel compared to the first four weeks of treatment with 5% BPO-acetone gel. Moreover, although *Montes 1983* claims success in the treatment of rosacea using a BPO-acetone gel, 25% of the patients in the study showed no improvement and 40% of the patients developed an irritation. Additionally, this study required increasing the amount of BPO administered to the patients from 5% to 10% after week four. The results of the *Montes 1983*

study make it clear that BPO would not be suitable for regular use in the treatment of rosacea, especially as a first line treatment of rosacea.

Other studies show that, when used in the treatment of rosacea, BPO is generally combined with a primary active agent such as clindamycin (Breneman et al., "Double-blind, randomized, vehicle-controlled clinical trial of once-daily benzoyl peroxide/clindamycin topical gel in the treatment of patients with severe rosacea," *Int. J. Derm.*, 43, 381-387 (2004); Gold et al., "Use of Benzoyl Peroxide/Clindamycin gel in the once daily treatment of moderate rosacea," *J. Amer. Acad. Dermat.*, 52(3), sup., P25 (2004); Leyden et al., "Blind photographic review for a double blind, multicenter, placebo-controlled study comparing Benzoyl Peroxide/Clindamycin and placebo for the treatment of rosacea," *J. Amer. Acad. Dermat.*, 52(3), sup., P14 (2004); Goldgar et al., "Treatment Options for Acne Rosacea," *J Amer. Fam. Physician*, 80(5), 461-468 (2009)).

BPO is generally identified as only a possible second-line treatment of rosacea following the use of another, different active. (Oge 2015, Table 5; Goldgar 2009, "Key Recommendations for Practice"). *Goldgar 2009*, in particular, recommends the use of BPO only as a tertiary therapy for the treatment of rosacea.

When BPO was used as the sole active agent for the treatment of rosacea, lesions were found to be unresponsive. (Gul 2008).

These previous rosacea treatments with BPO alone or in combination with other agents, have been shown to have several drawbacks such as irritation and intolerance phenomena, especially when they are administered for a prolonged period. (Crawford et al., "Rosacea: I. Etiology, pathogenesis, and subtype classification," *J. Am. Acad. Dermatol.*, 51, 327-341 (2004)). These treatments are only suppressive and not curative, acting especially on the pustulous spasms occurring during the inflammatory stage.

Such drawbacks associated with the treatment of rosacea involving the use of BPO result in exclusion of BPO from standard rosacea treatment methods. For example, "A Review of the Current Modalities for the Treatment of Papulopustular Rosacea" identifies metronidazole, ivermectin and azelaic acid as topical therapies that were proven effective for the treatment of rosacea. (McGregor et al., "A Review of the Current Modalities of the Treatment of Papulopustular Rosacea," *Dermatol. Clin.* (2017)). While *McGregor 2017* mentions alternate therapies, such as sodium sulfacetanide/sulfur cream, clindamycin, tretinoin, calcineurin inhibitors and oral tretinoin, that may have some effectiveness in the treatment of rosacea, notably, *McGregor 2017* does not include, or even mention, BPO in the long list of possible treatment therapies described therein. The absence of BPO as a known treatment for rosacea is also evident in other studies. (Feaster et al., "Clinical effectiveness of novel rosacea therapies," *Current Op. Pharmacol.*, 46, 14-18 (2019); Del Rosso et al., "Update on the Management of Rosacea from the American Acne & Rosacea Society (AARS); *J. Clinical & Aesthetic Dermat.*, 12 (6), 17-24 (2019)). The absence of BPO as a recognized first-line treatment for rosacea is especially evident in *Del Rosso*, which is a well-known and respected authority on the treatment of rosacea. The AARS review lists the Society's recommendation for rosacea treatment, including topical metronidazole, topical azelaic acid, oral tetracyclines, ivermectin, topical alpha agonists, and oral isotretinoin, as well as "alternative therapies," such as sulfacetamide/sulfur, calcineurin inhibitors, retinoids, and permethrin. (*See e.g.*, Table 1 of the AARS review.) BPO is not mentioned in the AARS review either as a leading, or even an alternative, therapeutic agent for the treatment of rosacea.

Considering the chronic nature of rosacea, there is a need for early onset of action, and a prolonged use treatment of the disease, its symptoms and associated conditions, in a safe and effective manner. Thus, there exists a need for compositions that show early onset of action, and improved efficacy in the treatment of rosacea, that impart greater tolerance to the active principles

and that reduce, substantially minimize or do not have the side effects described in the prior art. As described herein, patient reported outcomes demonstrate the unexpectedly superior therapeutic effects of treating the symptoms of rosacea, such as, for example, burning, itching, redness and burns, with the BPO composition of the present invention. The patient reported outcomes also demonstrate the unexpected decrease in the impact of papulopustular rosacea, such as embarrassment, self-consciousness and frustration.

Advantages and features of the present disclosure, and methods for accomplishing the same will be more clearly understood from exemplary embodiments described below with reference to any accompanying drawings. However, the present disclosure is not limited to the following exemplary embodiments and can be implemented in various different forms. The exemplary embodiments are provided only to provide sufficient disclosure of the present discoveries and to fully provide a person having ordinary skill in the art to which the present disclosure pertains within the technical field, and the present disclosure will be defined by any appended claims and combinations thereof.

As used herein, like reference numerals generally denote like elements throughout the present specification. Further, in the following description, a detailed explanation of well-known related technologies can be omitted to avoid unnecessarily obscuring the subject matter of the present disclosure.

As used herein, terms such as "including" and "having" are generally intended to allow other components to be included unless the terms are used in conjunction with the term "only."

As used herein, the term "topical use" is meant to encompass the topical administration of an exemplary composition by formulating said composition in any way known in the art, or in formulations disclosed herein, which are compatible with the skin, mucous membranes and/or the integuments.

As used herein, the term "treating" or "treatment" includes curing a condition, treating a condition, preventing or substantially preventing a condition, treating symptoms of a condition, curing symptoms of a condition, ameliorating, reducing and/or minimizing symptoms of a condition, treating effects of a condition, ameliorating, reducing and/or minimizing effects of a condition, and preventing and/or substantially preventing results of a condition,

As used herein, the term "pharmaceutical composition" refers to a composition comprising one or more active ingredients with other components such as, for example, pharmaceutically acceptable ingredients and/or excipients. The purpose of a pharmaceutical composition is to facilitate administration of an active ingredient to a subject.

As used herein, the terms "pharmaceutically active agent" or "active agent" or "active pharmaceutical ingredient" are interchangeable and mean the ingredient is a pharmaceutical drug, which is biologically- and/or chemically-active and is regulatory-approved or approvable as such.

As used herein, the term "ingredient" refers to a pharmaceutically acceptable ingredient, which is included or is amenable to be included in The FDA's Inactive Ingredient (IIG) database. Inactive ingredients can sometimes exhibit some therapeutic effects, although they are not drugs.

As used herein, "Patient Reported Outcome" and/or "PRO" refers to patient reported outcomes of Patient Assessment of Papulopustular Rosacea Signs and Symptoms (PAPSS) and/or Patient Assessment of Papulopustular Rosacea Impacts (PAPI) as determined from answers to relevant validated questionnaires provided by subjects of the studies described herein.

As used herein, "Patient Assessment of Papulopustular Rosacea Signs and Symptoms" and/or "PAPSS" refers to assessment by subjects of the studies described herein of various symptoms of rosacea, such as burning and/or stinging, itching, redness, flushing, bumps, spider

veins, swollen and/or sensitive skin, dry skin, roughness or scaling, thickening of the skin, and the like.

As used herein, "Patient Assessment of Papulopustular Rosacea Impacts" and/or "PAPI" refers to assessment by subjects of the studies described herein of various impacts of rosacea, such as embarrassment, self-consciousness, frustration, worry, low self-esteem, problems with interacting with people, anxiety and depression, and the like.

Whenever a numerical range is indicated herewith, it is meant to include any cited numeral (fractional or integral) within the indicated range. The phrases "ranging/ranges between" a first indicated number and a second indicated number and "ranging/ranges from" a first indicated number "to" a second indicated number are used herein interchangeable and are meant to include the first and second indicated numbers and all fractional and integral numerals therebetween.

The dimensions and values disclosed herein are not to be understood as being strictly limited to the exact numerical values recited. Instead, unless otherwise specified, each such dimension is intended to mean both the recited value and a functionally equivalent range surrounding that value. For example, a dimension disclosed as "10 μm" is intended to mean "about 10 μm."

As used herein, numbers and/or numerical ranges preceded by the term "about" should not be considered to be limited to the recited range. Rather, numbers and/or numerical ranges preceded by the term "about" should be understood to include a range accepted by those skilled in the art for any given element in formations according to the subject invention.

As used herein, when a numerical value is preceded by the term "about," the term "about" is intended to indicate +/- 10%.

As used herein, the singular form "a," "an" and "the" include plural references unless the context clearly dictates otherwise. For example, the term "a compound" or "at least one compound" can include a plurality of compounds, including combinations and/or mixtures thereof.

As used herein, the term "method" refers to manners, means, techniques and procedures for accomplishing a given task including, but not limited to, those manners, means, technical and procedures either known to, or readily developed from known manners, means, techniques and procedures by practitioners of the chemical, pharmacological, biological, biochemical and medical arts.

It is appreciated that certain features of the exemplary embodiments described herein, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the exemplary embodiments, which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable sub-combination or as suitable in any other described embodiment. Certain features described in the context of various embodiments are not to be considered essential features of those embodiments, unless the embodiment is inoperative without those elements.

An exemplary embodiment of this application is a regimen for the therapeutic treatment of rosacea, the regimen comprising topically applying to the skin of a subject in need of said treatment a pharmaceutical composition, the pharmaceutical composition comprising about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, wherein said pharmaceutical composition is applied once daily for a period of at least about 2 weeks, about 4 weeks, about 8 weeks or about 12 weeks, wherein a decrease in Patient Assessment of Papulopustular Rosacea Signs and Symptoms (PAPSS) is at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, and the like, after treatment with said pharmaceutical composition for about 4 weeks.

In another exemplary embodiment, the decrease in PAPSS is less than about 40%, less than about 30%, less than about 20%, less than about 10%, less than about 5%, and the like, after treatment with vehicle alone for about 4 weeks.

Another exemplary embodiment of this application is a regimen for the therapeutic treatment of rosacea, the regimen comprising topically applying to the skin of a subject in need of said treatment a pharmaceutical composition, the pharmaceutical composition comprising about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, wherein said pharmaceutical composition is applied once daily for a period of at least about 2 weeks, about 4 weeks, about 8 weeks or about 12 weeks, wherein a decrease in PAPSS is from about 50% to about 65%, from about 52% to about 63%, from about 54% to about 61%, from about 56% to about 59%, and the like, after treatment with said pharmaceutical composition for at least about 8 weeks.

In another exemplary embodiment, the decrease in PAPSS is from about 25% to about 40%, from about 27% to about 38%, from about 29% to about 36%, from about 27% to about 34%, from about 29% to about 32%, and the like, after treatment with vehicle alone for at least about 8 weeks.

In another exemplary embodiment, the papulopustular rosacea signs and symptoms are selected from burning, itching, redness, bumps, and combinations thereof, on the skin of a subject.

Another exemplary embodiment of this application is a regimen for the therapeutic treatment of rosacea, the regimen comprising topically applying to the skin of a subject in need of said treatment a pharmaceutical composition, the pharmaceutical composition comprising about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only

active ingredient in said pharmaceutical composition, wherein said pharmaceutical composition is applied once daily for a period of at least about 2 weeks, about 4 weeks, about 8 weeks or about 12 weeks, wherein a decrease in Patient Assessment of Papulopustular Rosacea Impacts (PAPI) is at least about 35%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, and the like, after treatment with said pharmaceutical composition for about 2 weeks.

In another exemplary embodiment, the decrease in PAPI is about 15%, about 20%, about 25%, about 30%, about 34%, and the like, after treatment with vehicle alone for about 2 weeks.

Another exemplary embodiment of this application is a regimen for the therapeutic treatment of rosacea, the regimen comprising topically applying to the skin of a subject in need of said treatment a pharmaceutical composition, the pharmaceutical composition comprising about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, wherein said pharmaceutical composition is applied once daily for a period of at least about 2 weeks, about 4 weeks, about 8 weeks or about 12 weeks, wherein a decrease in Patient Assessment of Papulopustular Rosacea Impacts (PAPI) is from about 60% to about 70%, from about 61% to about 69%, from about 62% to about 68%, from about 63% to about 67%, from about 64% to about 66%, and the like, after treatment with said pharmaceutical composition for at least about 8 weeks.

In another exemplary embodiments, the decrease in PAPI is about 30%, about 35%, about 45%, about 50%, about 55%, and the like, after treatment with vehicle alone for at least about 8 weeks.

In another exemplary embodiment, an average decrease in the PAPI after treatment with said pharmaceutical composition for at least about 8 weeks is approximately about 1.2

times to two times, preferably 1.5 times to two times, more preferably more than two times, an average decrease in the PAPI after treatment with vehicle alone.

In another exemplary embodiment, the papulopustular rosacea impact is selected from embarrassment, self-consciousness and frustration.

Another exemplary embodiment of this application is a pharmaceutical composition for use as a medicament for the therapeutic treatment of rosacea, the pharmaceutical composition comprising from about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, wherein said pharmaceutical composition is applied once daily for a period of at least about 2 weeks, about 4 weeks, about 8 weeks or about 12 weeks, wherein a decrease in Patient Assessment of Papulopustular Rosacea Signs and Symptoms (PAPSS) is at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least 80%, at least about 90%, and the like, after treatment with said pharmaceutical composition for about 4 weeks.

In another exemplary embodiment, the decrease in PAPSS is less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and the like, after treatment with vehicle alone for about 4 weeks.

Another exemplary embodiment of this application is a pharmaceutical composition for use as a medicament for the therapeutic treatment of rosacea, the pharmaceutical composition comprising from about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, wherein said pharmaceutical composition is applied once daily for a period of at least about 2 weeks, about 4 weeks, about 8 weeks or about 12 weeks, wherein a decrease in Patient Assessment of

Papulopustular Rosacea Impacts (PAPI) is from about 60% to about 70%, from about 61% to about 69%, from about 62% to about 68%, from about 63% to about 67%, from about 64% to about 68%, from about 65% to about 67%, and the like, after treatment with said pharmaceutical composition for at least about 8 weeks.

In another exemplary embodiment, the decrease in PAPI is about 30%, about 35%, about 45%, about 50%, about 55%, and the like, after treatment with vehicle alone for at least about 8 weeks.

Another exemplary embodiment of this application is the use of a pharmaceutical composition for the treatment of rosacea, the pharmaceutical composition comprising from about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, wherein said pharmaceutical composition is applied once daily for a period of at least about 2 weeks, about 4 weeks, about 8 weeks or about 12 weeks, wherein a decrease in Patient Assessment of Papulopustular Rosacea Signs and Symptoms (PAPSS) is from about 50% to about 65%, from about 52% to about 63%, from about 54% to about 61%, from about 56% to about 59%, and the like, after treatment with said pharmaceutical composition for at least about 8 weeks.

In another exemplary embodiment, the decrease in PAPSS is from about 25% to about 40%, from about 27% to about 38%, from about 29% to about 36%, from about 31% to about 34%, and the like, after treatment with vehicle alone for at least about 8 weeks.

Another exemplary embodiment of this application is the use of a pharmaceutical composition for the treatment of rosacea, the pharmaceutical composition comprising from about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, wherein said pharmaceutical

composition is applied once daily for a period of at least about 2 weeks, about 4 weeks, about 8 weeks or about 12 weeks, wherein a decrease in Patient Assessment of Papulopustular Rosacea Impacts (PAPI) is from about 60% to about 70%, from about 62% to about 68%, from about 64% to about 66%, and the like, after treatment with said pharmaceutical composition for at least about 8 weeks.

In another exemplary embodiment, the decrease in PAPI is about 30%, about 35%, about 45%, about 50%, about 55%, and the like, after treatment with vehicle alone for at least about 8 weeks.

In another exemplary embodiment, the benzoyl peroxide is the only active ingredient in said pharmaceutical composition and/or in the regimen and/or in the method of treatment. In another exemplary embodiment, the benzoyl peroxide is the sole active ingredient administered to the subject during the duration of the regimen.

In another exemplary embodiment, the pharmaceutical composition comprises about 2.5% w/w to about 10% w/w of benzoyl peroxide, preferably about 3.0% to about 10% of benzoyl peroxide, more preferably about 3% to about 5% of benzoyl peroxide, and more preferably about 5% w/w of benzoyl peroxide.

In another exemplary embodiment, the benzoyl peroxide is in a form selected from solid, solution, and suspension.

In another exemplary embodiment, the rosacea is any of erythematotelengietatic, papulopustular, phymatous or ocular rosacea.

In another exemplary embodiment, the pharmaceutical composition is a cream, cream gel, an emulsion, a gel or a foam; preferably a cream or an emulsion.

In another exemplary embodiment, the pharmaceutical composition can be an extended- and/or controlled-release formulation, and the extended-release and/or controlled-release effect is

obtained by any one of encapsulation, microencapsulation, microspheres and/or coating, or can be encapsulated and/or microencapsulated or included in a microsphere and/or a coating.

In some embodiments, said rosacea is papulopustular rosacea (i.e., inflammatory rosacea; Rapini et al. (2007). *Dermatology: 2-Volume Set.* St. Louis: Mosby and James, William et al. (2005). *Andrews' Diseases of the Skin: Clinical Dermatology.* (10th ed.). Saunders p. 245).

In some further embodiments, the composition further comprises at least one non pharmaceutical active additive selected from the group consisting of chelating agents, antioxidants, sunscreens, preservatives, fillers, electrolytes, humectants, dyes, mineral or organic acids or bases, fragrances, essential oils, moisturizers, vitamins, essential fatty acids, sphingolipids, self-tanning compounds, calmatives and skin-protecting agents, pro-penetrating agents and gelling agents, or a mixture and/or combination thereof.

In other embodiments, the composition is formulated into a topically applicable, physiologically acceptable medium comprising of: (a) at least one member selected from the group consisting of water, alcohols, oils, fatty substances and waxes; and (b) at least one additive selected from the group consisting of chelating agents, antioxidants, sunscreens, preservatives, fillers, electrolytes, humectants, dyes, mineral acids, mineral bases, organic acids, organic bases, fragrances, essential oils, moisturizers, vitamins, essential fatty acids, sphingolipids, self-tanning compounds, calmatives, skin-protecting agents, pro-penetrating agents, gelling agents, emulsifiers, co-emulsifiers, and mixtures and/or combinations thereof.

In some embodiments the composition is formulated as an emulsion (including an oil-in-water emulsion, a water-in-oil emulsion, multiple emulsions and microemulsions). In other embodiments, the composition is formulated as a cream.

The compositions described in exemplary embodiments herein are pharmaceutical compositions, and especially dermatological compositions, which can be in any galenical form

conventionally used for topical application. By addition of a fatty or oily phase, they can also be in the form of dispersions of the lotion or serum type, emulsions of liquid or semi-liquid consistency of the milk type obtained by dispersing a fatty phase in an aqueous phase (O/W) or conversely (W/O), or suspensions or emulsions of soft, semiliquid or solid consistency of the cream, gel or ointment type, or alternatively multiple emulsions (W/O/W or O/W/O), microemulsions, microcapsules, microparticles and/or vesicular dispersions of ionic and/or nonionic type, and/or wax/aqueous phase dispersions. These compositions are formulated according to the usual methods.

In further embodiments, the composition comprises, as a single pharmaceutical active agent, benzoyl peroxide in a solid form, for topical use in the treatment of rosacea, is an oil in water emulsion comprising a polyoxylstearate and a glycerylstearate. Various methods for the preparation of the BPO-containing compositions are described in U.S. Application Publication Nos. 2010/0016443, 2017/0281571 and 2018/0147165 and U.S. Patent No. 9,687,465.

In some embodiments, the ratio of said polyoxylstearate to said glycerylstearate is in the range of about 0.1:10 to about 10:0.1.

In yet further embodiments, said polyoxylstearate is selected from the group consisting of Polyoxyl-8 stearate, Polyoxyl-20 stearate, Polyoxyl-40 stearate, Polyoxyl-100 stearate and combinations and/or mixtures thereof.

In further embodiments, said glycerylstearate is selected from the group consisting of glyceryl mono-stearate, glyceryl di-stearate and combinations and/or mixtures thereof.

In other embodiments, said polyoxylstearate in said composition is in the range of from about 0.1% w/w to about 30% w/w.

In further embodiments, the amount of said glycerylstearate in said composition is in the range of from about 0.1% w/w to about 30% w/w.

In other embodiments, said composition further comprises at least one fatty alcohol.

In other embodiments, said at least one fatty alcohol is selected from the group consisting of octyl alcohol, 2-ethyl hexanol. nonyl alcohol, decyl alcohol, undecanol, dodecyl alcohol, tridecyl alcohol, tetradecyl alcohol, pentadecyl alcohol, cetyl alcohol, palmitoleyl alcohol, heptadecyl alcohol, cetostearyl alcohol, stearyl alcohol, isostearyl alcohol, elaidyl alcohol, oleyl alcohol, linoleyl alcohol, elaidolinolenyl alcohol, ricinoleyl alcohol, nonadecyl alcohol, arachidyl alcohol, heneicosyl alcohol. behenyl alcohol, erucyl alcohol, lignoceryl alcohol, ceryl alcohol, montanyl alcohol, cluytyl alcohol, myricyl alcohol, melissyl alcohol, geddyl alcohol, cetearyl alcohol and combinations and/or mixtures thereof.

In further embodiments, the amount of said at least one fatty alcohol in said composition is in the range of from about 0.2% w/w to about 50% w/w.

In yet other embodiments, said composition further comprises a polyacrylic acid homopolymer or copolymer.

In other embodiments, said oil in said oil in water emulsion is selected from the group consisting of paraffin oil, isopropyl myristate, caprylic/capric triglyceride, squalane, squalene, almond oil, castor oil, olive oil, jojoba oil, sunflower oil, soybean oil, grape seed oil, dimethicone, cyclomethicone and combinations and/or mixtures thereof.

In further embodiments, said oil in present in the composition in an amount in the range of from about 0.05% w/w to about 50% w/w.

In some embodiments, said water in said oil in water emulsion further comprises at least one water soluble humectant.

In other embodiments, said at least one water soluble humectant is selected from the group consisting of propylene glycol, glycerin, polyethylene glycol-X and combinations and/or mixtures thereof, where X is in the range of from about 200 to about 10,000.

In some embodiments, the composition comprises said solid BPO in a controlled and/or slowed release drug delivery system. In further embodiments, said controlled and/or slowed

release drug delivery system is an encapsulation in a microcapsule, wherein said solid BPO is embedded in said microcapsule. When referring to a "controlled and/or slowed release drug delivery system" it should be understood to relate to a delivery system (which in the present application is a topical delivery system) that enables the release of the pharmaceutical active agent in predetermined amounts over a specified period. In some embodiments, said system is a core-shell system of a microcapsule and/or a porous matrix structure, such as, for example, a microsponge. The term "embedded" should be understood to encompass an inert system that provides a barrier between the pharmaceutical active agent, i.e. BPO, and its surrounding environment in the composition. In some embodiments, said agent is entrapped and/or encapsulated in said controlled release system.

In some embodiments, said core of said microcapsule comprises or consists of said solid BPO.

In some further embodiments, said microcapsules are a core shell microcapsule. The shell comprises at least one inorganic polymer. In some other embodiments, said inorganic polymer of said shell is a metal oxide or semi-metal oxide shell (layer).

In some embodiments, said microcapsule comprises a metal oxide or semi-metal oxide coating or layer (shell) and a core comprising or consisting of solid BPO.

In some embodiments, said microcapsule comprises a metal oxide or semi-metal oxide coating or layer (shell) and a core comprising solid BPO is prepared by a process comprising the steps of:

(a) contacting a solid BPO particulate matter with an ionic additive and an aqueous medium to obtain a dispersion of said particulate matter having positive charges on its surface;

(b) subjecting the particulate matter to a coating procedure comprising precipitating a metal oxide salt onto the surface of the particulate matter to form a metal oxide layer thereon thereby to obtain particulate matter coated by a metal oxide coating layer;

(c) repeating step (b) at least 4 more times: and

(d) aging said coating layer.

As used herein, the term "solid BPO particulate matter" refers to a solid BPO having solubility in water of less than about 1% w/w, typically less than about 0.5% and at times less than about 0.1% w/w at room temperature (about 20°C). The "solid BPO particulate matter" constitutes the "core" of the particles obtained by the process. The solid BPO particulate matter, is, in some embodiments, in such a state of subdivision that it can be suspended in water, e.g., in the form of a finely-divided powder having a D_{90} (see definition below), in some embodiments in the range of from about 0.3 to about 50 microns. Such a particulate matter can be readily suspended in an aqueous systems by stirring, with or without the aid of a surfactant.

The terms "solid BPO particulate matter" and "particulate matter" will be used interchangeably.

In the present application, the terms "layer", "coating" or "shell" and similar terms, refer to a layer of metal oxide or semi-metal oxide formed around a particle or particulate matter. The layer or coating need not always be complete or uniform and need not necessarily lead to complete coverage of the particulate matter or particle surface. It is appreciated that upon repetition of the coating steps as the coating process proceeds a more uniform coating and more complete coverage of the particulate matter is obtained.

The term "dispersion," as used herein, in step (a) of the process refers to a solid dispersion of the particulate matter in the aqueous medium. Step (a) of the process can further comprise reducing the particle size of the particulate matter to the desired particle size, for example, by milling or homogenization.

The core (i.e., solid, BPO particulate matter) can be of any shape, for example, rod-like, plate-like, ellipsoidal, cubic, spherical shape, combinations thereof and the like.

Reference to the size of particles will be made through their D_{90}, which means that about 90% of the particles have the stated dimension or less (measured by volume). Thus, for example, for spherical particles stated to have a diameter of about 10 micrometer ("microns"), this means that the particles have a D_{90} of about 10 microns. The D_{90} can be measured by laser diffraction. For particles having a shape other than spheres, the D_{90} refers to the mean average of the diameter of a plurality of particles.

In the case of cores having a spherical shape, the D_{90} can be in the range of from about 0.3 to 90 microns, in some embodiments from about 0.3 to about 50 microns, in some other embodiments from about 1 to about 50 microns, in some further embodiments from about 5 to about 30 microns, and in some embodiments all values therebetween, including about 0.5 microns, about 1 micron, about 2 micron, about 3 micron, about 4 micron, about 5 micron, about 10 microns, about 20 microns, about 30 microns, about 40 microns, about 50 microns, about 60 microns, about 70 microns, about 80 microns, and the like. By the term "D_{90} can be in the range of from about 0.3 microns to about 90 microns" is meant that about 90% by volume of the particles (in this case the particle's core) can be less than or equal to a value in the range of from about 0.3 microns to about 90 microns.

For generally cubic-shaped cores or cores having a shape resembling that of a cube, the mean size of a side can be in the range of from about 0.3 to about 80 microns, in some embodiments from about 0.3 to about 40 microns, in some further embodiments from about 0.8 to about 40 microns, in some further embodiments from about 4 to about 15 microns.

For rod-like shaped, ellipsoidal-shaped and plate-like shaped cores, the largest dimension (that of the longest axis) is typically in the range of from about 10 to about 100 microns, in some embodiments from about 15 to about 50 microns; and the smallest dimension is typically in the range of from about 0.5 to about 20 microns, in some further embodiments from about 2 to about 10 microns.

As used herein, unless otherwise indicated, the term "particle" refers to the metal oxide or semi-metal oxide coated particulate matter.

It is appreciated that some of the particles obtained by the process can at times be formed from two or more original particles of the solid BPO particulate and can accordingly include at times more than one core, such cores being separated from each other by a metal oxide region.

The weight of the solid BPO particulate (core material) based on the total weight of the particle can be in the range of from about 99% w/w to about 50% w/w, in some embodiments in the range of from about 97% w/w to about 50% w/w. The core material can be in a crystalline form, amorphous form, or combination thereof. The core material can be a cosmetic, pharmaceutical or an agrochemical active ingredient.

EXEMPLARY EMBODIMENTS

BPO-containing compositions were prepared following the various preparation methods described in U.S. Application Publication Nos. 2010/0016443, 2017/0281571 and 2018/0147165 and U.S. Patent No. 9,687,465, the contents of which are incorporated herein, by reference, in their entirety.

Description: A multi-center, double-blind, randomized, vehicle-controlled, dose-range study of encapsulated 5% benzoyl peroxide (E-BPO) Cream and vehicle cream was performed to assess the efficacy and safety of E-BPO compared to vehicle. Study duration was 12 weeks (84 days) and included approximately 350 male and female patients afflicted with papulopustular rosacea. Patients were at least 18 years of age, and met the inclusion/exclusion criteria described herein.

Dosing: Patients were randomized in a 2:1 ratio to the study product or vehicle treatment group, respectively. Patients applied the study product once daily for 12 weeks on the face in a thin layer.

Clinical and Safety Evaluations will be performed at:

1. Visit 1/Screening
2. Visit 2/Baseline, Day 1
3. Visit 3/Week 2, Day 15
4. Visit 4/Week 4, Day 29
5. Visit 5/Week 8, Day 57
6. Visit 6/Week 12, Day 85

Patients were admitted into the study after a clinical diagnosis of rosacea.

Patients completed a Patient Reported Outcomes (PRO) questionnaire at Baseline and Visit 2, 3, 4, 5 and 6.

Patient Reported Outcomes (PRO):

Patient Reported Outcome (PRO) questionnaires, including Patient Assessment of Papulopustular Rosacea Signs and Symptoms (PAPSS) and Patient Assessment of Papulopustular Rosacea Impacts (PAPI), were administered to all patients during the designated study visits with instruction from the study staff that they be completed:

- Only by the patient without amendment or interpretation of the patient's response by a clinician or anyone else.
- Prior to any other assessments or procedures.

The PAPSS is a 4-item questionnaire that asks patients to assess the severity of their rosacea symptoms (burning, itching, redness, and bumps) in the 24 hours prior to assessment on an 11-point numeric rating scale (NRS) ranging from "0=none" to "10=worst possible symptom. Items can be scored individually as well as together to form a total score. In the subject study,

scores of the symptoms burning, itching and bumps were added to create a total score used to evaluate efficacy hypotheses.

The PAPI is a 3-item questionnaire that asks patients to assess the papulopustular rosacea related embarrassment, self-consciousness, and frustration in the 7 days prior to assessment on an 11-point NRS ranging from 0 ["not at all"] to 10 ["extremely"]. Items can be scored individually as well as together to form a total score.

RESULTS:

Baseline Characteristics:

The Baseline characteristics were similar among the treatment groups. Patients selected for the treatment groups of this study suffered from moderate and severe rosacea, with a numerically higher percentage of subjects suffering from moderate rosacea. The baseline numerical percentage of treatment groups suffering from moderate and severe rosacea were similar for 5% E-BPO Cream and for Vehicle Cream.

Patient Reported Outcome - PAPSS:

Patient reported outcomes of several papulopustular signs and symptoms - burning, itching, redness and burning - were recorded at Baseline and Weeks 2, 4, 8 and 12. Subjects treated with 5% E-BPO Cream and subjects treated with Vehicle Cream completed the PAPSS questionnaire, and rated the appearance of the papulopustular signs and symptoms on the numerical range scale from "0=none" to "10=worst possible symptom". The results for each of Weeks 2, 4, 8 and 12 are shown in Table 1 below, and presented in Figs. 1A to 1D.

Table 1: PAPSS Assessment

		5% E-BPO Cream			Vehicle Cream		
		Baseline	Change from Baseline	% Change from Baseline	Baseline	Change from Baseline	% Change from Baseline
Week 2	Burning	2.9	-0.9	-31.0	2.6	-0.7	-26.9
	Itching	3.3	--1.3	-39.4	3.1	-1.1	-35.5
	Redness	5.8	-1.9	-32.8	5.7	-1.0	-17.5
	Bumps	5.0	-2.0	-40.0	4.8	-1.0	-20.8
Week 4	Burning	2.9	-1.5	-51.7	2.6	-0.8	-30.8
	Itching	3.3	-1.8	-54.5	3.1	-1.2	-38.7
	Redness	5.8	-2.6	-44.8	5.7	-1.4	-24.6
	Bumps	5.0	-2.5	-50.0	4.8	-1.4	-29.2
Week 8	Burning	2.9	-1.8	-62.1	2.6	-1.0	-38.5
	Itching	3.3	-2.1	-63.6	3.1	-1.3	-41.9
	Redness	5.8	-3.0	-51.7	5.7	-1.8	-31.6
	Bumps	5.0	-3.2	-64.0	4.8	-1.8	-37.5
Week 12	Burning	2.9	-1.8	-62.1	2.6	-0.7	-26.9
	Itching	3.3	-2.1	-63.6	3.1	-1.3	-41.9
	Redness	5.8	-3.1	-53.4	5.7	-1.8	-31.6
	Bumps	5.0	-3.2	-64.0	4.8	-1.5	-31.3

The total assessment of three of the four symptoms - burning, itching and bumps - are shown in Table 2 below, and presented in Fig. 2.

Table 2: Total Change in PAPSS Assessment

		Baseline	Change from Baseline	% Change from Baseline
5% E-BPO Cream	Week 2	17.0	-6.1	-35.9
	Week 4	17.0	-8.4	-49.4
	Week 8	17.0	-10.1	-59.4
	Week 12	17.0	-10.2	-60.0
Vehicle Cream	Week 2	16.1	-3.7	-23.0
	Week 4	16.1	-4.8	-29.8
	Week 8	16.1	-5.9	-36.6
	Week 12	16.1	-5.2	-32.3

Patient Reported Outcome - PAPI:

Patient reported outcomes of several impacts of papulopustular rosacea - embarrassment, self-consciousness and frustration - were recorded at Baseline and Weeks 2, 4, 8 and 12. Subjects treated with 5% E-BPO Cream and subjects treated with Vehicle Cream completed the PAPSS questionnaire, and rated the appearance of the papulopustular signs and symptoms on the numerical range scale from "0=none" to "10=worst possible symptom". The results for each of Weeks 2, 4, 8 and 12 are shown in Table 3 below, and presented in Figs. 3A to 3D.

Table 3: PAPI Assessment

		5% E-BPO Cream			Vehicle Cream		
		Baseline	Change from Baseline	% Change from Baseline	Baseline	Change from Baseline	% Change from Baseline
Week 2	Embarrassment	5.8	-2.2	-37.9	5.7	-1.4	-24.6
	Self-consciousness	6.1	-2.2	-36.1	6.0	-1.5	-25.0
	Frustration	6.2	-2.5	-40.3	6.1	-1.4	-23.0
Week 4	Embarrassment	5.8	-2.7	-46.6	5.7	-1.8	-31.6
	Self-consciousness	6.1	-2.8	-48.3	6.0	-1.8	-31.6
	Frustration	6.2	-3.1	-53.4	6.1	-2.0	-35.1
Week 8	Embarrassment	5.8	-3.6	-62.1	5.7	-2.1	-36.58
	Self-consciousness	6.1	-3.6	-62.1	6.0	-2.3	-40.4
	Frustration	6.2	-4.0	-69.0	6.1	-2.5	-43.9
Week 12	Embarrassment	5.8	-3.5	-60.3	5.7	-2.1	-36.8
	Self-consciousness	6.1	-3.7	-63.8	6.0	-2.3	-40.4
	Frustration	6.2	-3.9	-67.2	6.1	-2.1	-36.8

The average assessment of the impact of papulopustular rosacea is shown in Table 4 below, and presented in Fig. 4.

Table 4: Average Change in PAPI Assessment

		Baseline	Change from Baseline	% Change from Baseline
5% E-BPO Cream	Week 2	6.03	-2.31	-38.25
	Week 4	6.03	-2.86	-47.35
	Week 8	6.03	-3.72	-61.59
	Week 12	6.03	-3.69	-61.09
Vehicle Cream	Week 2	5.92	-1.46	-24.66
	Week 4	5.92	-1.85	-31.25
	Week 8	5.92	-2.30	-38.85
	Week 12	5.92	-2.15	-36.32

As shown in Table 1 above, and FIGS. 1A to 1D, the decrease in signs and symptoms of papulopustular rosacea, such as burning, itching, redness and burning, based on patient reported outcome, decreases at a much higher rate when treated with 5% E-BPO cream compared to treatment with vehicle cream alone. For example, in as little as about 4 weeks, the percentage change from baseline for burning, itching redness and bumps is between about 40% and about 55% when treated with 5% E-BPO compared to a percentage decrease from baseline of less than about 40% when treated with vehicle alone.

This result is even more significant after treatment for about 8 weeks to about 12 weeks. For example, the patient assessment of signs and symptom is significantly improved by about 52% to about 64% in burning, itching, redness and bumps after treatment with 5% E-BPO whereas the patient reported improvement in burning, itching, redness and bumps is only from about 25% to about 42%. In addition, the 5% E-BPO cream works very fast and maximum improvement was achieved after as little as about 8 weeks of treatment. These results are summarized as a total change in signs and symptoms in Table 2 and FIG. 2.

Similar results are also observed for patient reported outcome for papulopustular rosacea-related impacts, such as embarrassment, self-consciousness and frustration. For

example, as shown in Table 3, and FIGS. 3A to 3D, the decrease in the psychological effects of embarrassment, self-consciousness and frustration on study subjects decreased significantly after treatment with 5% E-BPO. For example, the decrease in embarrassment, self-consciousness and frustration in study subjects decrease by about 60% to about 70% after treatment with 5% E-BPO after only about 8 weeks, whereas the decrease in these effects was less than about 45% after treatment with vehicle cream alone. The average decrease in these impacts after about 2 weeks, about 4 weeks, about 8 weeks and about 12 weeks is shown in Table 4 and FIG. 4.

Rapid onset of the decrease in feelings of embarrassment, self-consciousness and frustration was observed in study subjects. For example, as shown in Table 4, there was an improvement of about 40% in a patient's assessment of these feelings after treatment with 5% E-BPO for only about 2 weeks compared to a decrease of only about 25% after treatment with vehicle cream alone for about 2 weeks. As also shown in Table 4, the average improvement in PAPI values after treatment with 5% E-BPO after only about 8 weeks of treatment was approximately about twice the values observed after treatment with vehicle cream alone.

Although the exemplary embodiments of the present disclosure have been described in detail with reference to the accompanying examples and drawings, the present disclosure is not limited thereto and can be embodied in many different forms without departing from the technical concept of the present disclosure. Therefore, the exemplary embodiments of the present disclosure are provided for illustrative purposes only and are not intended to limit the technical concept of the present disclosure. The protective scope of the present disclosure should be construed based on any appended claims and combinations thereof, and all the technical concepts in the equivalent scope thereof should be construed as falling within the scope of the present disclosure. As various changes could be made in the above methods and compositions without departing from the scope of the invention, it is intended that all matter

contained in the above description shall be interpreted as illustrative and not in a limiting sense. Other embodiments within the scope of the claims herein will be apparent to one skilled in the art from consideration of the specification or practice of the exemplary embodiments disclosed herein. It is intended that the specification be considered exemplary only, with the scope and spirit of the described subject matter being indicated by the claims.

CLAIMS

What is claimed is:

1. A regimen for the therapeutic treatment of rosacea, the regimen comprising topically applying to the skin of a subject in need of said treatment a pharmaceutical composition, the pharmaceutical composition comprising about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, wherein said pharmaceutical composition is applied once daily for a period of at least about 2 weeks, about 4 weeks, about 8 weeks or about 12 weeks, wherein a decrease in Patient Assessment of Papulopustular Rosacea Signs and Symptoms (PAPSS) is at least about 30% after treatment with said pharmaceutical composition for about 2 weeks.

2. The regimen of claim 1, wherein the decrease in PAPSS is about 20% after treatment with vehicle alone after about 2 weeks.

3. A regimen for the therapeutic treatment of rosacea, the regimen comprising topically applying to the skin of a subject in need of said treatment a pharmaceutical composition, the pharmaceutical composition comprising about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, wherein said pharmaceutical composition is applied once daily for a period of at least about 2 weeks, about 4 weeks, about 8 weeks or about 12 weeks, wherein a decrease in Patient Assessment of Papulopustular Rosacea Signs and Symptoms (PAPSS) is at least about is at least about 40% after treatment with said pharmaceutical composition for about 4 weeks.

4. The regimen of claim 3, wherein the decrease in PAPSS is less than about 40% after treatment with vehicle alone for about 4 weeks.

5. A regimen for the therapeutic treatment of rosacea, the regimen comprising topically applying to the skin of a subject in need of said treatment a pharmaceutical composition, the pharmaceutical composition comprising about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, wherein said pharmaceutical composition is applied once daily for a period of at least about 2 weeks, about 4 weeks, about 8 weeks or about 12 weeks, wherein a decrease in PAPSS is from about 50% to about 65% after treatment with said pharmaceutical composition for at least about 8 weeks.

6. The regimen of claim 5, wherein the decrease in PAPSS is from about 25% to about 40% after treatment with vehicle alone for at least about 8 weeks.

7. The regimen of any one of claims 1-6, wherein the benzoyl peroxide is the sole active ingredient administered to the subject in need of said treatment during the duration of the regimen.

8. The regimen of any one of claims 1-7, wherein said pharmaceutical composition comprises about 2.5% w/w to about 10% w/w of benzoyl peroxide.

9. The regimen of any one of claims 1-8, wherein the pharmaceutical composition comprises about 5% w/w of benzoyl peroxide.

10. The regimen of any one of claims 1-9, wherein said benzoyl peroxide is in a form selected from solid, solution or suspension.

11. The regimen of any one of claims 1-10, wherein the rosacea is any of erythematotelengietatic, papulopustular, phymatous or ocular rosacea.

12. The regimen of any one of claims 1-11, wherein said pharmaceutical composition is a cream or an emulsion.

13. The regimen of any one of claims 1-12, wherein said pharmaceutical composition is an extended release formulation.

14. The regimen of claim 13, wherein the extended-release effect is obtained by encapsulation, microencapsulation, microspheres or coating.

15. The regimen of claim 14, wherein the benzoyl peroxide is encapsulated and/or microencapsulated.

16. The regimen of claim 14, wherein the benzoyl peroxide is included in a microsphere and/or a coating.

17. The regimen of claims 1-16, wherein the papulopustular rosacea signs and symptoms are selected from burning, itching, redness, bumps, and combinations thereof, on the skin of a subject.

18. A regimen for the therapeutic treatment of rosacea, the regimen comprising topically applying to the skin of a subject in need of said treatment a pharmaceutical composition, the pharmaceutical composition comprising about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, wherein said pharmaceutical composition is applied once daily for a period of at least about 2 weeks, about 4 weeks, about 8 weeks or about 12 weeks, wherein a decrease in Patient Assessment of Papulopustular Rosacea Impacts (PAPI) is at least about 35% after treatment with said pharmaceutical composition for about 2 weeks.

19. The regimen of claim 18, wherein the decrease in PAPI is at least about 40% after treatment with said pharmaceutical composition for about 2 weeks.

20. The regimen of any one of claims 18 and 19, wherein the decrease in PAPI impacts is about 23% after treatment with vehicle alone for about 2 weeks.

21. A regimen for the therapeutic treatment of rosacea, the regimen comprising topically applying to the skin of a subject in need of said treatment a pharmaceutical composition, the pharmaceutical composition comprising about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, wherein said pharmaceutical composition is applied once daily for a period of at least about 2 weeks, about 4 weeks, about 8 weeks or about 12 weeks, wherein a decrease in PAPI is from about 60% to about 70% after treatment with said pharmaceutical composition for at least about 8 weeks.

22. The regimen of claim 21, wherein the decrease in patient assessment of papulopustular rosacea impacts is about 35% after treatment with vehicle alone for at least about 8 weeks.

23. The regimen of any one of claims 18-22, wherein the benzoyl peroxide is the sole active ingredient administered to the subject in need of said treatment during the duration of the regimen.

24. The regimen of any one of claims 18-23, wherein said pharmaceutical composition comprises about 2.5% w/w to about 10% w/w of benzoyl peroxide.

25. The regimen of any one of claims 18-24, wherein the pharmaceutical composition comprises about 5% w/w of benzoyl peroxide.

26. The regimen of any one of claims 18-25, wherein said benzoyl peroxide is in a form selected from solid, solution or suspension.

27. The regimen of any one of claims 18-26, wherein the rosacea is any of erythematotelengietatic, papulopustular, phymatous or ocular rosacea.

28. The regimen of any one of claims 18-27, wherein said pharmaceutical composition is a cream or an emulsion.

29. The regimen of any one of claims 18-28, wherein said pharmaceutical composition is an extended release formulation.

30. The regimen of claim 29, wherein the extended-release effect is obtained by encapsulation, microencapsulation, microspheres or coating.

31. The regimen of claim 30, wherein the benzoyl peroxide is encapsulated and/or microencapsulated.

32. The regimen of claim 30, wherein the benzoyl peroxide is included in a microsphere and/or a coating.

33. The regimen of any one of claims 18-32, wherein an average decrease in the PAPI after treatment with said pharmaceutical composition for at least about 8 weeks is approximately about 1.2 times to two times an average decrease in the PAPI after treatment with vehicle alone.

34. The regimen of any one of claims 18-33, wherein the papulopustular rosacea impact is selected from embarrassment, self-consciousness and frustration.

35. A pharmaceutical composition for use as a medicament for the therapeutic treatment of rosacea, the pharmaceutical composition comprising from about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, wherein said pharmaceutical composition is applied once daily for a period of at least about 2 weeks, about 4 weeks, about 8 weeks or about 12 weeks, wherein a decrease in Patient Assessment of Papulopustular Rosacea Signs and Symptoms (PAPSS) is at least about 30% after treatment with said pharmaceutical composition for about 2 weeks.

36. The pharmaceutical composition of claim 35, wherein the decrease in PAPSS is about 20% after treatment with vehicle alone for about 2 weeks.

37. A pharmaceutical composition for use as a medicament for the therapeutic treatment of rosacea, the pharmaceutical composition comprising from about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, wherein said pharmaceutical composition is applied once daily for a period of at least about 2 weeks, about 4 weeks, about 8 weeks or about 12 weeks, wherein a decrease in Patient Assessment of Papulopustular Rosacea Signs and Symptoms (PAPSS) is at least about 40% after treatment with said pharmaceutical composition for about 4 weeks.

38. The pharmaceutical composition of claim 37, wherein the decrease in PAPSS is less than about 40% after treatment with vehicle alone for about 4 weeks.

39. The pharmaceutical composition of any one of claims 35-38, wherein said pharmaceutical composition comprises from about 2.5% w/w to about 10% w/w of benzoyl peroxide.

40. The pharmaceutical composition of any one of claims 35-39, wherein said pharmaceutical composition comprises about 5% of benzoyl peroxide.

41. The pharmaceutical composition of any one of claims 35-40, wherein said benzoyl peroxide is in a form selected from solid, solution or suspension.

42. The pharmaceutical composition of any one of claims 35-41, wherein the rosacea is any of erythematotelengietatic, papulopustular, phymatous or ocular rosacea.

43. The pharmaceutical composition of any one of claims 35-42, wherein said pharmaceutical composition is a cream or an emulsion.

44. The pharmaceutical composition of any one of claims 35-43, wherein said pharmaceutical composition is an extended release formulation.

45. The pharmaceutical composition of claim 44, wherein the extended-release effect is obtained by at least one of encapsulation, microencapsulation, microspheres, coating and combinations thereof.

46. The pharmaceutical composition of claim 45, wherein the benzoyl peroxide is encapsulated and/or microencapsulated.

47. The pharmaceutical composition of claim 45, wherein the benzoyl peroxide is included in a microsphere and/or a coating.

48. A pharmaceutical composition for use as a medicament for the therapeutic treatment of rosacea, the pharmaceutical composition comprising from about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, wherein said pharmaceutical composition is applied once daily for a period of at least about 2 weeks, about 4 weeks, about 8 weeks or about 12 weeks, wherein a decrease in Patient Assessment of Papulopustular Rosacea Impacts (PAPI) is from about 60% to about 70% after treatment with said pharmaceutical composition for at least about 8 weeks.

49. The pharmaceutical composition of claim 48, wherein the decrease in PAPI is about 35% after treatment with vehicle alone for at least about 8 weeks.

50. The pharmaceutical composition of any one of claims 48 and 49, wherein said pharmaceutical composition comprises from about 2.5% w/w to about 10% w/w of benzoyl peroxide.

51. The pharmaceutical composition of any one of claims 48-50, wherein said pharmaceutical composition comprises about 5% of benzoyl peroxide.

52. The pharmaceutical composition of any one of claims 48-51, wherein said benzoyl peroxide is in a form selected from solid, solution or suspension.

53. The pharmaceutical composition of any one of claims 48-52, wherein the rosacea is any of erythematotelengietatic, papulopustular, phymatous or ocular rosacea.

54. The pharmaceutical composition of any one of claims 48-53, wherein said pharmaceutical composition is a cream or an emulsion.

55. The pharmaceutical composition of any one of claims 48-54, wherein said pharmaceutical composition is an extended release formulation.

56. The pharmaceutical composition of claim 55, wherein the extended-release effect is obtained by at least one of encapsulation, microencapsulation, microspheres, coating and combinations thereof.

57. The pharmaceutical composition of claim 56, wherein the benzoyl peroxide is encapsulated and/or microencapsulated.

58. The pharmaceutical composition of claim 56, wherein the benzoyl peroxide is included in a microsphere and/or a coating.

59. Use of a pharmaceutical composition for the treatment of rosacea, the pharmaceutical composition comprising from about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, wherein said pharmaceutical composition is applied once daily for a period of at least about 2 weeks, about 4 weeks, about 8 weeks or about 12 weeks, wherein a decrease in Patient Assessment of Papulopustular Rosacea Signs and Symptoms (PAPSS) is from about 50% to about 65% after treatment with said pharmaceutical composition for at least about 8 weeks.

60. The use of claim 59, wherein the decrease in PAPSS is from about 25% to about 40% after treatment with vehicle alone for at least about 8 weeks.

61. The use of any one of claims 59-60, wherein said pharmaceutical composition comprises from about 2.5% w/w to about 10% w/w of benzoyl peroxide.

62. The use of any one of claims 59-61, wherein said pharmaceutical composition comprises about 5% of benzoyl peroxide.

63. The use of any one of claims 59-62, wherein said benzoyl peroxide is in a form selected from solid, solution or suspension.

64. The use of any one of claims 59-63, wherein the rosacea is any of erythematotelengietatic, papulopustular, phymatous or ocular rosacea.

65. The use of any one of claims 59-64, wherein said pharmaceutical composition is a cream or an emulsion.

66. The use of any one of claims 59-65, wherein said pharmaceutical composition is an extended release formulation.

67. The use of claim 66, wherein the extended-release effect is obtained by at least one of encapsulation, microencapsulation, microspheres, coating and combinations thereof.

68. The use of claim 67, wherein the benzoyl peroxide is encapsulated and/or microencapsulated.

69. The use of claim 67, wherein the benzoyl peroxide is included in a microsphere and/or a coating.

70. Use of a pharmaceutical composition for the treatment of rosacea, the pharmaceutical composition comprising from about 1% w/w to about 10% w/w benzoyl peroxide as an active ingredient, and a pharmaceutically acceptable carrier or excipient, wherein the benzoyl peroxide is the only active ingredient in said pharmaceutical composition, wherein said pharmaceutical composition is applied once daily for a period of at least about 2 weeks, about 4 weeks, about 8 weeks or about 12 weeks, wherein a decrease in

Patient Assessment of Papulopustular Rosacea Impacts (PAPI) is from about 60% to about 70% after treatment with said pharmaceutical composition for at least about 8 weeks.

71. The use of claim 70, wherein the decrease in PAPI is about 35% after treatment with vehicle alone for at least about 8 weeks.

72. The use of any one of claims 70 and 71, wherein said pharmaceutical composition comprises from about 2.5% w/w to about 10% w/w of benzoyl peroxide.

73. The use of any one of claims 70-72, wherein said pharmaceutical composition comprises about 5% of benzoyl peroxide.

74. The use of any one of claims 70-73, wherein said benzoyl peroxide is in a form selected from solid, solution or suspension.

75. The use of any one of claims 70-74, wherein the rosacea is any of erythematotelengietatic, papulopustular, phymatous or ocular rosacea.

76. The use of any one of claims 70-75, wherein said pharmaceutical composition is a cream or an emulsion.

77. The use of any one of claims 70-76, wherein said pharmaceutical composition is an extended release formulation.

78. The use of claim 77, wherein the extended-release effect is obtained by at least one of encapsulation, microencapsulation, microspheres, coating and combinations thereof.

79. The use of claim 78, wherein the benzoyl peroxide is encapsulated and/or microencapsulated.

80. The use of claim 78, wherein the benzoyl peroxide is included in a microsphere and/or a coating.

FIGURE 1A

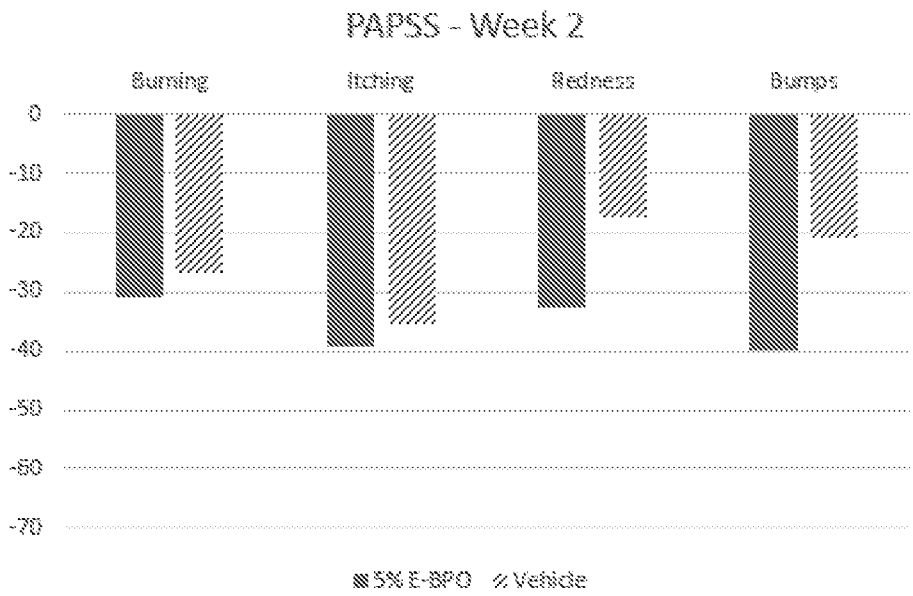

FIGURE 1B

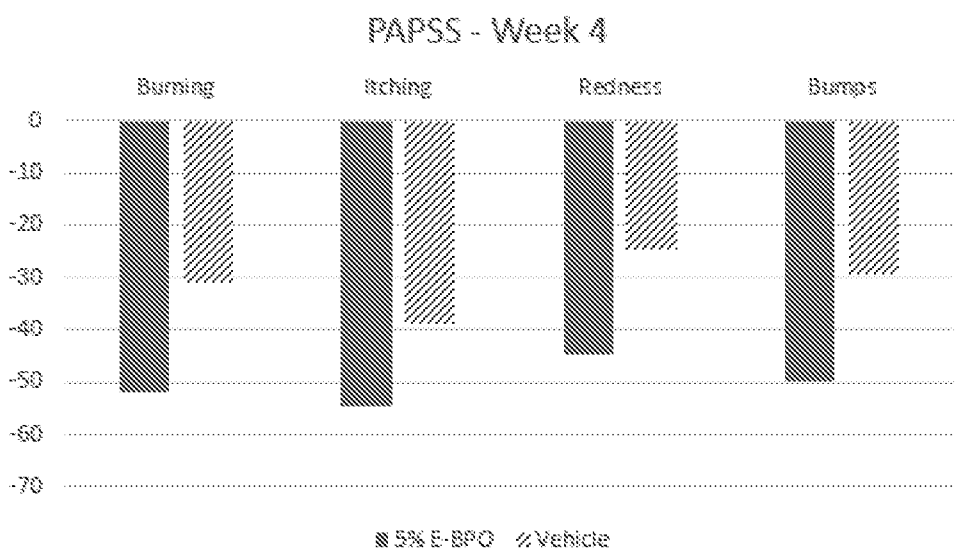

FIGURE 1C

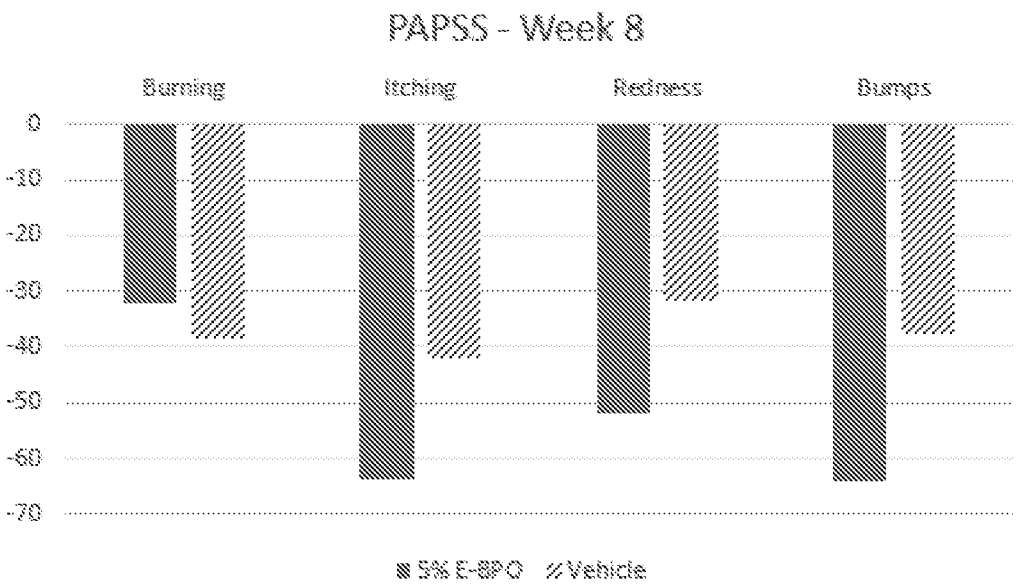

FIGURE 1D

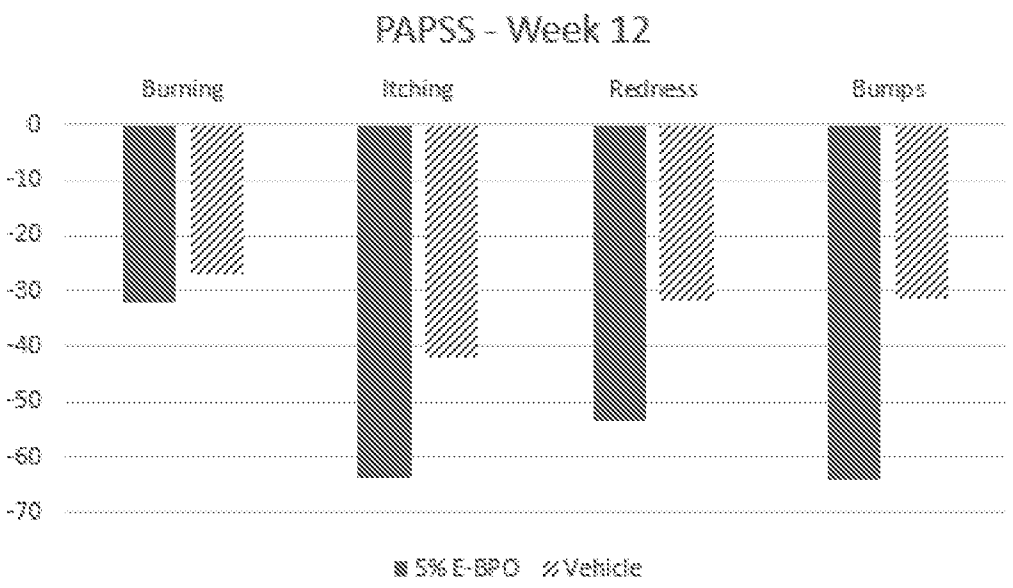

FIGURE 2

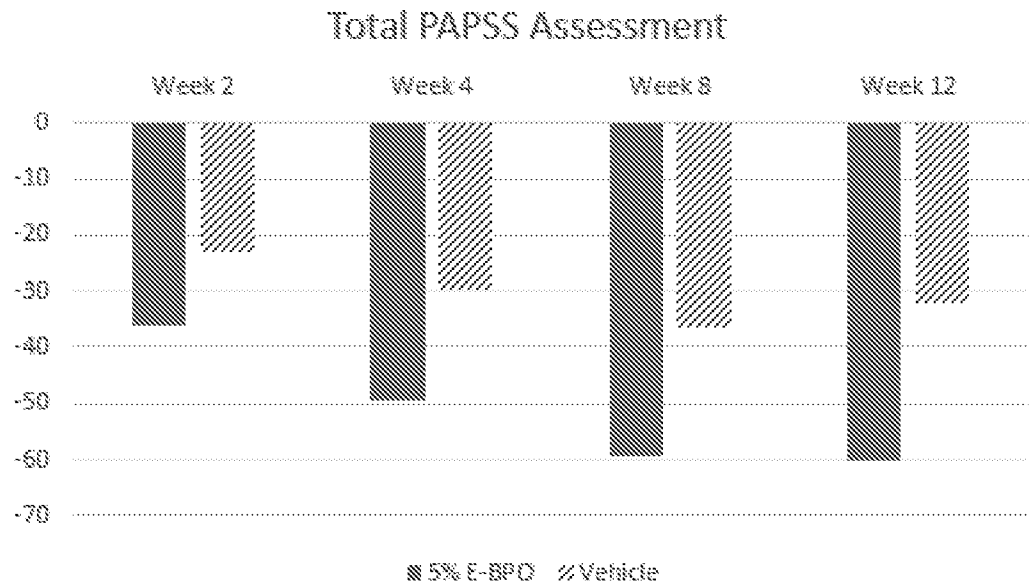

FIGURE 3A

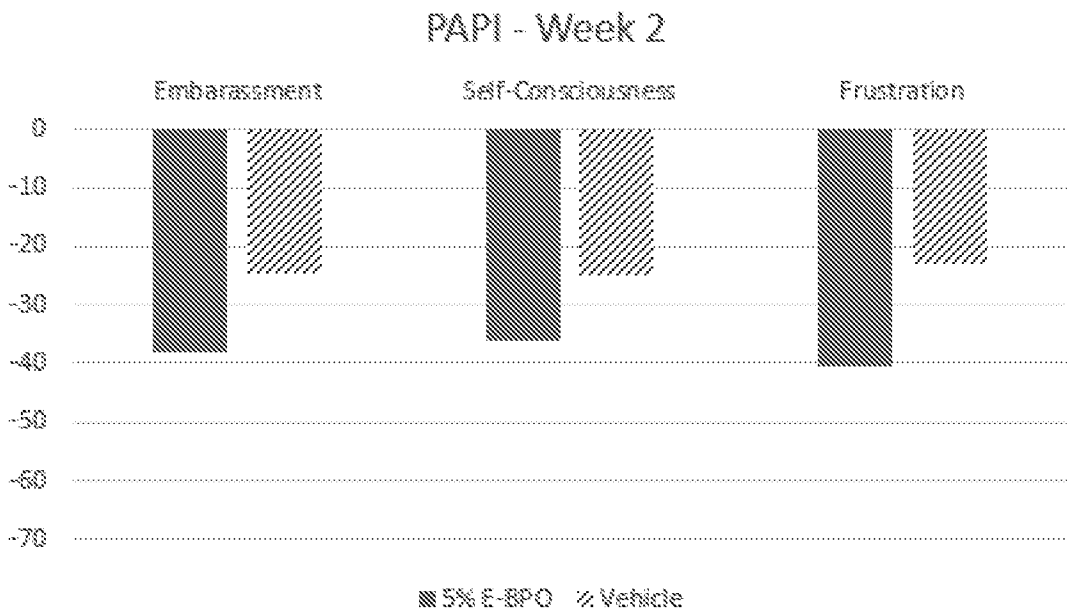

FIGURE 3B

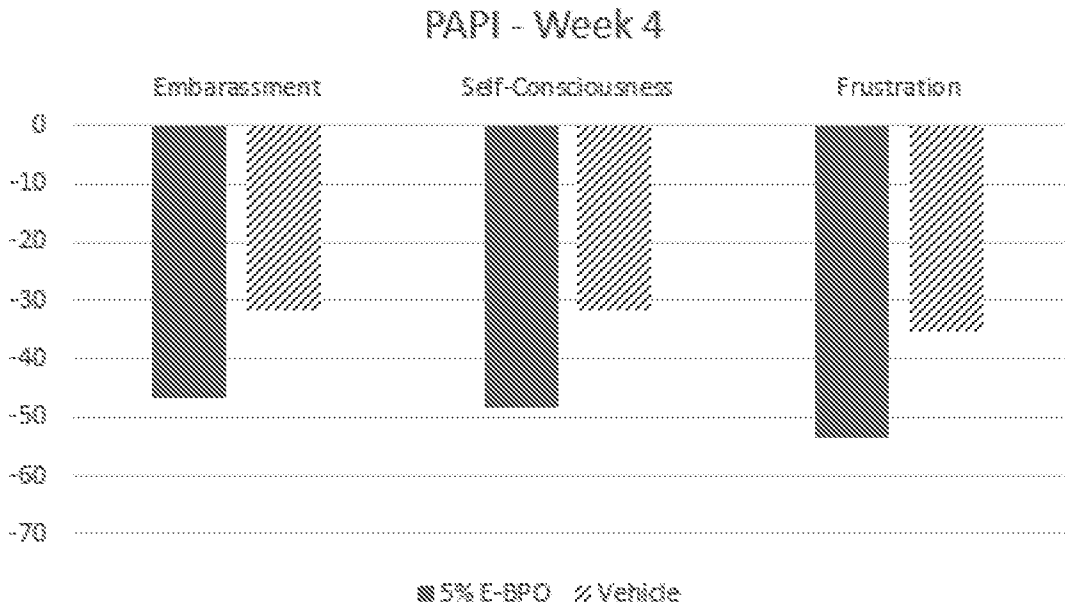

FIGURE 3C

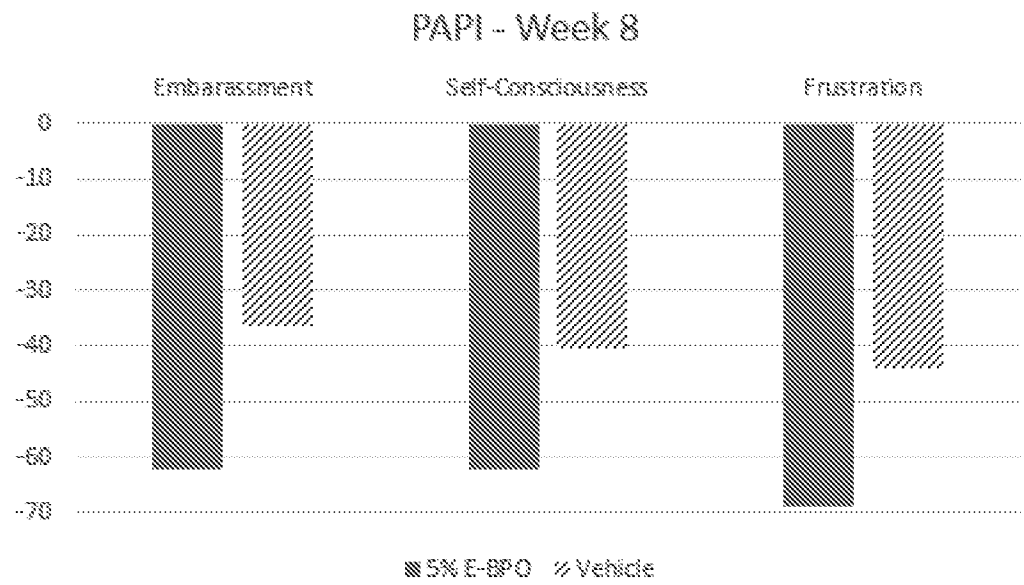

FIGURE 3D

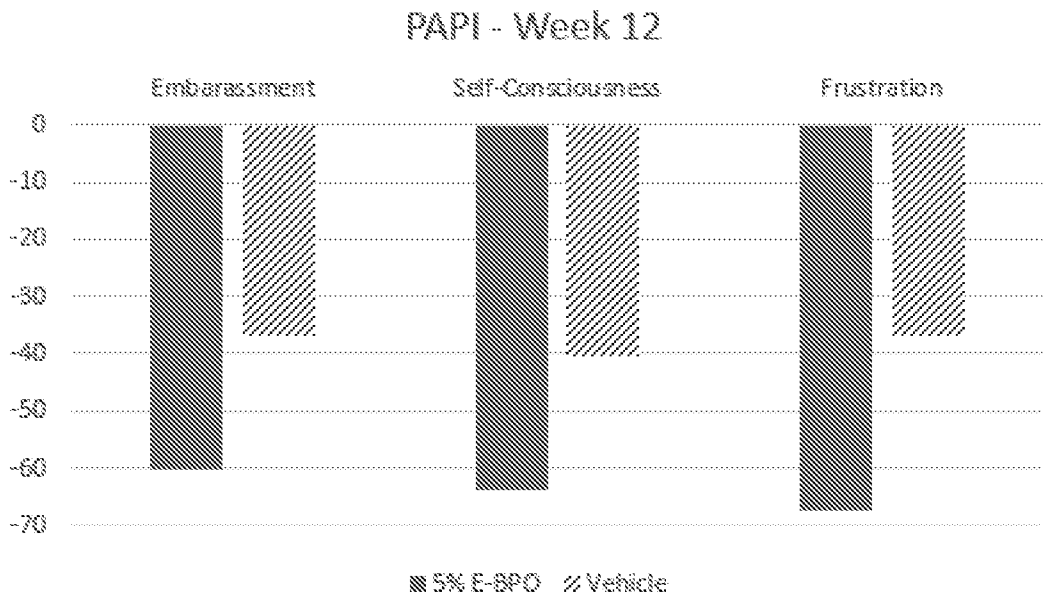

FIGURE 4