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(54) **Titre : EFFETS DE REMISSION DU TAPINAROF DANS LE TRAITEMENT DU PSORIASIS EN PLAQUES, DE LA DERMATITE
ATOPIQUE OU DE LA RADIODERMITE**
(54) **Title: REMITTIVE EFFECTS OF TAPINAROF IN THE TREATMENT OF PLAQUE PSORIASIS, ATOPIC DERMATITIS, OR
RADIATION DERMATITIS**

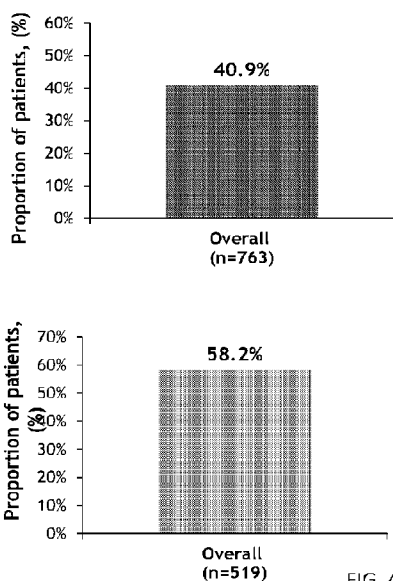


FIG. 4

(57) **Abstrégé/Abstract:**

Embodiments described herein are directed to methods for treating moderate to severe plaque psoriasis, atopic dermatitis, or radiation dermatitis in a subject comprising administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for an initial period of time until the plaque psoriasis, atopic dermatitis, or radiation dermatitis is clear at which time the administration is stopped, and reassessing the subject from about 3 months to about 12 months after administration is stopped to determine if further treatment is required. Also described is the remittive effect observed after once daily administration of 1% tapinarof cream.



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Abstract:

Embodiments described herein are directed to methods for treating moderate to severe plaque psoriasis, atopic dermatitis, or radiation dermatitis in a subject comprising administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for an initial period of time until the plaque psoriasis, atopic dermatitis, or radiation dermatitis is clear at which time the administration is stopped, and reassessing the subject from about 3 months to about 12 months after administration is stopped to determine if further treatment is required. Also described is the remittive effect observed after once daily administration of 1% tapinarof cream.

**REMITTIVE EFFECTS OF TAPINAROF IN THE TREATMENT OF PLAQUE
PSORIASIS, ATOPIC DERMATITIS, OR RADIATION DERMATITIS**

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to and benefit of U.S. Provisional Application No. 63/150,204 filed February 17, 2021, U.S. Provisional Application No. 63/260,322 filed August 17, 2021, U.S. Provisional Application No. 63/261,523 filed September 23, 2021, and U.S. Provisional Application No. 63/226,535 filed January 07, 2022, the entire contents of which are each hereby incorporated by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to methods of treating various chronic skin disorders and methods of achieving remission of the same.

SUMMARY

[0003] Embodiments of the invention are directed to methods for treating plaque psoriasis (PsO) in a subject in need thereof, comprising:

a. applying a thin layer of about 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for an initial period of time of at least 12 weeks, until the subject has a PGA score of 0, and a PASI score < the baseline PASI score and a DLQI score < the baseline DLQI score;

b. after the initial period of time, stop treating the subject with tapinarof for a remittive period of time of about 1 to about 7 months, wherein the remittive period of time is the time wherein the subject maintains a PGA score < 2; and

c. if, after the remittive period of time, the subject has a PGA score of ≥ 2 and the PASI score and DLQI score is $\geq$ the PASI score and DLQI score in step a. further applying a thin layer of 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for a further period of time, until the subject has a PGA score of 0; wherein

the 1.0% tapinarof topical cream composition does not prolong the QTc interval in the subject while applying the 1.0% tapinarof topical cream,

the plasma concentration of tapinarof in the subject is below 50 pg/mL while applying the 1.0% tapinarof topical cream, and

the subject selects a satisfaction rating of “agree” or “strongly agree” to one or more satisfaction questions selected from the group consisting of: 1) I can easily manage my psoriasis with the study drug; 2) The time spent applying the study drug every day was acceptable and did not affect my everyday life; 3) I am satisfied with how well the study drug worked for my psoriasis; 4) I have confidence in the study drug; 5) The study drug cleared my skin and kept my psoriasis from coming back; 6) If the study drug was available by prescription, I would recommend it to other patients with psoriasis; 7) If the study drug was available by a prescription, I would use it again or continue on it; 8) The study drug is easy to apply; 9) The study drug is not greasy; 10) The study drug quickly absorbs into my skin; 11) The study drug feels good on my skin; 12) I am satisfied with the look and feel of the study drug; 13) The study drug is more effective than other topical drugs I have used to treat my psoriasis; 14) The study drug is easier to use than other topical drugs I have used to treat my psoriasis; 15) I prefer the study drug to other topical drugs I have used to treat my psoriasis; 16) The study drug is more effective than systemic drugs I have used to treat my psoriasis; 17) The study drug is easier to use than systemic drugs I have used to treat my psoriasis; and 18) I prefer the study drug to systemic drugs I have used to treat my psoriasis.

[0004] In certain embodiments the plaque psoriasis is moderate or severe plaque psoriasis. In certain embodiments the initial period of time is about 12 weeks to about 52 weeks. In certain embodiments the remittive period is greater than 3 months and up to about 7 months. In certain embodiments the remittive period is about 4 months. In certain embodiments the further period of time is less than the initial period of time. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to three or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to five or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to ten or more of the satisfaction questions.

[0005] Embodiments of the invention are directed to a method for treating plaque psoriasis in a subject in need thereof, wherein the subject has achieved a PGA score of 0, a PASI score < their baseline PASI score, and a DLQI score < the baseline DLQI score, after applying a thin layer of about 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for an initial period of time of about 12 weeks to 52 weeks, comprising:

a. stopping treatment of the subject with tapinarof for a remittive period of time of about 1 to about 7 months, wherein the remittive period of time is the time wherein the subject has a PGA score < 2 , and

b. if, after the remittive period of time, the subject has a PGA score of > 2 and the PASI score and DLQI score is $>$ the PASI score and DLQI score in step a.; further applying a thin layer of 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for a further period of time until the subject has a PGA score of 0; wherein

the 1.0% tapinarof topical cream composition does not prolong the QTc interval in the subject while applying the 1.0% tapinarof topical cream,

the plasma concentration of tapinarof in the subject is below 50 pg/mL while applying the 1.0% tapinarof topical cream, and

the subject selects a satisfaction rating of “agree” or “strongly agree” to one or more satisfaction questions selected from the group consisting of:

1) I can easily manage my psoriasis with the study drug; 2) The time spent applying the study drug every day was acceptable and did not affect my everyday life; 3) I am satisfied with how well the study drug worked for my psoriasis; 4) I have confidence in the study drug; 5) The study drug cleared my skin and kept my psoriasis from coming back; 6) If the study drug was available by prescription, I would recommend it to other patients with psoriasis; 7) If the study drug was available by a prescription, I would use it again or continue on it; 8) The study drug is easy to apply; 9) The study drug is not greasy; 10) The study drug quickly absorbs into my skin; 11) The study drug feels good on my skin; 12) I am satisfied with the look and feel of the study drug; 13) The study drug is more effective than other topical drugs I have used to treat my psoriasis; 14) The study drug is easier to use than other topical drugs I have used to treat my psoriasis; 15) I prefer the study drug to other topical drugs I have used to treat my psoriasis; 16) The study drug is more effective than systemic drugs I have used to treat my psoriasis; 17) The study drug is easier to use than systemic drugs I have used to treat my psoriasis; and 18) I prefer the study drug to systemic drugs I have used to treat my psoriasis.

[0006] In certain embodiments the plaque psoriasis is moderate or severe plaque psoriasis. In certain embodiments the initial period of time is about 12 weeks to about 52 weeks. In certain embodiments the remittive period is greater than 3 months and up to about 7 months. In certain embodiments the remittive period is about 4 months. In certain

embodiments the further period of time is less than the initial period of time. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to three or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to five or more of the satisfaction questions.

[0007] Embodiments of the invention are directed to a method for treating plaque psoriasis in a subject in need thereof, wherein the subject has a PGA score of at least 1 point lower than baseline but has not achieved a PGA score of 0 after applying a thin layer of about 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for a period of time of about 12 weeks to about 52 weeks comprising continuing to applying a thin layer of about 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for an indefinite period of time, wherein the PGA score does not increase when applying a thin layer of about 1.0% tapinarof topical cream composition to the affected areas of the subject once a day;

wherein

the 1.0% tapinarof topical cream composition does not prolong the QTc interval in the subject while applying the 1.0% tapinarof topical cream,

the plasma concentration of tapinarof in the subject is below 50 pg/mL while applying the 1.0% tapinarof topical cream, and

the subject selects a satisfaction rating of “agree” or “strongly agree” to one or more satisfaction questions selected from the group consisting of: 1) I can easily manage my psoriasis with the study drug; 2) The time spent applying the study drug every day was acceptable and did not affect my everyday life; 3) I am satisfied with how well the study drug worked for my psoriasis; 4) I have confidence in the study drug; 5) The study drug cleared my skin and kept my psoriasis from coming back; 6) If the study drug was available by prescription, I would recommend it to other patients with psoriasis; 7) If the study drug was available by a prescription, I would use it again or continue on it; 8) The study drug is easy to apply; 9) The study drug is not greasy; 10) The study drug quickly absorbs into my skin; 11) The study drug feels good on my skin; 12) I am satisfied with the look and feel of the study drug; 13) The study drug is more effective than other topical drugs I have used to treat my psoriasis; 14) The study drug is easier to use than other topical drugs I have used to treat my psoriasis; 15) I prefer the study drug to other topical drugs I have used to treat my psoriasis; 16) The study drug is more effective than systemic drugs I have used to treat my psoriasis;

- 17) The study drug is easier to use than systemic drugs I have used to treat my psoriasis; and
18) I prefer the study drug to systemic drugs I have used to treat my psoriasis.

[0008] In certain embodiments the plaque psoriasis is moderate or severe plaque psoriasis. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to three or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to five or more of the satisfaction questions.

DESCRIPTION OF DRAWINGS

[0009] FIG. 1 provides a graph of the dosing over time.

[0010] FIG. 2 provides a graph of tapinarof and tapinarof sulfate (a metabolite of tapinarof) concentrations over time.

[0011] FIG. 3 depicts the phase 3 study design.

[0012] FIG. 4 shows the long-term extension of tapinarof treatment.

[0013] FIG. 5 presents the time to first disease worsening among patients entering with complete disease clearance (PGA=0) i.e., the remittive effect.

[0014] FIG. 6 presents the durability of the response up to 52 weeks.

[0015] FIG. 7 presents a depiction of the potential mechanism of clinical remittive effect with tapinarof.

[0016] FIG. 8 is an example of 1 representative target lesion of 1 tapinarof-treated patient from PSOARING 1 clinical trial. PGA and PASI are global efficacy assessments. DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; PP-NRS, Peak Pruritus Numeric Rating Scale.

[0017] FIG. 9 displays improvements in a patient’s clinical response for PGA, PASI, and DLQI during treatment with tapinarof cream in the pivotal (PSOARING 1) and LTE (PSOARING 3) trails.

[0018] FIG. 10 displays improvements in clinical response of a patient with plaque psoriasis treated with tapinarof cream and the remittive effect that persisted while off therapy for 24 weeks during the LTE trial.

[0019] FIG. 11 is a graph showing the mean change in %BSA during the LTE trial. Tapinarof-tapinarof subjects received tapinarof treatment during the pivotal trail and continued treatment during the LTE trail. Vehicle–tapinarof subjects received vehicle

treatment during the pivotal trial and transitioned to tapinarof treatment at the start of the LTE trial.

[0020] FIG. 12 is a graph showing the change in PASI score by visit during the LTE trial. Tapinarof-tapinarof subjects received tapinarof treatment during the pivotal trial and continued treatment during the LTE trial. Vehicle-tapinarof subjects received vehicle treatment during the pivotal trial and transitioned to tapinarof treatment at the start of the LTE trial.

[0021] FIG. 13 is a graph showing the mean DLQI scores of the two groups during the LTE trial. Tapinarof-tapinarof subjects received tapinarof treatment during the pivotal trial and continued treatment during the LTE trial. Vehicle-tapinarof subjects received vehicle treatment during the pivotal trial and transitioned to tapinarof treatment at the start of the LTE trial.

[0022] FIG. 14 is a graph showing the results of the Patient Satisfaction Questionnaire for Confidence and Satisfaction with the Efficacy of Tapinarof (n=599).

[0023] FIG. 15 is a graph showing the results of the Patient Satisfaction Questionnaire for Ease of Application and Cosmetic Elegance (n=599).

[0024] FIG. 16 is a graph showing the results of the Patient Satisfaction Questionnaire for patient preference for tapinarof versus previous topical therapies.

[0025] FIG. 17 is a graph showing the results of the Patient Satisfaction Questionnaire for patient preference for tapinarof versus previous systemic therapies.

[0026] FIG. 18 is a graph showing the patient reported tolerability scores for tapinarof cream during the course of the LTE trial.

[0027] FIGs 19A-G are graphs showing the mean investigator-assessed irritation scores for sensitive skin areas treated with tapinarof cream during the course of the LTE trial, FIG. 19A anal crux, FIG. 19B axillae, FIG. 19C face, FIG. 19D neck, FIG. 19E genitalia, FIG. 19F skin folds, and FIG. 19G inframammary areas.

DETAILED DESCRIPTION

[0028] Various aspects now will be described more fully hereinafter. Such aspects may, however, be embodied in many different forms and should not be construed as limited to the embodiments set forth herein; rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey its scope to those skilled in the art.

[0029] Where a range of values is provided, it is intended that each intervening value between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the disclosure. For example, if a range of 1 mg to 8 mg is stated, it is intended that 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, and 7 mg are also explicitly disclosed, as well as the range of values greater than or equal to 1 mg and the range of values less than or equal to 8 mg.

[0030] All percentages, parts and ratios are based upon the total weight of the topical compositions and all measurements made are at about 25 °C, unless otherwise specified.

[0031] The singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to a “subject” includes a single subject as well as two or more subjects; reference to an “excipient” includes a single excipient as well as two or more of the same or different excipients, and the like.

[0032] The word “about” when immediately preceding a numerical value means a range of plus or minus 10% of that value, e.g., “about 50” means 45 to 55, “about 25,000” means 22,500 to 27,500, etc., unless the context of the disclosure indicates otherwise, or is inconsistent with such an interpretation. For example, in a list of numerical values such as “about 49, about 50, about 55, “about 50” means a range extending to less than half the interval(s) between the preceding and subsequent values, e.g., more than 49.5 to less than 52.5. Furthermore, the phrases “less than about” a value or “greater than about” a value should be understood in view of the definition of the term “about” provided herein.

[0033] The terms “administer,” “administering” or “administration” as used herein refer to either directly administering a compound (also referred to as an agent of interest) or pharmaceutically acceptable salt of the compound (agent of interest) or a topical composition to a subject.

[0034] The term “applying a thin layer”, refers to rubbing enough of composition (e.g., 1% tapinarof cream composition) into the skin to cover the area requiring application until any residual cream is no longer visible.

[0035] The term “carrier” as used herein encompasses carriers, excipients, and diluents, meaning a material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material involved in carrying or transporting a pharmaceutical, cosmetic or other agent across a tissue layer such as the stratum corneum or stratum spinosum.

[0036] The terms “controlled,” “control,” “clear,” or “clearance,” when referring to the treatment of the symptoms of plaque psoriasis shall mean the symptoms are negligible or non-existent, i.e. PGA is 0 or 1. The terms “controlled,” “control,” “clear,” or “clearance,” when referring to the treatment of the symptoms of atopic dermatitis (AD), shall mean the symptoms are negligible or non-existent, i.e. IGA is 0 or 1. The terms “controlled,” “control,” “clear,” or “clearance,” when referring to the treatment of the symptoms of radiation dermatitis shall mean the symptoms are negligible or non-existent, i.e. Grade 1 classification.

[0037] The transitional term “comprising,” which is synonymous with “including,” “containing,” or “characterized by,” is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. By contrast, the transitional phrase “consisting of” excludes any element, step, or ingredient not specified in the claim. The transitional phrase “consisting essentially of” limits the scope of a claim to the specified materials or steps “and those that do not materially affect the basic and novel characteristic(s)” of the claimed invention. In embodiments or claims where the term comprising is used as the transition phrase, such embodiments can also be envisioned with replacement of the term “comprising” with the terms “consisting of” or “consisting essentially of.”

[0038] The term “disorder” is used in this disclosure to mean, and is used interchangeably with, the terms disease, condition, or illness, unless otherwise indicated.

[0039] The terms “effective amount” and “therapeutically effective amount” are used interchangeably in this disclosure and refer to an amount of a compound that, when administered to a subject, is capable of reducing a symptom of a disorder in a subject or enhance the texture, appearance, color, sensation, or hydration of the intended tissue treatment area. The actual amount which comprises the “effective amount” or “therapeutically effective amount” will vary depending on a number of conditions including, but not limited to, the severity of the disorder, the size and health of the patient, and the route of administration. A skilled medical practitioner can readily determine the appropriate amount using methods known in the medical arts.

[0040] The phrase “pharmaceutically acceptable” or “cosmetically acceptable” is employed herein to refer to those agents of interest/compounds, salts, compositions, dosage forms, etc., which are--within the scope of sound medical judgment--suitable for use in contact with the tissues of human beings and/or other mammals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a

reasonable benefit/risk ratio. In some aspects, pharmaceutically acceptable means approved by a regulatory agency of the federal or a state government, or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in mammals (e.g., animals), and more particularly, in humans.

[0041] The term “patient” and “subject” are interchangeable and may be taken to mean any human which may be treated with compounds of the present invention. In some embodiments, the patient or subject is an adult, adolescent, child or infant. In some embodiments, the patient or subject is an adolescent (i.e. 12-17 years old). In some embodiments, the patient or subject is 18 years old or older. In some embodiments, the patient or subject is between the age of 18 and 75.

[0042] The term “remittive effect” when referring to the treatment of plaque psoriasis refers to the time during which treatment with tapinarof has stopped and plaque psoriasis remains controlled for a period of time after cessation of treatment. Plaque psoriasis is controlled when the PGA score is 0 or 1. The term “remission” means that plaque psoriasis in itself is not completely cured, but the symptoms thereof are temporarily or perpetually alleviated or have disappeared, the symptoms may be measured by PGA, PASI, BSA, DLQI, and Patient Satisfaction questionnaire.

[0043] The term “remittive effect” when referring to the treatment of atopic dermatitis refers to the time during which treatment with tapinarof has stopped and atopic dermatitis remains controlled for a period of time after cessation of treatment. Atopic dermatitis is controlled when IGA score is 0 or 1. The term “remission” means that atopic dermatitis in itself is not completely cured, but the symptoms thereof are temporarily or perpetually alleviated or have disappeared, the symptoms may be measured by IGA, Itch/Pruritus, EASI, BSA, VAS for sleep or itch, and patient reported outcomes.

[0044] The term “remittive effect” when referring to the treatment of radiation dermatitis refers to the time during which treatment with tapinarof has stopped and radiation dermatitis remains controlled for a period of time after cessation of treatment. Radiation dermatitis is controlled when the classification is measured as Grade 1.

[0045] The term “salts” as used herein embraces pharmaceutically acceptable salts commonly used to form alkali metal salts of free acids and to form addition salts of free bases. The nature of the salt is not critical, provided that it is pharmaceutically acceptable. The term “salts” also includes solvates of addition salts, such as hydrates, as well as polymorphs of addition salts. Suitable pharmaceutically acceptable acid addition salts can be

prepared from an inorganic acid or from an organic acid. Non-limiting examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric, and phosphoric acid. Appropriate organic acids can be selected from aliphatic, cycloaliphatic, aromatic, arylaliphatic, and heterocyclyl containing carboxylic acids and sulfonic acids, for example formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, 3-hydroxybutyric, galactaric and galacturonic acid.

[0046] The term “treating” is used herein, for instance, in reference to methods of treating a skin disorder or a systemic condition, and generally includes the administration of a compound or composition which reduces the frequency of, or delays the onset of, symptoms of a medical condition or enhance the texture, appearance, color, sensation, or hydration of the intended tissue treatment area of the tissue surface in a subject relative to a subject not receiving the compound or composition. This can include reversing, reducing, or arresting the symptoms, clinical signs, and underlying pathology of a condition in a manner to improve or stabilize a subject’s condition. The term “treatment,” as used within the context of the present disclosure, is meant to include therapeutic treatment, as well as prophylactic or suppressive measures, for the treatment of psoriasis, atopic dermatitis, or radiation dermatitis. For example, the term treatment may include administration of tapinarof prior to or following the onset of psoriasis, atopic dermatitis, or radiation dermatitis thereby preventing or removing signs of the disease or disorder. As another example, administration of tapinarof after clinical manifestation of psoriasis, atopic dermatitis, or radiation dermatitis to combat the symptoms and/or complications of said disorders comprises “treatment” of the disease. In one embodiment, treatment of psoriasis in a subject comprises achieving remission of psoriasis in a subject. In one embodiment, treatment of psoriasis in a subject comprises inducing and maintaining remission of psoriasis in a subject. In another embodiment, treatment of psoriasis in a subject comprises maintaining remission of psoriasis in a subject. In one embodiment, treatment of atopic dermatitis in a subject comprises achieving remission of atopic dermatitis in a subject. In one embodiment, treatment of atopic dermatitis in a subject comprises inducing and maintaining remission of atopic dermatitis in a subject. In another embodiment, treatment of atopic dermatitis in a subject comprises maintaining

remission of atopic dermatitis in a subject. In one embodiment, treatment of radiation dermatitis in a subject comprises achieving remission of radiation dermatitis in a subject. In one embodiment, treatment of radiation dermatitis in a subject comprises inducing and maintaining remission of radiation dermatitis in a subject. In another embodiment, treatment of radiation dermatitis in a subject comprises maintaining remission of radiation dermatitis in a subject.

[0047] By hereby reserving the right to proviso out or exclude any individual members of any such group, including any sub-ranges or combinations of sub-ranges within the group, that can be claimed according to a range or in any similar manner, less than the full measure of this disclosure can be claimed for any reason. Further, by hereby reserving the right to proviso out or exclude any individual substituents, analogs, compounds, ligands, structures, or groups thereof, or any members of a claimed group, less than the full measure of this disclosure can be claimed for any reason. Throughout this disclosure, various patents, patent applications and publications are referenced. The disclosures of these patents, patent applications and publications in their entireties are incorporated into this disclosure by reference in order to more fully describe the state of the art as known to those skilled therein as of the date of this disclosure. This disclosure will govern in the instance that there is any inconsistency between the patents, patent applications and publications cited and this disclosure.

[0048] For convenience, certain terms employed in the specification, examples and claims are collected here. Unless defined otherwise, all technical and scientific terms used in this disclosure have the same meanings as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

[0049] Psoriasis is a common, chronic relapsing inflammatory skin disease with recurrent episodes of prominently erythematous and scaly patches (plaques). Approximately 2 to 3% of the global population is affected by psoriasis; those affected are predominantly adults, who are most often diagnosed between the ages of 18 to 35 years. Psoriasis disrupts daily activities such as work and/or school attendance, interpersonal relationships, recreational activities, and intimacy, thereby significantly impacting sufferers' quality of life. Furthermore, psoriasis sufferers can also have co-morbidities such as arthritis, depression, inflammatory bowel disease, and cardiovascular (CV) diseases.

[0050] Up to 80% of patients have mild to moderate plaque-type psoriasis, which is generally managed with topical treatments. Topically-applied corticosteroids and Vitamin

D analogs, alone or in combination, are the most commonly used products in the treatment of psoriasis. Vitamin D analogs are moderately efficacious as monotherapy, while application of topical corticosteroids – particularly the very potent ones – is restricted in terms of body areas that can be treated and the duration of use due to the well-known application site and systemic adverse drug reactions.

[0051] Although numerous topical treatment options are available, there still remains a need for a topical treatment that combines a high level of efficacy with an acceptable safety profile that permits application to a large body surface area (BSA) without restrictions on duration of treatment.

[0052] Tapinarof, also known as DMVT-505 and formerly known as GSK2894512, WBI-1001, or benvitimod, is a fully synthetic hydroxylated stilbene, new molecular entity and is a novel non-steroidal anti-inflammatory agent for the topical treatment of atopic dermatitis (AD), radiation dermatitis, and plaque psoriasis.

[0053] Psoriatic skin lesions and atopic dermatitis skin lesions contain elevated numbers of activated T-cells, which have a key role in the pathogenesis of inflammatory diseases through the proliferation and secretion of pro-inflammatory cytokines. Radiation dermatitis skin lesions contain an inflammatory infiltrate which consists of increased numbers and/or activation of inflammatory cells including, but not limited to T-cells and/or B-cells and/or neutrophils and/or antigen presenting cells and/or other cell lineages generally described as granulocytes and/or lymphocytes and/or macrophages. The drug likely mediates its effects via the aryl hydrocarbon receptor (AhR) agonist and nuclear factor erythroid 2-related factor 2 (Nrf2) because the pattern of pro-inflammatory mediators inhibited by tapinarof is different from that of corticosteroids, calcineurin inhibitors, vitamin D analogs, and other immunosuppressive agents commonly used to treat AD and psoriasis. Rather, the profile of biological responses elicited by tapinarof most closely matches that of the dual activation properties of coal tar, a common nonprescription treatment for psoriasis. Together, existing data identify tapinarof as a non-steroid, therapeutic AhR-modulating agent (TAMA), which is a unique mechanism of action compared with existing therapies. The efficacy of tapinarof in these inflammatory skin diseases is attributed to tapinarof binding to and activating the ligand-dependent transcription factor aryl hydrocarbon receptor (AhR), resulting in the downregulation of proinflammatory cytokines, restoration of the skin barrier through modulation of skin barrier protein expression, and regulation of gene expression in immune cells.

[0054] Clinical trials, described herein, have demonstrated a remittive effect with topical tapinarof therapy, defined as maintenance of disease control off therapy. In the Phase 2b clinical trial in patients with psoriasis, significant improvements were maintained for four weeks following the discontinuation of tapinarof treatment; this remittive effect was confirmed in the Phase 3 psoriasis program in which patients entering the long-term extension study with complete disease clearance (Physician Global Assessment [PGA] score = 0) maintained disease control off therapy for approximately 4 months before requiring retreatment with tapinarof (PGA score ≥ 2).

[0055] The observed remittive effect of tapinarof cream in patients with inflammatory skin diseases, including psoriasis and atopic dermatitis, results from tapinarof's binding to the ligand-dependent transcription factor aryl hydrocarbon receptor (AhR). Specifically, binding of tapinarof to AhR modulates T cell responses both through intrinsic control of T cell subset differentiation and via controlling the function of antigen presenting cells. Tapinarof modulated AhR signaling (i) promotes the conversion of Th17 cells to type 1 regulatory T cells, (ii) more generally regulates T cell polarization, T cell tolerance, T cell anergy, and/or T cell exhaustion, (iii) regulates T regulatory cell differentiation, polarization of T cells, and/or the generation of resident memory T cells, and (iv) regulates the balance of TH17 and type 1 regulatory T cells, (iii) regulates antigen presenting cell (APC) development, maturation, polarization, activation, and/or blockade of APC:T-cell interactions. More specifically, the efficacy of tapinarof is attributed to its specific binding and activation of AhR. This leads to the downregulation of pro-inflammatory Th17 cytokines (including interleukin IL-17A and IL-17F), increase in expression of skin barrier proteins related to keratinocyte differentiation, including filaggrin and loricrin, increase in antioxidant activity, and regulation of gene expression in immune cells. AhR is widely expressed in immune cells, including antigen-presenting cells (APCs), T cells, macrophages, mast cells, and other skin immune cells. In APCs, including Langerhans and dendritic cells (DCs), AhR expression is necessary for function and cytokine expression. Tapinarof-AhR has been shown to directly downregulate IL-17A and IL-17F, which likely explains its immediate therapeutic benefit in PsO. In addition, the remittive effect observed off therapy in the PSOARING trial program may be explained by the additional roles of AhR including modulation of T-cell responses through both intrinsic control of T-cell subset differentiation and via control of APCs' function that may contribute to the clinical remittive effect observed. AhR signaling via canonical and non-canonical pathways drives multiple tolerogenic mechanisms in DCs

(FIG. 7): AhR dampens expression of major histocompatibility complex class II expression in APCs, It alters production of cytokines involved in differentiation of effector and regulatory T cells (Tregs), AhR signaling in DCs controls expression of metabolites with immunoregulatory function, in particular, AhR promotes the expression of indoleamine 2,3-dioxygenase, an enzyme that catalyzes the production of kynurenine, itself an AhR agonist, which promotes FoxP3⁺ T-cell differentiation and suppresses inflammation in many contexts. Additionally, the specific binding and activation of AhR by tapinarof has been shown to inhibit T-cell expansion and Helper T cell (Th) 17-cell differentiation and reduce IL-17 production in T-cell assays. Ligand-dependent AhR activation has also been demonstrated to result in epigenetic modification of both the FoxP3 and IL-17 gene promoters leading to preferential differentiation of Tregs and inhibition of Th17 cells.

[0056] As these pathways are probed experimentally, further refinement/specific descriptions of cell (T-cell, APC) subset/differentiation are likely to be elucidated/described providing a clearer mechanism of action, i.e., subsets of tissue resident memory cells may be described by a combination of antigen biomarkers including CD45RO^{hi}, CD45RA^{low}, CD69^{hi}, CD103^{hi} and CD103^{low}.

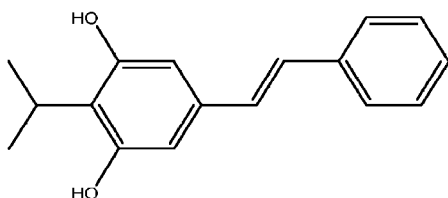
[0057] It was surprisingly and unexpectedly found that after treatment with 1% tapinarof cream formulation topically administered once daily for about 3 months the symptoms of plaque psoriasis remained improved in subjects not being treated for greater than 4 months. Though a similar trial (Cai et al., Chinese Medical Journal, 2020; 133(24)) observed improvement in symptoms after treatment had stopped, that trial dosed the subjects with a 1% tapinarof formulation twice a day. The 1% tapinarof cream formulation described herein was only applied once a day, therefore it was completely unexpected that application of half of the amount of tapinarof would lead to a remittive effect for a period of time greater than 3 months.

[0058] The tapinarof topical composition described herein does not show a tachyphylaxis effect as seen with other active ingredients. Tachyphylaxis is the decrease in response to successive doses of a drug, rendering it less effective. Such a surprising and unexpected characteristic of the tapinarof topical composition described herein allows for the continuous daily administration of the composition to the skin as well as the use in large body surface areas without concern for decreased efficacy over time and the potential increase of side effects as seen with other treatments. Without wishing to be bound by theory, the beneficial lack of tachyphylaxis is not due to an active metabolite, is not a characteristic of

vehicle cream alone, nor is it an artifact of patient non-compliance. Accordingly, the tapinarof topical composition described herein can continue to be administered to a patient in need thereof at the same dose and dose frequency to continue to achieve at least the same efficacy, if not improved efficacy, over time without increasing the risk of any potential side effects over time.

COMPOSITIONS

[0059] Embodiments of the invention are directed to topical compositions comprising 3,5-Dihydroxy-4-isopropyl-*trans*-stilbene or a pharmaceutically acceptable salt thereof. Throughout this disclosure 3,5-Dihydroxy-4-isopropyl-*trans*-stilbene is referred to as tapinarof, and is also known as (E)-2-isopropyl-5-styrylbenzene-1,3 diol, with the empirical formula $C_{17}H_{18}O_2$, a molecular weight of 254.32, and the following structure:



[0060] In embodiments, the topical composition is an emulsion. In embodiments, the topical composition is an oil-in-water emulsion. In embodiments, the topical composition is an oil-in-water emulsion cream having a viscosity of about 20,000 to 100,000 centipoise (cps), preferably about 20,000 to 60,000 cps and more preferably about 30,000 to 40,000 cps; a D50 of less than or equal to about 1 μm , preferably about 0.1 μm to about 0.6 μm , and more preferably about 0.2 μm to about 0.3 μm ; and a D90 of about 0.2 μm to about 1.5 μm , preferably about 0.4 μm to about 1 μm , and more preferably about 0.5 μm to about 0.6 μm of the oil droplets. In an embodiment, the topical composition of tapinarof or a pharmaceutically acceptable salt thereof, comprises an oil phase, and a water phase, creating an emulsion, and wherein the emulsion composition is homogenous. In an embodiment, tapinarof, or pharmaceutically acceptable salt thereof is solubilized in the oil phase of the emulsion composition. In embodiments, the oil phase is comprised of medium chain triglycerides, propylene glycol, non-ionic emulsifying wax, diethylene glycol monoethyl ether, polyoxyl stearyl ether-2, polysorbate 80, polyoxyl stearyl ether-20, benzoic acid, and butylated hydroxytoluene. In embodiments, the water phase is comprised of sodium citrate, edetate disodium, citric acid monohydrate, and water.

[0061] In certain embodiments described herein, the topical composition comprises about 1.0% tapinarof, or a pharmaceutically acceptable salt thereof. The tapinarof topical pharmaceutical oil-in-water emulsion compositions described in U.S. Patent No. 10,195,160, U.S. Publication No. 2018/0064656, and PCT Application No. PCT/US2021/038794 are each incorporated herein in its entirety.

[0062] In certain embodiments described herein, the topical composition comprises about 0.05% to about 2% 3,5-dihydroxy-4-isopropyl-trans-stilbene or a pharmaceutically acceptable salt thereof, about 2% to about 30% of an oil phase, about 55% to about 75% of an aqueous phase, about 1% to about 20% of a surfactant, and a dermatologically acceptable excipient selected from the group consisting of an antioxidant, a pH adjusting agent, a chelating agent, a preservative, a co-solvent and combinations thereof. In certain embodiments, the oil phase comprises medium chain triglycerides of a carbon length from six to twelve. In certain embodiments, the aqueous phase comprises water. In certain embodiments, the surfactant is selected from the group consisting of a non-ionic emulsifying wax NF, steareth-2, steareth-20, polysorbate 80, and combinations thereof. In certain embodiments described herein, the topical composition comprises about 50.00% to about 75.00% water, about 0.05% to about 0.50% sodium citrate, about 0.01% to about 2.00% citric acid, about 0.01% to about 1.00% disodium EDTA, about 5.00% to about 25.00% propylene glycol, about 0.10% to about 5.00% diethylene glycol monoethyl ether, about 0.01% to about 1.00% butylated hydroxytoluene, about 0.01% to about 1.00% benzoic acid, about 5.00% to about 10.00% emulsifying wax, about 5.00% to about 25.00% medium chain triglycerides (MCT), about 0.50% to about 5.00% polysorbate 80, about 0.50% to about 5.00% steareth 2, and about 0.50% to about 5.00% steareth 20. In preferred embodiments, the topical composition comprises 1.00% tapinarof, or a pharmaceutically acceptable salt thereof, 64.68% water, 0.19% sodium citrate, 0.08% citric acid, 0.10% disodium EDTA, 10.00% propylene glycol, 2.00% diethylene glycol monoethyl ether, 0.10% butylated hydroxytoluene, 0.25% benzoic acid, 7.20% emulsifying wax, 10.00% medium chain triglycerides (MCT), 1.50% polysorbate 80, 1.80% steareth 2, and 1.10% steareth 20. In another embodiment, the emulsifying wax is a proprietary blend known as "Polawax NF" (Registered Trademark) (Croda Inc, Edison, N.J., USA).

METHODS OF USING TOPICAL COMPOSITIONS TO TREAT PSORIASIS

[0063] Embodiments of the invention are directed to methods for treating plaque psoriasis in a subject in need thereof, comprising:

a. administering about 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for an initial period of time of at least 12 weeks, until the subject has a PGA score of 0, and a PASI score < the baseline PASI score and a DLQI score < the baseline DLQI score;

b. after the initial period of time, stop treating the subject with tapinarof for a remittive period of time of about 1 to about 7 months, wherein the remittive period of time is the time wherein the subject maintains a PGA score < 2; and

c. if, after the remittive period of time, the subject has a PGA score of ≥ 2 and the PASI score and DLQI score is $\geq$ the PASI score and DLQI score in step a. further administering 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for a further period of time, until the subject has a PGA score of 0;

wherein

the 1.0% tapinarof topical cream composition does not prolong the QTc interval in the subject while applying the 1.0% tapinarof topical cream; and

the plasma concentration of tapinarof in the subject is below 50 pg/mL while applying the 1.0% tapinarof topical cream.

[0064] Embodiments of the invention are directed to methods for treating plaque psoriasis in a subject in need thereof, comprising:

a. administering about 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for an initial period of time of at least 12 weeks, until the subject has a PGA score of 0, and a PASI score < the baseline PASI score and a DLQI score < the baseline DLQI score;

b. after the initial period of time, stop treating the subject with tapinarof for a remittive period of time of about 1 to about 7 months, wherein the remittive period of time is the time wherein the subject maintains a PGA score < 2; and

c. if, after the remittive period of time, the subject has a PGA score of ≥ 2 and the PASI score and DLQI score is $\geq$ the PASI score and DLQI score in step a. further administering 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for a further period of time, until the subject has a PGA score of 0;

wherein

the 1.0% tapinarof topical cream composition does not prolong the QTc interval in the subject while applying the 1.0% tapinarof topical cream; and

the plasma concentration of tapinarof in the subject is below 50 pg/mL while applying the 1.0% tapinarof topical cream.

[0065] Embodiments of the invention are directed to methods for treating plaque psoriasis in a subject in need thereof, comprising:

a. applying a thin layer of about 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for an initial period of time of at least 12 weeks, until the subject has a PGA score of 0, and a PASI score < the baseline PASI score and a DLQI score < the baseline DLQI score;

b. after the initial period of time, stop treating the subject with tapinarof for a remittive period of time of about 1 to about 7 months, wherein the remittive period of time is the time wherein the subject maintains a PGA score < 2; and

c. if, after the remittive period of time, the subject has a PGA score of ≥ 2 and the PASI score and DLQI score is $\geq$ the PASI score and DLQI score in step a. further applying a thin layer of 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for a further period of time, until the subject has a PGA score of 0;

wherein

the 1.0% tapinarof topical cream composition does not prolong the QTc interval in the subject while applying the 1.0% tapinarof topical cream; and

the plasma concentration of tapinarof in the subject is below 50 pg/mL while applying the 1.0% tapinarof topical cream.

[0066] Embodiments of the invention are directed to methods for treating plaque psoriasis in a subject in need thereof, comprising:

a. applying a thin layer of about 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for an initial period of time of at least 12 weeks, until the subject has a PGA score of 0, and a PASI score < the baseline PASI score and a DLQI score < the baseline DLQI score;

b. after the initial period of time, stop treating the subject with tapinarof for a remittive period of time of about 1 to about 7 months, wherein the remittive period of time is the time wherein the subject maintains a PGA score < 2; and

c. if, after the remittive period of time, the subject has a PGA score of ≥ 2 and the PASI score and DLQI score is $\geq$ the PASI score and DLQI score in step a. further applying a

thin layer of 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for a further period of time, until the subject has a PGA score of 0; wherein

the 1.0% tapinarof topical cream composition does not prolong the QTc interval in the subject while applying the 1.0% tapinarof topical cream,

the plasma concentration of tapinarof in the subject is below 50 pg/mL while applying the 1.0% tapinarof topical cream, and

the subject selects a satisfaction rating of “agree” or “strongly agree” to one or more satisfaction questions selected from the group consisting of: 1) I can easily manage my psoriasis with the study drug; 2) The time spent applying the study drug every day was acceptable and did not affect my everyday life; 3) I am satisfied with how well the study drug worked for my psoriasis; 4) I have confidence in the study drug; 5) The study drug cleared my skin and kept my psoriasis from coming back; 6) If the study drug was available by prescription, I would recommend it to other patients with psoriasis; 7) If the study drug was available by a prescription, I would use it again or continue on it; 8) The study drug is easy to apply; 9) The study drug is not greasy; 10) The study drug quickly absorbs into my skin; 11) The study drug feels good on my skin; 12) I am satisfied with the look and feel of the study drug; 13) The study drug is more effective than other topical drugs I have used to treat my psoriasis; 14) The study drug is easier to use than other topical drugs I have used to treat my psoriasis; 15) I prefer the study drug to other topical drugs I have used to treat my psoriasis; 16) The study drug is more effective than systemic drugs I have used to treat my psoriasis; 17) The study drug is easier to use than systemic drugs I have used to treat my psoriasis; and 18) I prefer the study drug to systemic drugs I have used to treat my psoriasis.

[0067] In certain embodiments the plaque psoriasis is moderate or severe plaque psoriasis.

[0068] In certain embodiments the initial period of time is about 12 weeks to about 52 weeks. In certain embodiments the initial period of time is about 12 weeks. In certain embodiments the initial period of time is about 16, about 24, about 28, about 32, about 36, about 40, about 44, about 48 or about 52 weeks. In certain embodiments the initial period of time is 16-40 weeks. In certain embodiments the initial period of time is 40 weeks. In certain embodiments the initial period is 52 weeks.

[0069] In certain embodiments the remittive period is greater than 3 months and up to about 7 months. In certain embodiments the remittive period of time is about 4 months,

about 5 months, about 6 months or about 7 months. In certain embodiments the remittive period is about 4 months.

[0070] In certain embodiments the further period of time is less than the initial period of time. In certain embodiments the further period of time is about 8 weeks to 16 weeks. In certain embodiments the further period of time is about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, or about 16 weeks.

[0071] In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to two or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to three or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to four or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to five or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to six or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to seven or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to eight or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to nine or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to ten or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to eleven or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to twelve or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to thirteen or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to fourteen or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to fifteen or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to sixteen or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to seventeen or more of the satisfaction questions. In certain embodiments the subject selects a

satisfaction rating of “agree” or “strongly agree” to eighteen or more of the satisfaction questions.

[0072] Embodiments of the invention are directed to a method for treating plaque psoriasis in a subject in need thereof, wherein the subject has achieved a PGA score of 0, a PASI score < their baseline PASI score, and a DLQI score < the baseline DLQI score, after applying a thin layer of about 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for an initial period of time of about 12 weeks to 52 weeks, comprising:

a. stopping treatment of the subject with tapinarof for a remittive period of time of about 1 to about 7 months, wherein the remittive period of time is the time wherein the subject has a PGA score < 2, and

b. if, after the remittive period of time, the subject has a PGA score of > 2 and the PASI score and DLQI score is > the PASI score and DLQI score in step a.; further applying a thin layer of 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for a further period of time until the subject has a PGA score of 0;
wherein

the 1.0% tapinarof topical cream composition does not prolong the QTc interval in the subject while applying the 1.0% tapinarof topical cream; and

the plasma concentration of tapinarof in the subject is below 50 pg/mL while applying the 1.0% tapinarof topical cream.

[0073] Embodiments of the invention are directed to a method for treating plaque psoriasis in a subject in need thereof, wherein the subject has achieved a PGA score of 0, a PASI score < their baseline PASI score, and a DLQI score < the baseline DLQI score, after administering about 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for an initial period of time of about 12 weeks to 52 weeks, comprising:

a. stopping treatment of the subject with tapinarof for a remittive period of time of about 1 to about 7 months, wherein the remittive period of time is the time wherein the subject has a PGA score < 2, and

b. if, after the remittive period of time, the subject has a PGA score of > 2 and the PASI score and DLQI score is > the PASI score and DLQI score in step a.; further administering 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for a further period of time until the subject has a PGA score of 0;
wherein

the 1.0% tapinarof topical cream composition does not prolong the QTc interval in the subject while applying the 1.0% tapinarof topical cream,

the plasma concentration of tapinarof in the subject is below 50 pg/mL while applying the 1.0% tapinarof topical cream, and

the subject selects a satisfaction rating of “agree” or “strongly agree” to one or more satisfaction questions selected from the group consisting of:

1) I can easily manage my psoriasis with the study drug; 2) The time spent applying the study drug every day was acceptable and did not affect my everyday life; 3) I am satisfied with how well the study drug worked for my psoriasis; 4) I have confidence in the study drug; 5) The study drug cleared my skin and kept my psoriasis from coming back; 6) If the study drug was available by prescription, I would recommend it to other patients with psoriasis; 7) If the study drug was available by a prescription, I would use it again or continue on it; 8) The study drug is easy to apply; 9) The study drug is not greasy; 10) The study drug quickly absorbs into my skin; 11) The study drug feels good on my skin; 12) I am satisfied with the look and feel of the study drug; 13) The study drug is more effective than other topical drugs I have used to treat my psoriasis; 14) The study drug is easier to use than other topical drugs I have used to treat my psoriasis; 15) I prefer the study drug to other topical drugs I have used to treat my psoriasis; 16) The study drug is more effective than systemic drugs I have used to treat my psoriasis; 17) The study drug is easier to use than systemic drugs I have used to treat my psoriasis; and 18) I prefer the study drug to systemic drugs I have used to treat my psoriasis.

[0074] Embodiments of the invention are directed to a method for treating plaque psoriasis in a subject in need thereof, wherein the subject has achieved a PGA score of 0, a PASI score < their baseline PASI score, and a DLQI score < the baseline DLQI score, after applying a thin layer of about 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for an initial period of time of about 12 weeks to 52 weeks, comprising:

a. stopping treatment of the subject with tapinarof for a remittive period of time of about 1 to about 7 months, wherein the remittive period of time is the time wherein the subject has a PGA score < 2, and

b. if, after the remittive period of time, the subject has a PGA score of > 2 and the PASI score and DLQI score is > the PASI score and DLQI score in step a.; further applying a

thin layer of 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for a further period of time until the subject has a PGA score of 0;

wherein

the 1.0% tapinarof topical cream composition does not prolong the QTc interval in the subject while applying the 1.0% tapinarof topical cream; and

the plasma concentration of tapinarof in the subject is below 50 pg/mL while applying the 1.0% tapinarof topical cream.

[0075] Embodiments of the invention are directed to a method for treating plaque psoriasis in a subject in need thereof, wherein the subject has achieved a PGA score of 0, a PASI score < their baseline PASI score, and a DLQI score < the baseline DLQI score, after applying a thin layer of about 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for an initial period of time of about 12 weeks to 52 weeks, comprising:

a. stopping treatment of the subject with tapinarof for a remittive period of time of about 1 to about 7 months, wherein the remittive period of time is the time wherein the subject has a PGA score < 2, and

b. if, after the remittive period of time, the subject has a PGA score of > 2 and the PASI score and DLQI score is > the PASI score and DLQI score in step a.; further applying a thin layer of 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for a further period of time until the subject has a PGA score of 0;

wherein

the 1.0% tapinarof topical cream composition does not prolong the QTc interval in the subject while applying the 1.0% tapinarof topical cream,

the plasma concentration of tapinarof in the subject is below 50 pg/mL while applying the 1.0% tapinarof topical cream, and

the subject selects a satisfaction rating of “agree” or “strongly agree” to one or more satisfaction questions selected from the group consisting of:

1) I can easily manage my psoriasis with the study drug; 2) The time spent applying the study drug every day was acceptable and did not affect my everyday life; 3) I am satisfied with how well the study drug worked for my psoriasis; 4) I have confidence in the study drug; 5) The study drug cleared my skin and kept my psoriasis from coming back; 6) If the study drug was available by prescription, I would recommend it to other patients with psoriasis; 7) If the study drug was available by a prescription, I would use it again or continue

on it; 8) The study drug is easy to apply; 9) The study drug is not greasy; 10) The study drug quickly absorbs into my skin; 11) The study drug feels good on my skin; 12) I am satisfied with the look and feel of the study drug; 13) The study drug is more effective than other topical drugs I have used to treat my psoriasis; 14) The study drug is easier to use than other topical drugs I have used to treat my psoriasis; 15) I prefer the study drug to other topical drugs I have used to treat my psoriasis; 16) The study drug is more effective than systemic drugs I have used to treat my psoriasis; 17) The study drug is easier to use than systemic drugs I have used to treat my psoriasis; and 18) I prefer the study drug to systemic drugs I have used to treat my psoriasis.

[0076] In certain embodiments the plaque psoriasis is moderate or severe plaque psoriasis.

[0077] In certain embodiments the initial period of time is about 12 weeks. In certain embodiments the initial period of time is 16-40 weeks. In certain embodiments the initial period of time is about 16, about 24, about 28, about 32, about 36, about 40, about 44, about 48 or about 52 weeks. In certain embodiments the initial period of time is 16-40 weeks. In certain embodiments the initial period of time is 40 weeks. In certain embodiments the initial period is 52 weeks.

[0078] In certain embodiments the remittive period is greater than 3 months and up to about 7 months. . In certain embodiments the remittive period of time is about 4 months, about 5 months, about 6 months or about 7 months. In certain embodiments the remittive period is about 4 months.

[0079] In certain embodiments the further period of time is less than the initial period of time. In certain embodiments the further period of time is 8 to 16 weeks. In certain embodiments the further period of time is about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, or about 16 weeks.

[0080] In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to two or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to three or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to four or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to five or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction

rating of “agree” or “strongly agree” to six or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to seven or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to eight or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to nine or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to ten or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to eleven or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to twelve or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to thirteen or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to fourteen or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to fifteen or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to sixteen or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to seventeen or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to eighteen or more of the satisfaction questions.

[0081] Embodiments of the invention are directed to a method for treating plaque psoriasis in a subject in need thereof, wherein the subject has a PGA score of at least 1 point lower than baseline but has not achieved a PGA score of 0 after administering 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for a period of time of about 12 weeks to about 52 weeks comprising continuing to applying a thin layer of about 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for an indefinite period of time, wherein the PGA score does not increase when administering about 1.0% tapinarof topical cream composition to the affected areas of the subject once a day;
wherein

the 1.0% tapinarof topical cream composition does not prolong the QTc interval in the subject while applying the 1.0% tapinarof topical cream and

the plasma concentration of tapinarof in the subject is below 50 pg/mL while applying the 1.0% tapinarof topical cream.

[0082] Embodiments of the invention are directed to a method for treating plaque psoriasis in a subject in need thereof, wherein the subject has a PGA score of at least 1 point lower than baseline but has not achieved a PGA score of 0 after administering about 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for a period of time of about 12 weeks to about 52 weeks comprising continuing to administering about 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for an indefinite period of time, wherein the PGA score does not increase when applying a thin layer of about 1.0% tapinarof topical cream composition to the affected areas of the subject once a day; wherein

the 1.0% tapinarof topical cream composition does not prolong the QTc interval in the subject while applying the 1.0% tapinarof topical cream,

the plasma concentration of tapinarof in the subject is below 50 pg/mL while applying the 1.0% tapinarof topical cream, and

the subject selects a satisfaction rating of “agree” or “strongly agree” to one or more satisfaction questions selected from the group consisting of: 1) I can easily manage my psoriasis with the study drug; 2) The time spent applying the study drug every day was acceptable and did not affect my everyday life; 3) I am satisfied with how well the study drug worked for my psoriasis; 4) I have confidence in the study drug; 5) The study drug cleared my skin and kept my psoriasis from coming back; 6) If the study drug was available by prescription, I would recommend it to other patients with psoriasis; 7) If the study drug was available by a prescription, I would use it again or continue on it; 8) The study drug is easy to apply; 9) The study drug is not greasy; 10) The study drug quickly absorbs into my skin; 11) The study drug feels good on my skin; 12) I am satisfied with the look and feel of the study drug; 13) The study drug is more effective than other topical drugs I have used to treat my psoriasis; 14) The study drug is easier to use than other topical drugs I have used to treat my psoriasis; 15) I prefer the study drug to other topical drugs I have used to treat my psoriasis; 16) The study drug is more effective than systemic drugs I have used to treat my psoriasis; 17) The study drug is easier to use than systemic drugs I have used to treat my psoriasis; and 18) I prefer the study drug to systemic drugs I have used to treat my psoriasis.

[0083] Embodiments of the invention are directed to a method for treating plaque psoriasis in a subject in need thereof, wherein the subject has a PGA score of at least 1 point lower than baseline but has not achieved a PGA score of 0 after applying a thin layer of about 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for a period of time of about 12 weeks to about 52 weeks comprising continuing to applying a thin layer of about 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for an indefinite period of time, wherein the PGA score does not increase when applying a thin layer of about 1.0% tapinarof topical cream composition to the affected areas of the subject once a day;
wherein

the 1.0% tapinarof topical cream composition does not prolong the QTc interval in the subject while applying the 1.0% tapinarof topical cream; and

the plasma concentration of tapinarof in the subject is below 50 pg/mL while applying the 1.0% tapinarof topical cream.

[0084] Embodiments of the invention are directed to a method for treating plaque psoriasis in a subject in need thereof, wherein the subject has a PGA score of at least 1 point lower than baseline but has not achieved a PGA score of 0 after applying a thin layer of about 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for a period of time of about 12 weeks to about 52 weeks comprising continuing to applying a thin layer of about 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for an indefinite period of time, wherein the PGA score does not increase when applying a thin layer of about 1.0% tapinarof topical cream composition to the affected areas of the subject once a day;
wherein

the 1.0% tapinarof topical cream composition does not prolong the QTc interval in the subject while applying the 1.0% tapinarof topical cream,

the plasma concentration of tapinarof in the subject is below 50 pg/mL while applying the 1.0% tapinarof topical cream, and

the subject selects a satisfaction rating of “agree” or “strongly agree” to one or more satisfaction questions selected from the group consisting of: 1) I can easily manage my psoriasis with the study drug; 2) The time spent applying the study drug every day was acceptable and did not affect my everyday life; 3) I am satisfied with how well the study drug worked for my psoriasis; 4) I have confidence in the study drug; 5) The study drug cleared

my skin and kept my psoriasis from coming back; 6) If the study drug was available by prescription, I would recommend it to other patients with psoriasis; 7) If the study drug was available by a prescription, I would use it again or continue on it; 8) The study drug is easy to apply; 9) The study drug is not greasy; 10) The study drug quickly absorbs into my skin; 11) The study drug feels good on my skin; 12) I am satisfied with the look and feel of the study drug; 13) The study drug is more effective than other topical drugs I have used to treat my psoriasis; 14) The study drug is easier to use than other topical drugs I have used to treat my psoriasis; 15) I prefer the study drug to other topical drugs I have used to treat my psoriasis; 16) The study drug is more effective than systemic drugs I have used to treat my psoriasis; 17) The study drug is easier to use than systemic drugs I have used to treat my psoriasis; and 18) I prefer the study drug to systemic drugs I have used to treat my psoriasis.

[0085] In certain embodiments the plaque psoriasis is moderate or severe plaque psoriasis.

[0086] In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to two or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to three or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to four or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to five or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to six or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to seven or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to eight or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to nine or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to ten or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to eleven or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to twelve or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to thirteen or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or

“strongly agree” to fourteen or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to fifteen or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to sixteen or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to seventeen or more of the satisfaction questions. In certain embodiments the subject selects a satisfaction rating of “agree” or “strongly agree” to eighteen or more of the satisfaction questions.

[0087] Embodiments described herein are directed to methods for developing a remittive effect in a subject with moderate to severe plaque psoriasis comprising administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for an initial period of time until the plaque psoriasis is clear at which time the administration is stopped, and reassessing the subject from about 3 months to about 12 months after administration is stopped to determine if further treatment is required.

[0088] Embodiments described herein are directed to methods for treating moderate to severe plaque psoriasis in a subject comprising administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for an initial period of time until the plaque psoriasis is clear at which time the administration is stopped, and reassessing the subject from about 3 months to about 12 months after administration is stopped to determine if further treatment is required. In embodiments described herein, the topical composition is administered in an initial period of time. In embodiments described herein, the initial period of time is about 16 weeks to about 40 weeks in duration. In certain embodiments, the initial period of time is about 40 weeks.

[0089] In embodiments described herein, reassessment of the subject occurs at about 4 months after administration. In certain embodiments, further treatment is initiated after reassessment of the subject. In certain embodiments, the further treatment comprises administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for a subsequent period of time until the plaque psoriasis is clear.

[0090] Embodiments described herein are directed to methods for inducing a remittive effect in a subject with moderate to severe plaque psoriasis, wherein the remittive effect can be temporary or permanent.

[0091] Embodiments described herein are directed to methods for achieving remission in a subject with moderate to severe plaque psoriasis comprising administering

about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day until the subject reaches a PGA score of 0, wherein administration of the about 1.0% tapinarof in a topical composition is stopped. In certain embodiments, the subject reaches a PGA score of 0 after about 4 weeks, 8 weeks or 12 weeks of treatment with the 1% Tapinarof topical composition once a day. In certain embodiments, once the subject reaches a PGA score of 0, the administration is stopped for about 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, or indefinitely. In certain embodiments, treatment is reinitiated when the subject reaches a PGA score of ≥ 2 , wherein treatment is continued until the subject achieves a PGA score of 0.

[0092] Embodiments described herein are directed to methods for treating a subject with moderate to severe plaque psoriasis who has achieved a PGA score of 0 after about 4 weeks, 8 weeks or 12 weeks of administration of about 1.0% tapinarof in a topical composition comprising stopping administration of the about 1.0% tapinarof in a topical composition for about 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, or indefinitely.

[0093] Embodiments described herein are directed to methods for achieving remission in a subject with moderate to severe plaque psoriasis comprising administering about 1.0% tapinarof in a topical composition to the affected areas of the subject having a PGA score of ≥ 1 once a day, wherein administration of the about 1.0% tapinarof in a topical composition is stopped when the subject reaches a PGA score of 0. In certain embodiments, the subject reaches a PGA score of 0 after about 4 weeks, 8 weeks or 12 weeks of treatment. In certain embodiments, once the subject reaches a PGA score of 0 the administration is stopped for about 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, or indefinitely. In certain embodiments, treatment is reinitiated when the subject reaches a PGA score of ≥ 2 , wherein treatment is continued until the subject achieves a PGA score of 0.

[0094] Embodiments described herein are directed to methods for maintaining remission of moderate to severe plaque psoriasis in a subject comprising administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for an initial period of time until the plaque psoriasis is clear at which time the administration is stopped and remission is achieved, wherein the plaque psoriasis is clear is defined as one or more symptom is alleviated.

[0095] Embodiments described herein are directed to methods for inducing remission of moderate to severe plaque psoriasis in a subject comprising administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for an initial period of time until the plaque psoriasis is clear at which time the administration is stopped and remission has been induced, wherein the plaque psoriasis is clear is defined as one or more symptom is alleviated.

[0096] In embodiments described herein, the treating moderate to severe plaque psoriasis in a subject is wherein one or more symptom of psoriasis is improved. In embodiments described herein, the one or more symptom of moderate to severe psoriasis is measured according to an assessment selected from Physician Global Assessment (PGA) score, Psoriasis Area and Severity Index (PASI), target lesion grading, percent body surface area (BSA) affected, Dermatology Quality of Life Index (DLQI), or Patient Satisfaction questionnaire. In certain embodiments, plaque psoriasis is treated when the Physician Global Assessment (PGA) score is 0 or 1. In certain embodiments, plaque psoriasis is treated when the Physician Global Assessment (PGA) score has improved from baseline by at least 2-grades and as described below. In certain embodiments, plaque psoriasis is treated when the Psoriasis Area and Severity Index (PASI) has improved from baseline by a decrease in total PASI score and as described below. In certain embodiments, plaque psoriasis is treated when the target lesion grading has improved from baseline and as described below. In certain embodiments, plaque psoriasis is treated when the percent body surface area (BSA) affected has improved from baseline and as described below. In certain embodiments, plaque psoriasis is treated when the Dermatology Quality of Life Index (DLQI) has improved from baseline and as described below. In certain embodiments, plaque psoriasis is treated when the Patient Satisfaction questionnaire has improved from baseline and as described below.

[0097] In embodiments described herein, reassessment of the subject results in further treatment when a new nidus (previous application site or other site) or aggravating psoriasis (such as erythema, scale, immersion) occurs. In embodiments described herein, reassessment of the subject results in further treatment when compared with baseline and the symptoms are no longer improved or clear.

[0098] In embodiments described herein, further treatment is required if the PGA score is greater than or equal to 2. In embodiments described herein, further treatment is required if the PGA score is greater than or equal to 3. In embodiments described herein, further treatment is required if the PGA score is greater than or equal to 4. In embodiments

described herein, further treatment is required if the Psoriasis Area and Severity Index (PASI) returns to baseline. In embodiments described herein, further treatment is required if the target lesion grading returns to baseline. In embodiments described herein, further treatment is required if the percent body surface area (BSA) affected returns to baseline. In embodiments described herein, further treatment is required if the Dermatology Quality of Life Index (DLQI) returns to baseline. In embodiments described herein, further treatment is required if the Patient Satisfaction questionnaire returns to baseline.

[0099] In embodiments described herein, further treatment comprises administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for a subsequent period of time until the plaque psoriasis is treated. In certain embodiments, the subsequent period of time is about 8 weeks to about 16 weeks. In certain embodiments, the subsequent period of time can be up to 52 weeks.

[0100] Embodiments of the invention are directed to methods of treating moderate to severe plaque psoriasis in a subject comprising topically administering to the subject in need thereof a topical composition containing tapinarof as described herein, wherein skin type does not affect the efficacy of the treatment. In some embodiments, the skin type is measured using the Fitzpatrick scale, wherein the subject's skin type is selected from the group consisting of Fitzpatrick skin type I, Fitzpatrick skin type II, Fitzpatrick skin type III, Fitzpatrick skin type IV, Fitzpatrick skin type V, and Fitzpatrick skin type VI. Fitzpatrick scale is a numerical classification schema for human skin color. The following list shows the six categories of the Fitzpatrick scale: Type I -always burns, never tans (palest, freckles); Type II - usually burns, tans minimally; Type III - sometimes mild burn, tans uniformly; Type IV - burns minimally, always tans well (moderate brown); Type V - very rarely burns, tans very easily (dark brown); or Type VI - never burns (deeply pigmented dark brown to darkest brown).

[0101] In embodiments described herein, the topically administering of the topical composition includes application to the skin of the body, arms, legs, back, chest, buttocks, neck, scalp, fingernails, or toenails where the moderate to severe plaque psoriasis lesions are present (or "affected area"). The topically administering of the topical composition includes applying enough of the topical composition to completely cover each lesion with a thin layer. In embodiments described herein, administration of the topical composition requires that the subject lightly rub the cream into the skin until it is no longer visible.

[0102] In embodiments described herein, the subject has been diagnosed with moderate to severe plaque psoriasis and has had stable disease for at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, or at least 12 months.

[0103] In embodiments described herein, the subject is younger than 18 years of age. In embodiments described herein, the subject is 18 years of age or older. In embodiments described herein, the subject is between the ages of 18 to 65 years old. In embodiments described herein, the subject is between the ages of 18 to 75 years old.

[0104] In embodiments described herein, the topical composition is administered once daily for up to 52 weeks. In embodiments described herein, the topical composition is administered once daily for about 52 weeks. In embodiments described herein, the topical composition is administered once daily for up to 48 weeks. In embodiments described herein, the topical composition is administered once daily for about 48 weeks. In embodiments described herein, the topical composition is administered once daily for up to 44 weeks. In embodiments described herein, the topical composition is administered once daily for about 44 weeks. In embodiments described herein, the topical composition is administered once daily for up to 40 weeks. In embodiments described herein, the topical composition is administered once daily for about 40 weeks. In embodiments described herein, the topical composition is administered once daily for up to 36 weeks. In embodiments described herein, the topical composition is administered once daily for about 36 weeks. In embodiments described herein, the topical composition is administered once daily for up to 32 weeks. In embodiments described herein, the topical composition is administered once daily for about 32 weeks. In embodiments described herein, the topical composition is administered once daily for up to 28 weeks. In embodiments described herein, the topical composition is administered once daily for about 28 weeks. In embodiments described herein, the topical composition is administered once daily for up to 24 weeks. In embodiments described herein, the topical composition is administered once daily for about 24 weeks. In embodiments described herein, the topical composition is administered once daily for up to 12 weeks. In embodiments described herein, the topical composition is administered once daily for about 12 weeks. In embodiments described herein, the topical composition is administered once daily for up to 8 weeks. In embodiments described herein, the topical composition is administered once daily for about 8 weeks. In embodiments described herein, the topical composition is administered once daily for up to 6 weeks. In embodiments described herein,

the topical composition is administered once daily for about 6 weeks. In embodiments described herein, the topical composition is administered once daily for up to 4 weeks. In embodiments described herein, the topical composition is administered once daily for about 4 weeks. In embodiments described herein, the topical composition is administered once daily until the moderate to severe plaque psoriasis is resolved.

[0105] In certain embodiments, the duration of treatment success (time off treatment) will correlate with the severity of baseline disease. For example, a subject with a baseline PGA score of 3 may have treatment success for about 4 weeks to about 12 weeks, a subject with a baseline PGA score of 2 may have treatment success for about 8 weeks to about 20 weeks, a subject with a baseline PGA score of 1 may have treatment success for about 12 weeks to about 24 weeks, and a subject with a baseline PGA score of 0 may have treatment success for about 20 weeks to about 52 weeks.

[0106] In embodiments described herein, the subject has been diagnosed with moderate to severe plaque psoriasis having a Physician Global Assessment (PGA) score of about 2, about 3, or about 4. In embodiments described herein, the subject has been diagnosed with moderate to severe mild to moderate plaque psoriasis having a Physician Global Assessment (PGA) score of greater than or equal to 2. A PGA score of 2 is a diagnosis of mild plaque psoriasis. A PGA score of 3 is a diagnosis of moderate plaque psoriasis. A PGA score of 4 is a diagnosis of severe plaque psoriasis. In embodiments described herein, the Physician Global Assessment (PGA) is used to assess the current state/severity of a subject's psoriasis. It is a static 5-point morphological assessment of overall disease severity, as determined by the investigator, using the clinical characteristics of erythema, plaque thickness, and scaling as guidelines. In certain embodiments, the PGA is assessed daily, weekly, or monthly and without reference to previous scores. The scoring system includes: Score of 0 represents clear skin with no signs of psoriasis, post-inflammatory hyperpigmentation may be present; Score of 1 represents almost clear skin with no thickening, normal to pink coloration, no to minimal focal scaling; Score of 2 represents mild psoriasis with just detectable to mild thickening, pink to light red coloration, predominantly fine scaling; Score of 3 represents moderate psoriasis with clearly distinguishable to moderate thickening, dull to bright red, clearly distinguishable erythema, moderate scaling; and Score of 4 represents severe psoriasis with severe thickening with hard edges, bright to deep dark red coloration, severe/coarse scaling covering almost all or all lesions. In embodiments described herein, the subject's Physician Global Assessment (PGA)

score improved by about 1 grade, about 2 grades, about 3 grades, about 4 grades, or about 5 grades. In embodiments described herein, the subject's Physician Global Assessment (PGA) score improved by about 2 grades. In embodiments described herein, the subject's Physician Global Assessment (PGA) score improved to a score of about 0 or clear. In embodiments described herein, the subject's Physician Global Assessment (PGA) score improved to a score of about 1 or almost clear. In certain embodiments, the subject achieved a score of about 0 or about 1 by week 1, week 2, week 3, week 4, week 5, week 6, week 7, week 8, week 9, week 10, week 11, or week 12. In certain embodiments, the subject achieved a 2-grade improvement by week 1, week 2, week 3, week 4, week 5, week 6, week 7, week 8, week 9, week 10, week 11, week 12, week 13, week 14, week 15, week 16, week 17, week 18, week 19, week 20, week 21, week 22, week 23, or week 24. In embodiments described herein, the subject has sustained improvement of PGA score after treatment has ended. In embodiments described herein, the subject has sustained improvement of PGA score about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after treatment has ended. In embodiments described herein, the subject does not experience worsening of PGA score about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after treatment has ended.

[0107] In certain embodiments, the subject achieved a PGA score of 0 or 1 at least once over a 52 week period of time. In certain embodiments, the subject achieved a PGA score of 0 at least once over a 52 week period of time. In certain embodiments, the subject achieved a PGA score of 0 or 1 at least once over a 44 week period of time. In certain embodiments, the subject achieved a PGA score of 0 at least once over a 44 week period of time. In certain embodiments, the subject did not experience worsening during a 52 week period of time.

[0108] In embodiments described herein, administration of the topical composition to a subject having severe plaque psoriasis is effectively treated wherein the subject achieved a "Clear" or "Almost Clear" rating according to the PGA with at least a 2

point improvement. In embodiments described herein, administration of the topical composition to a subject having moderate plaque psoriasis is effectively treated wherein the subject achieved a “Clear” or “Almost Clear” rating according to the PGA with at least a 2 point improvement. In embodiments described herein, administration of the topical composition to a subject having mild plaque psoriasis is effectively treated wherein the subject achieved a “Clear” rating according to the PGA.

[0109] In embodiments described herein, the subject has been diagnosed with moderate to severe plaque psoriasis having a percent body surface area (BSA) affected of about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 31%, about 32%, about 33%, about 34%, or about 35%. In preferred embodiments, the subject has been diagnosed with moderate to severe plaque psoriasis having a percent body surface area (BSA) affected of about 3% to about 20%. In embodiments described herein, body surface area (BSA) excludes the scalp, palms of the hands and soles of the feet. The assessment of the %BSA affected is an estimate of the percentage of total involved skin with psoriasis. The extent of BSA affected by psoriasis is a general indicator of disease severity. In embodiments described herein, one percent body surface area (1% BSA) is the equivalent of the total palmar surface of the palm plus 5 digits. The %BSA affected is calculated using the following regional body areas: Head and neck; Trunk, includes internal axillae and groin; Upper extremities, includes arms, external axillae, and hands; and Lower extremities, includes legs, buttocks, and feet. In embodiments described herein, body surface area (BSA) excludes the scalp, palms of the hands and soles of the feet. The %BSA assessment is utilized in the PASI. The %BSA affected by psoriasis is evaluated from 0 to 100%. In embodiments described herein, the subject's percent body surface area (BSA) affected is decreased. In certain embodiments, the subject achieved a decrease in the % BSA affected by week 1, week 2, week 3, week 4, week 5, week 6, week 7, week 8, week 9, week 10, week 11, week 12, week 13, week 14, week 15, week 16, week 17, week 18, week 19, week 20, week 21, week 22, week 23, or week 24. In embodiments described herein, the subject has sustained improvement of % BSA affected after treatment has ended. In embodiments described herein, the subject has sustained improvement of percent body surface area (BSA) affected about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7

weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after treatment has ended. In embodiments described herein, the subject does not experience worsening of % BSA affected about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after treatment has ended.

[0110] In embodiments described herein, the Psoriasis Area and Severity Index (PASI) is used to assess the severity of psoriasis that takes into account the overall severity of erythema (redness), thickness (induration), and scale (desquamation), as well as the extent of BSA affected with psoriasis. The 3 clinical signs are each graded on a 5 point scale (0 to 4) and the %BSA affected is scored on a 7-point scale (0 to 6) for each of the 4 specified body regions (head, upper extremities, trunk, and lower extremities). The individual scores are multiplied by a weighted factor for each body region; the sum of these scores gives the overall PASI score. Higher scores indicate more severe disease. PASI is a static assessment made without reference to previous scores. In embodiments described herein, the subject's Psoriasis Area and Severity Index (PASI) is improved by about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%. In embodiments described herein, the subject's Psoriasis Area and Severity Index (PASI) is improved by greater than or equal to 25%, greater than or equal to 50%, greater than or equal to 75%, or greater than or equal to 90%. In embodiments described herein, the subject's Psoriasis Area and Severity Index (PASI) is improved by greater than or equal to 50%. In embodiments described herein, the subject's Psoriasis Area and Severity Index (PASI) is improved by greater than or equal to 75%. In embodiments described herein, the subject's Psoriasis Area and Severity Index (PASI) is improved by greater than or equal to 90%. In certain embodiments, the subject achieved a greater than 50% improvement in PASI by week 1, week 2, week 3, week 4, week 5, week 6, week 7, week 8, week 9, week 10, week 11, week 12, week 13, week 14, week 15, week 16, week 17, week 18, week 19, week 20, week 21, week 22, week 23, or week 24. In certain embodiments, the subject achieved a greater than 75% improvement in PASI by week 1, week 2, week 3, week 4, week 5, week 6,

week 7, week 8, week 9, week 10, week 11, week 12, week 13, week 14, week 15, week 16, week 17, week 18, week 19, week 20, week 21, week 22, week 23, or week 24. In certain embodiments, the subject achieved a greater than 90% improvement in PASI by week 1, week 2, week 3, week 4, week 5, week 6, week 7, week 8, week 9, week 10, week 11, week 12, week 13, week 14, week 15, week 16, week 17, week 18, week 19, week 20, week 21, week 22, week 23, or week 24. In embodiments described herein, the subject has sustained improvement of PASI after treatment has ended. In embodiments described herein, the subject has sustained improvement of PASI about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after treatment has ended. In embodiments described herein, the subject does not experience worsening of PASI about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after treatment has ended.

[0111] In embodiments described herein, the target lesion grading is determined by measuring a single target lesion at baseline to assess efficacy in treating a discrete area rather than an overall average of all areas. For that single target lesion, the severity of erythema, scaling, and plaque thickness is assessed on a 5-point scale ranging from 0 (=none) to 4 (=severe). The maximum score was 15, with higher scores indicating more severe disease. In embodiments described herein, the subject's target lesion grading improved by about 1 point, about 2 points, 3 points, about 4 points, about 5 points, about 6 points, about 7 points, about 8 points, about 9 points, about 10 points, about 11 points, about 12 points, about 13 points, about 14 points, or about 15 points. In certain embodiments, the subject achieved an improvement in target lesion grading by week 1, week 2, week 3, week 4, week 5, week 6, week 7, week 8, week 9, week 10, week 11, week 12, week 13, week 14, week 15, week 16, week 17, week 18, week 19, week 20, week 21, week 22, week 23, or week 24. In embodiments described herein, the subject has sustained improvement of target lesion grading after treatment has ended. In embodiments described herein, the subject has sustained improvement of target lesion grading about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10

weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after treatment has ended. In embodiments described herein, the subject does not experience worsening of target lesion grading about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after treatment has ended.

[0112] In embodiments described herein, subjects record changes using the Dermatology Quality of Life Index (DLQI) questionnaire. The DLQI is a simple dermatology-specific 10 question validated questionnaire to assess the impact of the disease on a subject's quality of life. The DLQI has become an important outcome measure in dermatology clinical trials and is the most frequently used instrument in studies of randomized controlled trials in dermatology. The DLQI can be analyzed as a total score (where a higher score indicates greater impairment in quality of life) and can also be scored for the following dimensions: Symptoms and Feelings (items 1 and 2), Daily Activities (items 3 and 4), Leisure (items 5 and 6), Work and School (item 7), Personal Relationships (items 8 and 9), and Treatment (item 10). In certain embodiments, the subject reported an improvement on the impact of one or more daily activities assessed by the DLQI by week 1, week 2, week 3, week 4, week 5, week 6, week 7, week 8, week 9, week 10, week 11, week 12, week 13, week 14, week 15, week 16, week 17, week 18, week 19, week 20, week 21, week 22, week 23, or week 24. In embodiments described herein, the subject has sustained improvement on the impact of one or more daily activities assessed by the DLQI after treatment has ended. In embodiments described herein, the subject has sustained improvement of one or more daily activities assessed by the DLQI about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after treatment has ended. IV. In embodiments described herein, the subject does not experience worsening of one or more daily activities assessed by the DLQI about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks,

about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after treatment has ended.

[0113] In embodiments described herein, the Patient Satisfaction questionnaire includes the questions provided below, wherein the subject selects one of the following: Strongly Agree, Agree, Neutral, Disagree, or Strongly Disagree.

1. I can easily manage my psoriasis with the study drug
2. The time spent applying the study drug every day was acceptable and did not affect my everyday life
3. I am satisfied with how well the study drug worked for my psoriasis
4. I have confidence in the study drug
5. The study drug cleared my skin and kept my psoriasis from coming back
6. If the study drug was available by prescription, I would recommend it to other patients with psoriasis
7. If the study drug was available by a prescription, I would use it again or continue on it
8. The study drug is easy to apply
9. The study drug is not greasy
10. The study drug quickly absorbs into my skin
11. The study drug feels good on my skin
12. I am satisfied with the look and feel of the study drug

The below questions # 13-18 are comparing the study drug to other drugs used to treat psoriasis in the past. A topical drug is a drug that is applied to the skin like creams, ointments, lotions, gels, foams, sprays. A systemic drug is a drug that is taken by mouth like a capsule or tablet or injected through the skin with a needle like a shot or through a vein by a healthcare practitioner.

Subject is asked if they have used other topical drugs to treat psoriasis in the past? If yes, they answer questions 13-15. If no, they skip to question 16.

13. The study drug is more effective than other topical drugs I have used to treat my psoriasis
14. The study drug is easier to use than other topical drugs I have used to treat my psoriasis
15. I prefer the study drug to other topical drugs I have used to treat my psoriasis

Subject is asked if they have used systemic drugs to treat psoriasis in the past?

16. The study drug is more effective than systemic drugs I have used to treat my psoriasis

17. The study drug is easier to use than systemic drugs I have used to treat my psoriasis

18. I prefer the study drug to systemic drugs I have used to treat my psoriasis

[0114] In embodiments described herein, the one or more symptoms improved by about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after administering the topical composition. In embodiments described herein, the one or more symptoms improved by about 2 weeks of administering the topical composition. In embodiments described herein, the one or more symptoms improved by about 4 weeks of administering the topical composition. In embodiments described herein, the one or more symptoms improved by about 8 weeks of administering the topical composition. In embodiments described herein, the one or more symptoms improved by about 12 weeks of administering the topical composition.

[0115] In some embodiments, it was surprisingly found that the topical composition may produce long lasting effects on the skin and may modify the long-term course of moderate to severe plaque psoriasis. Specifically, in certain embodiments, the improvement of the symptoms seen during administration of the topical composition may be maintained long after the final administration of the topical composition. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 2 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 3 weeks after administration of the topical composition has ceased. In embodiments described herein, the

one or more symptoms remain improved and the remittive effect lasted about 4 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 8 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 12 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 16 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 20 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 24 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 28 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 32 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 36 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 42 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 48 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 52 weeks after administration of the topical composition has ceased.

[0116] It was surprisingly found that the topical composition may produce long lasting effects on the skin and may modify the long-term course of moderate to severe plaque psoriasis. Specifically, in certain embodiments, the symptoms do not worsen after the final administration of the topical composition. In embodiments described herein, the one or more symptoms do not worsen about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 2 weeks after

administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 3 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 4 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 8 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 12 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 16 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 20 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 24 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 28 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 32 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 36 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 42 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 48 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 52 weeks after administration of the topical composition has ceased.

[0117] In embodiments described herein, the topical composition can be used in a long-term treatment regimen, compared with topical corticosteroids which can only be used for 2-4 weeks. In embodiments described herein, the topical composition can be used for greater than 12 weeks.

[0118] Plaque psoriasis is a chronic disease which typically requires daily treatment for the duration of the subject's life. Available treatments, such are corticosteroids, have high side effects and cannot be administered for longer than 2 weeks at a time, after which time a rest phase from treatment must be taken before treatment can resume. Surprisingly, the tapinarof topical composition described herein is safe to use daily for an extended period of time which is greater than 2 weeks. In embodiments described herein, the

tapinarof topical composition described herein can be continuously administered to the subject for greater than 2 weeks, greater than 1 month, greater than 2 months, greater than 3 months, greater than 4 months, or longer and during such period of administration, efficacy of the treatment is maintained (e.g., no loss of efficacy over time). Additionally, current treatments are only applied to the areas of the skin where there is an active lesion. Surprisingly, the tapinarof topical composition described herein can be safely applied to all areas of the skin without any limit as to total amount of body surface area receives treatment, for example, the subject can apply to active lesions as well as clear regions. In embodiments described herein, the tapinarof topical composition described herein can be administered to any or all of the following regions: back, elbows, knees, legs, soles of the feet, scalp, face, palms, genitals, or chest.

[0119] Embodiments described herein are directed to methods for treating a subject with moderate to severe plaque psoriasis comprising administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for an indefinite amount of time, wherein the subject reaches a PGA score of 1 or improves by at least 1 grade. In embodiments described herein, the subject maintains an improved PGA score but does not reach 0. In embodiments described herein, the subject achieves an improved PGA score of 0 after 4 months of administration of the tapinarof topical composition.

METHODS OF USING TOPICAL COMPOSITIONS TO TREAT ATOPIC DERMATITIS

[0120] Embodiments described herein are directed to methods for developing a remittive effect in a subject with moderate to severe atopic dermatitis comprising administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for an initial period of time until the atopic dermatitis is clear at which time the administration is stopped, and reassessing the subject from about 3 months to about 12 months after administration is stopped to determine if further treatment is required.

[0121] Embodiments described herein are directed to methods for treating moderate to severe atopic dermatitis in a subject comprising administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for an initial period of time until the atopic dermatitis is clear at which time the administration is stopped, and reassessing the subject from about 3 months to about 12 months after administration is stopped to determine if further treatment is required.

[0122] In embodiments described herein, the topical composition is administered in an initial period of time. In embodiments described herein, the initial period of time is about 8 weeks to about 40 weeks in duration. In certain embodiments, the initial period of time is about 40 weeks.

[0123] In embodiments described herein, reassessment of the subject occurs at about 4 months after administration. In certain embodiments, further treatment is initiated after reassessment of the subject. In certain embodiments, the further treatment comprises administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for a subsequent period of time until the atopic dermatitis is clear.

[0124] Embodiments described herein are directed to methods for inducing a remittive effect in a subject with atopic dermatitis, wherein the remittive effect can be temporary or permanent.

[0125] Embodiments described herein are directed to methods for achieving remission in a subject with atopic dermatitis comprising administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day until the subject reaches an IGA score of 0, wherein administration of the about 1.0% tapinarof in a topical composition is stopped. In certain embodiments, the subject reaches an IGA score of 0 at 12 weeks. In certain embodiments, the administration is stopped for about 4 months or indefinitely. In certain embodiments, treatment is reinitiated when the subject reaches a IGA score of ≥ 2 , wherein treatment is continued until the subject achieves a IGA score of 0.

[0126] Embodiments described herein are directed to methods for treating a subject with atopic dermatitis who has achieved an IGA score of 0 after about 4 weeks, 8 weeks, or 12 weeks of administration of about 1.0% tapinarof in a topical composition comprising stopping administration of the about 1.0% tapinarof in a topical composition for about 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, or indefinitely.

[0127] Embodiments described herein are directed to methods for achieving remission in a subject with atopic dermatitis comprising administering about 1.0% tapinarof in a topical composition to the affected areas of the subject having a IGA score of ≥ 1 once a day, wherein administration of the about 1.0% tapinarof in a topical composition is stopped when the subject reaches a IGA score of 0. In certain embodiments, the subject reaches a IGA score of 0 after about 4 weeks, 8 weeks or 12 weeks of treatment. In certain embodiments, once the subject reaches a IGA score of 0 the administration is stopped for about 4 months, 5

months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, or indefinitely. In certain embodiments, treatment is reinitiated when the subject reaches a IGA score of ≥ 2 , wherein treatment is continued until the subject achieves a IGA score of 0. Embodiments described herein are directed to methods for maintaining remission of moderate to severe atopic dermatitis in a subject comprising administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for an initial period of time until the atopic dermatitis is clear at which time the administration is stopped and remission is achieved, wherein the atopic dermatitis is clear is defined as one or more symptom is alleviated.

[0128] Embodiments described herein are directed to methods for inducing remission of atopic dermatitis in a subject comprising administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for an initial period of time until the atopic dermatitis is clear at which time the administration is stopped and remission has been induced, wherein the atopic dermatitis is clear is defined as one or more symptom is alleviated.

[0129] In embodiments described herein, further treatment comprises administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for a subsequent period of time until the atopic dermatitis is treated. In certain embodiments, the subsequent period of time is about 8 weeks to about 16 weeks. In certain embodiments, the subsequent period of time can be up to 52 weeks.

[0130] In embodiments described herein, the treating moderate to severe atopic dermatitis in a subject is wherein one or more symptom of atopic dermatitis is improved. In embodiments described herein, the one or more symptom of atopic dermatitis is measured according to an assessment selected from Investigator Global Assessment (IGA) score, daily Itch/Pruritus numeric rating scale, Eczema Area and Severity Index (EASI), total severity score, percent body surface area (BSA) affected, sleep quality, dry/rough skin, red/discolored skin, flaky skin, visual analogue scale (VAS) for sleep, visual analogue scale (VAS) for itch, peak pruritus numerical rating scale (PP-NRS), and patient reported outcomes.

[0131] In embodiments described herein, the topically administering of the topical composition includes application to the skin of the body, arms, legs, back, chest, buttocks, neck, scalp, fingernails, or toenails where the atopic dermatitis lesions are present (or “affected area”). The topically administering of the topical composition includes applying enough of the topical composition to completely cover each lesion with a thin layer. In

embodiments described herein, administration of the topical composition requires that the subject lightly rub the cream into the skin until it is no longer visible.

[0132] In embodiments described herein, the subject has been diagnosed with atopic dermatitis and has had stable disease for at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, or at least 12 months. In embodiments described herein, the subject has been diagnosed with atopic dermatitis and has had stable disease for at least 6 months for ages 6 years old and older. In embodiments described herein, the subject has been diagnosed with atopic dermatitis and has had stable disease for 3 months for ages 2 to 5 years old.

[0133] In embodiments described herein, the subject is between the ages of 2 or older. In embodiments described herein, the subject is younger than 18 years of age. In embodiments described herein, the subject is 18 years of age or older. In embodiments described herein, the subject is between the ages of 18 to 65 years old. In embodiments described herein, the subject is between the ages of 18 to 75 years old.

[0134] In embodiments described herein, the topical composition is administered once daily for up to 52 weeks. In embodiments described herein, the topical composition is administered once daily for about 52 weeks. In embodiments described herein, the topical composition is administered once daily for up to 48 weeks. In embodiments described herein, the topical composition is administered once daily for about 48 weeks. In embodiments described herein, the topical composition is administered once daily for up to 44 weeks. In embodiments described herein, the topical composition is administered once daily for about 44 weeks. In embodiments described herein, the topical composition is administered once daily for up to 40 weeks. In embodiments described herein, the topical composition is administered once daily for about 40 weeks. In embodiments described herein, the topical composition is administered once daily for up to 36 weeks. In embodiments described herein, the topical composition is administered once daily for about 36 weeks. In embodiments described herein, the topical composition is administered once daily for up to 32 weeks. In embodiments described herein, the topical composition is administered once daily for about 32 weeks. In embodiments described herein, the topical composition is administered once daily for up to 28 weeks. In embodiments described herein, the topical composition is administered once daily for about 28 weeks. In embodiments described herein, the topical composition is administered once daily for up to 24 weeks. In embodiments described herein, the topical composition is administered once daily for about 24 weeks. In embodiments

described herein, the topical composition is administered once daily for up to 12 weeks. In embodiments described herein, the topical composition is administered once daily for about 12 weeks. In embodiments described herein, the topical composition is administered once daily for up to 8 weeks. In embodiments described herein, the topical composition is administered once daily for about 8 weeks. In embodiments described herein, the topical composition is administered once daily for up to 6 weeks. In embodiments described herein, the topical composition is administered once daily for about 6 weeks. In embodiments described herein, the topical composition is administered once daily for up to 4 weeks. In embodiments described herein, the topical composition is administered once daily for about 4 weeks. In embodiments described herein, the topical composition is administered once daily until the atopic dermatitis is resolved.

[0135] In embodiments described herein, the Investigator's Global Assessment (IGA) is used for assessing the current state/severity of a subject's AD. It uses a static 5-point morphological assessment of overall disease severity, as determined by the investigator, using the clinical characteristics of erythema, infiltration, papulation, oozing, and crusting as guidelines. In certain embodiments, the IGA is made daily, weekly, or monthly and without reference to previous scores. The scoring system ranges from 0 (–Clear) to 4 (–Severe). In embodiments described herein, the subject's Investigator Global Assessment (IGA) score improved by about 1 grade, about 2 grades, about 3 grades, about 4 grades, or about 5 grades. In embodiments described herein, the subject's IGA score improved by about 2 grades. In embodiments described herein, the subject's IGA score improved to a score of about 0 or about 1. In embodiments described herein, the subject's IGA score improved to a score of about 1 or almost clear. In certain embodiments, the subject achieved a score of about 0 or about 1 by week 1, week 2, week 3, week 4, week 5, week 6, week 7, week 8, week 9, week 10, week 11, or week 12. In certain embodiments, the subject achieved a 2-grade improvement by week 1, week 2, week 3, week 4, week 5, week 6, week 7, week 8, week 9, week 10, week 11, week 12, week 13, week 14, week 15, week 16, week 17, week 18, week 19, week 20, week 21, week 22, week 23, or week 24. In embodiments described herein, the subject has sustained improvement of IGA score after treatment has ended. In embodiments described herein, the subject has sustained improvement of IGA score about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19

weeks, about 20 weeks, or up to 52 weeks after treatment has ended. In embodiments described herein, the subject does not experience worsening of IGA score about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after treatment has ended.

[0136] In certain embodiments, the duration of treatment success (time off treatment) will correlate with the severity of baseline disease. For example, a subject with a baseline IGA score of 3 may have treatment success for about 4 weeks to about 12 weeks, a subject with a baseline IGA score of 2 may have treatment success for about 8 weeks to about 20 weeks, a subject with a baseline IGA score of 1 may have treatment success for about 12 weeks to about 24 weeks, and a subject with a baseline IGA score of 0 may have treatment success for about 20 weeks to about 52 weeks.

[0137] In certain embodiments, the subject achieved a IGA score of 0 or 1 at least once over a 52 week period of time. In certain embodiments, the subject achieved a IGA score of 0 at least once over a 52 week period of time. In certain embodiments, the subject achieved a IGA score of 0 or 1 at least once over a 44 week period of time. In certain embodiments, the subject achieved a IGA score of 0 at least once over a 44 week period of time. In certain embodiments, the subject did not experience worsening during a 52 week period of time.

[0138] In embodiments described herein, administration of the topical composition to a subject having moderate to severe atopic dermatitis is effectively treated wherein the subject achieved a “Clear” or “Almost Clear” rating according to the IGA with at least a 2 point improvement.

[0139] Pruritus is the most frequent symptom of AD and potentially has the greatest effect on quality of life. In embodiments described herein, the daily Itch/Pruritus numeric rating scale is subject-reported and obtained from the itch item on the Daily Sign and Symptom Severity Diary. In embodiments described herein, the subject’s Itch/Pruritus numeric rating scale is improved by about 1 point, about 2 points, about 3 points, about 4 points, or about 5 points. In embodiments described herein, the subject’s Itch/Pruritus numeric rating scale is improved by 3 points.

[0140] The assessment of the %BSA affected is an estimate of the percentage of total involved skin with atopic dermatitis. The extent of BSA affected by AD is a general

indicator of disease severity. In embodiments described herein, one percent body surface area (1% BSA) is the equivalent of the total palmar surface of the palm plus 5 digits. The %BSA affected is calculated using the following regional body areas: Head and neck; Trunk, includes internal axillae and groin; Upper extremities, includes arms, external axillae, and hands; and Lower extremities, includes legs, buttocks, and feet. The %BSA assessment is utilized in the EASI. The %BSA affected by atopic dermatitis is evaluated from 0 to 100%. In embodiments described herein, the subject's percent body surface area (BSA) affected is decreased. In certain embodiments, the subject achieved a decrease in the % BSA affected by week 1, week 2, week 3, week 4, week 5, week 6, week 7, week 8, week 9, week 10, week 11, week 12, week 13, week 14, week 15, week 16, week 17, week 18, week 19, week 20, week 21, week 22, week 23, or week 24. In embodiments described herein, the subject has sustained improvement of % BSA affected after treatment has ended. In embodiments described herein, the subject has sustained improvement of percent body surface area (BSA) affected about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after treatment has ended. In embodiments described herein, the subject does not experience worsening of % BSA affected about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after treatment has ended.

[0141] In embodiments described herein, the Eczema Area and Severity Index (EASI) is measured using a scoring system for assessing the severity of AD that takes into account the overall severity of erythema, infiltration/ papulation, excoriation, and lichenification, as well as the extent of BSA affected with AD. The 4 clinical signs are each graded on a 4-point scale (0 to 3) for each of the 4 specified body regions (head and neck, upper extremities, lower extremities, and trunk). The EASI is a static assessment made without reference to previous scores. In embodiments described herein, the subject's Eczema Area and Severity Index (EASI) is improved by about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about

100%. In embodiments described herein, the subject's Eczema Area and Severity Index (EASI) is improved by greater than or equal to 25%, greater than or equal to 50%, or greater than or equal to 75%. In embodiments described herein, the subject's Eczema Area and Severity Index (EASI) is improved by greater than or equal to 50%. In embodiments described herein, the subject's Eczema Area and Severity Index (EASI) is improved by greater than or equal to 75%. In embodiments described herein, the subject's Eczema Area and Severity Index (EASI) is improved by greater than or equal to 90%. In certain embodiments, the subject achieved a greater than 50% improvement in EASI by week 1, week 2, week 3, week 4, week 5, week 6, week 7, week 8, week 9, week 10, week 11, week 12, week 13, week 14, week 15, week 16, week 17, week 18, week 19, week 20, week 21, week 22, week 23, or week 24. In certain embodiments, the subject achieved a greater than 75% improvement in EASI by week 1, week 2, week 3, week 4, week 5, week 6, week 7, week 8, week 9, week 10, week 11, week 12, week 13, week 14, week 15, week 16, week 17, week 18, week 19, week 20, week 21, week 22, week 23, or week 24. In certain embodiments, the subject achieved a greater than 90% improvement in EASI by week 1, week 2, week 3, week 4, week 5, week 6, week 7, week 8, week 9, week 10, week 11, week 12, week 13, week 14, week 15, week 16, week 17, week 18, week 19, week 20, week 21, week 22, week 23, or week 24. In embodiments described herein, the subject has sustained improvement of EASI after treatment has ended. In embodiments described herein, the subject has sustained improvement of EASI about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after treatment has ended. In embodiments described herein, the subject does not experience worsening of EASI about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after treatment has ended.

[0142] In embodiments described herein, the total severity score (TSS) is determined by measuring a single target lesion measuring at least 3 cm at baseline and was representative of subject disease, but not located on hands, feet or genitalia. The single target lesion selected to assess efficacy in treating a discrete area rather than an overall average of

all areas. For the single target lesion, the severity of erythema, induration/papulation, lichenification, oozing/crusting, and scaling was assessed on a 4-point scale and TSS was calculated. The maximum score was 15, with higher scores indicating more severe disease. In embodiments described herein, the subject's total severity score improved by about 1 point, about 2 points, 3 points, about 4 points, about 5 points, about 6 points, about 7 points, about 8 points, about 9 points, about 10 points, about 11 points, about 12 points, about 13 points, about 14 points, or about 15 points. In certain embodiments, the subject achieved an improvement in total severity score by week 1, week 2, week 3, week 4, week 5, week 6, week 7, week 8, week 9, week 10, week 11, week 12, week 13, week 14, week 15, week 16, week 17, week 18, week 19, week 20, week 21, week 22, week 23, or week 24. In embodiments described herein, the subject has sustained improvement of total severity score after treatment has ended. In embodiments described herein, the subject has sustained improvement of total severity score about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after treatment has ended. In embodiments described herein, the subject does not experience worsening of total severity score about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after treatment has ended.

[0143] In embodiments described herein, the peak pruritus numerical rating scale (PP-NRS) is used to measure itch intensity. The maximum score was 10, with higher scores indicating worst itch imaginable itch. In embodiments described herein, the subject's total severity score improved by about 1 point, about 2 points, 3 points, about 4 points, about 5 points, about 6 points, about 7 points, about 8 points, about 9 points, or about 10 points. In certain embodiments, the subject achieved an improvement in total severity score by week 1, week 2, week 3, week 4, week 5, week 6, week 7, week 8, week 9, week 10, week 11, week 12, week 13, week 14, week 15, week 16, week 17, week 18, week 19, week 20, week 21, week 22, week 23, or week 24. In embodiments described herein, the subject has sustained improvement of total severity score after treatment has ended. In embodiments described herein, the subject has sustained improvement of total severity score about 1 week, about 2

weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after treatment has ended. In embodiments described herein, the subject does not experience worsening of total severity score about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after treatment has ended.

[0144] In embodiments described herein, patient reported outcomes were measured using the Daily Sign and Symptom Severity Diary and the Expanded Patient-Oriented Eczema Measure (POEM).

[0145] In embodiments described herein, the self-administered Daily Sign and Symptom Severity Diary assesses the severity of 11 disease-related signs and symptoms (1. skin that is itchy, 2. discolored, 3. bleeding, 4. oozing, 5. cracked, 6. scaly, 7. flaky, 8. dry/rough, 9. painful, 10. burning, and 11. stinging). Response options are on an 11-point numeric rating scale (NRS) and range from 0 (Absent) to 10 (Worst Imaginable). In embodiments described herein, the recall period was the previous 24 hours. In embodiments described herein, the subject's assessment of itchy skin, red/discolored skin, bleeding, weeping or oozing skin, cracked skin, scaly skin, flaky skin, dry or rough skin, painful skin, burning skin, or burning skin, each improved by about 1 point, about 2 points, 3 points, about 4 points, about 5 points, about 6 points, about 7 points, about 8 points, about 9 points, about 10 points, or about 11 points. In certain embodiments, the subject reported an improvement on one or more symptoms assessed by the Daily Sign and Symptom Severity Diary by week 1, week 2, week 3, week 4, week 5, week 6, week 7, week 8, week 9, week 10, week 11, week 12, week 13, week 14, week 15, week 16, week 17, week 18, week 19, week 20, week 21, week 22, week 23, or week 24. In embodiments described herein, the subject has sustained improvement on one or more symptoms assessed by the Daily Sign and Symptom Severity Diary after treatment has ended. In embodiments described herein, the subject has sustained improvement on one or more symptoms assessed by the Daily Sign and Symptom Severity Diary about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks,

about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after treatment has ended. In embodiments described herein, the subject does not experience worsening of one or more daily activities assessed by the Daily Sign and Symptom Severity Diary about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after treatment has ended.

[0146] In embodiments described herein, the subject assessed disease severity using the self-administered Expanded Patient-Oriented Eczema Measure (POEM). In embodiments described herein, the Expanded POEM assessed seven symptoms (1. skin that is itchy, 2. bleeding, 3. weeping/oozing, 4. cracked, 5. flaking, 6. dry/rough, and 7. disturbed sleep) measured using a 5-point scale of frequency of occurrence during the previous week. The 3 questions to assess sleep quality were directed to the frequency of waking at night difficulty falling asleep due to the atopic dermatitis. Individual responses were scored from 0 to 4. Improvement in sleep and improvement in itch were also measured using a visual analogue scale (VAS). In embodiments described herein, the subject's assessment of itchy skin, bleeding, weeping/oozing, cracked skin, flaking skin, dry/rough skin, and disturbed sleep each improved by about 1 point, about 2 points, 3 points, or about 4 points. In embodiments described herein, the subject's assessment of sleep quality is improved. In embodiments described herein, the subject's assessment of disturbed sleep improved. In certain embodiments, the subject reported an improvement on one or more symptoms assessed by POEM by week 1, week 2, week 3, week 4, week 5, week 6, week 7, week 8, week 9, week 10, week 11, week 12, week 13, week 14, week 15, week 16, week 17, week 18, week 19, week 20, week 21, week 22, week 23, or week 24. In embodiments described herein, the subject has sustained improvement on the impact of one or more daily activities assessed by POEM after treatment has ended. In embodiments described herein, the subject has sustained improvement of one or more daily activities assessed by POEM about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after treatment has ended. In embodiments described herein, the subject does not experience worsening of one or more

daily activities assessed by POEM about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after treatment has ended.

[0147] In embodiments described herein, the one or more symptoms improved by about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after administering the topical composition. In embodiments described herein, the one or more symptoms improved by about 2 weeks of administering the topical composition. In embodiments described herein, the one or more symptoms improved by about 4 weeks of administering the topical composition. In embodiments described herein, the one or more symptoms improved by about 8 weeks of administering the topical composition. In embodiments described herein, the one or more symptoms improved by about 12 weeks of administering the topical composition.

[0148] In some embodiments, it was surprisingly found that the topical composition may produce long lasting effects on the skin and may modify the long-term course of moderate to severe atopic dermatitis. Specifically, in certain embodiments, the improvement of the symptoms seen during administration of the topical composition may be maintained long after the final administration of the topical composition. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 2 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 3 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 4 weeks after administration of the topical composition has ceased. In embodiments described herein, the

one or more symptoms remain improved and the remittive effect lasted about 8 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 12 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 16 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 20 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 24 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 28 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 32 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 36 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 42 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 48 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 52 weeks after administration of the topical composition has ceased.

[0149] It was surprisingly found that the topical composition may produce long lasting effects on the skin and may modify the long-term course of moderate to severe atopic dermatitis. Specifically, in certain embodiments, the symptoms do not worsen after the final administration of the topical composition. In embodiments described herein, the one or more symptoms do not worsen about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 2 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 3 weeks after administration of the topical

composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 4 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 8 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 12 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 16 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 20 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 24 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 28 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 32 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 36 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 42 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 48 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 52 weeks after administration of the topical composition has ceased.

[0150] In embodiments described herein, the topical composition can be used in a long-term treatment regimen, compared with topical corticosteroids which can only be used for 2-4 weeks. In embodiments described herein, the topical composition can be used for greater than 12 weeks.

[0151] Atopic dermatitis is a chronic disease which typically requires daily treatment for the duration of the subject's life. Available treatments, such are corticosteroids, have high side effects and cannot be administered for longer than 2 weeks at a time, after which time a rest phase from treatment must be taken before treatment can resume. Surprisingly, the tapinarof topical composition described herein is safe to use daily for an extended period of time which is greater than 2 weeks. In embodiments described herein, the tapinarof topical composition described herein can be continuously administered to the subject for greater than 2 weeks, greater than 1 month, greater than 2 months, greater than 3

months, greater than 4 months, or longer. Additionally, current treatments are only applied to the areas of the skin where there is an active lesion. Surprisingly, the tapinarof topical composition described herein can be safely applied to all areas of the skin without any limit as to total amount of body surface area receives treatment, for example, the subject can apply to active lesions as well as clear regions. In embodiments described herein, the tapinarof topical composition described herein can be administered to any or all of the following regions: back, elbows, knees, legs, soles of the feet, scalp, face, palms, genitals, or chest.

[0152] Embodiments described herein are directed to methods for treating a subject with atopic dermatitis comprising administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for an indefinite amount of time, wherein the subject reaches an IGA score of 1 or improves by at least 1 grade. In embodiments described herein, the subject maintains an improved IGA score but does not reach 0. In embodiments described herein, the subject achieves an improved IGA score of 0 after 4 months of administration of the tapinarof topical composition.

METHODS OF USING TOPICAL COMPOSITIONS TO TREAT RADIATION DERMATITIS

[0153] Embodiments described herein are directed to methods for developing a remittive effect in a subject with radiation dermatitis comprising administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for an initial period of time until the radiation dermatitis is clear at which time the administration is stopped, and reassessing the subject from about 3 months to about 12 months after administration is stopped to determine if further treatment is required.

[0154] Embodiments described herein are directed to methods for treating radiation dermatitis in a subject comprising administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for an initial period of time until the radiation dermatitis is clear at which time the administration is stopped, and reassessing the subject from about 3 months to about 12 months after administration is stopped to determine if further treatment is required.

[0155] In embodiments described herein, the topical composition is administered in an initial period of time. In embodiments described herein, the initial period of time is about 16 weeks to about 40 weeks in duration. In certain embodiments, the initial period of time is about 40 weeks.

[0156] In embodiments described herein, reassessment of the subject occurs at about 4 months after administration. In certain embodiments, further treatment is initiated

after reassessment of the subject. In certain embodiments, the further treatment comprises administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for a subsequent period of time until the radiation dermatitis is clear.

[0157] Embodiments described herein are directed to methods for inducing a remittive effect in a subject with radiation dermatitis, wherein the remittive effect can be temporary or permanent.

[0158] Embodiments described herein are directed to methods for achieving remission in a subject with radiation dermatitis comprising administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day until the subject reaches a National Cancer Institute classification of Grade 1, wherein administration of the about 1.0% tapinarof in a topical composition is stopped. In certain embodiments, the subject reaches a National Cancer Institute classification of Grade 1 at 12 weeks. In certain embodiments, the administration is stopped for about 4 months or indefinitely.

[0159] Embodiments described herein are directed to methods for treating a subject with radiation dermatitis who has achieved a National Cancer Institute classification of Grade 1 after 12 weeks of administration of about 1.0% tapinarof in a topical composition comprising stopping administration of the about 1.0% tapinarof in a topical composition for about 4 months.

[0160] Embodiments described herein are directed to methods for maintaining remission of radiation dermatitis in a subject comprising administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for an initial period of time until the radiation dermatitis is clear at which time the administration is stopped and remission is achieved, wherein one or more symptom is alleviated.

[0161] Embodiments described herein are directed to methods for inducing remission of radiation dermatitis in a subject comprising administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for an initial period of time until the radiation dermatitis is clear at which time the administration is stopped and remission has been induced, wherein one or more symptom is alleviated.

[0162] In embodiments described herein, the treating radiation dermatitis in a subject is wherein one or more symptom of radiation dermatitis is improved. In embodiments described herein, the one or more symptom of radiation dermatitis is measured according to an assessment selected from erythema, desquamation, patchy skin, moist desquamation confined to skin folds and creases, moderate swelling, confluent, moist desquamation greater

than 1.5 cm diameter, which is not confined to the skin folds, pitting edema (severe swelling), skin necrosis, or ulceration of full-thickness dermis (middle layer of skin).

[0163] The National Cancer Institute (USA) has developed 4 criteria for the classification of acute radiation dermatitis: Grade 1 – Faint erythema and/or desquamation; Grade 2 – Moderate to brisk erythema or patchy, moist desquamation confined to skin folds and creases, and/or Moderate swelling; Grade 3 – Confluent, moist desquamation greater than 1.5 cm diameter, which is not confined to the skin folds, and/or Pitting edema (severe swelling); and Grade 4 – Skin necrosis or ulceration of full-thickness dermis (middle layer of skin).

[0164] In embodiments described herein, the topically administering of the topical composition includes application to the skin of the body, arms, legs, back, chest, buttocks, neck, scalp, fingernails, or toenails where the radiation dermatitis lesions are present (or “affected area”). The topically administering of the topical composition includes applying enough of the topical composition to completely cover each lesion with a thin layer. In embodiments described herein, administration of the topical composition requires that the subject lightly rub the cream into the skin until it is no longer visible.

[0165] In embodiments described herein, the subject is younger than 18 years of age. In embodiments described herein, the subject is 18 years of age or older. In embodiments described herein, the subject is between the ages of 18 to 65 years old. In embodiments described herein, the subject is between the ages of 18 to 75 years old.

[0166] In embodiments described herein, the topical composition is administered once daily for up to 52 weeks. In embodiments described herein, the topical composition is administered once daily for about 52 weeks. In embodiments described herein, the topical composition is administered once daily for up to 48 weeks. In embodiments described herein, the topical composition is administered once daily for about 48 weeks. In embodiments described herein, the topical composition is administered once daily for up to 44 weeks. In embodiments described herein, the topical composition is administered once daily for about 44 weeks. In embodiments described herein, the topical composition is administered once daily for up to 40 weeks. In embodiments described herein, the topical composition is administered once daily for about 40 weeks. In embodiments described herein, the topical composition is administered once daily for up to 36 weeks. In embodiments described herein, the topical composition is administered once daily for about 36 weeks. In embodiments described herein, the topical composition is administered once daily for up to 32 weeks. In

embodiments described herein, the topical composition is administered once daily for about 32 weeks. In embodiments described herein, the topical composition is administered once daily for up to 28 weeks. In embodiments described herein, the topical composition is administered once daily for about 28 weeks. In embodiments described herein, the topical composition is administered once daily for up to 24 weeks. In embodiments described herein, the topical composition is administered once daily for about 24 weeks. In embodiments described herein, the topical composition is administered once daily for up to 12 weeks. In embodiments described herein, the topical composition is administered once daily for about 12 weeks. In embodiments described herein, the topical composition is administered once daily for up to 8 weeks. In embodiments described herein, the topical composition is administered once daily for about 8 weeks. In embodiments described herein, the topical composition is administered once daily for up to 6 weeks. In embodiments described herein, the topical composition is administered once daily for about 6 weeks. In embodiments described herein, the topical composition is administered once daily for up to 4 weeks. In embodiments described herein, the topical composition is administered once daily for about 4 weeks. In embodiments described herein, the topical composition is administered once daily until the radiation dermatitis is resolved.

[0167] In certain embodiments, the subject achieved a classification of Grade 1 by week 1, week 2, week 3, week 4, week 5, week 6, week 7, week 8, week 9, week 10, week 11, week 12, week 13, week 14, week 15, week 16, week 17, week 18, week 19, week 20, week 21, week 22, week 23, or week 24. In embodiments described herein, the subject has sustained classification of Grade 1 after treatment has ended. In embodiments described herein, the subject has sustained classification of Grade 1 for about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after treatment has ended. In embodiments described herein, the subject does not experience worsening to Grades 2-4 for about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after treatment has ended.

[0168] In embodiments described herein, the one or more symptoms improved by about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after administering the topical composition. In embodiments described herein, the one or more symptoms improved by about 2 weeks of administering the topical composition. In embodiments described herein, the one or more symptoms improved by about 4 weeks of administering the topical composition. In embodiments described herein, the one or more symptoms improved by about 8 weeks of administering the topical composition. In embodiments described herein, the one or more symptoms improved by about 12 weeks of administering the topical composition.

[0169] In some embodiments, it was surprisingly found that the topical composition may produce long lasting effects on the skin and may modify the long-term course of radiation dermatitis. Specifically, in certain embodiments, the improvement of the symptoms seen during administration of the topical composition may be maintained long after the final administration of the topical composition. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 2 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 3 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 4 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 8 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 12 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 16 weeks after administration of the topical

composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 20 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 24 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved and the remittive effect lasted about 28 weeks after administration of the topical composition has ceased.

[0170] It was surprisingly found that the topical composition may produce long lasting effects on the skin and may modify the long-term course of radiation dermatitis. Specifically, in certain embodiments, the symptoms do not worsen after the final administration of the topical composition. In embodiments described herein, the one or more symptoms do not worsen about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, or up to 52 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 2 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 3 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 4 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 8 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 12 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 16 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 20 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 24 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms do not worsen about 28 weeks after administration of the topical composition has ceased.

[0171] In embodiments described herein, the topical composition can be used in a long-term treatment regimen, compared with topical corticosteroids which can only be used

for 2-4 weeks. In embodiments described herein, the topical composition can be used for greater than 12 weeks.

[0172] Radiation dermatitis typically requires daily treatment but available treatments, such as corticosteroids, have high side effects and cannot be administered for longer than 2 weeks at a time, after which time a rest phase from treatment must be taken before treatment can resume. Surprisingly, the tapinarof topical composition described herein is safe to use daily for an extended period of time which is greater than 2 weeks. In embodiments described herein, the tapinarof topical composition described herein can be continuously administered to the subject for greater than 2 weeks, greater than 1 month, greater than 2 months, greater than 3 months, greater than 4 months, or longer. Additionally, current treatments are only applied to the areas of the skin where there is an active lesion. Surprisingly, the tapinarof topical composition described herein can be safely applied to all areas of the skin without any limit as to total amount of body surface area receives treatment, for example, the subject can apply to active lesions as well as clear regions. In embodiments described herein, the tapinarof topical composition described herein can be administered to any or all of the following regions: back, elbows, knees, legs, soles of the feet, scalp, face, palms, genitals, or chest.

[0173] Embodiments described herein are directed to methods for treating a subject with radiation dermatitis comprising administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for an indefinite amount of time, wherein the subject reaches a National Cancer Institute classification of Grade 2 or improves by at least 1 grade. In embodiments described herein, the subject maintains an improved classification but does not reach Grade 1. In embodiments described herein, the subject achieves an improved classification of Grade 1 after 4 months of administration of the tapinarof topical composition.

ADDITIONAL METHODS OF USE

[0174] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the tapinarof has an effect on antigen presenting cell (APC) development, maturation, polarization, activation, or blockade of APC:T-cell interactions.

[0175] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the tapinarof induces T cell polarization, T cell tolerance, T cell anergy, or T cell exhaustion.

[0176] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the tapinarof blocks regulation of T cell differentiation, polarization of T cells, or generation of resident memory T cells.

[0177] In embodiments described herein, the tapinarof topical composition is used to treat skin conditions where APC and T cells play a role in disease pathogenesis. In certain embodiments, the disease is psoriasis, atopic dermatitis, or radiation dermatitis.

[0178] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the tapinarof induces disease remittance via alteration of the APC:T cell balance.

[0179] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the tapinarof induces disease remittance via alteration of the TH17:Treg cell balance.

[0180] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the tapinarof induces disease remittance via alteration of the TH1:Treg cell balance.

[0181] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the tapinarof induces disease remittance via alteration of the Th2:Treg cell balance.

[0182] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the tapinarof induces disease remittance via alteration of the Teffector:Treg cell balance.

[0183] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the tapinarof results in disease remittance through AhR modulation of APC:T cell interactions.

[0184] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the tapinarof suppresses or alters the proliferation (growth) of one or more cell type selected from the group consisting of antigen presenting cells, T cells (CD3), T-helper cells (CD4), T-suppressor cells (CD8), T-helper-17 T-cells (TH-17), T-helper-2 T-cells (TH-2), T-helper-1 T-cells (TH-1), memory resident T-cells (Trm), and regulatory T-cells (Treg).

[0185] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the

tapinarof suppresses or alters the development of one or more cell type selected from the group consisting of antigen presenting cells, T cells (CD3), T-helper cells (CD4), T-suppressor cells (CD8), T-helper-17 T-cells (TH-17), T-helper-2 T-cells (TH-2), T-helper-1 T-cells (TH-1), memory resident T-cells (Trm), and regulatory T-cells (Treg).

[0186] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the tapinarof suppresses or alters the differentiation of one or more cell type selected from the group consisting of antigen presenting cells, T cells (CD3), T-helper cells (CD4), T-suppressor cells (CD8), T-helper-17 T-cells (TH-17), T-helper-2 T-cells (TH-2), T-helper-1 T-cells (TH-1), memory resident T-cells (Trm), and regulatory T-cells (Treg).

[0187] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the tapinarof suppresses or alters the maturation of one or more cell type selected from the group consisting of antigen presenting cells, T cells (CD3), T-helper cells (CD4), T-suppressor cells (CD8), T-helper-17 T-cells (TH-17), T-helper-2 T-cells (TH-2), T-helper-1 T-cells (TH-1), memory resident T-cells (Trm), and regulatory T-cells (Treg).

[0188] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the tapinarof suppresses or alters the activation of one or more cell type selected from the group consisting of antigen presenting cells, T cells (CD3), T-helper cells (CD4), T-suppressor cells (CD8), T-helper-17 T-cells (TH-17), T-helper-2 T-cells (TH-2), T-helper-1 T-cells (TH-1), memory resident T-cells (Trm), and regulatory T-cells (Treg).

[0189] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the tapinarof suppresses or alters the biologic behavior of one or more cell type selected from the group consisting of antigen presenting cells, T cells (CD3), T-helper cells (CD4), T-suppressor cells (CD8), T-helper-17 T-cells (TH-17), T-helper-2 T-cells (TH-2), T-helper-1 T-cells (TH-1), memory resident T-cells (Trm), and regulatory T-cells (Treg).

[0190] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the tapinarof suppresses or alters the migration and/or chemotaxis of one or more cell type selected from the group consisting of antigen presenting cells, T cells (CD3), T-helper cells

(CD4), T-suppressor cells (CD8), T-helper-17 T-cells (TH-17), T-helper-2 T-cells (TH-2), T-helper-1 T-cells (TH-1), memory resident T-cells (Trm), and regulatory T-cells (Treg).

[0191] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the tapinarof suppresses or alters the polarization of one or more cell type selected from the group consisting of antigen presenting cells, T cells (CD3), T-helper cells (CD4), T-suppressor cells (CD8), T-helper-17 T-cells (TH-17), T-helper-2 T-cells (TH-2), T-helper-1 T-cells (TH-1), memory resident T-cells (Trm), and regulatory T-cells (Treg).

[0192] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the tapinarof suppresses or alters the gene expression of one or more cell type selected from the group consisting of antigen presenting cells, T cells (CD3), T-helper cells (CD4), T-suppressor cells (CD8), T-helper-17 T-cells (TH-17), T-helper-2 T-cells (TH-2), T-helper-1 T-cells (TH-1), memory resident T-cells (Trm), and regulatory T-cells (Treg).

[0193] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the tapinarof suppresses or alters the protein expression of and/or the post translational modification of proteins expressed by one or more cell type selected from the group consisting of antigen presenting cells, T cells (CD3), T-helper cells (CD4), T-suppressor cells (CD8), T-helper-17 T-cells (TH-17), T-helper-2 T-cells (TH-2), T-helper-1 T-cells (TH-1), memory resident T-cells (Trm), and regulatory T-cells (Treg).

[0194] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the tapinarof suppresses or alters the interaction of antigen presenting cells with one or more cell type selected from the group consisting of T-lymphocytes, macrophages, keratinocytes, vascular endothelial cells, mast cells, neutrophils, eosinophils, basophils, and B-lymphocytes.

[0195] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the tapinarof suppresses or alters the interaction of T cells (CD3) with one or more cell type selected from the group consisting of antigen presenting cells, macrophages, keratinocytes, vascular endothelial cells, mast cells, neutrophils, eosinophils, basophils, and B-lymphocytes.

[0196] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the

tapinarof suppresses or alters the interaction of T cells (CD4) with one or more cell type selected from the group consisting of antigen presenting cells, macrophages, keratinocytes, vascular endothelial cells, mast cells, neutrophils, eosinophils, basophils, and B-lymphocytes.

[0197] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the tapinarof suppresses or alters the interaction of T cells (CD8) with one or more cell type selected from the group consisting of antigen presenting cells, macrophages, keratinocytes, vascular endothelial cells, mast cells, neutrophils, eosinophils, basophils, and B-lymphocytes.

[0198] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the tapinarof suppresses or alters the interaction of T-helper-17 T cells (TH-17) with one or more cell type selected from the group consisting of antigen presenting cells, macrophages, keratinocytes, vascular endothelial cells, mast cells, neutrophils, eosinophils, basophils, and B-lymphocytes.

[0199] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the tapinarof suppresses or alters the interaction of T-helper-2 T cells (TH-2) with one or more cell type selected from the group consisting of antigen presenting cells, macrophages, keratinocytes, vascular endothelial cells, mast cells, neutrophils, eosinophils, basophils, and B-lymphocytes.

[0200] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the tapinarof suppresses or alters the interaction of T-helper-1 T cells (TH-1) with one or more cell type selected from the group consisting of antigen presenting cells, macrophages, keratinocytes, vascular endothelial cells, mast cells, neutrophils, eosinophils, basophils, and B-lymphocytes.

[0201] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the tapinarof suppresses or alters the interaction of memory resident T cells (Trm) with one or more cell type selected from the group consisting of antigen presenting cells, macrophages, keratinocytes, vascular endothelial cells, mast cells, neutrophils, eosinophils, basophils, and B-lymphocytes.

[0202] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the tapinarof suppresses or alters the interaction of regulatory T cells (Treg) with one or more cell type selected from the group consisting of antigen presenting cells, macrophages, keratinocytes, vascular endothelial cells, mast cells, neutrophils, eosinophils, basophils, and B-lymphocytes.

[0203] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the tapinarof induces or alters the tolerance/anergy of one or more cell type selected from the group consisting T cells (CD3), T-helper cells (CD4), T-suppressor cells (CD8), T-helper-17 T-cells (TH-17), T-helper-2 T-cells (TH-2), T-helper-1 T-cells (TH-1), memory resident T-cells (Trm), and regulatory T-cells (Treg).

[0204] In embodiments described herein, the method of treating a skin condition comprises topically administering the tapinarof composition described herein, wherein the tapinarof alters the exhaustion of one or more cell type selected from the group consisting of antigen presenting cells, T cells (CD3), T-helper cells (CD4), T-suppressor cells (CD8), T-helper-17 T-cells (TH-17), T-helper-2 T-cells (TH-2), T-helper-1 T-cells (TH-1), memory resident T-cells (Trm), and regulatory T-cells (Treg).

Additional embodiments:

Embodiment 1: A method for treating moderate to severe plaque psoriasis in a subject comprising administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for an initial period of time until the plaque psoriasis is clear at which time the administration is stopped, and reassessing the subject from about 3 months to about 12 months after administration is stopped to determine if further treatment is required.

Embodiment 2: The method of Embodiment 1, wherein the initial period of time is about 16 weeks to about 40 weeks.

Embodiment 3: The method of Embodiment 1, wherein plaque psoriasis is clear when the Physician Global Assessment (PGA) score is 0 or 1.

Embodiment 4: The method of Embodiment 1, wherein further treatment is required if the PGA score is greater than or equal to 2.

Embodiment 5: The method of Embodiment 4, wherein further treatment comprises administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for a subsequent period of time until the plaque psoriasis is clear.

Embodiment 6: The method of Embodiment 5, wherein the subsequent period of time is about 8 weeks to about 16 weeks.

Embodiment 7: The method of Embodiment 2, wherein the initial period of time is about 40 weeks.

Embodiment 8: The method of Embodiment 7, wherein reassessment of the subject occurs at about 4 months after administration.

Embodiment 9: The method of Embodiment 8, wherein further treatment is initiated.

Embodiment 10: The method of Embodiment 9, wherein further treatment comprises administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for a subsequent period of time until the plaque psoriasis is clear.

Embodiment 11: A method for treating moderate to severe atopic dermatitis in a subject comprising administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for an initial period of time until the atopic dermatitis is clear at which time the administration is stopped, and reassessing the subject from about 3 months to about 12 months after administration is stopped to determine if further treatment is required.

Embodiment 12: The method of Embodiment 11, wherein the initial period of time is about 16 weeks to about 40 weeks.

Embodiment 13: The method of Embodiment 11, wherein atopic dermatitis is clear when the Investigator Global Assessment (IGA) score is 0 or 1.

Embodiment 14: The method of Embodiment 11, wherein further treatment is required if the IGA score is greater than or equal to 2.

Embodiment 15: The method of Embodiment 14, wherein further treatment comprises administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for a subsequent period of time until the atopic dermatitis is clear.

Embodiment 16: The method of Embodiment 15, wherein the subsequent

period of time is about 8 weeks to about 16 weeks.

Embodiment 17: The method of Embodiment 12, wherein the initial period of time is about 40 weeks.

Embodiment 18: The method of Embodiment 17, wherein reassessment of the subject occurs at about 4 months after administration.

Embodiment 19: The method of Embodiment 18, wherein further treatment is initiated.

Embodiment 20: The method of Embodiment 19, wherein further treatment comprises administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for a subsequent period of time until the atopic dermatitis is clear.

Embodiment 21: A method for treating radiation dermatitis in a subject comprising administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for an initial period of time until the radiation dermatitis is clear at which time the administration is stopped, and reassessing the subject from about 3 months to about 12 months after administration is stopped to determine if further treatment is required.

Embodiment 22: The method of Embodiment 21, wherein the initial period of time is about 16 weeks to about 40 weeks.

Embodiment 23: The method of Embodiment 21, wherein radiation dermatitis is clear when the Grade Classification score is 1.

Embodiment 24: The method of Embodiment 21, wherein further treatment is required if the Grade Classification score is greater than or equal to 2.

Embodiment 25: The method of Embodiment 24, wherein further treatment comprises administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for a subsequent period of time until the radiation dermatitis is clear.

Embodiment 26: The method of Embodiment 25, wherein the subsequent period of time is about 8 weeks to about 16 weeks.

Embodiment 27: The method of Embodiment 22, wherein the initial period of time is about 40 weeks.

Embodiment 28: The method of Embodiment 27, wherein reassessment of the

subject occurs at about 4 months after administration.

Embodiment 29: The method of Embodiment 28, wherein further treatment is initiated.

Embodiment 30: The method of Embodiment 29, wherein further treatment comprises administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for a subsequent period of time until the radiation dermatitis is clear.

Embodiment 31: A method for achieving remission in a subject with moderate to severe plaque psoriasis comprising administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day until the subject reaches a PGA score of 0, wherein administration of the about 1.0% tapinarof in a topical composition is stopped.

Embodiment 32: The method of Embodiment 31, wherein the subject reaches a PGA score of 0 at about 4 weeks, 8 weeks, or 12 weeks.

Embodiment 33: The method of Embodiment 31, wherein the administration is stopped for about 4 months or indefinitely.

Embodiment 34: A method for treating a subject with moderate to severe plaque psoriasis who has achieved a PGA score of 0 after 12 weeks of administration of about 1.0% tapinarof in a topical composition comprising stopping administration of the about 1.0% tapinarof in a topical composition for about 4 months.

Embodiment 35: A method for treating a subject with moderate to severe plaque psoriasis comprising administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for an indefinite amount of time, wherein the subject reaches a PGA score of 1 or improves by at least 1 grade.

Embodiment 36: The method of Embodiment 35, wherein the subject maintains an improved PGA score but does not reach 0.

Embodiment 37: The method of Embodiment 35, wherein the subject achieves an improved PGA score of 0 after 4 months of administration of the tapinarof topical composition.

Embodiment 38: A method for achieving remission in a subject with atopic dermatitis comprising administering about 1.0% tapinarof in a topical composition to the

affected areas of the subject once a day until the subject reaches an IGA score of 0, wherein administration of the about 1.0% tapinarof in a topical composition is stopped.

Embodiment 39: The method of Embodiment 38, wherein the subject reaches a IGA score of 0 at about 4 weeks, 8 weeks, or 12 weeks.

Embodiment 40: The method of Embodiment 38, wherein the administration is stopped for about 4 months or indefinitely.

Embodiment 41: A method for treating a subject with atopic dermatitis who has achieved a PGA score of 0 after 12 weeks of administration of about 1.0% tapinarof in a topical composition comprising stopping administration of the about 1.0% tapinarof in a topical composition for about 4 months.

Embodiment 42: A method for treating a subject with atopic dermatitis comprising administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for an indefinite amount of time, wherein the subject reaches an IGA score of 1 or improves by at least 1 grade.

Embodiment 43: The method of Embodiment 42, wherein the subject maintains an improved IGA score but does not reach 0.

Embodiment 44: The method of Embodiment 42, wherein the subject achieves an improved IGA score of 0 after 4 months of administration of the tapinarof topical composition.

Embodiment 45: A method for achieving remission in a subject with radiation dermatitis comprising administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day until the subject reaches a National Cancer Institute classification of Grade 1, wherein administration of the about 1.0% tapinarof in a topical composition is stopped.

Embodiment 46: The method of Embodiment 45, wherein the subject reaches a National Cancer Institute classification of Grade 1 at 12 weeks.

Embodiment 47: The method of Embodiment 45, wherein the administration is stopped for an indefinite amount of time.

Embodiment 48: A method for treating a subject with atopic dermatitis who has achieved a National Cancer Institute classification of Grade 1 after 12 weeks of

administration of about 1.0% tapinarof in a topical composition comprising stopping administration of the about 1.0% tapinarof in a topical composition for about 4 months.

Embodiment 49: A method for treating a subject with atopic dermatitis comprising administering about 1.0% tapinarof in a topical composition to the affected areas of the subject once a day for about 4 months or indefinitely, wherein the subject reaches a National Cancer Institute classification of Grade 2 or improves by at least 1 grade.

Embodiment 50: The method of Embodiment 49, wherein the subject maintains an improved classification but does not reach Grade 1.

Embodiment 51: The method of Embodiment 49, wherein the subject achieves an improved National Cancer Institute classification of Grade 1 after 4 months of administration of the tapinarof topical composition.

[0205] Although the present invention has been described in considerable detail with reference to certain preferred embodiments thereof, other versions are possible. Therefore, the spirit and scope of the appended claims should not be limited to the description and the preferred versions contained within this specification. Various aspects of the present invention will be illustrated with reference to the following non-limiting examples.

EXAMPLES

Example 1- A Long-Term, Open-Label, Extension Study to Evaluate the Safety and Efficacy of Tapinarof Cream, 1% for the Treatment of Plaque Psoriasis in Adults

[0206] Background

[0207] Psoriasis is a common, chronic relapsing inflammatory skin disease with recurrent episodes of prominently erythematous and scaly patches. Approximately 2% to 3% of the global population is affected by psoriasis; those affected are predominantly adults, who are most often diagnosed between the ages of 18 to 35 years.

[0208] Up to 80% of patients have mild to moderate plaque type psoriasis, which is generally managed with topical treatments such as corticosteroids and/or vitamin D analogs. However, there remains a need for an efficacious and safe topical treatment that permits application to a large body surface area (BSA) for an unrestricted treatment duration.

[0209] Tapinarof cream, 1% is an oil in water emulsion intended for topical application to psoriatic skin lesions. The drug likely mediates its effects via the aryl hydrocarbon receptor (AhR) agonist and nuclear factor erythroid 2 related factor 2 because

the pattern of proinflammatory mediators inhibited by tapinarof is different from that of corticosteroids, vitamin D analogs, and other immunosuppressive agents commonly used to treat psoriasis. The profile of biological responses elicited by tapinarof most closely matches that of the dual activation properties of coal tar, a common nonprescription treatment for psoriasis. Existing data identify tapinarof as a nonsteroidal therapeutic AhR modulating agent, which has a unique mechanism of action compared with existing therapies. Additional details, including evaluation of tapinarof cream, 1% in nonclinical and clinical trials, can be found in the study protocol.

[0210] Study Rationale

[0211] This 40 week, Phase 3, open label extension study was conducted as part of a clinical development program to evaluate the long term safety and continued efficacy of tapinarof cream, 1% for the topical treatment of plaque psoriasis in adults. Subjects in this study were enrolled from those subjects who completed 1 of 2 Phase 3 pivotal efficacy and safety studies (Study DMVT 505 3001 or Study DMVT 505 3002) and met the predefined criteria to enroll into this extension study. The results of this extension study are intended to support product registration in the United States.

[0212] Rationale for Study Design and Dose

[0213] The once daily topical application of tapinarof cream, 1% administered in the pivotal Phase 3 studies was continued in this open label extension study.

[0214] Tapinarof cream, 1% is intended for long term use in non-life threatening inflammatory dermatologic conditions. Therefore, the 40 week duration of long term use of tapinarof cream, 1% in this extension study, in addition to the treatment received during the double blinded (DB), pivotal Phase 3 study, was expected to be an adequate duration to assess safety and efficacy of repeated treatment courses of tapinarof cream, 1% as recommended in the ICH E1 guideline on the extent of population exposure to assess clinical safety for drugs intended for long term treatment of non-life threatening conditions. The ICH E1 guideline recommends subject be treated with the intended clinical dose and followed for adverse events (AEs) for at least 1 year for a minimum of 100 subjects and for at least 6 months for a minimum of 300 subjects. This interim analysis includes 235 subjects exposed to tapinarof cream, 1% for 1 year and 450 subjects exposed to tapinarof cream, 1% for 6 months.

[0215] Objective: To evaluate the safety and tolerability of tapinarof cream, 1% in adults with plaque psoriasis. Endpoints: Incidence, frequency, and nature of AEs, adverse

events of special interest (AESIs), and serious adverse events (SAEs), Change over time in clinical laboratory tests and frequency of clinically significant abnormal test results, Change over time in vital signs and frequency of clinically significant abnormal results, Local Tolerability Scale (LTS) scores by severity summarized by visit.

[0216] Objective: To describe the efficacy of tapinarof cream, 1% over an extended period of time in adults with plaque psoriasis, including duration of treatment success, durability of response and duration of remittive effect. Endpoints: Proportion of subjects who experienced a Physician Global Assessment (PGA) ≥ 2 at least 1 time in the study and the median time from Visit 1 date to first worsening (PGA ≥ 2) for subjects entering the study with a PGA score of clear (0), Proportion of subjects who achieved a PGA score of 0 at least 1 time in the study and the median time from Visit 1 date to first achieving a PGA score of 0 for subjects entering the study with a PGA score ≥ 1 , Duration of each treatment episode defined as time from each PGA ≥ 2 (or PGA ≥ 1 for the first episode) to each subsequent treatment success (PGA score of 0), Duration of each treatment success (PGA score of 0) to each subsequent worsening (PGA ≥ 2), Proportion of subjects who never achieved a PGA ≥ 2 throughout the study, Proportion of subjects who never achieved a PGA score of 0 or 1 throughout the study, Proportion of subjects who never achieved a PGA score of 0 throughout the study, PGA scores by visit (Observed Cases [OC] and Last Observed Carried Forward [LOCF]), Change and percent change from baseline in percent of body surface area (%BSA) affected by visit (OC and LOCF), Change and percent change in Psoriasis Area and Severity Index (PASI) score by visit (OC and LOCF).

[0217] Objective: To describe the effect of tapinarof cream, 1% on psoriasis symptom severity and the associated impact on daily activities and attitudes in adults with plaque psoriasis. Endpoints: Change in disease impact on daily activities, as measured by the Dermatology Life Quality Index (DLQI) total and individual dimension scores.

[0218] Complete disease clearance is defined as the proportion of patients achieving PGA of 0 (clear).

[0219] Remittive effect is defined as the duration of efficacy maintenance, which is time at which patient has a PGA score of 0 (clear) or 1 (almost clear) while off therapy after having achieved complete disease clearance (PGA=0).

[0220] Response is defined as the proportion of patients who entered the trial with a PGA ≥ 2 and achieved a PGA of 0 (clear) or 1 (almost clear) at least once during trial.

[0221] Durability of response (absence of tachyphylaxis) is defined as the maintenance of efficacy while on treatment, defined as the proportion of patients who achieved a PGA score of 0 or 1 at least once during the trial and trends in PASI score and percentage of body surface area (%BSA) affected over time.

[0222] Tolerability is defined as the local tolerability using a patient-reported 5-point scale for burning/stinging and itching, and an investigator-assessed 5-point scale for dryness, erythema, and peeling.

[0223] Study Design

[0224] This was a long term, open label, multicenter study to evaluate the safety and efficacy of topical tapinarof cream, 1% in adults with plaque psoriasis. Subjects in this extension study completed treatment with tapinarof cream, 1% or vehicle cream in 1 of 2 DB, randomized, pivotal Phase 3 efficacy and safety studies (Study DMVT 505 3001 or Study DMVT 505 3002). This extension study consisted of up to 40 weeks of treatment and a 4 week, safety follow up period. See Figure 3.

[0225] At the completion of the Week 12 visit of the DB, pivotal Phase 3 study, eligibility of the subjects opting to enroll in this extension study was confirmed. Study visits during the treatment period for all subjects occurred every 4 weeks ($\pm$ 3 days). A phone call was performed at Week 2 (Day 15). Unscheduled visits may have occurred, as needed. Subjects who withdrew from this study before Week 40 returned to the study center for an Early Termination visit. The total duration of this extension study participation was 44 weeks. Subjects in this study were treated as follows based on their PGA score from the Week 12 visit in the DB, pivotal Phase 3 study (Study DMVT 505 3001 or Study DMVT 505 3002).

[0226] Subjects entering with a $\text{PGA} \geq 1$ received treatment with tapinarof cream, 1% until they achieve a $\text{PGA} = 0$, at which time treatment was discontinued and subjects were monitored for durability of response (remittive response). If/when disease worsening occurred, as evidenced by a $\text{PGA} \geq 2$, treatment was re initiated and continued until a $\text{PGA} = 0$ was observed.

[0227] Subjects entering with a $\text{PGA} = 0$ had treatment discontinued and were monitored for remittive response. If/when disease worsening occurred, as evidenced by a $\text{PGA} \geq 2$, treatment was re initiated and continued until a $\text{PGA} = 0$ was observed.

[0228] This treatment and re treatment pattern of use was continued until the end of the study (i.e., subjects may have received study drug up until the Week 40 visit.

[0229] Study drug (tapinarof cream, 1%) was dispensed, and subjects were instructed on how to apply it. Study drug was dispensed to subjects during the study visits and was to be administered at home between study visits as instructed by site personnel. Subjects were instructed to apply study drug once daily to all affected areas, including newly appearing lesions and lesions or affected areas that improved during the study. Subjects applied sufficient study drug to cover completely each lesion with a thin layer and recorded the time of study drug application in a daily diary provided by the study site. (Note that subjects were allowed, but not required, to treat fingernails, toenails, palms, soles, and scalp lesions with study drug; however, efficacy analyses did not include assessment of improvement of psoriasis in these areas.) Subjects were instructed to maintain the approximate dosing time chosen at the beginning of the study for their full study participation. Study drug application instructions were reviewed at subsequent study visits. During study visits, subjects applied the daily dose of study drug while at the site under the supervision of site personnel, after efficacy and safety assessments had been completed. The time of the dose application and assessments depended on the time of the study visit (either morning or afternoon visit). Therefore, the timing of the study visit may have led to a change in the subject's chosen dosing time; if this occurred, it was not considered a protocol deviation. The subject should have resumed their chosen dosing time the day following any such clinic visit application.

[0230] Rescue medications may have been initiated with consultation of the Medical Monitor.

[0231] Safety assessments included AEs, AESIs, SAEs, local (application site) tolerability, clinical laboratory tests, vital signs, physical examinations, and Investigator assessed LTS. Efficacy assessments included a 5 point static PGA (0 [clear], 1 [almost clear], 2 [mild], 3 [moderate], 4 [severe]), %BSA affected, the PASI, and subject reported DLQI.

[0232] Inclusion Criteria

[0233] Each subject had to meet all of the following criteria to be eligible to participate in the study:

[0234] Completed the 12 week treatment period in 1 of the 2 pivotal Phase 3 studies (Study DMVT 505 3001 or Study DMVT 505 3002)

[0235] Male or female

[0236] Female subjects of childbearing potential and male subjects who were engaging in sexual activity that could have led to pregnancy should have used one of the following acceptable birth control methods while on study and for 4 weeks after the last exposure to study drug. Acceptable contraception methods were:

[0237] Female subject or male subject's female partner was surgically sterile (bilateral tubal ligation, hysterectomy, bilateral oophorectomy) for a minimum of 3 months prior to the first dose of study drug

[0238] Female subject or male subject's female partner had an intrauterine device in place for at least 3 months prior to the first dose of study drug

[0239] Double barrier methods (e.g., condom plus diaphragm, condom or diaphragm plus spermicide) starting at least 14 days prior to the first dose of study drug

[0240] Subjects who claimed abstinence as their method of contraception were allowed, provided they agreed to use a double barrier method (e.g., condom plus diaphragm, condom or diaphragm plus spermicide) should they have become sexually active from Screening to 1 month after the last dose of study drug

[0241] Surgical sterilization of male subject or female subject's male partner (vasectomy) a minimum of 3 months prior to first dose of study drug

[0242] Female subject or male subject's female partner was taking hormonal contraceptives starting at least 3 months prior to the first dose of study drug. If hormonal contraceptives were started < 3 months prior to the first dose of study drug, subjects must have agreed to use a double barrier method (e.g., condom plus diaphragm, condom or diaphragm plus spermicide) from Screening through 3 months after the initiation of hormonal contraceptives.

[0243] These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The Investigator was responsible for ensuring that subjects understood how to properly use these methods of contraception.

[0244] Non childbearing potential was defined as premenarchal or premenopausal females with a documented bilateral tubal ligation, bilateral oophorectomy (removal of the ovaries) or hysterectomy, or hysteroscopic sterilization; or postmenopausal females defined as a cessation of menses for at least 12 months without an alternative medical cause. In questionable cases, a blood sample with simultaneous follicle stimulating hormone > 40 mIU/mL was confirmatory. Documented verbal history from the subject was acceptable.

[0245] Female subjects of childbearing potential must have had a negative urine pregnancy test at Baseline (Day 1).

[0246] Capable of giving signed informed consent, as applicable, which included compliance with the requirements and restrictions listed in the ICF; written informed consent must have been obtained prior to any study related procedures.

[0247] Exclusion Criteria

[0248] A subject who met any of the following criteria was excluded and considered ineligible for participation in this extension study:

[0249] Used a prohibited concomitant product or procedure to treat psoriasis during the pivotal study

[0250] Had an SAE that was potentially related to treatment or experienced an AE that led to permanent discontinuation of treatment in the pivotal study

[0251] History of or ongoing serious illness or medical, physical, or psychiatric condition(s) that, in the Investigator's opinion, may have interfered with the subject's completion of the study

[0252] Known hypersensitivity to tapinarof or excipients

[0253] Investigational Product: tapinarof cream, 1%. Excipients in tapinarof cream are propylene glycol, diethylene glycol monoethyl ether, polysorbate 80, medium chain triglycerides, emulsifying wax nonionic, polyoxyl stearyl ether 2, polyoxyl stearyl ether 20, benzoic acid, butylated hydroxytoluene, purified water, sodium citrate, citric acid monohydrate, and edetate disodium.

[0254] Treatment by Physician Global Assessment Score

[0255] Subjects entering with a PGA ≥ 1 received treatment with tapinarof cream, 1% until they achieved a PGA = 0. If/when disease worsening occurred, as evidenced by a PGA ≥ 2 , treatment was re initiated and continued until a PGA = 0 was observed.

[0256] Subjects entering with a PGA = 0 had treatment discontinued and were monitored for durability of response (remittive response). If/when disease worsening occurred, as evidenced by a PGA ≥ 2 , treatment was re initiated and continued until a PGA = 0 was observed.

[0257] This treatment and re treatment pattern of use continued until the end of the study (i.e., subjects may have received study drug up until the Week 40 visit). Subjects who experienced suspected disease worsening between scheduled study visits may have

contacted the study site to arrange an unscheduled visit. Upon confirmation of disease worsening, subjects would have restarted treatment with study drug.

[0258] Disease Worsening (Physician Global Assessment Score ≥ 2) During the Study

[0259] If disease worsening was suspected between scheduled study visits, an unscheduled visit may have been performed.

[0260] If disease worsening (i.e., PGA ≥ 2) was not confirmed, the subject continued to be assessed at routine, scheduled visits (see Table 2).

[0261] For each confirmed episode of disease worsening (i.e., PGA ≥ 2) during the study (at either a scheduled or unscheduled visit), a treatment course of study drug (once daily) was initiated and continued until the subject achieved a PGA = 0, as assessed at scheduled visits, approximately every 4 weeks.

[0262] Subjects subsequently achieving a PGA = 0 stopped study drug and then were assessed at routine, scheduled visits.

[0263] Subjects who then experience suspected disease worsening between scheduled study visits may have contacted the study site to arrange an unscheduled visit.

[0264] If disease worsening was not confirmed, the subject continued to be assessed at routine, scheduled visits.

[0265] If disease worsening was confirmed (i.e., PGA ≥ 2) at the unscheduled visit, subjects initiated another treatment course of study drug (once daily) until a PGA = 0 was achieved at which time the subject stopped study drug and continued to be assessed at routine, scheduled visits.

[0266] This treatment and re treatment pattern of use continued until the end of the study.

[0267] Application of Study Drug

[0268] Study drug was dispensed to subjects requiring treatment at the study visits specified in the Schedule of Assessments.

[0269] Subjects took the tubes home and self-administered study drug (or had caregiver apply if necessary), except on clinic visit days (when study drug was applied under supervision at the site), to affected areas, once daily.

[0270] Subjects were instructed to apply study drug as follows:

[0271] For subjects with a PGA > 0 , once daily application to affected areas including those areas treated in the DB, pivotal Phase 3 study; subjects were to choose the

application time they preferred and applied the study drug at that time each day of study participation.

[0272] Subjects with a PGA = 0 did not receive treatment but if they worsen and experienced a PGA $\geq$ 2, study drug was applied once daily to newly affected areas only.

[0273] If a subject missed a daily dose, it was recorded as a protocol deviation. The subject was to continue dosing the next day and was not to apply more than once daily to make up for the missed dose on the previous day.

[0274] If the chosen application time was in the evening, the dose was applied at least 30 minutes prior to bedtime.

[0275] Study drug was to be applied to dry, clean skin.

[0276] Subjects had to wash hands after application unless treating lesions on the hands or fingernails.

[0277] Study drug was applied to all lesions, including newly appearing lesions and lesions that had improved during the study, if applicable.

[0278] Subjects were allowed, but not required, to treat fingernails, toenails, palms, soles, and scalp lesions with study drug; however, efficacy analyses did not include assessment of improvement of psoriasis in these areas. If using study drug on the scalp, no other treatment for scalp psoriasis was permitted during the study.

[0279] If there was residual cream visible on the disease affected lesional skin, then, the subject was instructed to continue to lightly rub the cream into the skin until it was no longer visible.

[0280] If study drug was applied to the subject by another person, that person was to thoroughly wash his/her hands after application. When possible, use of disposable gloves was recommended.

[0281] Subjects recorded the time of study drug application in their daily diary.

[0282] Subjects were to avoid swimming, bathing, showering, or strenuous activities for at least 2 hours after application of study drug.

[0283] On study visit days, study drug was applied in the clinic under the supervision of site personnel and after safety and efficacy assessments had been completed.

[0284] Note: The time of the dose and assessments on clinic visit days depended on the time of the clinic visit. Therefore, the timing of the clinic visit could have differed from the subject's chosen dosing time. The intention was to allow flexibility to accommodate subjects' schedules.

[0285] Subjects were instructed/reminded on how to apply study drug at each clinic visit (except during the final treatment visit).

[0286] Efficacy Assessments

[0287] To minimize interobserver variability, Investigators and evaluators/raters were trained on each of the required assessments during an Investigator meeting, site initiation visit, and/or by utilizing online assessments before enrolling subjects at their study site. Only trained evaluators/raters were permitted to perform the efficacy assessments. To the fullest extent possible, the same Investigator (or designated evaluator/rater) performed all efficacy assessments for an individual subject throughout the study. If it was not possible for the same evaluator/rater to continue performing assessments, it was recommended that the primary and subsequent evaluator/rater both examine and discuss their respective scoring during at least 1 visit.

[0288] Assessments Completed by the Investigator

[0289] Physician Global Assessment

[0290] The PGA was used to assess the primary efficacy endpoint in this study. The PGA is a clinical tool for assessing the current state/severity of a subject's psoriasis at a given time point. It is a static, 5 point, morphological assessment of overall disease severity, as determined by the Investigator, using the clinical characteristics of erythema, scaling, and plaque thickness/elevation as guidelines; higher PGA scores represent more severe disease (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, and 4 = severe). The BSA affected was not considered in scoring of the PGA. Variations of the PGA are frequently used in clinical studies because it is a simple assessment, similar to those used in clinical practice. The PGA was performed first, prior to the %BSA, PASI, and LTS assessments.

[0291] Body Surface Area Affected

[0292] The %BSA affected is an estimate of the percentage of total involved skin with psoriasis. For the purpose of clinical estimation, the total palmar surface of the subject's palm and digits was assumed to be approximately equivalent to 1% BSA. The %BSA affected by psoriasis was evaluated (from 0% to 100%). Details on calculation of approximate %BSA involvement in each subject (total and individual) can be found in Appendix 2 of the protocol. Percent BSA is a static assessment made without reference to previous scores.

[0293] At Screening, Baseline, and for all efficacy assessments, lesions on the subject's scalp, palms, fingernails, toenails, and soles were not included in the calculation of %BSA affected as these areas were excluded from the efficacy analyses.

[0294] Psoriasis Area and Severity Index

[0295] The PASI scoring system is a widely used, standard, clinical tool for assessing the severity of psoriasis that takes into account the overall severity of erythema (redness), induration (plaque thickness), scale, and the extent of %BSA affected with psoriasis. The 3 clinical signs are each graded on a 5 point scale (0 to 4) and the %BSA affected is scored on a 7 point scale (0 to 6) for each of the 4 specified body regions (head, upper extremities, trunk, and lower extremities). Individual scores are multiplied by a weighted factor for each body region; the sum of these scores gives the overall PASI score. Higher scores indicate more severe disease. PASI is a static assessment made without reference to previous scores. Details on PASI calculation can be found in Appendix 2 of the protocol.

[0296] Assessments Completed by Subject

[0297] Dermatology Life Quality Index

[0298] Subjects completed the DLQI questionnaire. The DLQI is a simple, validated, dermatology specific, 10 question questionnaire to assess the impact of the disease on a subject's quality of life. The DLQI is an important outcome measure in dermatology clinical trials and is the most frequently used instrument in randomized, controlled dermatology trials. The DLQI can be analyzed as a total score (where a higher score indicates greater impairment in quality of life) and can also be scored for the following dimensions: Symptoms and Feelings (Items 1 and 2), Daily Activities (Items 3 and 4), Leisure (Items 5 and 6), Work and School (Item 7), Personal Relationships (Items 8 and 9), and Treatment (Item 10).

[0299] Patient Satisfaction Questionnaire

[0300] Subjects completed the Patient Satisfaction Questionnaire.

Table 1: Extension Study Efficacy Endpoints

For subjects entering the study with a PGA score of clear (0):	• Proportion of subjects who experienced $\text{PGA} \geq 2$ at least 1 time during the study • Proportion of subjects who never experienced $\text{PGA} \geq 2$ throughout the study • Time to first worsening ($\text{PGA} \geq 2$), defined as days from the date of Visit 1 to the date of first occurrence of $\text{PGA} \geq 2$. Subjects who never experienced $\text{PGA} \geq 2$ throughout the study were censored at the date of their last PGA assessment.
For subjects entering the study with a PGA score ≥ 1 :	• Proportion of subjects who achieved $\text{PGA} = 0$ at least 1 time during the study • Proportion of subjects who never experienced $\text{PGA} = 0$ throughout the study • Time to achieving a $\text{PGA} = 0$, defined as days from date of Visit 1 to the date of first occurrence of $\text{PGA} = 0$. Subjects who never achieved $\text{PGA} = 0$ throughout the study were censored at the date of their last PGA assessment.
For subjects entering the study with a PGA score ≥ 2 :	• Proportion of subjects who achieved $\text{PGA} = 0$ or 1 at least 1 time during the study • Proportion of subjects who never achieved $\text{PGA} = 0$ or 1 throughout the study

Endpoints summarized over subjects in the ITT population:	• Duration (days) of treatment episodes, defined as time (days) from date of each $\text{PGA} \geq 2$ (or $\text{PGA} \geq 1$ for the first episode) to 1 day before each subsequent treatment success ($\text{PGA} = 0$). The date of the last PGA assessment was used as the end date for episodes ongoing at the end of this extension study. All 1st episodes were summarized, then all 2nd episodes, etc. Additionally, each subject was characterized by an average duration of episodes and these averages were summarized over the entire ITT population. • Duration (days) of treatment successes, defined as time (days) from date of $\text{PGA} = 0$ to 1 day before each $\text{PGA} \geq 2$. The date of the last PGA assessment was used as the end date for episodes of treatment success ongoing at the end of this extension study. All 1st treatment successes were summarized, then all 2nd treatment successes, etc. Additionally, each subject was characterized by an average duration of treatment success and these averages were summarized over the entire ITT population. Both durations of treatment episodes/successes were summarized by Baseline PGA scores. • PGA scores and change from baseline values by visit (OC and LOCF) • Absolute values, change and percent change from baseline in %BSA affected by visit (OC and LOCF) • Absolute values, change and percent change from baseline in PASI score by visit (OC and LOCF) • Proportion of subjects with $\geq 50\%$ improvement in PASI score (PASI50) from Baseline by visit (OC and LOCF) • Proportion of subjects with $\geq 75\%$ improvement in PASI score (PASI75) from Baseline by visit (OC and LOCF) • Proportion of subjects with $\geq 90\%$ improvement in PASI score (PASI90) from Baseline by visit (OC and LOCF)
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[0301] All efficacy parameters were summarized over the ITT analysis set overall and by DB assigned treatment group. Summaries of efficacy endpoints by visit were performed using OC and LOCF methods.

[0302] Time to event parameters, such as the time from treatment success to subsequent worsening ($\text{PGA} \geq 2$) or duration of treatment episode, were summarized by the Kaplan Meier product limit method using OC.

[0303] The remaining efficacy endpoints were summarized descriptively: continuous data included the mean, SD, minimum, maximum, median, and number of observations; descriptive summary statistics for categorical data included frequency counts and percentages.

[0304] For the following efficacy outcomes:

[0305] Proportions of subjects who achieved PGA = 0 at least 1 time during the study (for subjects entering the study with a PGA $\geq$ 1)

[0306] Proportions of subjects who experienced PGA $\geq$ 2 at least 1 time during the study (for subjects entering the study with a PGA = 0)

[0307] PGA scores at Week 40 (LOCF)

[0308] %BSA affected absolute value and change from baseline to Week 40 (LOCF)

[0309] PASI absolute value and change from baseline to Week 40 (LOCF)

[0310] Subgroup analyses were generated for Baseline PGA, age (< 65 and $\geq$ 65 years old), sex, race (White, Other), Baseline %BSA affected (< 10%, $\geq$ 10%), duration of disease (< 5 years, 5 to 10 years, > 10 years), country (United States and Canada).

[0311] Health Related Quality of Life

[0312] The DLQI is a 10 item subject reported outcome, 6 domain measure that assessed the extent to which the skin condition had affected the subject's quality of life over the past week. The total score (0 to 30) is the sum of 10 questions with each ranging from 0 to 3. The DLQI was assessed at 4 week intervals. If one question was left unanswered, this was scored as 0 and the scores were summed and expressed as usual out of a maximum of 30. If $\geq$ 2 questions were left unanswered, the total DLQI score was considered missing.

[0313] When summarizing the domain scores, if a domain contains 2 questions and the answer to one of the questions was missing, that domain was scored as the answer to the non-missing question. If all the answers to questions in a domain were missing, the domain was not scored.

[0314] DLQI total score and sub scores on DLQI domains and their changes from baseline as well as percent change from baseline values were summarized descriptively. Additional details of the analysis of the DLQI are provided in the SAP.

[0315] Patient Satisfaction Questionnaire

[0316] Responses for each question of the Patient Satisfaction Questionnaire assessed at Week 40 (or Early Termination visit) were summarized overall and by DB assigned treatment group.

[0317] Disposition of Subjects is described in Table 2.

Table 2 Baseline Patient Demographics and Characteristics in Phase 3

	Overall (n=763)	Tapinarof→Tapinarof* (n=508)	Vehicle→Tapinarof* (n=255)
Age, years, mean (SD)	50.7 (12.9)	50.5 (12.9)	51.0 (12.9)
Male, n (%)	448 (58.7)	304 (59.8)	144 (56.5)
Weight, kg, mean (SD)	92.4 (23.9)	92.6 (25.1)	92.1 (21.3)
BMI, kg/m ² , mean (SD)	31.7 (7.7)	31.6 (8.1)	31.8 (7.0)
PGA, n (%) [†]			
0 - Clear	79 (10.4)	74 (14.6)	5 (2.0)
1 - Almost clear	161 (21.1)	144 (28.3)	17 (6.7)
2 - Mild	247 (32.4)	187 (36.8)	60 (23.5)
3 - Moderate	249 (32.6)	93 (18.3)	156 (61.2)
4 - Severe	23 (3.0)	7 (1.4)	16 (6.3)
PASI, mean (SD)	4.8 (4.7)	3.3 (3.5)	7.7 (5.4)
BSA affected, %, mean (SD)	4.6 (5.6)	3.3 (4.7)	7.3 (6.2)

*Tapinarof Tapinarof: patients previously assigned to tapinarof in the pivotal trials who enrolled in Phase 3;

Vehicle Tapinarof: patients previously assigned to vehicle in the pivotal trials who enrolled in Phase 3.

†Four patients (3 tapinarof, 1 vehicle) did not have a baseline PGA, PASI, and BSA value and are listed as missing. ITT population.

BMI, body mass index; BSA, body surface area; ITT, intention-to-treat; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment, SD, standard deviation.

[0318] A total of 763 subjects were enrolled from the DB, pivotal Phase 3 studies (Study DMVT 505 3001 and Study DMVT 5050 3002) of which 508 subjects received tapinarof cream, 1% and 255 subjects received vehicle cream. This is an interim analysis based on a cut of the data that occurred on 25 November 2020. Data from all enrolled subjects at the time of the data cut are included in this interim analysis which includes 671 subjects who completed assessments up to 14 weeks and 349 subjects who completed assessments up to 40 weeks. The combination of subjects treated during one of the 2 DB, pivotal Phase 3 studies plus this extension study results in 235 and 450 subjects who were treated with the intended clinical dose and followed for AEs for a least 1 year or 6 months, respectively, as per ICH E1 guidelines. An additional 114 subjects who were previously randomized to vehicle cream in the DB, pivotal Phase 3 studies have also been exposed to tapinarof cream, 1% for at least 6 months in this extension study.

[0319] Although all subjects enrolled in this extension study received tapinarof cream, 1% if they met the PGA criteria, data are presented using the 2 randomized cohorts from the DB, pivotal Phase 3 studies: tapinarof cream, 1% and vehicle cream. Data from both cohorts combined are presented as overall.

[0320] A total of 763 subjects with chronic psoriasis were enrolled in this extension study, and as of the data cutoff date, 743 subjects received and 20 subjects had not yet received treatment with tapinarof cream, 1%. Seventy eight subjects entered this 40 week extension study with a PGA = 0.

[0321] Of the 763 subjects, 260 (34.1%) completed the study (tapinarof cream, 1%: 34.3%; vehicle cream: 33.7%). Two hundred and thirteen subjects permanently discontinued this extension study. The most common reasons for premature treatment discontinuation prior to Week 40 were withdrawal of consent (10.9% overall; 9.6% and 13.3% in the tapinarof cream, 1% and vehicle cream, respectively), lost to follow up (6.2% overall; 6.7% and 5.1%, respectively), and AEs (5.8% overall; 5.7% and 5.9%, respectively).

[0322] Of the total enrolled ITT population, 763 subjects participated in this extension study for a mean (SD) of 231.6 (87.62) days; the number of days in the study was similar between the 2 DB assigned treatment groups.

[0323] Efficacy Analysis

[0324] All efficacy endpoints were analyzed using the ITT population.

[0325] Note: Visit 1 of this extension study is considered the Baseline visit which is also the last assessment completed as part of the DB, pivotal Phase 3 studies (Week 12). There was also a Baseline visit at the beginning of the DB, pivotal Phase 3 studies.

[0326] Upon entering this extension study, 4 subjects had missing Baseline PGA, %BSA, and PASI values. Subject 1034 004 signed an ICF prior to being deemed ineligible; this subject was discontinued prior to receiving tapinarof cream, 1%. Due to factors related to COVID 19 limiting in clinic visits, the Baseline visit for Subject 1038 016 was conducted virtually and was conducted by phone for Subject 1905 009 and Subject 2002 007.

[0327] Proportion of Subjects who Experienced a PGA ≥ 2 at Least 1 Time in the Study and the Median Time from Visit 1 Date to First Worsening for Subjects Entering this Extension Study with a PGA = 0

[0328] Table 3 presents the proportion of subjects who experienced a PGA ≥ 2 at least once after entering this extension study with a PGA = 0; Table 4 presents the time to that PGA ≥ 2 . Of the 78 subjects who entered this extension study with a PGA = 0, 73 had

been randomized to tapinarof cream, 1% in the DB, pivotal Phase 3 studies and 5 had been randomized to vehicle cream. A $\text{PGA} \geq 2$ was experienced by 75.6% of these subjects ($n = 78$) at least once at the data cutoff date for this interim analysis. Seventeen subjects randomized to tapinarof cream, 1% in the DB, pivotal Phase 3 studies did not experience a $\text{PGA} \geq 2$ at the time of the interim analysis. Of this group, 2 subjects completed the study, 10 were ongoing, and 5 had an early termination. In addition, of the 5 subjects previously randomized to vehicle cream who entered with $\text{PGA} = 0$, there were 2 subjects who did not receive tapinarof cream, 1% at the time of the data cutoff date.

[0329] The median (95% confidence interval [CI]) time to first worsening ($\text{PGA} \geq 2$) was 115 days (85.0, 162.0; Table 3).

Table 3: Analysis of Efficacy Endpoint, Proportion of Subjects Experiencing $\text{PGA} \geq 2$; Subjects Entering the Extension Study with $\text{PGA} = 0$ (ITT Population, Observed Cases)

	Tapinarof Cream, 1% (Pivotal) (N = 73)	Vehicle Cream (Pivotal) (N = 5)	Overall (N = 78)
Proportion of subjects who experienced $\text{PGA} \geq 2$ at least 1 time during the study, n/N (%)	56/73 (76.7)	3/5 (60.0)	59/78 (75.6)
Proportion of subjects who never experienced $\text{PGA} \geq 2$ throughout the study, n/N (%)	17/73 (23.3)	2/5 (40.0)	19/78 (24.4)

DB = double blinded; ITT = Intent-to-Treat; PGA = Physician Global Assessment.

Table 4: Analysis of Efficacy Endpoint, Time to First Worsening ($\text{PGA} \geq 2$); Subjects Entering this Extension Study with a $\text{PGA} = 0$ (ITT Population, Observed Cases)

	Tapinarof Cream, 1% (Pivotal) (N = 73)	Vehicle Cream (Pivotal) (N = 5)	Overall (N = 78)
Time to First Worsening (PGA $\geq$ 2; Days) [1]			
Kaplan-Meier Estimates			
N	73	5	78
Number of Subjects with 1st Worsening	56	3	59
25th percentile (95% CI)	54 (29.0, 76.0)	66 (42.0, NE)	54 (29.0, 66.0)
Median (95% CI)	114 (85.0, 142.0)	281 (42.0, NE)	115 (85.0, 162.0)
75th percentile (95% CI)	196 (168.0, 309.0)	NE (NE, NE)	222 (169.0, 309.0)

[1] Days from date of Baseline visit to the date of first occurrence of PGA $\geq$ 2. Subjects who never experienced PGA $\geq$ 2 throughout the study were censored at the date of their last PGA assessment.

CI – confidence interval; DB – double blinded; ITT – Intent-to-Treat; NE – not estimable; PGA – Physician Global Assessment.

[0330] Proportion of Subjects who Achieved a PGA = 0 at Least 1 Time in the Study and the Median Time from Baseline Visit to First Achieving a PGA = 0 for Subjects Entering this Extension Study with a PGA $\geq$ 1

[0331] Table 5 presents the proportion of subjects who achieved a PGA = 0 at least once after entering this extension study with a PGA $\geq$ 1; Table 6 presents the time to that PGA = 0. Of the 681 subjects who entered this extension study with a PGA $\geq$ 1, 32.5% of those subjects experienced a PGA = 0 at least once during the study. The proportions were similar between the DB assigned treatment groups (tapinarof cream, 1%: 32.2%; vehicle cream: 32.9%).

[0332] The median (95% CI) time to first achieving PGA = 0 was not estimable; however, the 25th percentile (95% CI) was 141 days (113.0, 169.0). Subjects who were randomized to vehicle cream during the DB, pivotal Phase 3 studies achieved their first PGA = 0 (169 days) later than those subjects who were randomized to tapinarof cream, 1% (113 days; Table 6).

Table 5: Analysis of Efficacy Endpoint, Proportion of Subjects Achieving PGA = 0; Subjects Entering the Extension Study with a PGA $\geq$ 1 (ITT Population, Observed Cases).

	Tapinarof Cream, 1% (Pivotal) (N = 432)	Vehicle Cream (Pivotal) (N = 249)	Overall (N = 681)
Proportion of subjects who achieved PGA = 0 at least 1 time during the study, n/N (%)	139/432 (32.2)	82/249 (32.9)	221/681 (32.5)
Proportion of subjects who never achieved PGA = 0 throughout the study, n/N (%)	293/432 (67.8)	167/249 (67.1)	460/681 (67.5)

DB = double blinded; ITT = Intent-to-Treat; PGA = Physician Global Assessment

Table 6: Analysis of Efficacy Endpoint, Time to First Achieving PGA = 0; Subjects Entering the Extension Study with PGA ≥ 1 (ITT Population, Observed Cases)

	Tapinarof Cream, 1% (Pivotal) (N = 432)	Vehicle Cream (Pivotal) (N = 249)	Overall (N = 681)
Time to First Achieving PGA = 0 (Days) [1]			
Kaplan-Meier Estimates			
N	432	249	681
Number of Subjects with 1st Achieving	139	82	221
25th percentile (95% CI)	113 (89.0, 148.0)	169 (119.0, 206.0)	141 (113.0, 169.0)
Median (95% CI)	NE (NE, NE)	313 (283.0, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)

CI = confidence interval; DB = double blinded; ITT = Intent-to-Treat; NE = not estimable; PGA = Physician Global Assessment.

[0333] Proportion of Subjects who Achieved PGA = 0 or 1 at Least 1 Time in the Study for Subjects Entering the Extension Study with PGA ≥ 2

[0334] Table 7 presents the proportion of subjects achieving a PGA = 0 or 1 who entered this extension study with PGA ≥ 2. Of the 520 subjects who entered this extension study with a PGA ≥ 2, 57.3% of those subjects experienced a PGA = 0 or 1 at least once during the study. The proportions were similar between the DB assigned treatment groups (tapinarof cream, 1%: 53.5%; vehicle cream: 62.1%).

Table 7: Analysis of Efficacy Endpoint, Proportion of Subjects Achieving a PGA = 0 or 1; Subjects Entering the Extension Study with PGA ≥ 2 (ITT Population, Observed Cases)

	Tapinarof Cream, 1% (Pivotal) (N = 288)	Vehicle Cream (Pivotal) (N = 232)	Overall (N = 520)
Proportion of subjects who achieved PGA = 0 or 1 at least 1 time during the study, n/N (%)	154/288 (53.5)	144/232 (62.1)	298/520 (57.3)
Proportion of subjects who never achieved PGA = 0 or 1 throughout the study, n/N (%)	134/288 (46.5)	88/232 (37.9)	222/520 (42.7)

DB = double blinded; ITT = Intent-to-Treat; PGA = Physician Global Assessment.

[0335] Duration of Treatment Episodes

[0336] The duration of each treatment episode is defined as the time from each $\text{PGA} \geq 2$ (or $\text{PGA} \geq 1$ for the first episode [Baseline]) to each subsequent treatment success ($\text{PGA} = 0$). Table 8 presents the durations of treatment episodes. Treatment episodes that were ongoing as of the last known PGA evaluation were right censored, thus the treatment duration was stopped due to the subject reaching the end of the study, not because the subject achieved a $\text{PGA} = 0$. At the time of the data cutoff date for this interim analysis, 96.3% of subjects required one treatment episode with a mean (SD) duration of 163.1 (97.10) days. The treatment episode data were right censored for 66.4% of these subjects. The mean (SD) duration of the first treatment episode was approximately 19 days longer in the group of subjects who were randomized to vehicle cream in the DB, pivotal Phase 3 studies (175.5 [92.74] days) compared with subjects randomized to tapinarof cream, 1% (156.6 [98.77] days).

[0337] The overall mean (SD) durations of the second and third treatment episodes continued to shorten (74.0 [55.35] and 50.4 [41.38] days, respectively); however, this is primarily due to the number of subjects' data requiring right censoring for this interim analysis (60.2% and 75.0% for the second and third treatment episodes, respectively). Only 1 subject required a fourth treatment episode.

[0338] Overall, the mean (SD) total duration of treatment episodes for each subject was 177.6 (90.38) days.

Table 8: Analysis of Efficacy Endpoint, Duration of Treatment Episodes (ITT Population, Observed Cases)

	Tapinarof Cream, 1% (Pivotal) (N = 508)	Vehicle Cream (Pivotal) (N = 255)	Overall (N = 763)
Duration of 1st Episode (days)			
Number of subjects	484	251	735
Number of subjects without censoring [1]	166	81	247
Number of subjects with right censoring [1]	318	170	488
Mean (SD)	156.6 (98.77)	175.5 (92.74)	163.1 (97.10)
Median	147.5	196.0	169.0
Minimum, Maximum	1, 307	1, 294	1, 307
Duration of 2nd Episode (days)			
Number of subjects	94	39	133
Number of subjects without censoring [1]	34	19	53
Number of subjects with right censoring [1]	60	20	80
Mean (SD)	80.7 (58.54)	57.8 (43.31)	74.0 (55.35)
Median	60.5	38.0	57.0
Minimum, Maximum	1, 225	1, 169	1, 225
Duration of 3rd Episode (days)			
Number of subjects	9	7	16
Number of subjects without censoring [1]	2	2	4
Number of subjects with right censoring [1]	7	5	12
Mean (SD)	49.6 (52.51)	51.6 (24.51)	50.4 (41.38)
Median	28.0	56.0	32.5
Minimum, Maximum	1, 138	26, 86	1, 138
Duration of 4th Episode (days)			
Number of subjects	0	1	1
Number of subjects with right censoring [1]	0	1	1
Mean (SD)	---	1.0 (NE)	1.0 (NE)
Median	---	1.0	1.0

	Tapinarof Cream, 1% (Pivotal) (N = 508)	Vehicle Cream (Pivotal) (N = 255)	Overall (N = 763)
Minimum, Maximum	---	1, 1	1, 1
Duration of Last Episode for Each Subject (days)			
Number of subjects	484	251	735
Number of subjects without censoring [1]	99	55	154
Number of subjects with right censoring [1]	385	196	581
Mean (SD)	157.6 (99.25)	171.4 (96.61)	162.4 (98.51)
Median	168.0	195.0	169.0
Minimum, Maximum	1, 307	1, 294	1, 307
Average Duration of Episodes for Each Subject (days)			
N	484	251	735
Mean (SD)	157.1 (97.16)	173.4 (93.60)	162.7 (96.20)
Median	140.5	195.0	168.0
Minimum, Maximum	1, 307	1, 294	1, 307
Total Duration of Treatment Episodes for Each Subject (days)			
N	484	251	735
Mean (SD)	173.2 (92.39)	185.9 (85.95)	177.6 (90.38)
Median	196.0	197.0	197.0
Minimum, Maximum	1, 307	1, 294	1, 307

[1] Right censoring indicates that the treatment episode was ongoing as of the last known PGA evaluation that treatments could be scheduled.

DB = double blinded; ITT = Intent-to-Treat; NE = not estimable; PGA = Physician Global Assessment; SD = standard deviation.

[0339] Table 9 presents the durations of treatment episodes by Baseline visit PGA score upon entering this extension study. Overall, the mean (SD) duration of the first treatment episode increased with increasing Baseline PGA score: PGA = 0: 92.9 (67.74) days, PGA = 1: 133.5 (100.06) days, PGA = 2: 177.8 (92.43) days, PGA = 3: 180.8 (93.84) days, and PGA = 4: 187.4 (102.04) days. Of note, the percentage of subjects affected by right censoring also increased with increasing PGA score (PGA = 0 [40.0%], PGA = 1 [47.8%], PGA = 2 [72.1%], PGA = 3 [77.1%], and PGA = 4 [82.6%]). Overall, the mean (SD) total duration of treatment for each subject were PGA = 0: 109.2 (61.94) days, PGA =

1: 165.9 (90.32) days, PGA = 2: 188.8 (87.61) days, PGA = 3: 187.9 (90.62) days, and PGA = 4: 191.1 (99.63) days.

Table 9: Analysis of Efficacy Endpoint, Duration of Treatment Episodes by Baseline PGA Score (ITT Population, Observed Cases)

Baseline PGA = 0			
	Tapinarof Cream, 1% (Pivotal) (N = 73)	Vehicle Cream (Pivotal) (N = 5)	Overall (N = 78)
Duration of 1st Episode (days)			
Number of subjects	53	2	55
Number of subjects without censoring [1]	31	2	33
Number of subjects with right censoring [1]	22	0	22
Mean (SD)	91.7 (66.66)	126.0 (120.21)	92.9 (67.74)
Median	65.0	126.0	65.0
Minimum, Maximum	25, 253	41, 211	25, 253
Duration of 2nd Episode (days)			
Number of subjects	18	1	19
Number of subjects without censoring [1]	10	1	11
Number of subjects with right censoring [1]	8	0	8
Mean (SD)	44.9 (26.43)	28.0 (NE)	44.1 (25.97)
Median	43.0	28.0	42.0
Minimum, Maximum	1, 92	28, 28	1, 92
Duration of 3rd Episode (days)			
Number of subjects	1	0	1
Number of subjects with right censoring [1]	1	0	1
Mean (SD)	61.0 (NE)	---	61.0 (NE)
Median	61.0	---	61.0
Minimum, Maximum	61, 61	---	61, 61
Duration of Last Episode for Each Subject (days)			
Number of subjects	53	2	55

Number of subjects without censoring [1]	22	2	24
Number of subjects with right censoring [1]	31	0	31
Mean (SD)	88.8 (67.68)	119.5 (129.40)	89.9 (68.95)
Median	63.0	119.5	63.0
Minimum, Maximum	1, 253	28, 211	1, 253
Average Duration of Episodes for Each Subject (days)			
N	53	2	55
Mean (SD)	90.2 (65.67)	122.8 (124.80)	91.4 (66.93)
Median	63.0	122.8	63.0
Minimum, Maximum	27, 253	35, 211	27, 253
Total Duration of Treatment Episodes for Each Subject (days)			
N	53	2	55
Mean (SD)	108.1 (61.26)	140.0 (100.41)	109.2 (61.94)
Median	94.0	140.0	94.0
Minimum, Maximum	27, 253	69, 211	27, 253
Baseline PGA = 1			
	Tapinarof Cream, 1% (Pivotal) (N = 144)	Vehicle Cream (Pivotal) (N = 17)	Overall (N = 161)
Duration of 1st Episode (days)			
Number of subjects	144	17	161
Number of subjects without censoring [1]	75	9	84
Number of subjects with right censoring [1]	69	8	77
Mean (SD)	132.6 (99.69)	141.1 (105.95)	133.5 (100.06)
Median	85.5	112.0	87.0
Minimum, Maximum	1, 291	27, 284	1, 291
Duration of 2nd Episode (days)			
Number of subjects	45	4	49
Number of subjects without censoring [1]	18	1	19
Number of subjects with right censoring [1]	27	3	30

Mean (SD)	97.9 (62.19)	104.0 (61.27)	98.4 (61.51)
Median	83.0	109.5	85.0
Minimum, Maximum	1, 225	28, 169	1, 225
Duration of 3rd Episode (days)			
Number of subjects	7	0	7
Number of subjects without censoring [1]	2	0	2
Number of subjects with right censoring [1]	5	0	5
Mean (SD)	54.9 (56.83)	---	54.9 (56.83)
Median	28.0	---	28.0
Minimum, Maximum	1, 138	---	1, 138
Duration of Last Episode for Each Subject (days)			
Number of subjects	144	17	161
Number of subjects without censoring [1]	43	6	49
Number of subjects with right censoring [1]	101	11	112
Mean (SD)	145.2 (96.38)	159.0 (93.38)	146.7 (95.87)
Median	144.0	134.0	141.0
Minimum, Maximum	1, 291	28, 284	1, 291
Average Duration of Episodes for Each Subject (days)			
Number of subjects	144	17	161
Mean (SD)	138.9 (94.99)	150.0 (97.54)	140.1 (95.01)
Median	112.0	112.0	112.0
Minimum, Maximum	1, 291	28, 284	1, 291
Total Duration of Treatment Episodes for Each Subject (days)			
Number of subjects	144	17	161
Mean (SD)	165.9 (90.68)	165.5 (89.94)	165.9 (90.32)
Median	194.5	140.0	193.0
Minimum, Maximum	1, 291	45, 284	1, 291
Baseline PGA = 2 (Mild)			
	Tapinarof Cream, 1% (Pivotal) (N = 188)	Vehicle Cream (Pivotal) (N = 60)	Overall (N = 248)
Duration of 1st Episode (days)			

Number of subjects	187	60	247
Number of subjects without censoring [1]	47	22	69
Number of subjects with right censoring [1]	140	38	178
Mean (SD)	179.2 (94.49)	173.2 (86.28)	177.8 (92.43)
Median	197.0	194.0	197.0
Minimum, Maximum	1, 307	27, 294	1, 307
Duration of 2nd Episode (days)			
Number of subjects	26	13	39
Number of subjects without censoring [1]	5	7	12
Number of subjects with right censoring [1]	21	6	27
Mean (SD)	78.2 (54.89)	46.0 (42.39)	67.5 (52.79)
Median	84.5	27.0	59.0
Minimum, Maximum	1, 180	1, 120	1, 180
Duration of 3rd Episode (days)			
Number of subjects	1	2	3
Number of subjects without censoring [1]	0	1	1
Number of subjects with right censoring [1]	1	1	2
Mean (SD)	1.0 (NE)	42.5 (19.09)	28.7 (27.50)
Median	1.0	42.5	29.0
Minimum, Maximum	1, 1	29, 56	1, 56
Duration of Last Episode for Each Subject (days)			
Number of subjects	187	60	247
Number of subjects without censoring [1]	25	15	40
Number of subjects with right censoring [1]	162	45	207
Mean (SD)	175.4 (98.91)	166.2 (95.09)	173.2 (97.88)
Median	197.0	194.0	197.0
Minimum, Maximum	1, 307	1, 294	1, 307
Average Duration of Episodes for Each Subject (days)			

Number of subjects	187	60	247
Mean (SD)	177.3 (95.45)	169.8 (89.68)	175.5 (93.95)
Median	197.0	194.0	197.0
Minimum, Maximum	1, 307	24, 294	1, 307
Total Duration of Treatment Episodes for Each Subject (days)			
Number of Subjects	187	60	247
Mean (SD)	190.1 (90.58)	184.6 (78.19)	188.8 (87.61)
Median	223.0	196.5	200.0
Minimum, Maximum	1, 307	27, 294	1, 307
Baseline PGA = 3 (Moderate)			
	Tapinarof Cream, 1% (Pivotal) (N = 93)	Vehicle Cream (Pivotal) (N = 156)	Overall (N = 249)
Duration of 1st Episode (days)			
Number of subjects	93	156	249
Number of subjects without censoring [1]	11	46	57
Number of subjects with right censoring [1]	82	110	192
Mean (SD)	187.1 (95.90)	177.1 (92.70)	180.8 (93.84)
Median	198.0	195.5	197.0
Minimum, Maximum	1, 305	1, 292	1, 305
Duration of 2nd Episode (days)			
Number of subjects	5	20	25
Number of subjects without censoring [1]	1	10	11
Number of subjects with right censoring [1]	4	10	14
Mean (SD)	68.2 (77.66)	56.4 (37.29)	58.8 (46.15)
Median	30.0	55.5	55.0
Minimum, Maximum	1, 196	1, 142	1, 196
Duration of 3rd Episode (days)			
Number of subjects	0	5	5
Number of subjects without censoring [1]	0	1	1
Number of subjects with right censoring [1]	0	4	4

Mean (SD)	---	55.2 (27.44)	55.2 (27.44)
Median	---	57.0	57.0
Minimum, Maximum	---	26, 86	26, 86
Duration of 4th Episode (days)			
Number of subjects	0	1	1
Number of subjects with right censoring [1]	0	1	1
Mean (SD)	---	1.0 (NE)	1.0 (NE)
Median	---	1.0	1.0
Minimum, Maximum	---	1, 1	1, 1
Duration of Last Episode for Each Subject (days)			
Number of subjects	93	156	249
Number of subjects without censoring [1]	7	31	38
Number of subjects with right censoring [1]	86	125	211
Mean (SD)	182.2 (99.93)	171.4 (97.39)	175.4 (98.29)
Median	198.0	195.0	197.0
Minimum, Maximum	1, 305	1, 292	1, 305
Average Duration of Episodes for Each Subject (days)			
Number of subjects	93	156	249
Mean (SD)	184.7 (96.36)	174.0 (94.06)	178.0 (94.87)
Median	198.0	195.0	197.0
Minimum, Maximum	1, 305	1, 292	1, 305
Total Duration of Treatment Episodes for Each Subject (days)			
Number of subjects	93	156	249
Mean (SD)	190.8 (95.50)	186.1 (87.86)	187.9 (90.62)
Median	200.0	197.5	198.0
Minimum, Maximum	1, 305	1, 292	1, 305
Baseline PGA = 4 (Severe)			
	Tapinarof Cream, 1% (Pivotal) (N = 7)	Vehicle Cream (Pivotal) (N = 16)	Overall (N = 23)
Duration of 1st Episode (days)			
Number of subjects	7	16	23

Number of subjects without censoring [1]	2	2	4
Number of subjects with right censoring [1]	5	14	19
Mean (SD)	132.9 (100.39)	211.3 (96.13)	187.4 (102.04)
Median	113.0	267.0	225.0
Minimum, Maximum	16, 280	29, 287	16, 287
Duration of 2nd Episode (days)			
Number of subjects	0	1	1
Number of subjects with right censoring [1]	0	1	1
Mean (SD)	---	85.0 (NE)	85.0 (NE)
Median	---	85.0	85.0
Minimum, Maximum	---	85, 85	85, 85
Duration of Last Episode for Each Subject (days)			
Number of subjects	7	16	23
Number of subjects without censoring [1]	2	1	3
Number of subjects with right censoring [1]	5	15	20
Mean (SD)	132.9 (100.39)	211.4 (96.04)	187.5 (101.99)
Median	113.0	267.0	225.0
Minimum, Maximum	16, 280	29, 287	16, 287
Average Duration of Episodes for Each Subject (days)			
Number of subjects	7	16	23
Mean (SD)	132.9 (100.39)	211.3 (96.08)	187.5 (102.01)
Median	113.0	267.0	225.0
Minimum, Maximum	16, 280	29, 287	16, 287
Total Duration of Treatment Episodes for Each Subject (days)			
Number of subjects	7	16	23
Mean (SD)	132.9 (100.39)	216.6 (90.82)	191.1 (99.63)
Median	113.0	267.0	225.0
Minimum, Maximum	16, 280	29, 287	16, 287

[1] Right censoring indicates that the treatment episode was ongoing as of the last known PGA evaluation that treatments could have been scheduled.

DB = double blinded; ITT = Intent-to-Treat; NE = not estimable; PGA = Physician Global Assessment; SD = standard deviation

[0340] Duration of Treatment Success

[0341] The duration of treatment success (treatment-free interval or remittive response) is defined as the time from each PGA = 0 to each subsequent worsening (PGA $\geq$ 2). Table 10 presents the durations of treatment successes. Treatment successes that were ongoing as of the last known PGA evaluation were right censored resulting in the treatment-free interval being stopped due to the subject reaching the end of the study, not because the subject had worsening disease. As of the data cutoff date for this interim analysis, 299 subjects (39.2%) experienced at least one treatment success with a mean (SD) duration of 100.0 (78.49) days. The treatment success data were right censored for 37.8% of these subjects. The mean duration of the first treatment success was approximately 10 days longer in the group of subjects who were randomized to tapinarof cream, 1% in the DB, pivotal Phase 3 studies (103.0 [80.13] days) compared with subjects randomized to vehicle cream (92.8 [74.32] days).

[0342] The overall mean (SD) durations of the second and third treatment successes continued to shorten (65.4 [60.68] days and 30.0 [26.46] days, respectively); however, this is primarily due to the number of subjects' data requiring right censoring for this interim analysis (45.7% and 66.7% for the second and third treatment successes, respectively).

[0343] Overall, the mean (SD) total duration of treatment success for each subject was 119.3 (81.80) days.

Table 10: Analysis of Efficacy Endpoint, Duration of Treatment Success (ITT Population, Observed Cases)

	Tapinarof Cream, 1% (Pivotal) (N = 508)	Vehicle Cream (Pivotal) (N = 255)	Overall (N = 763)
Duration of 1st Success (days)			
Number of subjects	212	87	299
Number of subjects without censoring [1]	140	46	186
Number of subjects with right censoring [1]	72	41	113
Mean (SD)	103.0 (80.13)	92.8 (74.32)	100.0 (78.49)
Median	84.0	85.0	84.0
Minimum, Maximum	1, 309	1, 309	1, 309

	Tapinarof Cream, 1% (Pivotal) (N = 508)	Vehicle Cream (Pivotal) (N = 255)	Overall (N = 763)
Duration of 2nd Success (days)			
Number of subjects	57	24	81
Number of subjects without censoring [1]	34	10	44
Number of subjects with right censoring [1]	23	14	37
Mean (SD)	76.5 (63.07)	39.1 (45.75)	65.4 (60.68)
Median	56.0	28.0	41.0
Minimum, Maximum	1, 257	1, 170	1, 257
Duration of 3rd Success (days)			
Number of subjects	12	3	15
Number of subjects without censoring [1]	4	1	5
Number of subjects with right censoring [1]	8	2	10
Mean (SD)	32.7 (28.40)	19.3 (15.89)	30.0 (26.46)
Median	28.5	28.0	28.0
Minimum, Maximum	1, 85	1, 29	1, 85
Duration of Last Success for Each Subject (days)			
Number of subjects	212	87	299
Number of subjects without censoring [1]	109	30	139
Number of subjects with right censoring [1]	103	57	160
Mean (SD)	101.5 (83.51)	80.5 (77.32)	95.4 (82.18)
Median	82.5	56.0	64.0
Minimum, Maximum	1, 309	1, 309	1, 309
Average Duration of Treatment Success for Each Subject (days)			
Number of subjects	212	87	299
Mean (SD)	102.4 (77.90)	86.8 (72.58)	97.9 (76.60)
Median	84.0	64.0	84.0
Minimum, Maximum	1, 309	1, 309	1, 309
Total Duration of Treatment Success for Each Subject (days)			
Number of subjects	212	87	299
Mean (SD)	125.4 (83.22)	104.3 (76.62)	119.3 (81.80)
Median	116.5	97.0	112.0

	Tapinarof Cream, 1% (Pivotal) (N = 508)	Vehicle Cream (Pivotal) (N = 255)	Overall (N = 763)
Minimum, Maximum	1, 309	1, 309	1, 309

[1] Right censoring indicates that treatment success was ongoing as of the last known PGA evaluation. DB = double blinded; ITT = Intent-to-Treat; PGA = Physician Global Assessment; SD = standard deviation.

[0344] Table 11 presents the duration of treatment successes by Baseline visit PGA upon entering this extension study. Overall, the mean (SD) duration of the first treatment success decreased with increasing Baseline PGA score from PGA = 0 to PGA = 3: PGA = 0: 125.1 (91.87) days, PGA = 1: 107.2 (76.62) days, PGA = 2: 90.4 (72.34) days, and PGA = 3: 68.8 (57.40) days. The overall mean (SD) duration of the first treatment success was 104.5 (56.36) days for subjects with a Baseline PGA = 4. Of note, the percentage of subjects affected by right censoring increased with increasing PGA score (PGA = 0 [24.4%], PGA = 1 [36.5%], PGA = 2 [40.8%], PGA = 3 [50.8%], and PGA = 4 [75.0%]). Overall, the mean (SD) total duration of treatment success for each subject also decreased with increasing Baseline PGA score from PGA = 0 to PGA = 3: PGA = 0: 167.9 (84.48) days, PGA = 1: 124.5 (78.53) days, PGA = 2: 98.0 (74.01) days, and PGA = 3: 75.5 (57.18) days. The overall mean (SD) total duration of treatment success was 104.5 (56.36) days for subjects with a Baseline PGA = 4.

Table 11: Analysis of Efficacy Endpoint, Duration of Treatment Success by Baseline PGA Score (ITT Population, Observed Cases)

Baseline PGA = 0 (Clear)			
	Tapinarof Cream, 1% (Pivotal) (N = 73)	Vehicle Cream (Pivotal) (N = 5)	Overall (N = 78)
Duration of 1st Success (days)			
Number of subjects	73	5	78
Number of subjects without censoring [1]	56	3	59
Number of subjects with right censoring [1]	17	2	19
Mean (SD)	120.3 (87.83)	195.2 (130.61)	125.1 (91.87)
Median	112.0	280.0	112.0
Minimum, Maximum	1, 309	41, 309	1, 309

Duration of 2nd Success (days)			
Number of subjects	32	2	34
Number of subjects without censoring [1]	22	1	23
Number of subjects with right censoring [1]	10	1	11
Mean (SD)	89.1 (67.03)	63.5 (88.39)	87.6 (67.05)
Median	71.0	63.5	71.0
Minimum, Maximum	1, 257	1, 126	1, 257
Duration of 3rd Success (days)			
Number of subjects	10	1	11
Number of subjects without censoring [1]	4	0	4
Number of subjects with right censoring [1]	6	1	7
Mean (SD)	36.2 (29.31)	1.0 (NE)	33.0 (29.76)
Median	28.5	1.0	28.0
Minimum, Maximum	1, 85	1, 1	1, 85
Duration of Last Success for Each Subject (days)			
Number of subjects	73	5	78
Number of subjects without censoring [1]	40	1	41
Number of subjects with right censoring [1]	33	4	37
Mean (SD)	118.0 (93.58)	174.4 (158.72)	121.6 (98.44)
Median	112.0	280.0	112.0
Minimum, Maximum	1, 309	1, 309	1, 309
Average Duration of Treatment Success for Each Subject (days)			
Number of subjects	73	5	78
Mean (SD)	119.7 (82.74)	191.0 (136.91)	124.2 (87.66)
Median	98.0	280.0	98.0
Minimum, Maximum	1, 309	21, 309	1, 309
Total Duration of Treatment Success for Each Subject (days)			
Number of subjects	73	5	78
Mean (SD)	164.3 (82.24)	220.8 (109.21)	167.9 (84.48)
Median	168.0	280.0	170.0
Minimum, Maximum	1, 309	42, 309	1, 309
Baseline PGA = 1 (Almost Clear)			

	Tapinarof Cream, 1% (Pivotal) (N = 73)	Vehicle Cream (Pivotal) (N = 5)	Overall (N = 78)
Duration of 1st Success (days)			
Number of subjects	76	9	85
Number of subjects without censoring [1]	49	5	54
Number of subjects with right censoring [1]	27	4	31
Mean (SD)	106.3 (77.57)	115.0 (71.74)	107.2 (76.62)
Median	86.0	127.0	90.0
Minimum, Maximum	1, 280	1, 241	1, 280
Duration of 2nd Success (days)			
Number of subjects	18	1	19
Number of subjects without censoring [1]	10	0	10
Number of subjects with right censoring [1]	8	1	9
Mean (SD)	71.6 (58.68)	144.0 (NE)	75.4 (59.40)
Median	52.0	144.0	56.0
Minimum, Maximum	1, 189	144, 144	1, 189
Duration of 3rd Success (days)			
Number of subjects	2	0	2
Number of subjects with right censoring [1]	2	0	2
Mean (SD)	15.0 (19.80)	---	15.0 (19.80)
Median	15.0	---	15.0
Minimum, Maximum	1, 29	---	1, 29
Duration of Last Success for Each Subject (days)			
Number of subjects	76	9	85
Number of subjects without censoring [1]	39	4	43
Number of subjects with right censoring [1]	37	5	42
Mean (SD)	107.2 (79.80)	118.9 (72.32)	108.5 (78.72)
Median	85.5	136.0	90.0
Minimum, Maximum	1, 280	1, 241	1, 280
Average Duration of Treatment Success for Each Subject (days)			
Number of subjects	76	9	85

Mean (SD)	106.8 (76.36)	116.9 (71.80)	107.9 (75.54)
Median	92.5	127.0	98.0
Minimum, Maximum	1, 280	1, 241	1, 280
Total Duration of Treatment Success for Each Subject (days)			
Number of subjects	76	9	85
Mean (SD)	123.7 (78.29)	131.0 (85.06)	124.5 (78.53)
Median	116.5	136.0	120.0
Minimum, Maximum	1, 280	1, 253	1, 280
Baseline PGA = 2 (Mild)			
	Tapinarof Cream, 1% (Pivotal) (N = 188)	Vehicle Cream (Pivotal) (N = 60)	Overall (N = 248)
Duration of 1st Success (days)			
Number of subjects	49	22	71
Number of subjects without censoring [1]	29	13	42
Number of subjects with right censoring [1]	20	9	29
Mean (SD)	81.3 (71.03)	110.8 (72.69)	90.4 (72.34)
Median	57.0	115.5	83.0
Minimum, Maximum	1, 281	1, 253	1, 281
Duration of 2nd Success (days)			
Number of subjects	6	10	16
Number of subjects without censoring [1]	1	2	3
Number of subjects with right censoring [1]	5	8	13
Mean (SD)	27.3 (30.06)	34.7 (51.14)	31.9 (43.41)
Median	25.0	27.5	27.5
Minimum, Maximum	1, 83	1, 170	1, 170
Duration of 3rd Success (days)			
Number of subjects	0	1	1
Number of subjects with right censoring [1]	0	1	1
Mean (SD)	---	29.0 (NE)	29.0 (NE)
Median	---	29.0	29.0
Minimum, Maximum	---	29, 29	29, 29

Duration of Last Success for Each Subject (days)			
Number of subjects	49	22	71
Number of subjects without censoring [1]	24	4	28
Number of subjects with right censoring [1]	25	18	43
Mean (SD)	76.1 (72.82)	79.8 (77.74)	77.3 (73.84)
Median	56.0	44.5	56.0
Minimum, Maximum	1, 281	1, 253	1, 281
Average Duration of Treatment Success for Each Subject (days)			
Number of subjects	49	22	71
Mean (SD)	78.7 (71.03)	94.6 (65.57)	83.6 (69.31)
Median	57.0	87.0	66.5
Minimum, Maximum	1, 281	1, 253	1, 281
Total Duration of Treatment Success for Each Subject (days)			
Number of subjects	49	22	71
Mean (SD)	84.6 (71.17)	127.9 (73.01)	98.0 (74.01)
Median	78.0	136.5	84.0
Minimum, Maximum	1, 281	1, 253	1, 281
Baseline PGA = 3 (Moderate)			
	Tapinarof Cream, 1% (Pivotal) (N = 93)	Vehicle Cream (Pivotal) (N = 156)	Overall (N = 249)
Duration of 1st Success (days)			
Number of subjects	12	49	61
Number of subjects without censoring [1]	6	24	30
Number of subjects with right censoring [1]	6	25	31
Mean (SD)	62.6 (55.19)	70.3 (58.38)	68.8 (57.40)
Median	43.0	56.0	56.0
Minimum, Maximum	1, 171	1, 247	1, 247
Duration of 2nd Success (days)			
Number of subjects	1	11	12
Number of subjects without censoring [1]	1	7	8
Number of subjects with right censoring [1]	0	4	4
Mean (SD)	57.0 (NE)	29.2 (18.23)	31.5 (19.15)
Median	57.0	28.0	28.5

Minimum, Maximum	57, 57	1, 62	1, 62
Duration of 3rd Success (days)			
Number of subjects	0	1	1
Number of subjects with right censoring [1]	0	1	1
Mean (SD)	---	28.0 (NE)	28.0 (NE)
Median	---	28.0	28.0
Minimum, Maximum	---	28, 28	28, 28
Duration of Last Success for Each Subject (days)			
Number of subjects	12	49	61
Number of subjects without censoring [1]	6	20	26
Number of subjects with right censoring [1]	6	29	35
Mean (SD)	65.2 (54.03)	63.8 (59.74)	64.1 (58.23)
Median	56.0	49.0	51.0
Minimum, Maximum	1, 171	1, 247	1, 247
Average Duration of Treatment Success for Each Subject (days)			
Number of subjects	12	49	61
Mean (SD)	63.9 (54.43)	67.1 (57.99)	66.4 (56.88)
Median	48.3	51.0	51.0
Minimum, Maximum	1, 171	1, 247	1, 247
Total Duration of Treatment Success for Each Subject (days)			
Number of subjects	12	49	61
Mean (SD)	67.3 (54.20)	77.4 (58.26)	75.5 (57.18)
Median	56.5	81.0	64.0
Minimum, Maximum	1, 171	1, 247	1, 247
Baseline PGA = 4 (Severe)			
	Tapinarof Cream, 1% (Pivotal) (N = 7)	Vehicle Cream (Pivotal) (N = 16)	Overall (N = 23)
Duration of 1st Success (days)			
Number of subjects	2	2	4
Number of subjects without censoring [1]	0	1	1
Number of subjects with right censoring [1]	2	1	3
Mean (SD)	119.5 (79.90)	89.5 (47.38)	104.5 (56.36)
Median	119.5	89.5	93.0

Minimum, Maximum	63, 176	56, 123	56, 176
Duration of Last Success for Each Subject (days)			
Number of subjects	2	2	4
Number of subjects without censoring [1]	0	1	1
Number of subjects with right censoring [1]	2	1	3
Mean (SD)	119.5 (79.90)	89.5 (47.38)	104.5 (56.36)
Median	119.5	89.5	93.0
Minimum, Maximum	63, 176	56, 123	56, 176
Average Duration of Treatment Success for Each Subject (days)			
Number of subjects	2	2	4
Mean (SD)	119.5 (79.90)	89.5 (47.38)	104.5 (56.36)
Median	119.5	89.5	93.0
Minimum, Maximum	63, 176	56, 123	56, 176
Total Duration of Treatment Success for Each Subject (days)			
Number of subjects	2	2	4
Mean (SD)	119.5 (79.90)	89.5 (47.38)	104.5 (56.36)
Median	119.5	89.5	93.0
Minimum, Maximum	63, 176	56, 123	56, 176

[1] Right censoring indicates that treatment success was ongoing at the end of the study.

DB = double blinded; ITT = Intent-to-Treat; NE = not estimable; PGA = Physician Global Assessment; SD = standard deviation.

[0345] Physician Global Assessment Score, Percent of Body Surface Area Affected, and Psoriasis Area and Severity Index

[0346] Physician Global Assessment

[0347] Table 12 presents PGA score and change from baseline at Week 16 and Week 40 as performed using OC and LOCF methods. Overall subjects' baseline PGA scores were similarly distributed among moderate (32.8%), mild (32.7%), and almost clear (21.2%). The majority of subjects who were randomized to vehicle cream in the DB, pivotal Phase 3 studies entered this extension study with a Baseline PGA = 3 (61.4%) compared with 18.4% of subjects randomized to tapinarof cream, 1%. The majority of subjects randomized to tapinarof cream, 1% in the DB, pivotal Phase 3 studies entered with a PGA score of either a 2 (37.2%) or 1 (28.5%).

[0348] At Week 16 using the OC method, 19.1% and 32.2% of subjects randomized to tapinarof cream, 1% in the DB, pivotal Phase 3 studies had a PGA = 0 or PGA = 1, respectively; and 12.9% and 28.2% of subjects randomized to vehicle cream had a PGA = 0 or PGA = 1, respectively. Using the LOCF method, 18.1% and 30.4% of subjects randomized to tapinarof cream, 1% in the DB, pivotal Phase 3 studies had a PGA = 0 or PGA = 1, respectively; and 12.7% and 25.8% of subjects randomized to vehicle cream had a PGA = 0 or PGA = 1.

[0349] At Week 40 using the OC method, 17.4% and 30.1% of subjects randomized to tapinarof cream, 1% in the DB, pivotal Phase 3 studies had a PGA = 0 or PGA = 1, respectively; and 23.9% and 31.9% of subjects randomized to vehicle cream had a PGA = 0 or PGA = 1, respectively. Using the LOCF method, 15.4% and 30.0% of subjects randomized to tapinarof cream, 1% in the DB, pivotal Phase 3 studies had a PGA = 0 or PGA = 1, respectively; and 16.7% and 27.4% of subjects randomized to vehicle cream had a PGA = 0 or PGA = 1, respectively.

Table 12: Summary of PGA Scores Observed Values and Change from Baseline at Week 16 and Week 40 (ITT Population, Observed Cases and Last Observation Carried Forward)

	Tapinarof Cream, 1% (Pivotal) (N = 508)	Vehicle Cream (Pivotal) (N = 255)	Overall (N = 763)
Baseline			
Observed Value, n (%)			
N	505	254	759
4 – Severe	7 (1.4)	16 (6.3)	23 (3.0)
3 – Moderate	93 (18.4)	156 (61.4)	249 (32.8)
2 – Mild	188 (37.2)	60 (23.6)	248 (32.7)
1 – Almost Clear	144 (28.5)	17 (6.7)	161 (21.2)
0 – Clear	73 (14.5)	5 (2.0)	78 (10.3)
Week 16, Observed Cases			
Observed Value, n (%)			
N	419	209	628
4 – Severe	4 (1.0)	1 (0.5)	5 (0.8)
3 – Moderate	54 (12.9)	32 (15.3)	86 (13.7)
2 – Mild	146 (34.8)	90 (43.1)	236 (37.6)
1 – Almost Clear	135 (32.2)	59 (28.2)	194 (30.9)
0 – Clear	80 (19.1)	27 (12.9)	107 (17.0)
Change from Baseline, n (%)			

	Tapinarof Cream, 1% (Pivotal) (N = 508)	Vehicle Cream (Pivotal) (N = 255)	Overall (N = 763)
N	418	209	627
+4 = Worsened by 4	0 (0.0)	0 (0.0)	0 (0.0)
+3 = Worsened by 3	5 (1.2)	0 (0.0)	5 (0.8)
+2 = Worsened by 2	23 (5.5)	2 (1.0)	25 (4.0)
+1 = Worsened by 1	63 (15.1)	6 (2.9)	69 (11.0)
0 = No Change	187 (44.7)	59 (28.2)	246 (39.2)
-1 = Improved by 1	109 (26.1)	81 (38.8)	190 (30.3)
-2 = Improved by 2	29 (6.9)	48 (23.0)	77 (12.3)
-3 = Improved by 3	1 (0.2)	12 (5.7)	13 (2.1)
-4 = Improved by 4	1 (0.2)	1 (0.5)	2 (0.3)
Week 16, Last Observation Carried Forward			
Observed Value, n (%)			
N	493	252	745
4 – Severe	6 (1.2)	5 (2.0)	11 (1.5)
3 – Moderate	74 (15.0)	45 (17.9)	119 (16.0)
2 – Mild	174 (35.3)	105 (41.7)	279 (37.4)
1 – Almost Clear	150 (30.4)	65 (25.8)	215 (28.9)
0 – Clear	89 (18.1)	32 (12.7)	121 (16.2)
Change from Baseline, n (%)			
N	491	251	742
+4 = Worsened by 4	0 (0.0)	0 (0.0)	0 (0.0)
+3 = Worsened by 3	5 (1.0)	0 (0.0)	5 (0.7)
+2 = Worsened by 2	25 (5.1)	3 (1.2)	28 (3.8)
+1 = Worsened by 1	77 (15.7)	9 (3.6)	86 (11.6)
0 = No Change	223 (45.4)	74 (29.5)	297 (40.0)
-1 = Improved by 1	122 (24.8)	97 (38.6)	219 (29.5)
-2 = Improved by 2	37 (7.5)	54 (21.5)	91 (12.3)
-3 = Improved by 3	1 (0.2)	13 (5.2)	14 (1.9)
-4 = Improved by 4	1 (0.2)	1 (0.4)	2 (0.3)
Week 40, Observed Cases			
Observed Value, n (%)			
N	236	113	349
4 – Severe	1 (0.4)	0 (0.0)	1 (0.3)
3 – Moderate	42 (17.8)	15 (13.3)	57 (16.3)
2 – Mild	81 (34.3)	35 (31.0)	116 (33.2)
1 – Almost Clear	71 (30.1)	36 (31.9)	107 (30.7)
0 – Clear	41 (17.4)	27 (23.9)	68 (19.5)
Change from Baseline, n (%)			

	Tapinarof Cream, 1% (Pivotal) (N = 508)	Vehicle Cream (Pivotal) (N = 255)	Overall (N = 763)
N	236	113	349
+4 = Worsened by 4	0 (0.0)	0 (0.0)	0 (0.0)
+3 = Worsened by 3	3 (1.3)	0 (0.0)	3 (0.9)
+2 = Worsened by 2	20 (8.5)	1 (0.9)	21 (6.0)
+1 = Worsened by 1	48 (20.3)	7 (6.2)	55 (15.8)
0 = No Change	86 (36.4)	19 (16.8)	105 (30.1)
-1 = Improved by 1	58 (24.6)	41 (36.3)	99 (28.4)
-2 = Improved by 2	19 (8.1)	27 (23.9)	46 (13.2)
-3 = Improved by 3	2 (0.8)	17 (15.0)	19 (5.4)
-4 = Improved by 4	0 (0.0)	1 (0.9)	1 (0.3)
Week 40, Last Observation Carried Forward			
Observed Value, n (%)			
N	493	252	745
4 – Severe	7 (1.4)	4 (1.6)	11 (1.5)
3 – Moderate	91 (18.5)	55 (21.8)	146 (19.6)
2 – Mild	171 (34.7)	82 (32.5)	253 (34.0)
1 – Almost Clear	148 (30.0)	69 (27.4)	217 (29.1)
0 – Clear	76 (15.4)	42 (16.7)	118 (15.8)
Change from Baseline, n (%)			
N	491	251	742
+4 = Worsened by 4	0 (0.0)	0 (0.0)	0 (0.0)
+3 = Worsened by 3	4 (0.8)	0 (0.0)	4 (0.5)
+2 = Worsened by 2	34 (6.9)	3 (1.2)	37 (5.0)
+1 = Worsened by 1	95 (19.3)	13 (5.2)	108 (14.6)
0 = No Change	211 (43.0)	71 (28.3)	282 (38.0)
-1 = Improved by 1	110 (22.4)	84 (33.5)	194 (26.1)
-2 = Improved by 2	31 (6.3)	57 (22.7)	88 (11.9)
-3 = Improved by 3	5 (1.0)	22 (8.8)	27 (3.6)
-4 = Improved by 4	1 (0.2)	1 (0.4)	2 (0.3)

DB = double blinded; ITT = Intent-to-Treat; PGA = Physician Global Assessment.

[0350] Body Surface Area

[0351] Table 13 presents %BSA affected, change from baseline, and percent change from Baseline at Week 16 and Week 40 as performed using OC and LOCF methods. FIG. 11 shows the change in %BSA affected throughout the duration of the trial. Overall subjects' Baseline mean (SD) %BSA affected was 4.65% (5.601) with 3.31% (4.743) for

subjects who were randomized to tapinarof cream 1% in the DB, pivotal Phase 3 studies and 7.30% (6.208) for subjects who were randomized to vehicle cream.

[0352] The %BSA affected decreased over time overall and in both DB assigned treatment groups with no loss of effect observed. At Week 16 using the OC method, the mean (SD) %BSA affected was 1.97% (2.694) for subjects randomized to tapinarof cream, 1% in the DB, pivotal Phase 3 studies and 2.89% (4.028) for subjects randomized to vehicle cream. Overall, the mean (SD) %BSA affected was 2.28% (3.226). Using the LOCF method resulted in mean (SD) %BSA affected of 2.54% (4.579) and 3.36% (4.546), for subjects randomized to tapinarof cream, 1% cream or vehicle cream in the DB, pivotal Phase 3 studies, respectively. The overall mean (SD) %BSA affected was 2.82% (4.581).

[0353] At Week 40 using the OC method, the mean (SD) %BSA affected was 1.75% (2.714) for subjects randomized to tapinarof cream, 1% in the DB, pivotal Phase 3 studies and 2.07% (3.703) for subjects randomized to vehicle cream. Overall, the mean (SD) %BSA affected was 1.85% (3.067). Using the LOCF method resulted in mean (SD) %BSA affected of 2.44% (4.645) and 2.99% (4.472) for subjects randomized to tapinarof cream, 1% cream or vehicle cream in the DB, pivotal Phase 3 studies, respectively. The overall mean (SD) %BSA affected was 2.63% (4.592).

Table 13: Summary of Percent BSA Affected Observed Values, Change from Baseline, and Percent Change from Baseline at Week 16 and Week 40 (ITT Population, Observed Cases and Last Observation Carried Forward)

	Tapinarof Cream 1% (Pivotal) (N = 508)			Vehicle Cream (Pivotal) (N = 255)			Overall (N = 763)		
	Observed	CFBL	Percent CFBL	Observed	CFBL	Percent CFBL	Observed	CFBL	Percent CFBL
Baseline									
N	505			254			759		
Mean (SD)	3.31 (4.743)			7.30 (6.208)			4.65 (5.601)		
Median	2.00			5.65			3.00		
Minimum, Maximum	0.0, 66.0			0.0, 45.0			0.0, 66.0		
Week 16, Observed Cases									
N	419	418	350	209	209	204	628	627	554
Mean (SD)	1.97 (2.694)	-0.97 (3.090)	-18.46 (86.088)	2.89 (4.028)	-4.40 (5.043)	-53.18 (77.450)	2.28 (3.226)	-2.11 (4.175)	-31.25 (84.617)
Median	1.00	-0.23	-36.96	1.50	-3.18	-66.67	1.02	-1.00	-50.00
Minimum, Maximum	0.0, 20.8	-27.1, 10.5	-100.0, 525.0	0.0, 22.0	-27.1, 14.3	-100.0, 841.2	0.0, 22.0	-27.1, 14.3	-100.0, 841.2

	Tapinarof Cream 1% (Pivotal) (N = 508)			Vehicle Cream (Pivotal) (N = 255)			Overall (N = 763)		
	Observed	CFBL	Percent CFBL	Observed	CFBL	Percent CFBL	Observed	CFBL	Percent CFBL
Week 16, Last Observation Carried Forward									
N	493	491	420	252	251	246	745	742	666
Mean (SD)	2.54 (4.579)	-0.77 (3.330)	-5.67 (150.062)	3.36 (4.546)	-3.96 (5.028)	-47.15 (81.350)	2.82 (4.581)	-1.85 (4.259)	-20.99 (130.491)
Median	1.00	-0.20	-33.33	1.80	-2.98	-63.42	1.20	-0.96	-46.13
Minimum, Maximum	0.0, 66.0	-27.1, 17.2	-100.0, 2278.6	0.0, 26.2	-27.1, 14.3	-100.0, 841.2	0.0, 66.0	-27.1, 17.2	-100.0, 2278.6
Week 40, Observed Cases									
N	236	236	197	113	113	110	349	349	307
Mean (SD)	1.75 (2.714)	-0.93 (3.100)	-21.60 (126.790)	2.07 (3.703)	-5.30 (5.594)	-60.22 (102.651)	1.85 (3.067)	-2.35 (4.556)	-35.43 (119.977)
Median	0.68	-0.49	-57.39	0.80	-4.49	-86.06	0.72	-1.50	-67.00
Minimum, Maximum	0.0, 17.6	-17.8, 12.6	-100.0, 1194.3	0.0, 23.0	-29.0, 10.8	-100.0, 860.0	0.0, 23.0	-29.0, 12.6	-100.0, 1194.3
Week 40, Last Observation Carried Forward									
N	493	491	420	252	251	246	745	742	666
Mean (SD)	2.44 (4.645)	-0.88 (3.834)	-0.11 (183.058)	2.99 (4.472)	-4.33 (5.702)	-43.91 (109.158)	2.63 (4.592)	-2.04 (4.833)	-16.29 (161.095)
Median	1.00	-0.30	-46.61	1.00	-3.30	-75.06	1.00	-1.00	-55.78
Minimum, Maximum	0.0, 66.0	-27.1, 17.2	-100.0, 2278.6	0.0, 26.2	-29.0, 14.3	-100.0, 860.0	0.0, 66.0	-29.0, 17.2	-100.0, 2278.6

BSA = body surface area; CFBL = change from baseline; DB = double blinded; ITT = Intent-to-Treat; PGA = Physician Global Assessment; SD = standard deviation.

[0354] Psoriasis Area and Severity Index

[0355] Table 14 presents observed PASI score, change from baseline, and percent change from baseline at Week 16 and Week 40 as performed using OC and LOCF methods. FIG. 12 shows the change in PASI score throughout the duration of the trial. Overall subjects' Baseline mean (SD) PASI score was 4.76 (4.724) with 3.28 (3.531) for subjects who were randomized to tapinarof cream, 1% in the DB, pivotal Phase 3 studies and 7.69 (5.387) for subjects who were randomized to vehicle cream.

[0356] PASI score decreased over time overall and in both DB assigned treatment groups with no loss of effect observed. At Week 16 using the OC method, the mean (SD) PASI score was 2.38 (2.652) for subjects randomized to tapinarof cream, 1% in the DB, pivotal Phase 3 studies and 2.95 (3.020) for subjects randomized to vehicle cream. Overall, the mean (SD) PASI score was 2.57 (2.791). Using the LOCF method resulted in mean (SD)

PASI score of 2.74 (3.324) and 3.47 (3.794) for subjects randomized to tapinarof cream, 1% cream or vehicle cream in the DB, pivotal Phase 3 studies, respectively. The overall mean (SD) PASI was 2.99 (3.504).

[0357] At Week 40 using the OC method, the mean (SD) PASI score was 2.38 (2.672) for subjects randomized to tapinarof cream, 1% in the DB, pivotal Phase 3 studies and 2.31 (3.008) for subjects randomized to vehicle cream. Overall, the mean (SD) PASI score was 2.36 (2.781). Using the LOCF method resulted in mean (SD) PASI score of 2.80 (3.443) and 3.28 (3.937) for subjects randomized to tapinarof cream, 1% cream or vehicle cream in the DB, pivotal Phase 3 studies, respectively. The overall mean (SD) PASI score was 2.97 (3.622).

Table 14: Summary of PASI Observed Values, Change from Baseline, and Percent Change from Baseline at Week 16 and Week 40 (ITT Population, Observed Cases and Last Observation Carried Forward)

	Tapinarof Cream 1% (Pivotal) (N = 508)			Vehicle Cream (Pivotal) (N = 255)			Overall (N = 763)		
	Observed	CFBL	Percent CFBL	Observed	CFBL	Percent CFBL	Observed	CFBL	Percent CFBL
Baseline									
N	505			254			759		
Mean (SD)	3.28 (3.531)			7.69 (5.387)			4.76 (4.724)		
Median	2.30			6.40			3.40		
Minimum, Maximum	0.0, 28.8			0.0, 28.2			0.0, 28.8		
Week 16, Observed Cases									
N	412	411	342	207	207	202	619	618	544
Mean (SD)	2.38 (2.652)	-0.67 (2.888)	-7.79 (106.357)	2.95 (3.020)	-4.59 (4.294)	-55.09 (47.486)	2.57 (2.791)	-1.99 (3.889)	-25.35 (91.988)
Median	1.60	-0.40	-30.00	2.10	-3.80	-64.02	1.80	-1.00	-44.72
Minimum, Maximum	0.0, 18.0	-20.4, 10.8	-100.0, 600.0	0.0, 16.2	-18.2, 9.7	-100.0, 323.3	0.0, 18.0	-20.4, 10.8	-100.0, 600.0
Week 16, Last Observation Carried Forward									
N	491	489	416	250	250	245	741	739	661
Mean (SD)	2.74 (3.324)	-0.54 (2.930)	-3.20 (106.527)	3.47 (3.794)	-4.24 (4.221)	-51.02 (48.996)	2.99 (3.504)	-1.80 (3.841)	-20.93 (92.505)
Median	1.80	-0.20	-25.00	2.40	-3.80	-59.38	1.80	-0.90	-40.91
Minimum, Maximum	0.0, 28.8	-20.4, 14.0	-100.0, 600.0	0.0, 23.5	-18.2, 9.7	-100.0, 323.3	0.0, 28.8	-20.4, 14.0	-100.0, 600.0

	Tapinarof Cream 1% (Pivotal) (N = 508)			Vehicle Cream (Pivotal) (N = 255)			Overall (N = 763)		
	Observed	CFBL	Percent CFBL	Observed	CFBL	Percent CFBL	Observed	CFBL	Percent CFBL
Week 40, Observed Cases									
N	236	236	196	113	113	110	349	349	306
Mean (SD)	2.38 (2.672)	-0.51 (3.189)	8.49 (222.467)	2.31 (3.008)	-5.53 (4.957)	-60.12 (62.520)	2.36 (2.781)	-2.14 (4.506)	-16.18 (184.734)
Median	1.60	-0.30	-35.24	1.40	-4.80	-76.39	1.60	-1.20	-56.70
Minimum, Maximum	0.0, 18.5	-14.7, 14.4	-100.0, 2700.0	0.0, 17.5	-28.2, 6.4	-100.0, 300.0	0.0, 18.5	-28.2, 14.4	-100.0, 600.0
Week 40, Last Observation Carried Forward									
N	492	490	417	251	251	246	743	741	663
Mean (SD)	2.80 (3.443)	-0.48 (3.360)	11.96 (184.055)	3.28 (3.937)	-4.42 (4.814)	-48.42 (68.495)	2.97 (3.622)	-1.81 (4.332)	-10.45 (154.519)
Median	1.80	-0.20	-27.27	2.00	-3.90	-68.66	1.80	-0.90	-44.44
Minimum, Maximum	0.0, 28.8	-20.4, 14.4	-100.0, 2700.0	0.0, 23.5	-28.2, 9.7	-100.0, 481.6	0.0, 28.8	-28.2, 14.4	-100.0, 2700.0

CFBL = change from baseline; DB = double blinded; ITT = Intent-to-Treat; PASI = Psoriasis Area and Severity Index; PGA = Physician Global Assessment; SD = standard deviation.

[0358] Table 15 presents subjects who achieved a reduction of $\geq 75\%$ from Baseline in the PASI (PASI75) at Week 16 and Week 40 as performed using OC and LOCF methods.

[0359] There was continued efficacy in subjects randomized to tapinarof cream, 1% in the DB, pivotal Phase 3 studies and a greater percentage of subjects with reductions of $\geq 75\%$ from Baseline in those randomized to vehicle cream, as expected based on the Baseline differences of the 2 DB assigned treatment groups. At Week 16 using the OC method, 141 subjects (22.8%) achieved a reduction of $\geq 75\%$ from Baseline in their PASI score: 17.0% of subjects randomized to tapinarof cream, 1% in the DB, pivotal Phase 3 studies and 34.3% of subjects randomized to vehicle cream. Using the LOCF method, 158 subjects (21.3%) achieved a reduction of $\geq 75\%$ from Baseline in their PASI score: 15.9% of subjects randomized to tapinarof cream, 1% in the DB, pivotal Phase 3 studies and 32.0% of subjects randomized to vehicle cream.

[0360] At Week 40 using the OC method, 108 subjects (30.9%) achieved a reduction of $\geq 75\%$ from Baseline in their PASI score: 21.2% of subjects randomized to tapinarof cream, 1% in the DB, pivotal Phase 3 studies and 51.3% of subjects randomized to

vehicle cream. Using the LOCF, 188 subjects (25.3%) achieved a reduction of $\geq 75\%$ from Baseline in their PASI score: 16.9% of subjects randomized to tapinarof cream, 1% in the DB, pivotal Phase 3 studies and 41.8% of subjects randomized to vehicle cream.

Table 15: Summary of PASI75 Response Rate at Week 16 and Week 40 (ITT Population, Observed Cases and Last Observation Carried Forward)

	Tapinarof Cream, 1% (Pivotal) (N = 508)	Vehicle Cream (Pivotal) (N = 255)	Overall (N = 763)
Week 16, Observed Cases			
PASI75 Responder [1], n/N (%)	70/412 (17.0)	71/207 (34.3)	141/619 (22.8)
Standard error of percentage responder	1.85	3.30	1.69
PASI75 Non-Responder [1], n/N (%)	342/412 (83.0)	136/207 (65.7)	478/619 (77.2)
Standard error of percentage non-responder	1.85	3.30	1.69
Week 16, Last Observation Carried Forward			
PASI75 Responder [1], n/N (%)	78/491 (15.9)	80/250 (32.0)	158/741 (21.3)
Standard error of percentage responder	1.65	2.95	1.50
PASI75 Non-Responder [1], n/N (%)	413/491 (84.1)	170/250 (68.0)	583/741 (78.7)
Standard error of percentage non-responder	1.65	2.95	1.50
Week 40, Observed Cases			
PASI75 Responder [1], n/N (%)	50/236 (21.2)	58/113 (51.3)	108/349 (30.9)
Standard error of percentage responder	2.66	4.70	2.47
PASI75 Non-Responder [1], n/N (%)	186/236 (78.8)	55/113 (48.7)	241/349 (69.1)
Standard error of percentage non-responder	2.66	4.70	2.47
Week 40, Last Observation Carried Forward			
PASI75 Responder [1], n/N (%)	83/492 (16.9)	105/251 (41.8)	188/743 (25.3)
Standard error of percentage responder	1.69	3.11	1.59
PASI75 Non-Responder [1], n/N (%)	409/492 (83.1)	146/251 (58.2)	555/743 (74.7)
Standard error of percentage non-responder	1.69	3.11	1.59

[1] Response defined as achieving a reduction of 75% or greater from Baseline in the PASI. Missing cases were imputed by last observation carried forward.

DB = double blinded; ITT = Intent-to-Treat; PASI = Psoriasis Area and Severity Index; PASI75 = 75% improvement in PASI score; PGA = Physician Global Assessment.

[0361] Table 16 presents subjects who achieved a reduction of $\geq 90\%$ from Baseline in the PASI (PASI90) at Week 16 and Week 40 as performed using OC and LOCF methods.

[0362] There was continued efficacy in subjects randomized to tapinarof cream, 1% in the DB, pivotal Phase 3 studies and a greater percentage of subjects with reductions of $\geq 90\%$ from Baseline in those randomized to vehicle cream, as expected based on the Baseline differences of the 2 DB assigned treatment groups. At Week 16 using the OC method, 89 subjects (14.4%) achieved a reduction of $\geq 90\%$ from Baseline in their PASI score: 13.6% of subjects randomized to tapinarof cream, 1% in the DB, pivotal Phase 3 studies and 15.9% of subjects randomized to vehicle cream. Using the LOCF method, 102 subjects (13.8%) achieved a reduction of $\geq 90\%$ from Baseline in their PASI score: 13.0% of subjects randomized to tapinarof cream, 1% in the DB, pivotal Phase 3 studies and 15.2% of subjects randomized to vehicle cream.

[0363] At Week 40 using the OC method, 62 subjects (17.8%) achieved a reduction of $\geq 90\%$ from Baseline in their PASI score: 13.1% of subjects randomized to tapinarof cream, 1% in the DB, pivotal Phase 3 studies and 27.4% of subjects randomized to vehicle cream. Using the LOCF method, 107 subjects (14.4%) achieved a reduction of $\geq 90\%$ from Baseline in their PASI score: 11.2% of subjects randomized to tapinarof cream, 1% in the DB, pivotal Phase 3 studies and 20.7% of subjects randomized to vehicle cream.

Table 16: Summary of PASI90 Response Rate at Week 16 and Week 40 (ITT Population, Observed Cases and Last Observation Carried Forward)

	Tapinarof Cream, 1% (Pivotal) (N = 508)	Vehicle Cream (Pivotal) (N = 255)	Overall (N = 763)
Week 16, Observed Cases			
PASI90 Responder [1], n/N (%)	56/412 (13.6)	33/207 (15.9)	89/619 (14.4)
Standard error of percentage responder	1.69	2.54	1.41
PASI90 Non-Responder [1], n/N (%)	356/412 (86.4)	174/207 (84.1)	530/619 (85.6)
Standard error of percentage non-responder	1.69	2.54	1.41
Week 16, Last Observation Carried Forward			
PASI90 Responder [1], n/N (%)	64/491 (13.0)	38/250 (15.2)	102/741 (13.8)

Standard error of percentage responder	1.52	2.27	1.27
PASI90 Non-Responder [1], n/N (%)	427/491 (87.0)	212/250 (84.8)	639/741 (86.2)
Standard error of percentage non-responder	1.52	2.27	1.27
Week 40, Observed Cases			
PASI90 Responder [1], n/N (%)	31/236 (13.1)	31/113 (27.4)	62/349 (17.8)
Standard error of percentage responder	2.20	4.20	2.05
PASI90 Non-Responder [1], n/N (%)	205/236 (86.9)	82/113 (72.6)	287/349 (82.2)
Standard error of percentage non-responder	2.20	4.20	2.05
Week 40, Last Observation Carried Forward			
PASI90 Responder [1], n/N (%)	55/492 (11.2)	52/251 (20.7)	107/743 (14.4)
Standard error of percentage responder	1.42	2.56	1.29
PASI90 Non-Responder [1], n/N (%)	437/492 (88.8)	199/251 (79.3)	636/743 (85.6)
Standard error of percentage non-responder	1.42	2.56	1.29

[1] Response defined as achieving a reduction of 90% or greater from Baseline in the PASI. Missing cases imputed by last observation carried forward.

DB = double blinded; ITT = Intent-to-Treat; PASI = Psoriasis Area and Severity Index; PASI90 = 90% improvement in PASI score; PGA = Physician Global Assessment.

[0364] Health Related Quality of Life Endpoint, Dermatology Life Quality Index

[0365] Table 17 presents the DLQI total score observed values, change from baseline, and percent change from baseline for Week 16 and Week 40. FIG. 13 shows the change in mean DQLI score throughout the duration of the trial. Overall subjects' Baseline mean (SD) DLQI total score was 4.3 (5.11) with 3.3 (4.33) for subjects who were randomized to tapinarof cream 1% in the DB, pivotal Phase 3 studies and 6.2 (5.97) for subjects who were randomized to vehicle cream.

[0366] DLQI scores decreased in both DB assigned treatment groups during this extension study with greater decreases in those subjects randomized to vehicle cream in the DB, pivotal Phase 3 studies, as expected based on the Baseline differences of the 2 DB assigned treatment groups. At Week 16 using the OC method, the mean (SD) DLQI total score was 2.0 (3.23) for subjects randomized to tapinarof cream, 1% in the DB, pivotal Phase 3 studies and 3.0 (5.19) for subjects randomized to vehicle cream. Overall, the mean (SD) DLQI total score was 2.3 (4.02).

[0367] By Week 40 using the OC method, the overall score and the scores from each DB assigned treatment group were ≤ 2.0 . The Week 40 mean (SD) DLQI total score

was 1.6 (2.36) for subjects randomized to tapinarof cream, 1% in the DB, pivotal Phase 3 studies and 2.0 (4.23) for subjects randomized to vehicle cream. Overall, the mean (SD) DLQI total score was 1.7 (3.09).

Table 17: Summary of Health Related Quality of Life Endpoint, DLQI Total Score Observed Values, Change from Baseline, and Percent Change from Baseline at Week 16 and Week 40 (ITT Population, Observed Cases)

	Tapinarof Cream, 1% (Pivotal) (N = 508)			Vehicle Cream (Pivotal) (N = 255)			Overall (N = 763)		
	Observed	CFBL	Percent CFBL	Observed	CFBL	Percent CFBL	Observed	CFBL	Percent CFBL
Baseline									
N	504			253			757		
Mean (SD)	3.3 (4.33)			6.2 (5.97)			4.3 (5.11)		
Median	2.0			4.0			2.0		
Minimum, Maximum	0, 26			0, 30			0, 30		
Week 16									
N	418	416	307	209	208	188	627	624	495
Mean (SD)	2.0 (3.23)	-1.0 (3.83)	-21.3 (115.97)	3.0 (5.19)	-3.1 (5.56)	-45.9 (102.00)	2.3 (4.02)	-1.7 (4.58)	-30.7 (111.41)
Median	1.0	0.0	-50.0	1.0	-3.0	-73.0	1.0	-1.0	-60.0
Minimum, Maximum	0, 26	-24, 21	-100.0, 800.0	0, 30	-27, 23	-100.0, 850	0, 30	-27, 23	-100.0, 850.0
Week 40									
N	235	235	170	113	113	102	348	348	272
Mean (SD)	1.6 (2.36)	-1.1 (3.04)	-25.0 (110.42)	2.0 (4.23)	-3.9 (4.57)	-69.2 (52.62)	1.7 (3.09)	-2.0 (3.83)	-41.6 (95.37)
Median	1.0	0.0	-61.3	0.0	-3.0	-88.9	1.0	-1.0	-72.1
Minimum, Maximum	0, 14	-13, 12	-100.0, 600.0	0, 29	-23, 6	-100.0, 300.0	0, 29	-23, 12	-100.0, 600.0

CFBL – change from baseline; DB – double blinded; DLQI – Dermatology Life Quality Index;
ITT = Intent-to-Treat; PGA = Physician Global Assessment; SD = standard deviation.

[0368] Health Related Quality of Life Endpoint, Patient Satisfaction Questionnaire

[0369] As of the data cutoff date for this interim analysis, 403 Patient Satisfaction Questionnaires had been completed; the results are presented in Table 18.

[0370] The majority of subjects (83.4%) strongly agreed (49.9%) or agreed (33.5%) that they could easily manage their psoriasis with tapinarof cream, 1% and were satisfied (82.4%) with how well tapinarof cream, 1% worked for their psoriasis (strongly

agreed: 52.9%; agreed: 29.5%). Subjects randomized to tapinarof cream, 1% in the DB, pivotal Phase 3 studies and subjects randomized to vehicle cream responded similarly.

[0371] Of the 353 subjects (88.3%) that had used other topical drugs to treat their psoriasis in the past, 51.5% strongly agreed and 29.3% agreed that tapinarof cream, 1% was more effective than those other topical drugs and 79.2% of subjects preferred tapinarof cream, 1% (strongly agreed: 53.0%; agreed: 26.2%) to the other topical drugs they have used to treat their psoriasis in the past.

[0372] Of the 137 subjects (34.2%) that had used systemic drugs to treat their psoriasis in the past, 31.2% strongly agreed and 18.1% agreed that tapinarof cream, 1% was more effective than those systemic drugs and 63.0% of subjects preferred tapinarof cream, 1% (strongly agreed: 37.0%; agreed: 26.1%) to those systemic drugs they have used to treat their psoriasis in the past.

Table 18: Summary of Patient Satisfaction Questionnaire at Week 40 or Early Termination Visit (ITT Population)

Observed Value, n (%)	Tapinarof Cream, 1% (Pivotal) (N = 508)	Vehicle Cream (Pivotal) (N = 255)	Overall (N = 763)
Question 1: I can easily manage my psoriasis with the study drug.			
Number of Subjects with Known Answer, n	264	139	403
Strongly Agree	129 (48.9)	72 (51.8)	201 (49.9)
Agree	93 (35.2)	42 (30.2)	135 (33.5)
Neutral	20 (7.6)	11 (7.9)	31 (7.7)
Disagree	11 (4.2)	11 (7.9)	22 (5.5)
Strongly Disagree	11 (4.2)	3 (2.2)	14 (3.5)
Question 2: The time spent applying the study drug every day was acceptable and did not affect my everyday life.			
Number of Subjects with Known Answer, n	264	139	403
Strongly Agree	147 (55.7)	75 (54.0)	222 (55.1)
Agree	96 (36.4)	52 (37.4)	148 (36.7)
Neutral	12 (4.5)	11 (7.9)	23 (5.7)
Disagree	7 (2.7)	1 (0.7)	8 (2.0)
Strongly Disagree	2 (0.8)	0 (0.0)	2 (0.5)
Question 3: I am satisfied with how well the study drug worked for my psoriasis.			
Number of Subjects with Known Answer, n	264	139	403
Strongly Agree	139 (52.7)	74 (53.2)	213 (52.9)

Observed Value, n (%)	Tapinarof Cream, 1% (Pivotal) (N = 508)	Vehicle Cream (Pivotal) (N = 255)	Overall (N = 763)
Agree	81 (30.7)	38 (27.3)	119 (29.5)
Neutral	20 (7.6)	9 (6.5)	29 (7.2)
Disagree	16 (6.1)	14 (10.1)	30 (7.4)
Strongly Disagree	8 (3.0)	4 (2.9)	12 (3.0)
Question 4: I have confidence in the study drug.			
Number of Subjects with Known Answer, n	264	139	403
Strongly Agree	141 (53.4)	72 (51.8)	213 (52.9)
Agree	78 (29.5)	40 (28.8)	118 (29.3)
Neutral	27 (10.2)	14 (10.1)	41 (10.2)
Disagree	13 (4.9)	10 (7.2)	23 (5.7)
Strongly Disagree	5 (1.9)	3 (2.2)	8 (2.0)
Question 5: The study drug cleared by skin and kept my psoriasis from coming back.			
Number of Subjects with Known Answer, n	264	139	403
Strongly Agree	73 (27.7)	42 (30.2)	115 (28.5)
Agree	90 (34.1)	42 (30.2)	132 (32.8)
Neutral	56 (21.2)	23 (16.5)	79 (19.6)
Disagree	31 (11.7)	22 (15.8)	53 (13.2)
Strongly Disagree	14 (5.3)	10 (7.2)	24 (6.0)
Question 6: If the study drug was available by prescription, I would recommend it to other patients with psoriasis.			
Number of Subjects with Known Answer, n	264	139	403
Strongly Agree	139 (52.7)	72 (51.8)	211 (52.4)
Agree	81 (30.7)	39 (28.1)	120 (29.8)
Neutral	26 (9.8)	16 (11.5)	42 (10.4)
Disagree	10 (3.8)	10 (7.2)	20 (5.0)
Strongly Disagree	8 (3.0)	2 (1.4)	10 (2.5)
Question 7: If the study drug was available by a prescription, I would use it again or continue on it.			
Number of Subjects with Known Answer, n	264	139	403
Strongly Agree	139 (52.7)	75 (54.0)	214 (53.1)
Agree	78 (29.5)	36 (25.9)	114 (28.3)
Neutral	20 (7.6)	10 (7.2)	30 (7.4)
Disagree	18 (6.8)	12 (8.6)	30 (7.4)
Strongly Disagree	9 (3.4)	6 (4.3)	15 (3.7)

Observed Value, n (%)	Tapinarof Cream, 1% (Pivotal) (N = 508)	Vehicle Cream (Pivotal) (N = 255)	Overall (N = 763)
Question 8: The study drug is easy to apply.			
Number of Subjects with Known Answer, n	264	139	403
Strongly Agree	158 (59.8)	80 (57.6)	238 (59.1)
Agree	97 (36.7)	52 (37.4)	149 (37.0)
Neutral	7 (2.7)	4 (2.9)	11 (2.7)
Disagree	0 (0.0)	2 (1.4)	2 (0.5)
Strongly Disagree	2 (0.8)	1 (0.7)	3 (0.7)
Question 9: The study drug is not greasy.			
Number of Subjects with Known Answer, n	264	139	403
Strongly Agree	130 (49.2)	59 (42.4)	189 (46.9)
Agree	105 (39.8)	61 (43.9)	166 (41.2)
Neutral	22 (8.3)	12 (8.6)	34 (8.4)
Disagree	6 (2.3)	7 (5.0)	13 (3.2)
Strongly Disagree	1 (0.4)	0 (0.0)	1 (0.2)
Question 10: The study drug quickly absorbs into my skin.			
Number of Subjects with Known Answer, n	264	139	403
Strongly Agree	122 (46.2)	53 (38.1)	175 (43.4)
Agree	114 (43.2)	70 (50.4)	184 (45.7)
Neutral	19 (7.2)	12 (8.6)	31 (7.7)
Disagree	7 (2.7)	4 (2.9)	11 (2.7)
Strongly Disagree	2 (0.8)	0 (0.0)	2 (0.5)
Question 11: The study drug feels good on my skin.			
Number of Subjects with Known Answer, n	264	139	403
Strongly Agree	117 (44.3)	50 (36.0)	167 (41.4)
Agree	100 (37.9)	54 (38.8)	154 (38.2)
Neutral	39 (14.8)	28 (20.1)	67 (16.6)
Disagree	6 (2.3)	5 (3.6)	11 (2.7)
Strongly Disagree	2 (0.8)	2 (1.4)	4 (1.0)
Question 12: I am satisfied with the look and feel of the study drug.			
Number of Subjects with Known Answer, n	259	135	394
Strongly Agree	124 (47.9)	61 (45.2)	185 (47.0)
Agree	97 (37.5)	54 (40.0)	151 (38.3)
Neutral	34 (13.1)	15 (11.1)	49 (12.4)

Observed Value, n (%)	Tapinarof Cream, 1% (Pivotal) (N = 508)	Vehicle Cream (Pivotal) (N = 255)	Overall (N = 763)
Disagree	3 (1.2)	4 (3.0)	7 (1.8)
Strongly Disagree	1 (0.4)	1 (0.7)	2 (0.5)
Have you used other topical drugs to treat your psoriasis in the past?			
Number of Subjects with Known Answer, n	263	137	400
Yes	232 (88.2)	121 (88.3)	353 (88.3)
No	31 (11.8)	16 (11.7)	47 (11.8)
Question 13: The study drug is more effective than other topical drugs I have used to treat my psoriasis.			
Number of Subjects with Known Answer, n	232	123	355
Strongly Agree	117 (50.4)	66 (53.7)	183 (51.5)
Agree	68 (29.3)	36 (29.3)	104 (29.3)
Neutral	30 (12.9)	14 (11.4)	44 (12.4)
Disagree	11 (4.7)	6 (4.9)	17 (4.8)
Strongly Disagree	6 (2.6)	1 (0.8)	7 (2.0)
Question 14: The study drug is easier to use than other topical drugs I have used to treat my psoriasis.			
Number of Subjects with Known Answer, n	232	123	355
Strongly Agree	72 (31.0)	46 (37.4)	118 (33.2)
Agree	76 (32.8)	38 (30.9)	114 (32.1)
Neutral	77 (33.2)	32 (26.0)	109 (30.7)
Disagree	6 (2.6)	6 (4.9)	12 (3.4)
Strongly Disagree	1 (0.4)	1 (0.8)	2 (0.6)
Question 15: I prefer the study drug to other topical drugs I have used to treat my psoriasis.			
Number of Subjects with Known Answer, n	232	123	355
Strongly Agree	120 (51.7)	68 (55.3)	188 (53.0)
Agree	65 (28.0)	28 (22.8)	93 (26.2)
Neutral	32 (13.8)	16 (13.0)	48 (13.5)
Disagree	10 (4.3)	9 (7.3)	19 (5.4)
Strongly Disagree	5 (2.2)	2 (1.6)	7 (2.0)
Have you used systemic drugs to treat your psoriasis in the past?			
Number of Subjects with Known Answer, n	263	138	401
Yes	90 (34.2)	47 (34.1)	137 (34.2)

Observed Value, n (%)	Tapinarof Cream, 1% (Pivotal) (N = 508)	Vehicle Cream (Pivotal) (N = 255)	Overall (N = 763)
No	173 (65.8)	91 (65.9)	264 (65.8)
Question 16: The study drug is more effective than systemic drugs I have used to treat my psoriasis.			
Number of Subjects with Known Answer, n	90	48	138
Strongly Agree	33 (36.7)	10 (20.8)	43 (31.2)
Agree	16 (17.8)	9 (18.8)	25 (18.1)
Neutral	23 (25.6)	16 (33.3)	39 (28.3)
Disagree	10 (11.1)	9 (18.8)	19 (13.8)
Strongly Disagree	8 (8.9)	4 (8.3)	12 (8.7)
Question 17: The study drug is easier to use than systemic drugs I have used to treat my psoriasis.			
Number of Subjects with Known Answer, n	90	48	138
Strongly Agree	29 (32.2)	15 (31.3)	44 (31.9)
Agree	28 (31.1)	14 (29.2)	42 (30.4)
Neutral	19 (21.1)	9 (18.8)	28 (20.3)
Disagree	10 (11.1)	6 (12.5)	16 (11.6)
Strongly Disagree	4 (4.4)	4 (8.3)	8 (5.8)
Question 18: I prefer the study drug to systemic drugs I have used to treat my psoriasis.			
Number of Subjects with Known Answer, n	90	48	138
Strongly Agree	38 (42.2)	13 (27.1)	51 (37.0)
Agree	23 (25.6)	13 (27.1)	36 (26.1)
Neutral	14 (15.6)	10 (20.8)	24 (17.4)
Disagree	10 (11.1)	8 (16.7)	18 (13.0)
Strongly Disagree	5 (5.6)	4 (8.3)	9 (6.5)

cream. Data from both cohorts combined are presented as overall.

DB = double blinded; ET = early termination; ITT = Intent-to-Treat; PGA = Physician Global Assessment.

[0373] Discussion

[0374] Tapinarof cream, 1% is a nonsteroidal, first in class, therapeutic aryl hydrocarbon receptor modulating agent being developed for the topical treatment of plaque psoriasis in adults. It has the potential to fulfill an unmet medical need as an efficacious topical therapy without restrictions on treatment duration or application site (i.e., use on sensitive areas). This long term extension study confirms the results of the DB, pivotal Phase

3 studies demonstrating that tapinarof cream, 1% has favorable safety, tolerability and efficacy profiles that support long term use for the management of psoriasis.

[0375] This report describes a planned interim analysis of this extension study in adults rolling over from the DB, pivotal Phase 3 studies which evaluated tapinarof cream, 1% or vehicle cream in the treatment of plaque psoriasis for 12 weeks. The safety, tolerability, efficacy, durability, and remittive effect of topical tapinarof cream, 1% applied once daily for up to 40 weeks were evaluated in this open label, Phase 3, multicenter long term extension study. Moreover, this extension study was designed to evaluate extended, intermittent use of tapinarof cream, 1% which is more reflective of ‘real world’ application in clinical practice.

[0376] Study Population and Baseline Characteristics

[0377] Eligibility consisted of those subjects who completed the 12 week treatment period in 1 of the 2 DB, pivotal Phase 3 studies (DMVT 505 3001 or DMVT 505 3002). A total of 763 subjects were enrolled, which included 508 subjects previously randomized to tapinarof cream, 1% and 255 subjects previously randomized to vehicle cream. The population included 235 subjects exposed to tapinarof cream, 1% and followed for 1 year and 450 subjects followed for 6 months which exceeds ICH E1 exposure requirements for safety follow up (ICH, 1994). The full spectrum of PGA scores (clear to severe) was represented at study entry. Subjects previously randomized to vehicle cream in the DB, pivotal Phase 3 studies entered this extension study with a higher disease burden reflective of an untreated population while subjects previously randomized to tapinarof cream, 1% entered with less severe disease reflective of tapinarof cream, 1%’s statistically significant efficacy in the DB, pivotal Phase 3 studies.

[0378] The impact of COVID 19 on this study was minimal. No subjects were discontinued due to a positive COVID 19 diagnosis and discontinuations due to other COVID 19 related reasons occurred in < 1% of subjects.

[0379] Efficacy

[0380] Efficacy measures included standard assessments for PGA, %BSA affected, and PASI. Furthermore, the study design allowed for assessment of durability (no loss of effect while on therapy) and remittive effect (maintenance of effect when off therapy).

[0381] Approximately 40% of the study population achieved complete clearance (PGA = 0) at least once during this extension study; this included 78 subjects that entered the study with a PGA= 0 and an additional 221 subjects that entered with a PGA ≥ 1. The high

rate of disease clearance with a topical therapy demonstrates a significant opportunity for the care of patients suffering from plaque psoriasis.

[0382] Assessment of response over time showed a similar pattern of improvement for PGA, %BSA affected, and PASI. Subjects previously randomized to tapinarof cream, 1% in the DB, pivotal Phase 3 studies demonstrated continued improvement beyond the initial 12 weeks of treatment they received in the DB, pivotal Phase 3 studies before achieving a plateauing of the effect at approximately Week 12 of this extension study (total duration of treatment of 24 weeks). Subjects previously randomized to vehicle cream in the DB, pivotal Phase 3 studies achieved a similar response to those previously randomized to tapinarof cream, 1% in PGA = 0 or 1, mean %BSA affected, and mean PASI score by approximately Weeks 24 to 28. Importantly, these beneficial clinical effects did not decline over time, demonstrating that tachyphylaxis was not observed. The durability of effect while on treatment was consistent across all measures of efficacy.

[0383] The protocol directed the treatment of subjects entering with a PGA ≥ 1 until they achieved a PGA = 0, at which time treatment was suspended. If/when the subject had worsening of disease (PGA ≥ 2), the subject would re initiate treatment until a PGA = 0 was achieved. This pattern of treatment, suspension, and re treatment allowed for characterization of a remittive effect, defined as maintenance of clear/almost clear (PGA = 0 or 1) while off therapy. In those subjects entering with a PGA = 0 (n = 78), the median time to worsening of disease was 115 days with a 95% CI ranging from 85 to 162 days. For subjects either entering with or achieving a PGA = 0 (n = 299), the average treatment free interval was > 3 months (mean 97.9 days). The treatment free period is underestimated since some data were censored, meaning that the remittive period ended due to the subject reaching the end of the extension study, not because the subject had worsening disease.

[0384] The subject reported DLQI and Patient Satisfaction Questionnaire illustrate the impact of tapinarof cream, 1% in this population. Quality of life measures improved for both DB assigned treatment groups. Initially, greater improvements were observed for subjects previously randomized to vehicle cream in the DB, pivotal Phase 3 studies compared with subjects randomized to tapinarof cream, 1%; however, over time the quality of life improved measurements converged for the 2 DB assigned treatment groups. At Week 40, the overall mean DLQI was 1.7 out of scale that ranges from 0 to 30 with lower scores representing improvement in quality of life measures. The Patient Satisfaction

Questionnaire showed a consistently positive perception of tapinarof cream, 1% across all parameters including questions relating to application, ease of use, and disease management.

[0385] Final Data Analysis

[0386] Tapinarof provides for a long-term extension of efficacy measured as complete disease clearance (PGA=0) and response rate. Improvements in efficacy were observed beyond the 12 week pivotal trials. FIG. 4 graphically depicts that 40.9% of patients achieved complete disease clearance at least once during the study, including patients who entered with PGA=0 (n=79) and patients entering with $\text{PGA} \geq 1$ who achieved PGA=0 at least once during the study (n=233), and that 58.2% of patients entering with $\text{PGA} \geq 2$ achieved a PGA score of 0 or 1 at least once during the study. As can be seen in FIG. 5, the median time to $\text{PGA} \geq 2$ off tapinarof was approximately 4 months (115 days) for patients entering with PGA=0 (95% CI: 85 to 168 days) and among patients entering with, or achieving, a PGA=0 (n=312), the mean total duration of remittive effect was approximately 4 months (130 days).

[0387] FIG. 6 and Table 19 presents the durability of response of up to 52 weeks, demonstrating no tachyphylaxis over time while on therapy. Patients previously treated with vehicle in the 12-week pivotal trials achieved similar responses to patients previously treated with tapinarof. Overall, at baseline, 10.4% of participants had PGA=0 and 31.6% had PGA=0 or 1; at Week 40, 16.9% had PGA=0 and 44.3% had PGA=0 or 1.

Table 19: Durability of Response up to 52 weeks

No. of Subjects	Wk. 0	Wk. 4	Wk. 8	Wk. 12	Wk. 16	Wk. 20	Wk. 24	Wk. 28	Wk. 32	Wk. 36	Wk. 40
Overall	240	273	330	334	336	358	346	336	339	340	330
Tapinarof→Tapinarof	18	216	243	233	239	250	236	230	233	225	224
Vehicle→Tapinarof	22	57	87	101	97	108	110	106	106	115	106

[0388] Safety

[0389] All subjects were included in this interim analysis of safety with exposures in this extension study of up to 40 weeks. Tapinarof cream, 1% was generally safe and well tolerated with long term use. The AE profile was consistent with previous studies and no new safety signals emerged over time. There was a low study discontinuation rate (5.8%) even with extended exposure. All SAEs were reported by the Investigator as not related to study drug. This includes one death from myocardial infarction in a subject with a long standing cardiovascular history who received study drug for 15 weeks.

[0390] AEsIs of contact dermatitis, folliculitis, and headache were further assessed with long term dosing. Folliculitis remained the most commonly reported TEAE. Importantly, severity did not worsen nor did the incidence increase with long term dosing, and there was a low rate of study discontinuation (1.2%). Similarly, there was no change in the profile of contact dermatitis with regard to severity and incidence and the study discontinuation rate was 1.4%. Headache was a low frequency event with no study discontinuations and negligible impact on treatment.

[0391] Tolerability was assessed subjectively via subject and objectively via Investigator throughout the 40 weeks of the study. The patient-reported local tolerability scale utilized for self-reported tolerability assessment is shown in Table 20, while the investigator-assessed local tolerability scale utilized is shown in Table 21.

Table 20. Patient-Reported Local Tolerability Scale (Burning/Stinging and Itching)

Score	Severity	Description
0	None	Normal, no discomfort
1	Slight	An awareness, but no discomfort and no intervention required
2	Mild	Noticeable discomfort that causes intermittent awareness
3	Moderate	A noticeable discomfort that causes intermittent awareness and interferes occasionally with normal daily activities
4	Strong/Severe	A definite continuous discomfort that interferes with normal daily activities

Table 21. Investigator-Assessed Local Tolerability Scale (Dryness, Erythema and Peeling)

Score	Severity	Description
0	No irritation	No evidence of local irritation/intolerance
1	Mild	Minimal erythema and/or edema, slight glazed appearance
2	Moderate	Definite erythema and/or edema with peeling and/or cracking but does not require treatment modification
3	Severe	Erythema, edema glazing with fissures, few vesicles or papules
4	Very Severe	Strong reaction spreading beyond the treated area, bullous reaction, erosions

[0392] FIG. 18 and FIG. 19 show the tolerability scores reported by the patient and investigator, respectively. These assessments demonstrated a high degree of correlation

and both indicated a well-tolerated cream regardless of anatomic region applied, including sensitive areas of the body. There were no clinically relevant trends in laboratory values or vital signs throughout this extension study.

[0393] Together, these interim data confirm the favorable safety profile of tapinarof cream, 1% with long term use in adults with plaque psoriasis.

[0394] Final analysis provided in Table 22 demonstrates that tapinarof 1% once daily cream was well-tolerated long-term. AEs were consistent with the pivotal trials, with no new safety signals observed with long-term use. TEAEs were mostly mild to moderate, at application sites, and associated with a low discontinuation rate (5.4%). Incidence and severity of folliculitis and contact dermatitis were mild to moderate and associated with low discontinuation rates (1.2% and 1.4%, respectively).

Table 22

Patients, n (%)	Overall (n=763)	Tapinarof→Tapinarof (n=508)	Vehicle→Tapinarof (n=255)
Study discontinuation due to TEAEs	41 (5.4)	26 (5.1)	15 (5.9)
Treatment-emergent AESI†			
Folliculitis	183 (24.0)	124 (24.4)	59 (23.1)
Dermatitis contact	45 (5.9)	24 (4.7)	21 (8.2)
Headache	15 (2.0)	10 (2.0)	5 (2.0)
Study discontinuation due to AESI			
Folliculitis	9 (1.2)	6 (1.2)	3 (1.2)
Dermatitis contact	11 (1.4)	7 (1.4)	4 (1.6)
Headache	0	0	0

†Investigator-specified, may represent multiple MedDRA-preferred terms. ITT population. All AEs reported in the study are considered as TEAE. A patient is counted once only for each MedDRA-preferred term. AE, adverse event; AESI, adverse event of special interest; ITT, intent-to-treat; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

[0395] Overall Conclusions

[0396] The interim analysis of this long term extension study demonstrated tapinarof cream, 1% to be generally safe and well tolerated over 40 weeks of once daily application when meeting PGA criteria for treatment. Safety remains consistent over time with a similar AE profile as observed in the DB, pivotal Phase 3 studies and no emergence of new safety signals with long-term use. Tapinarof cream, 1% was well tolerated in all skin locations with extended exposure, including sensitive areas.

[0397] Complete clearance of disease (PGA = 0) was achieved by 39.2% of subjects (299 of 763 subjects) indicating efficacy continues beyond the 12 week treatment period from the DB, pivotal Phase 3 studies. Efficacy measures did not decline with continued use over time (i.e., no tachyphylaxis). Similar improvements from Baseline were observed in both DB assigned treatment groups with similar effects on PGA, %BSA, and PASI between groups by Week 40.

[0398] A treatment-free interval (remittive effect) was observed in subjects that stopped treatment after achieving a PGA = 0. In subjects entering the study with a PGA = 0 (n = 78), the median time to PGA $\geq$ 2 was approximately 4 months (115 days). Across subjects either entering with or achieving a PGA = 0 (n = 299), the average treatment free interval was approximately 3 months (mean 97.9 days).

[0399] Quality of life measures by DLQI demonstrated improvements from Baseline in both DB assigned treatment groups with similar scores by Week 40.

[0400] As mentioned, tapinarof is a novel therapeutic aryl hydrocarbon receptor modulating agent (TAMA) in clinical development for the topical treatment of psoriasis and atopic dermatitis. The efficacy of tapinarof in these inflammatory skin diseases is attributed to tapinarof binding to and activating the ligand-dependent transcription factor aryl hydrocarbon receptor (AhR), resulting in the downregulation of proinflammatory cytokines, normalization of the skin barrier through modulation of skin barrier protein expression, and regulation of gene expression in immune cells. AhR modulates T cell responses both through intrinsic control of T cell subset differentiation and via controlling the function of antigen presenting cells. In addition, AhR signaling promotes the conversion of Th17 cells to type 1 regulatory T cells. Aberrant immune responses underpin the pathogenesis of both PsO and AD, and the wide expression of AhR in immune cells makes it an attractive target given the essential role of AhR in regulating inflammatory responses and skin homeostasis. Tapinarof cream 1% once-daily demonstrated statistically significant efficacy vs vehicle at 12 weeks and was well-tolerated in adults with mild to severe plaque psoriasis in two identical Phase 3

trials, PSOARING 1 and 2. A potential remittive effect was observed in a 12-week phase 2b trial in which efficacy with tapinarof cream 1% was maintained for 4 weeks after treatment cessation. This remittive effect was confirmed in a long-term extension of up to 40 weeks' open-label treatment according to Physician Global Assessment (PGA) score following completion of the 12-week double-blind period in PSOARING 1/2; tapinarof cream 1% demonstrated a high rate of complete disease clearance and a remittive effect of ~4 months off-therapy, with no tachyphylaxis observed over 52 weeks. These clinical data support the role of AhR in skin immune homeostasis. Given the multitude of AhR-dependent immunoregulatory mechanisms, AhR is an attractive target for novel immunotherapies with the potential to extend therapeutic efficacy following treatment discontinuation; this may provide a unique clinical benefit to patients.

[0401] In these two identical, double-blind 12-week pivotal trials (PSOARING 1 and 2), tapinarof cream 1% QD demonstrated significant efficacy versus vehicle and was well tolerated in adults with mild to severe plaque psoriasis. Tapinarof 1% QD showed maintenance of efficacy after treatment discontinuation in a 12-week phase 2b study, warranting investigation of potential remittive effect. Here we present the full results from PSOARING 3, the long-term, open-label, multicenter extension trial assessing the safety, efficacy, tolerability, durability of response, and duration of remittive effect of tapinarof cream 1% QD in adults with mild to moderate plaque psoriasis.

[0402] Materials & Methods: Eligible patients completing PSOARING 1 or 2 could enroll in PSOARING 3 for 40 weeks of open-label treatment followed by 4 weeks of follow-up, thus receiving up to 52 weeks of treatment. Patients entering with Physician Global Assessment (PGA) score ≥ 1 received tapinarof 1% QD until complete disease clearance (PGA=0). Patients entering with, or achieving, PGA=0 discontinued treatment and were monitored for the duration of remittive effect: off-therapy maintenance of PGA=0/1 (clear/almost clear). Patients with disease worsening (PGA ≥ 2) were re-treated with tapinarof until PGA=0. Patients were followed for durability of response on-therapy (no tachyphylaxis). Safety assessments included treatment-emergent adverse events (TEAEs) and patient- and investigator-rated local tolerability. Efficacy endpoints included median time from PGA=0 to first worsening, and proportion of patients with PGA=0/1 after treatment.

[0403] Results: 763 patients were enrolled in PSOARING 3, representing 91.6% of eligible patients from the pivotal trials. TEAEs were consistent with the interim analysis and pivotal trials, with no new safety signals observed with long-term use in PSOARING 3.

TEAEs were mostly at application sites, mild to moderate in severity, and associated with a low rate of discontinuation (5.8%). Most common TEAEs were folliculitis (22.7%), contact dermatitis (5.5%), and upper respiratory tract infection (4.7%). Incidence and severity of folliculitis and contact dermatitis remained stable with long-term use and were associated with low discontinuation rates (1.2% and 1.4%, respectively). Efficacy measures continued to improve beyond the 12-week pivotal trials: 58.2% of patients entering with $\text{PGA} \geq 2$ achieved $\text{PGA}=0/1$ at least once during PSOARING 3. Complete disease clearance ($\text{PGA}=0$) was achieved by 40.9% of patients ($n=312$). For patients entering with $\text{PGA}=0$ ($n=79$), the median duration of remittive effect was 4 months (115 days). Among patients entering with, or achieving, a $\text{PGA}=0$ ($n=312$), the mean total duration of remittive effect was approximately 4 months (130 days). Durability of response was demonstrated for up to 52 weeks of treatment, indicating no tachyphylaxis based on the proportion of patients achieving a PGA score of 0 or 1, and maintenance of improvements in % body surface area affected and the Psoriasis Area and Severity Index over time.

[0404] Conclusions: Tapinarof cream 1% QD was well tolerated during long-term use, with a safety profile consistent with the previously reported interim analysis and pivotal trials. The confirmed high rate of complete disease clearance, ~4-month remittive effect off-therapy, and no tachyphylaxis are key attributes establishing tapinarof as an effective and novel non-steroidal topical psoriasis therapy.

[0405] Example 2- Decline in Tapinarof Plasma Concentrations during a Course of Treatment

[0406] Most drugs follow standard pharmacokinetics where repeated dosing leads to accumulation and eventual achievement of “steady-state.” This term, “steady-state,” implies dosing has continued long enough for the amount of drug administered to equal the amount of drug excreted as shown in FIG. 1.

[0407] Unlike most drugs, plasma concentrations of tapinarof have been observed to decrease over the duration of treatment across all clinical studies. This unique PK profile is characterized by the highest plasma concentrations being observed on the first day or week of the treatment period followed by a subsequent decline to undetectable or near undetectable levels in the plasma after multiple weeks of dosing. Accumulation of drug after multiple dosing has not been observed in any clinical study with tapinarof.

[0408] The term steady-state is not applicable to tapinarof because drug concentrations at “steady state” represent a lower level of exposure than drug concentrations

seen in the first week of dosing. In the maximal use study with serial PK sampling, a 10-fold decline in concentrations of tapinarof was observed between Days 1 and 29; concentrations of tapinarof sulfate (a metabolite of tapinarof) were not quantifiable. (FIG. 2). This decline is further supported by serial PK data collected from previous clinical studies over 28 days of dosing and over 21 days of dosing. Of note, the reduction in exposure over time appears to occur regardless of formulation, since early studies with a different formulation of tapinarof demonstrated the same effect.

[0409] The reason for the decrease in plasma concentrations over time is unknown. Without wishing to be bound by theory, as the skin heals, there may be less penetration of the drug through the stratum corneum and into the systemic circulation since the barrier is restored. Another possibility is induction of CYP1A1/2 enzymes in the skin by tapinarof, which could lead to metabolism of tapinarof in the skin and subsequently decreased levels of tapinarof over the course of treatment; although this mechanism is generally not supported by animal data. Preclinical studies in rats and minipigs show that while CYP1A1/2 are induced in skin or liver, no changes in systemic exposures are observed with repeat dosing compared to single doses. Preclinical studies show that CYP1A1/2 do not play a significant role in metabolic clearance. Furthermore, in vitro studies in human skin microsomes show no metabolic turnover.

[0410] The formulation may also play a role. In vitro skin penetration studies show that with improvements in formulation, the amount of drug in dermis increases over time while skin flux decreases. Formulation F with the addition of medium chain triglycerides demonstrated in vitro an increased accumulation into dermis with a decreased amount into the receiving fluid compared to earlier formulations. It should be noted that subjects in clinical studies were instructed to apply study drug to all affected areas including newly appearing lesions and lesions/areas that improved during the study. Therefore, the decreasing concentrations would not be explained by subjects discontinuing study drug once their skin improved. Regardless of the exact mechanism, the plasma exposure of tapinarof has not been shown to be correlated with commonly observed AEs. This PK profile of decreasing concentrations with continued dosing is both uncommon and unexpected. This phenomenon is not generally observed with other drugs, regardless of dosing route. See Duobrii package insert, Vectical Ointment package insert, Bryhali Lotion package insert (all topical treatments for psoriasis). In each of the foregoing, there is accumulation over time

with steady-state being reached later in the course of treatment, as would be expected based on standard principles of pharmacokinetics and drug elimination.

[0411] Example 3: Patient Satisfaction with Tapinarof Cream 1% Once Daily for Plaque Psoriasis in a Long-Term Extension Trial

[0412] Patient dissatisfaction with current therapies is an important barrier to optimal care of psoriasis (52% of psoriasis patients have reported dissatisfaction with their treatment) and there is a need for efficacious, tolerable, easy to use, topical therapies that can be used long-term, including on sensitive skin areas. Tapinarof 1% is a cosmetically elegant once daily (QD) topical cream that does not contain added fragrance and is free of petrolatum, parabens, and gluten. The vehicle is specifically designed to reduce skin irritation and optimize the delivery of tapinarof to the target site. Tapinarof cream 1% QD demonstrated significant efficacy and was well tolerated, as demonstrated by favorable patient-reported local tolerability and investigator-assessed irritation scores, including on sensitive skin areas, in 1,025 adults with mild-to-severe plaque psoriasis in two 12-week pivotal phase 3 trials, PSOARING 1 (NCT03956355) and PSOARING 2 (NCT03983980). Improvement in psoriasis in a patient achieving the regulatory primary endpoint prior to enrolling in PSOARING 3 is shown in FIG. 8. PSOARING 3 (NCT04053387) is a 40-week long-term open-label extension trial to assess the efficacy, durability of response on therapy, duration of remittive effect off therapy, safety, and tolerability of tapinarof.

[0413] Objective: Given that patient dissatisfaction with current therapies has a significant impact on disease management, we assessed patient satisfaction using a Patient Satisfaction Questionnaire; here we present the results from PSOARING 3, a long-term open-label extension trial of tapinarof cream 1% QD.

[0414] Patients completing PSOARING 1 and PSOARING 2 were eligible to enroll in PSOARING 3 for up to 40 weeks of open-label treatment with tapinarof cream 1% QD, followed by 4 weeks of follow-up. The Patient Satisfaction Questionnaire was designed to assess patients' satisfaction with the efficacy, formulation elegance, application ease, impact on daily life, and preference for tapinarof versus prior psoriasis therapies. The questionnaire included a series of 18 questions with responses on a scale of strongly agree, agree, neutral, disagree, or strongly disagree. Patient Satisfaction Questionnaire responses were assessed at Week 40 (or Early Termination Visit) and summarized overall.

[0415] Tapinarof cream 1% QD demonstrated continued and substantial improvement in efficacy with long-term use, beyond the improvements already observed in

the 12-week pivotal trials, PSOARING 1 and 2. FIG. 9 and FIG. 10 show improvement in plaque psoriasis in patients who achieved the regulatory primary endpoint after enrollment in PSOARING 3. Both patients achieved the desired remittive effect, being off treatment for 24 weeks prior to commencing with treatment again. Overall, 40.9% of patients (312/763) achieved complete disease clearance at least once during the study; this included 233 patients who entered the study with a PGA of ≥ 1 and 79 patients who entered with a PGA of 0. The median duration of remittive effect while off therapy for patients who entered the study with a PGA of 0 was 115 days, and the mean total duration of remittive effect for patients who entered with, or achieved, a PGA of 0 was 130 days. Durability of response of up to 52 weeks was demonstrated with intermittent use of tapinarof cream 1% QD, indicating no observation of tachyphylaxis (defined as loss of response) while on therapy. Tapinarof cream 1% QD was well tolerated with long-term use and had a safety profile consistent with previous studies.

[0416] Results of Patient Satisfaction Questionnaire: 91.6% of eligible patients (n=763) completing PSOARING 1 and 2 elected to enroll in PSOARING 3. Patient Satisfaction Questionnaires were completed by 78.5% of patients (599/763) in PSOARING 3. Patients consistently reported high satisfaction rates across all parameters, including patients' satisfaction with the efficacy, formulation elegance, application ease, impact on daily life, and preference for tapinarof versus prior psoriasis therapies.

[0417] Most patients either strongly agreed or agreed with all questions on confidence and satisfaction with the efficacy of tapinarof (FIG. 14). 85.8% felt they could easily manage their psoriasis with tapinarof, and 83.6% were satisfied with how well tapinarof worked. 62.9% either strongly agreed or agreed that tapinarof cleared their skin and kept psoriasis from coming back, beyond the already observed 40.9% of patients who achieved complete disease clearance and a ~4-month remittive effect. 84.1% had confidence in tapinarof, and 84.0% would recommend tapinarof to other patients with psoriasis. 82.5% of patients would use tapinarof again or continue on tapinarof if it was available.

[0418] Patients were consistently very satisfied with the tapinarof formulation and elegance (FIG. 15). 93.2% were satisfied with the time spent applying tapinarof cream, and 96.3% considered it easy to apply. In addition, most patients either strongly agreed or agreed that tapinarof was not greasy (89.0%), quickly absorbed (89.5%), and felt good on their skin (79.9%). 87.7% were very satisfied with the look and feel of tapinarof.

[0419] For patients who reported having used other topical drugs to treat psoriasis in the past, 81.7% considered tapinarof to be more effective than prior therapies, and 65.3%

considered tapinarof easier to use (FIG. 16). 81.1% of patients preferred tapinarof to other topical drugs used to treat their psoriasis in the past. For patients who reported having used systemic drugs to treat psoriasis in the past, 55.3% considered tapinarof to be more effective than prior therapies, and 63.8% considered tapinarof to be easier to use (FIG. 17). Most patients (67.8%) also preferred tapinarof to systemic drugs used to treat their psoriasis in the past.

[0420] Conclusion: Patient satisfaction data from PSOARING 3 demonstrate a consistent and highly positive perception of tapinarof cream 1% QD across all patient relevant parameters, including satisfaction with the efficacy, formulation elegance, application ease, impact on daily life, and preference for tapinarof versus prior psoriasis therapies.

CLAIMS

What is claimed:

1. A method for treating plaque psoriasis in a subject in need thereof, comprising
 - a. applying a thin layer of about 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for an initial period of time of at least 12 weeks, until the subject has a PGA score of 0, and a PASI score < the baseline PASI score and a DLQI score < the baseline DLQI score;
 - b. after the initial period of time, stop treating the subject with tapinarof for a remittive period of time of about 1 to about 7 months, wherein the remittive period of time is the time wherein the subject maintains a PGA score < 2; and
 - c. if, after the remittive period of time, the subject has a PGA score of ≥ 2 and the PASI score and DLQI score is $\geq$ the PASI score and DLQI score in step a. further applying a thin layer of 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for a further period of time, until the subject has a PGA score of 0;

wherein

the 1.0% tapinarof topical cream composition does not prolong the QTc interval in the subject while applying the 1.0% tapinarof topical cream,

the plasma concentration of tapinarof in the subject is below 50 pg/mL while applying the 1.0% tapinarof topical cream, and

the subject selects a satisfaction rating of “agree” or “strongly agree” to one or more satisfaction questions selected from the group consisting of: 1) I can easily manage my psoriasis with the study drug; 2) The time spent applying the study drug every day was acceptable and did not affect my everyday life; 3) I am satisfied with how well the study drug worked for my psoriasis; 4) I have confidence in the study drug; 5) The study drug cleared my skin and kept my psoriasis from coming back; 6) If the study drug was available by prescription, I would recommend it to other patients with psoriasis; 7) If the study drug was available by a prescription, I would use it again or continue on it; 8) The study drug is easy to

apply; 9) The study drug is not greasy; 10) The study drug quickly absorbs into my skin; 11) The study drug feels good on my skin; 12) I am satisfied with the look and feel of the study drug; 13) The study drug is more effective than other topical drugs I have used to treat my psoriasis; 14) The study drug is easier to use than other topical drugs I have used to treat my psoriasis; 15) I prefer the study drug to other topical drugs I have used to treat my psoriasis; 16) The study drug is more effective than systemic drugs I have used to treat my psoriasis; 17) The study drug is easier to use than systemic drugs I have used to treat my psoriasis; and 18) I prefer the study drug to systemic drugs I have used to treat my psoriasis.

2. A method for treating plaque psoriasis in a subject in need thereof, wherein the subject has achieved a PGA score of 0, a PASI score $<$ their baseline PASI score, and a DLQI score $<$ the baseline DLQI score, after applying a thin layer of about 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for an initial period of time of about 12 weeks to 52 weeks, comprising

a. stopping treatment of the subject with tapinarof for a remittive period of time of about 1 to about 7 months, wherein the remittive period of time is the time wherein the subject has a PGA score < 2 , and

b. if, after the remittive period of time, the subject has a PGA score of ≥ 2 and the PASI score and DLQI score is $\geq$ the PASI score and DLQI score in step a.; further applying a thin layer of 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for a further period of time until the subject has a PGA score of 0;

wherein

the 1.0% tapinarof topical cream composition does not prolong the QTc interval in the subject while applying the 1.0% tapinarof topical cream,

the plasma concentration of tapinarof in the subject is below 50 pg/mL while applying the 1.0% tapinarof topical cream, and

the subject selects a satisfaction rating of “agree” or “strongly agree” to one or more satisfaction questions selected from the group consisting of:

1) I can easily manage my psoriasis with the study drug; 2) The time spent applying the study drug every day was acceptable and did not affect my everyday life; 3) I am satisfied with how

well the study drug worked for my psoriasis; 4) I have confidence in the study drug; 5) The study drug cleared my skin and kept my psoriasis from coming back; 6) If the study drug was available by prescription, I would recommend it to other patients with psoriasis; 7) If the study drug was available by a prescription, I would use it again or continue on it; 8) The study drug is easy to apply; 9) The study drug is not greasy; 10) The study drug quickly absorbs into my skin; 11) The study drug feels good on my skin; 12) I am satisfied with the look and feel of the study drug; 13) The study drug is more effective than other topical drugs I have used to treat my psoriasis; 14) The study drug is easier to use than other topical drugs I have used to treat my psoriasis; 15) I prefer the study drug to other topical drugs I have used to treat my psoriasis; 16) The study drug is more effective than systemic drugs I have used to treat my psoriasis; 17) The study drug is easier to use than systemic drugs I have used to treat my psoriasis; and 18) I prefer the study drug to systemic drugs I have used to treat my psoriasis.

3. A method for treating plaque psoriasis in a subject in need thereof, wherein the subject has a PGA score of at least 1 point lower than baseline but has not achieved a PGA score of 0 after applying a thin layer of about 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for a period of time of about 12 weeks to about 52 weeks comprising continuing to applying a thin layer of about 1.0% tapinarof topical cream composition to the affected areas of the subject once a day for an indefinite period of time, wherein the PGA score does not increase when applying a thin layer of about 1.0% tapinarof topical cream composition to the affected areas of the subject once a day;
wherein

the 1.0% tapinarof topical cream composition does not prolong the QTc interval in the subject while applying the 1.0% tapinarof topical cream,

the plasma concentration of tapinarof in the subject is below 50 pg/mL while applying the 1.0% tapinarof topical cream, and

the subject selects a satisfaction rating of “agree” or “strongly agree” to one or more satisfaction questions selected from the group consisting of: 1) I can easily manage my psoriasis with the study drug; 2) The time spent applying the study drug every day was acceptable and did not affect my everyday life; 3) I am satisfied with how well the study drug

worked for my psoriasis; 4) I have confidence in the study drug; 5) The study drug cleared my skin and kept my psoriasis from coming back; 6) If the study drug was available by prescription, I would recommend it to other patients with psoriasis; 7) If the study drug was available by a prescription, I would use it again or continue on it; 8) The study drug is easy to apply; 9) The study drug is not greasy; 10) The study drug quickly absorbs into my skin; 11) The study drug feels good on my skin; 12) I am satisfied with the look and feel of the study drug; 13) The study drug is more effective than other topical drugs I have used to treat my psoriasis; 14) The study drug is easier to use than other topical drugs I have used to treat my psoriasis; 15) I prefer the study drug to other topical drugs I have used to treat my psoriasis; 16) The study drug is more effective than systemic drugs I have used to treat my psoriasis; 17) The study drug is easier to use than systemic drugs I have used to treat my psoriasis; and 18) I prefer the study drug to systemic drugs I have used to treat my psoriasis.

4. The method of claim [0003], wherein the plaque psoriasis is moderate or severe plaque psoriasis.

5. The method of claim [0003] wherein the initial period of time is about 12 weeks to about 52 weeks.

6. The method of claim [0003] wherein the remittive period is greater than 3 months and up to about 7 months.

7. The method of claim [0003] wherein the remittive period is about 4 months.

8. The method of claim [0003] wherein the further period of time is less than the initial period of time.

9. The method of claim [0003] wherein the subject selects a satisfaction rating of “agree” or “strongly agree” to three or more of the satisfaction questions.

10. The method of claim [0003] wherein the subject selects a satisfaction rating of “agree” or “strongly agree” to five or more of the satisfaction questions.

11. The method of claim [0003] wherein the subject selects a satisfaction rating of “agree” or “strongly agree” to ten or more of the satisfaction questions.

12. The method of claim 2, wherein the plaque psoriasis is moderate or severe plaque psoriasis.

13. The method of claim 2 wherein the remittive period is greater than 3 months and up to about 7 months.
14. The method of claim 2 wherein the remittive period is about 4 months.
15. The method of claim 2 wherein the further period of time is less than the initial period of time.
16. The method of claim 2 wherein the subject selects a satisfaction rating of “agree” or “strongly agree” to three or more of the satisfaction questions.
17. The method of claim 2 wherein the subject selects a satisfaction rating of “agree” or “strongly agree” to five or more of the satisfaction questions.
18. The method of claim 3, wherein the plaque psoriasis is moderate or severe plaque psoriasis.
19. The method of claim 3 wherein the subject selects a satisfaction rating of “agree” or “strongly agree” to three or more of the satisfaction questions.
20. The method of claim 3 wherein the subject selects a satisfaction rating of “agree” or “strongly agree” to five or more of the satisfaction questions.

1/20

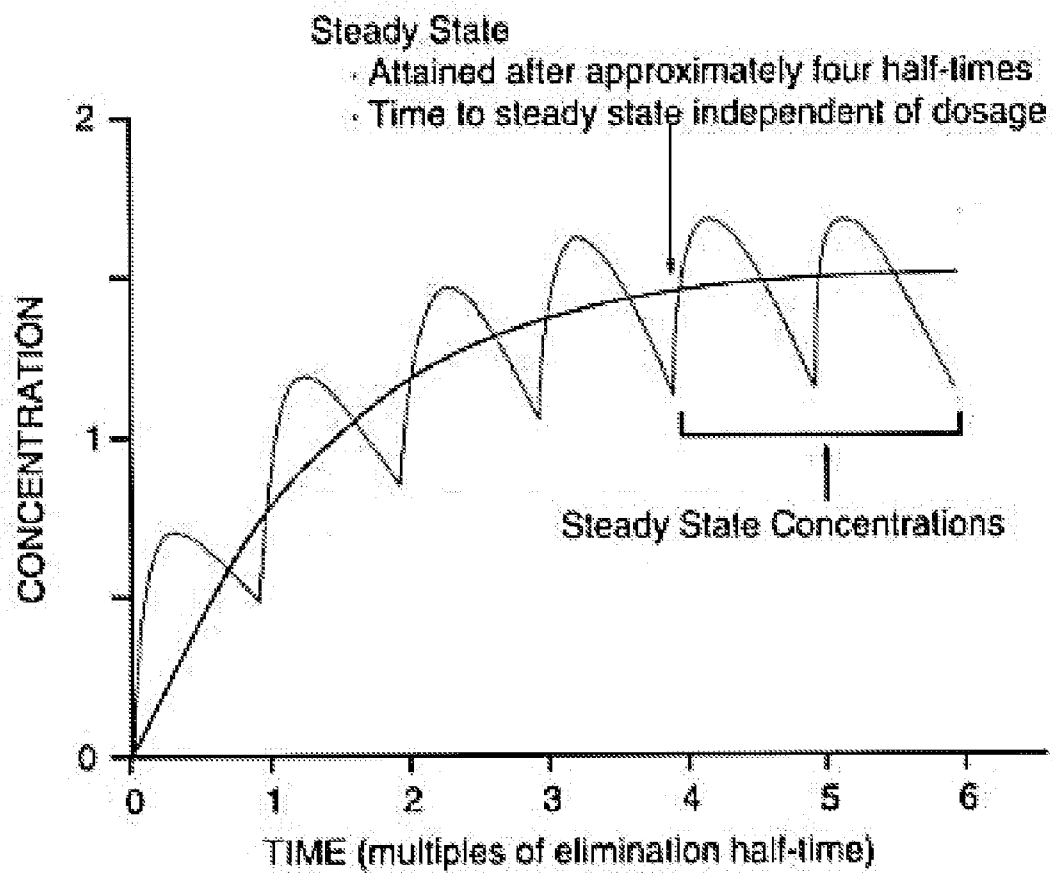


FIG. 1

2/20

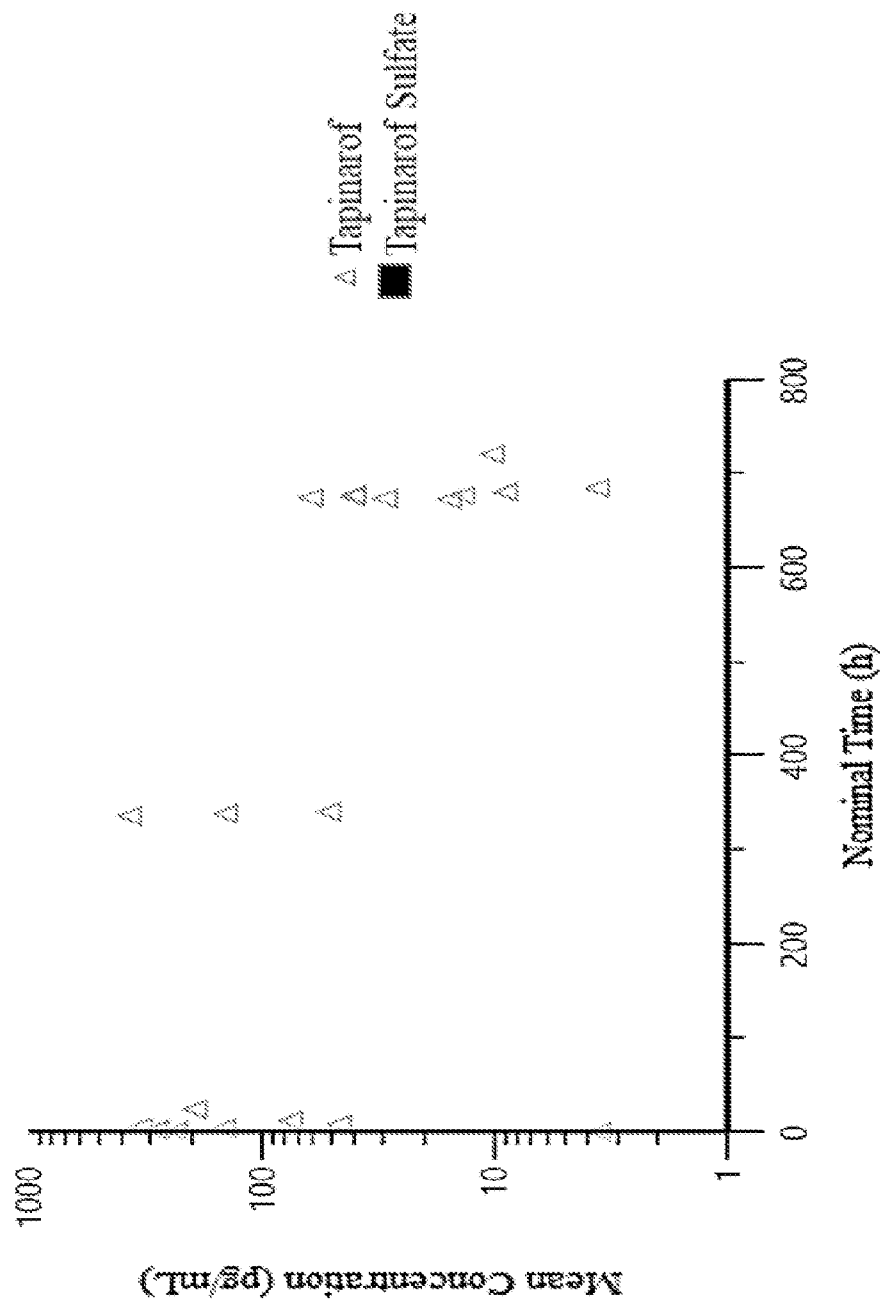


FIG. 2

3/20

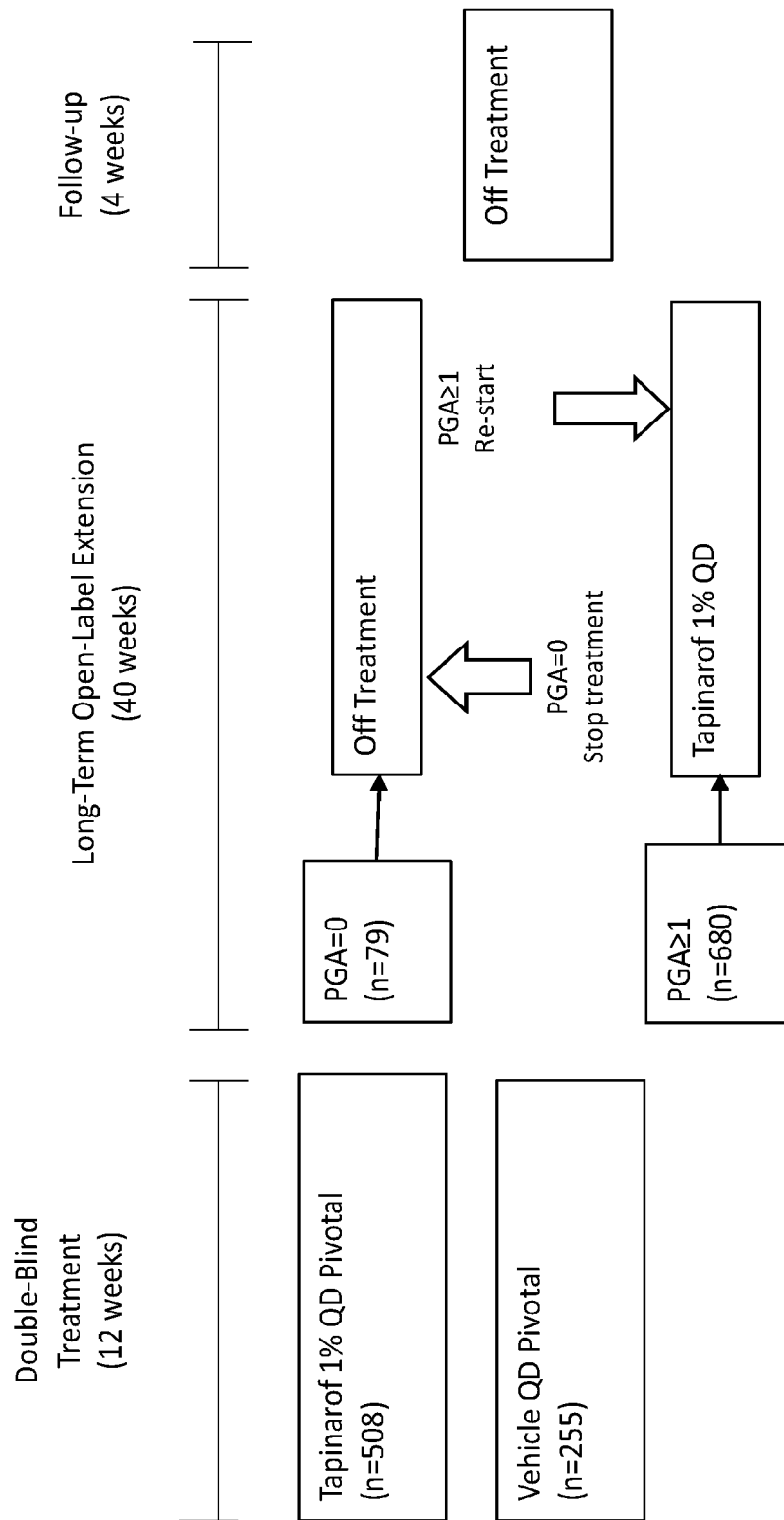


FIG. 3

4/20

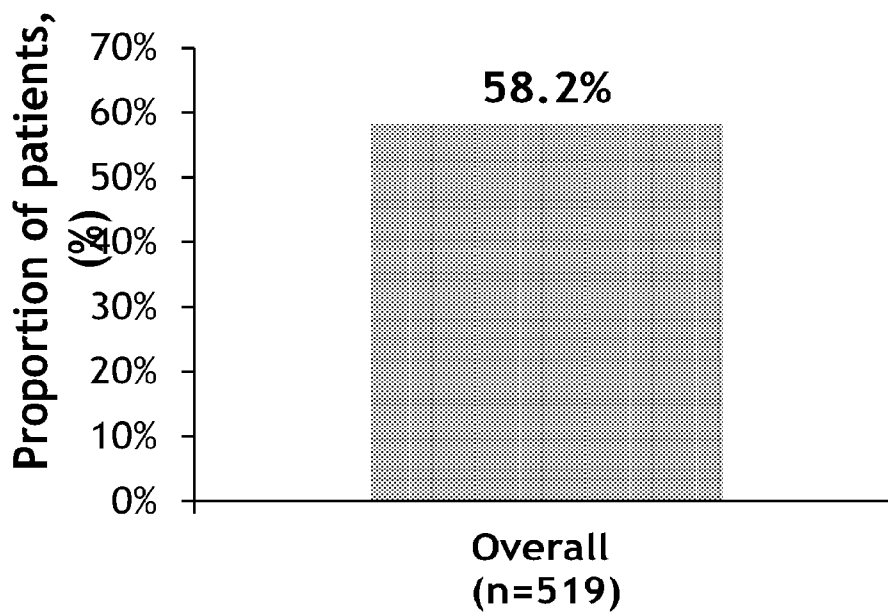
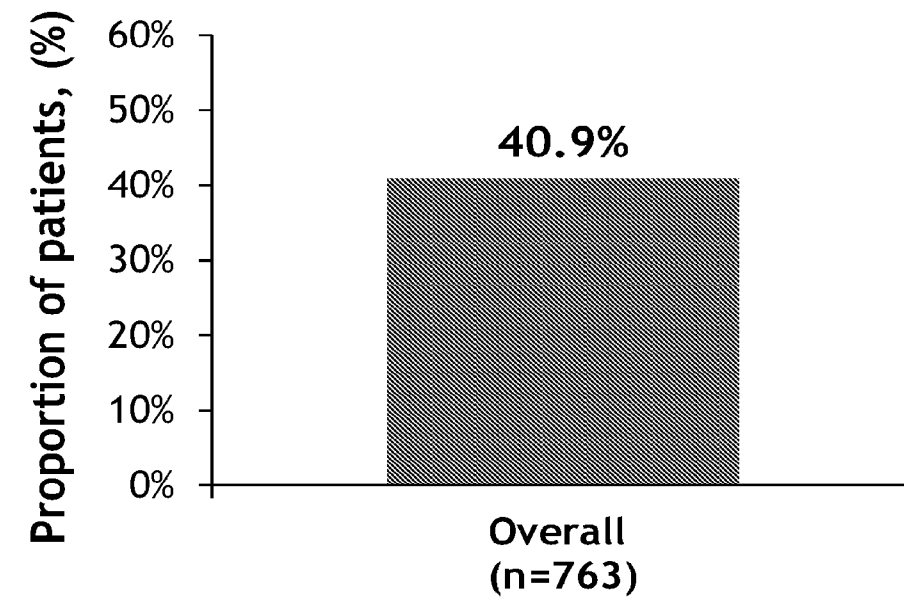


FIG. 4

5/20

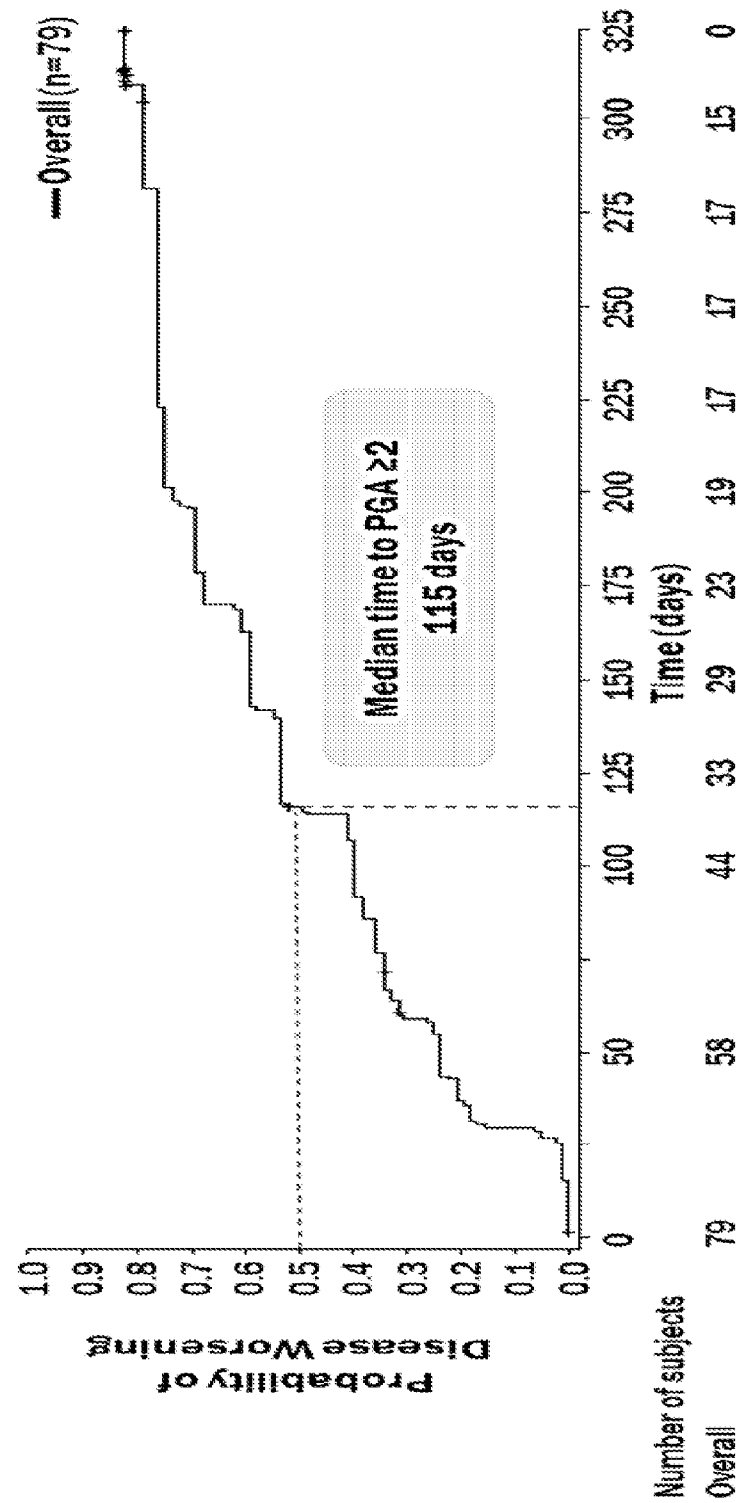


FIG. 5

6/20

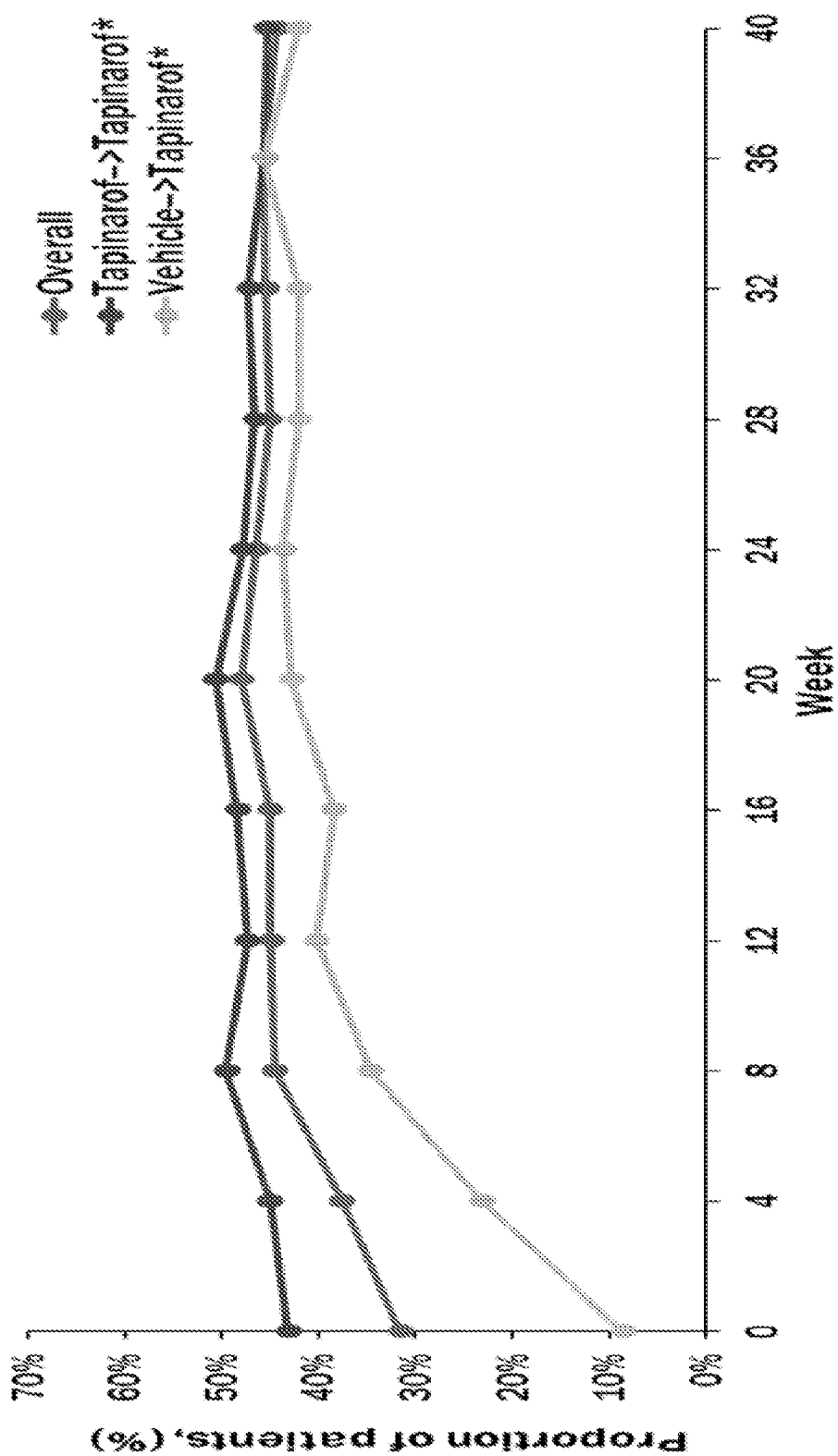


FIG. 6

7/20

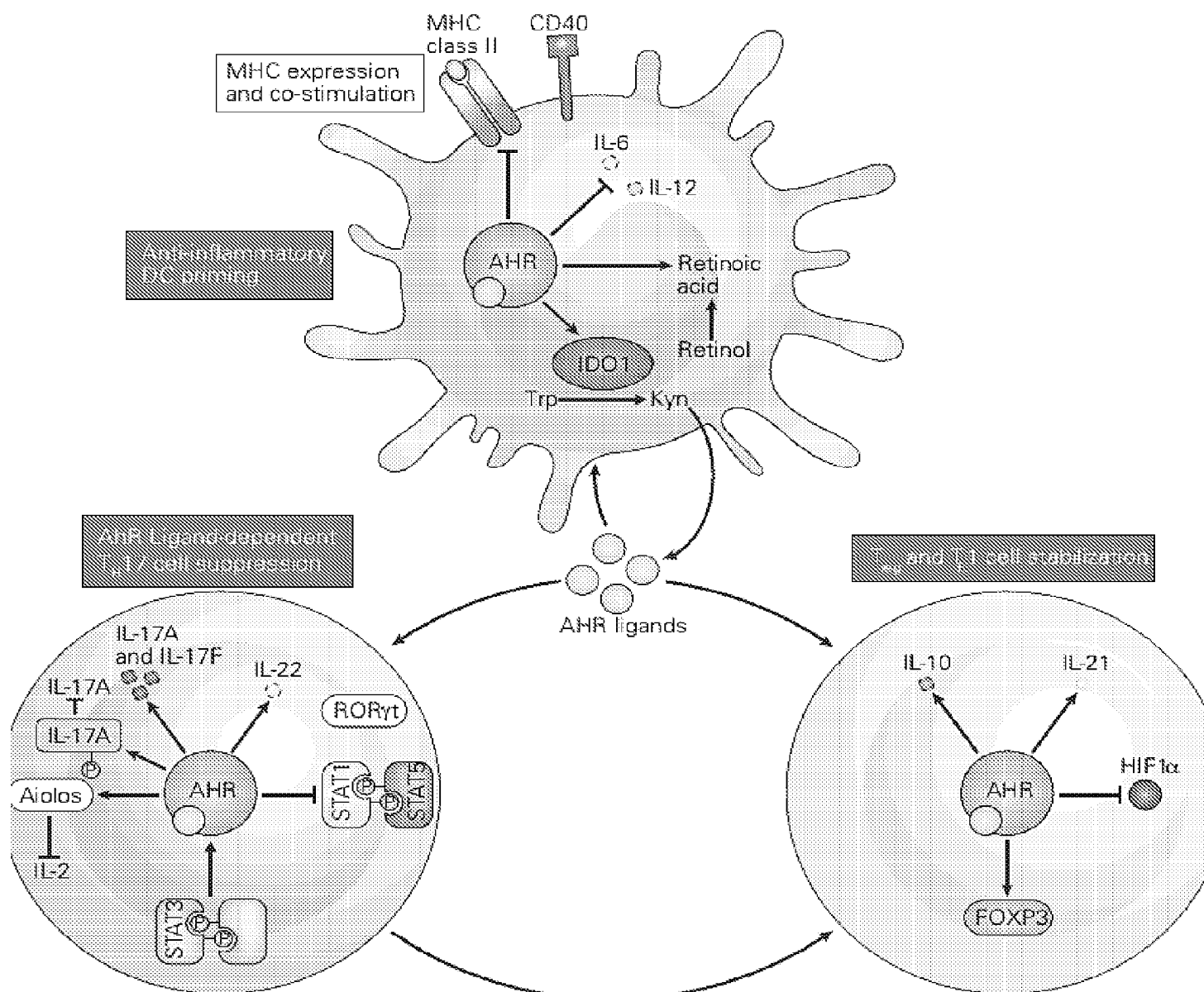


FIG. 7

8/20

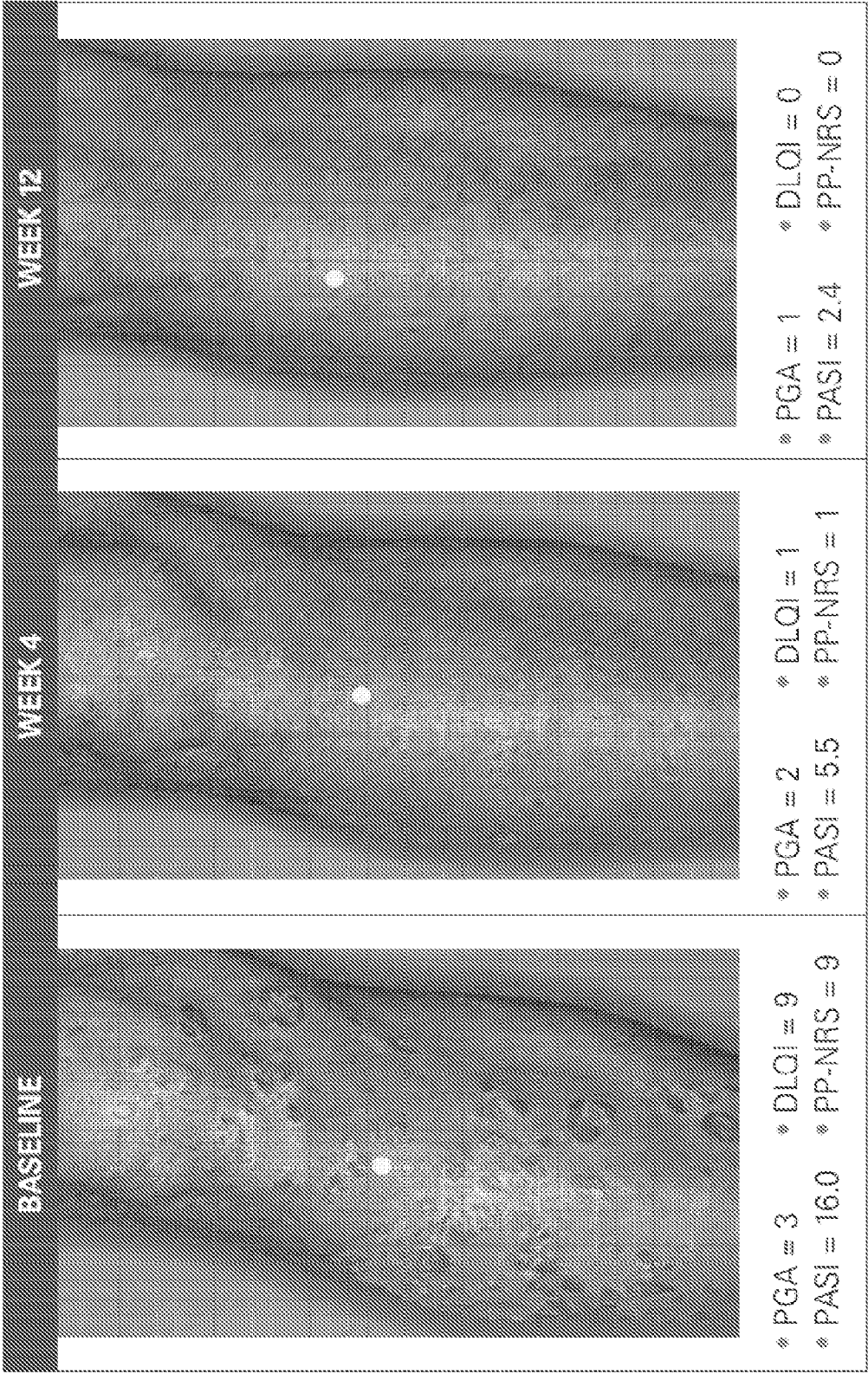


FIG. 8

9/20

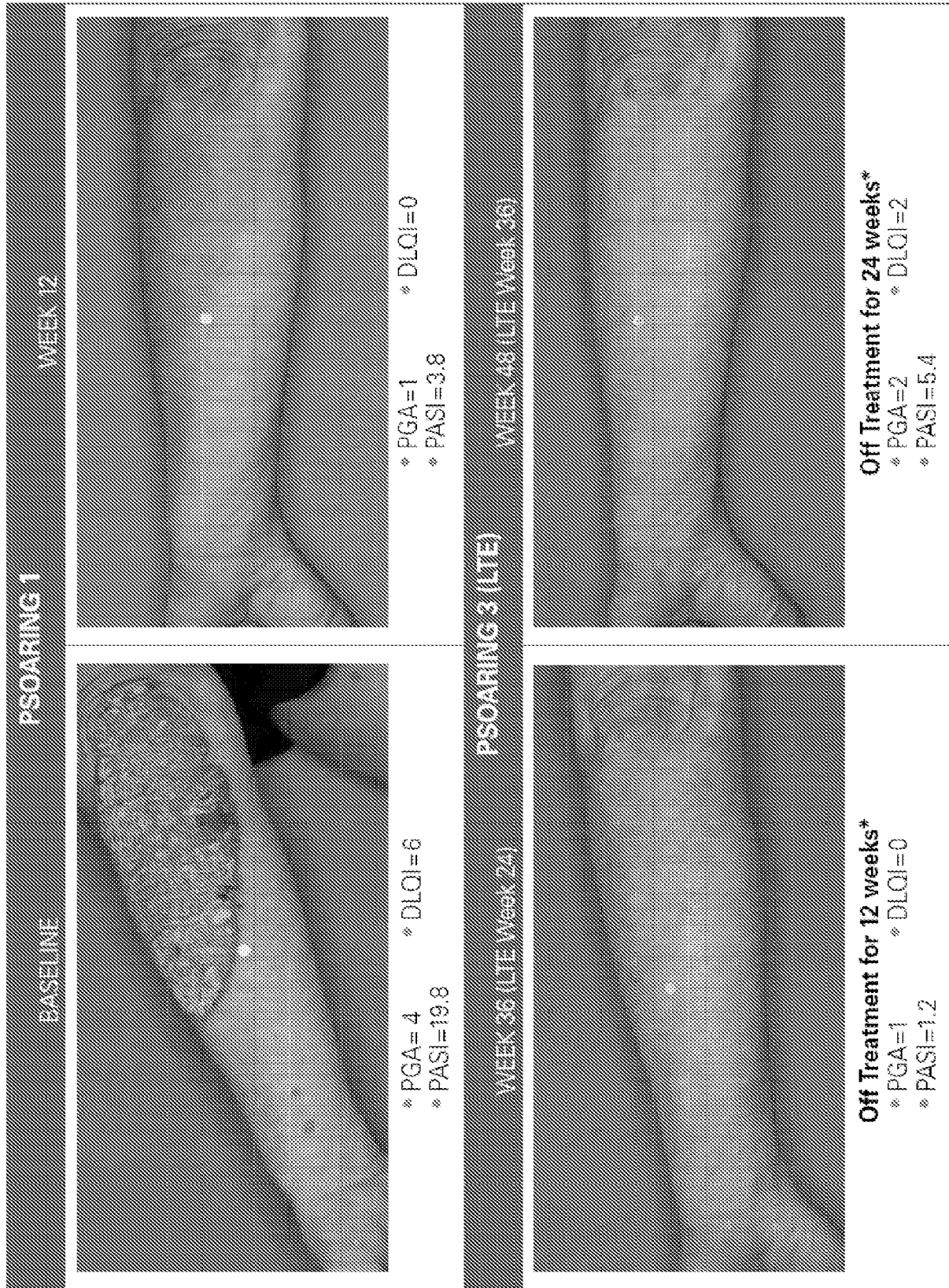


FIG. 9

10/20

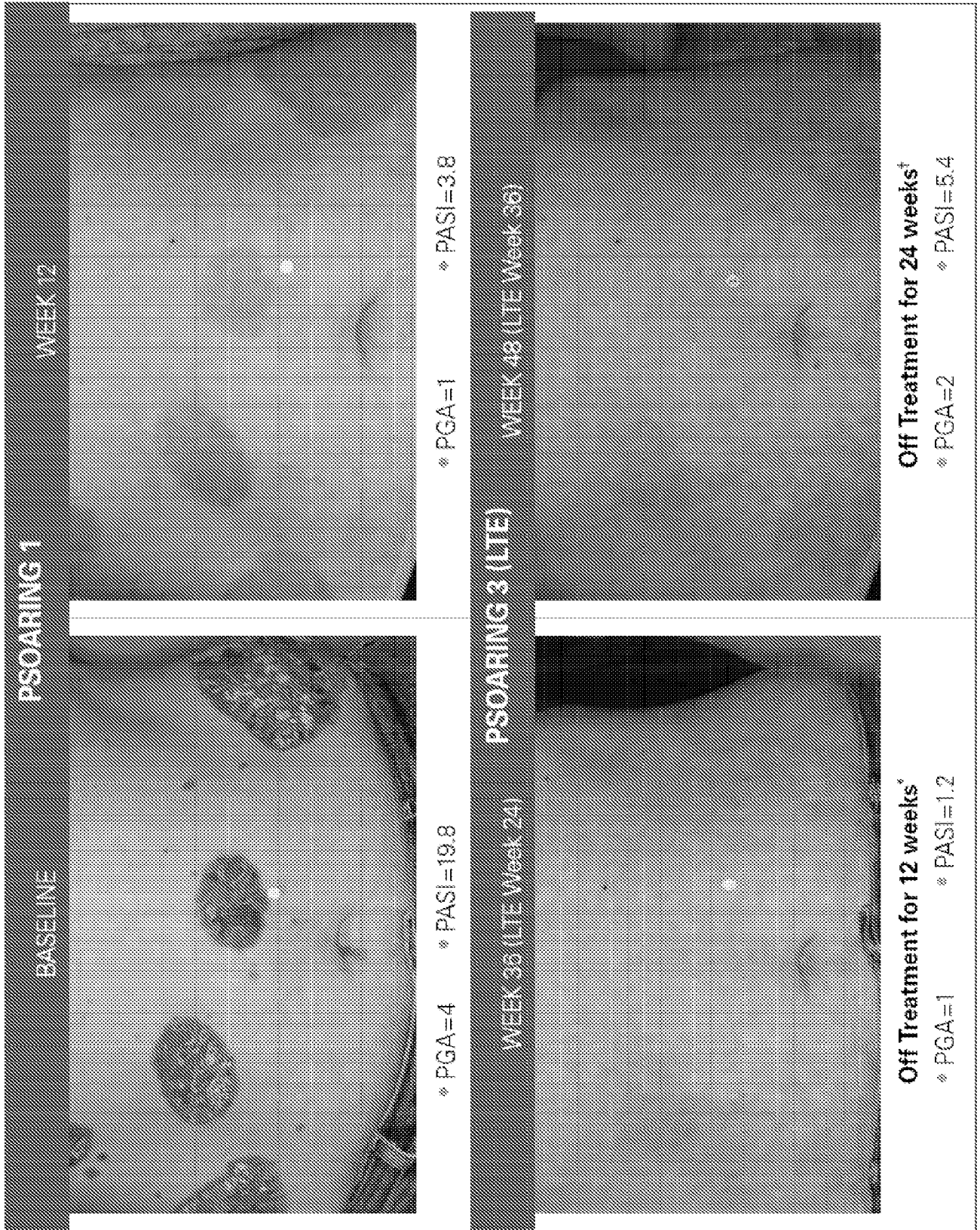


FIG. 10

11/20

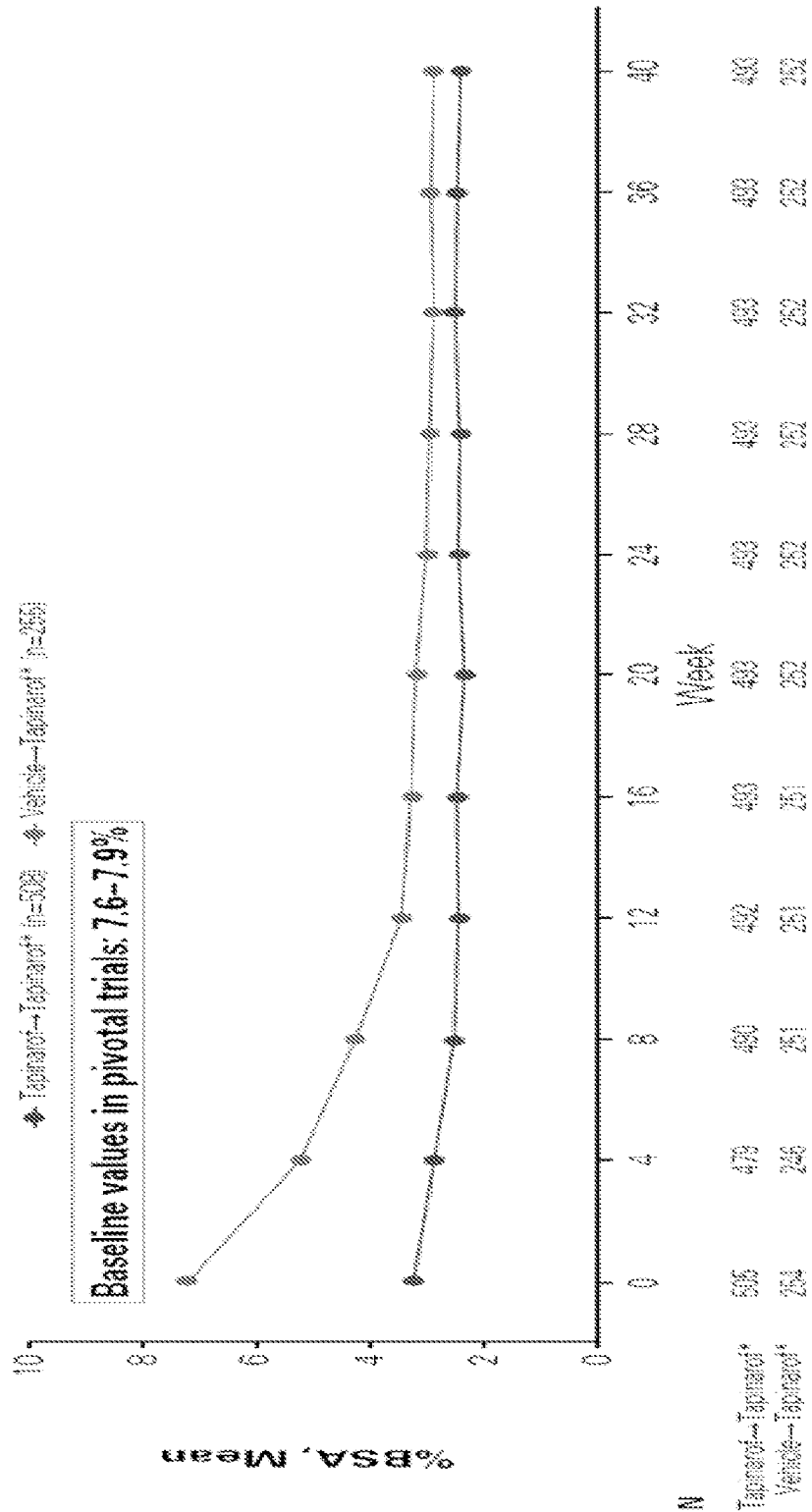


FIG. 11

12/20

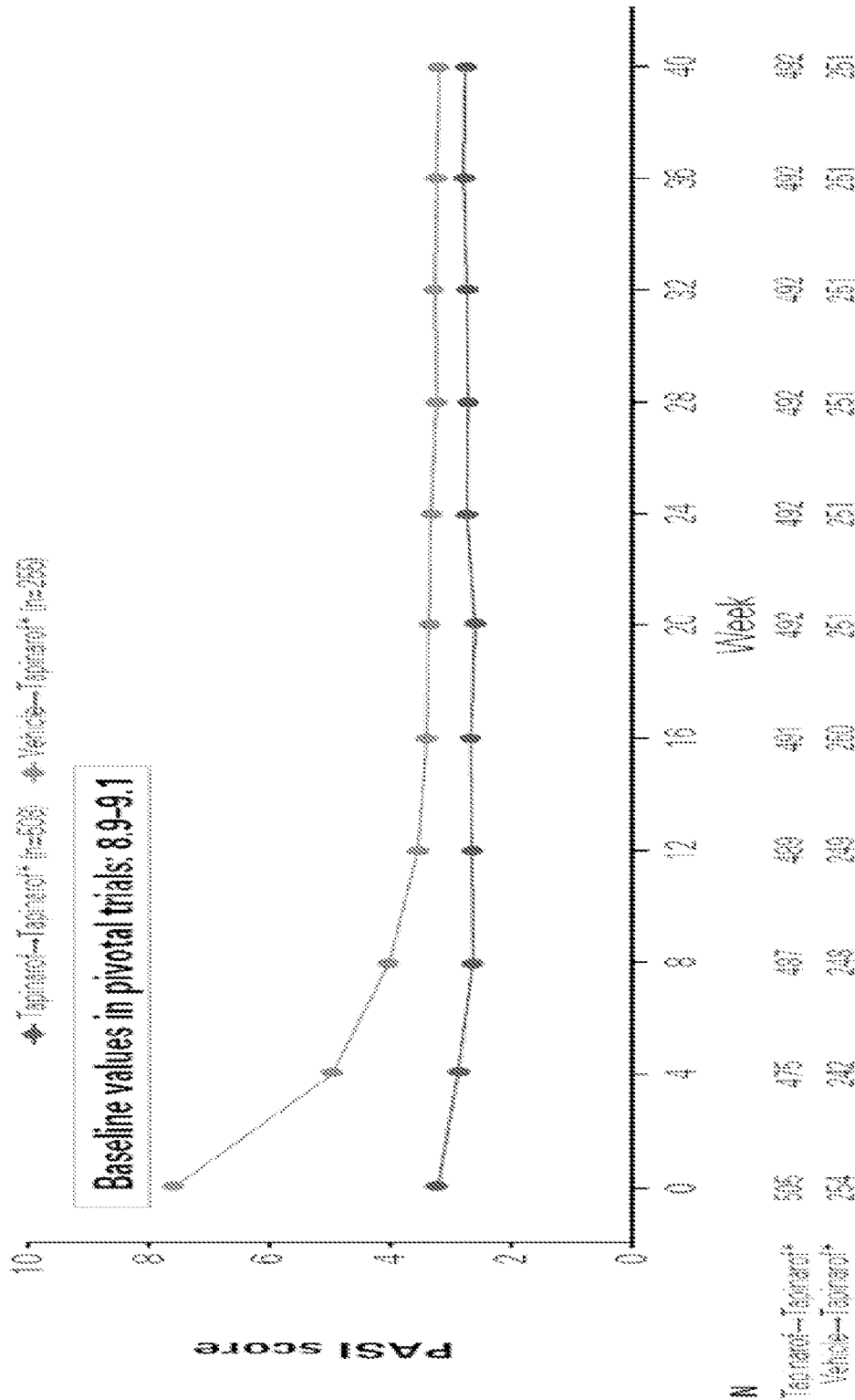


FIG. 12

13/20

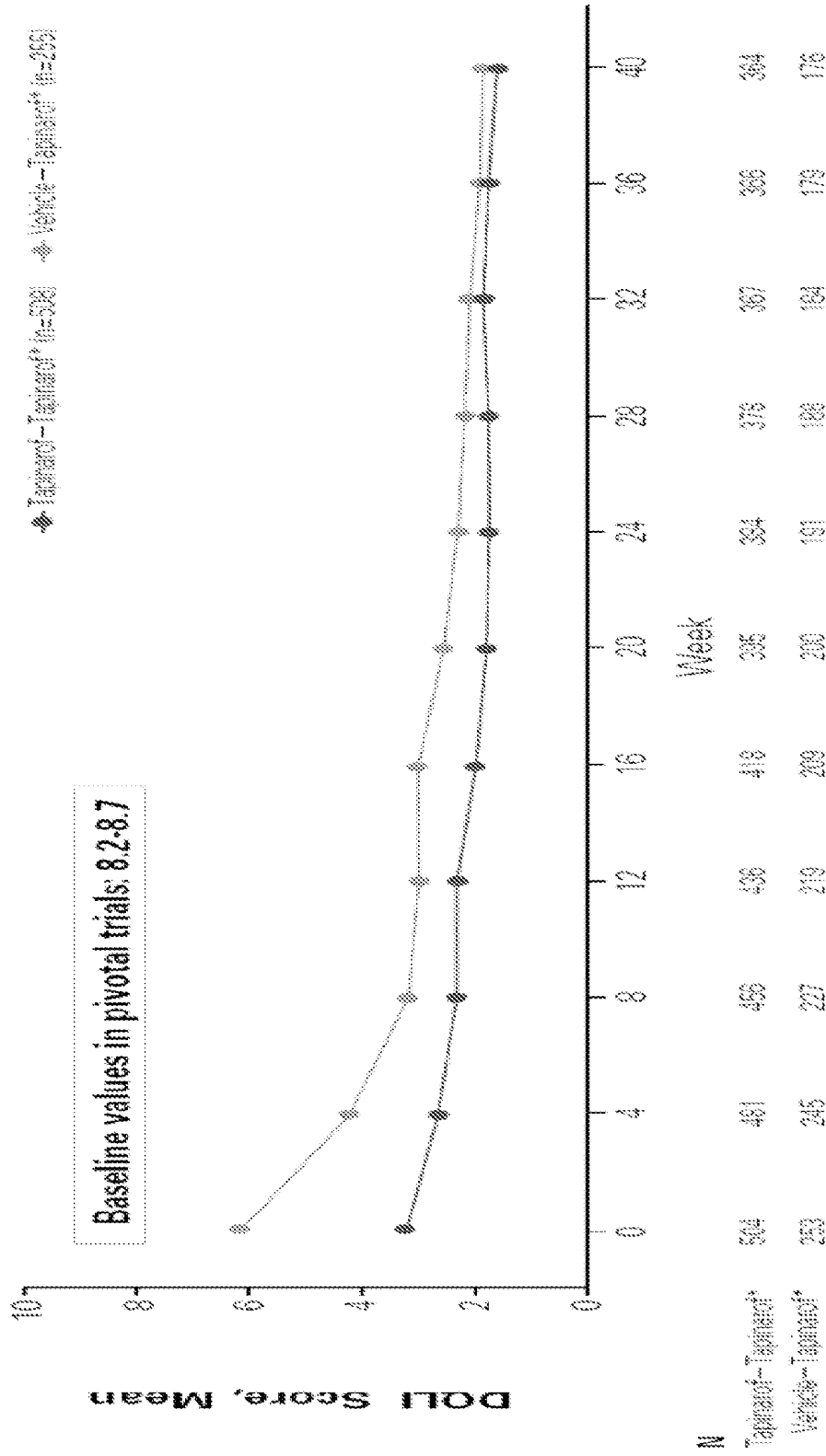


FIG. 13

14/20

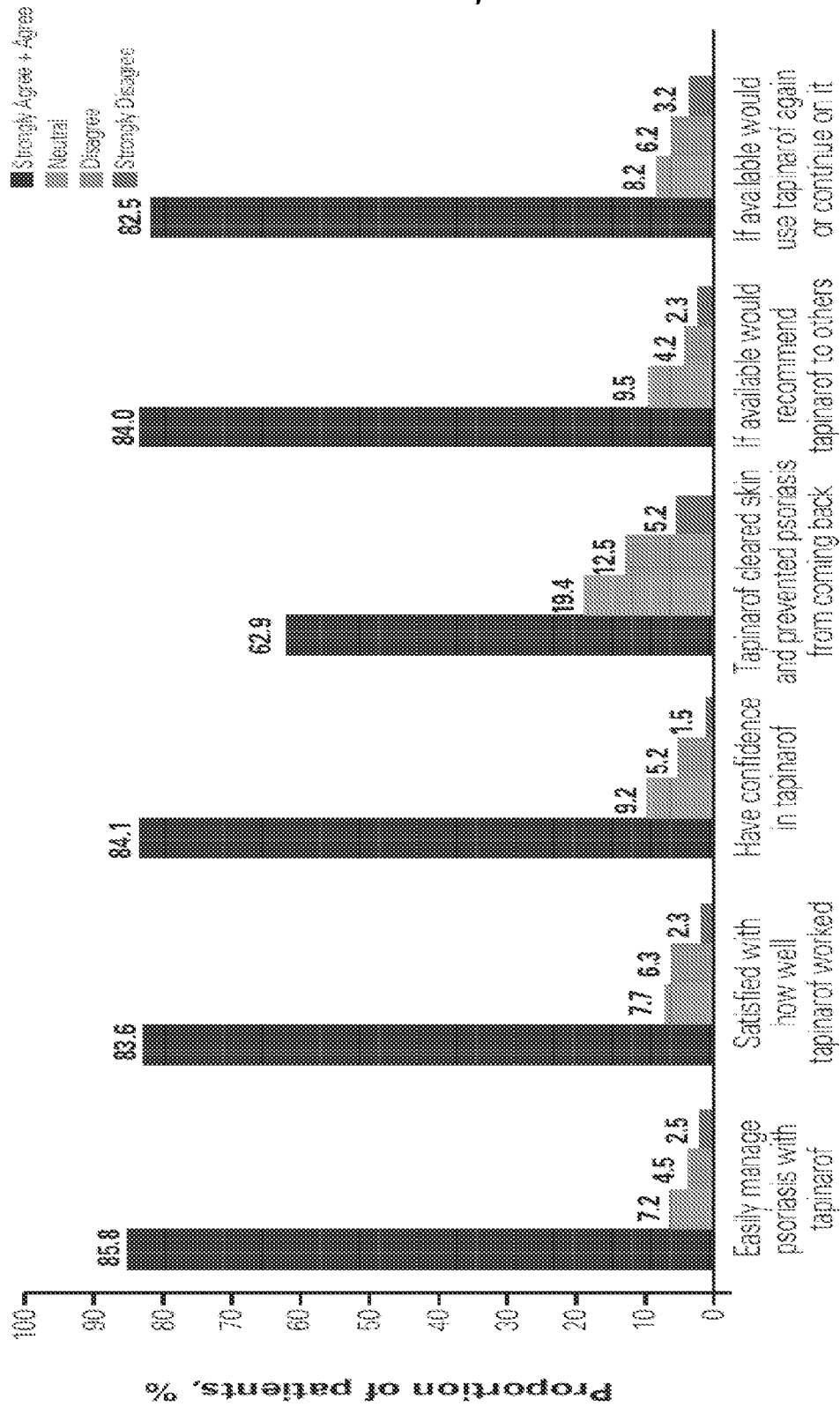


FIG. 14

15/20

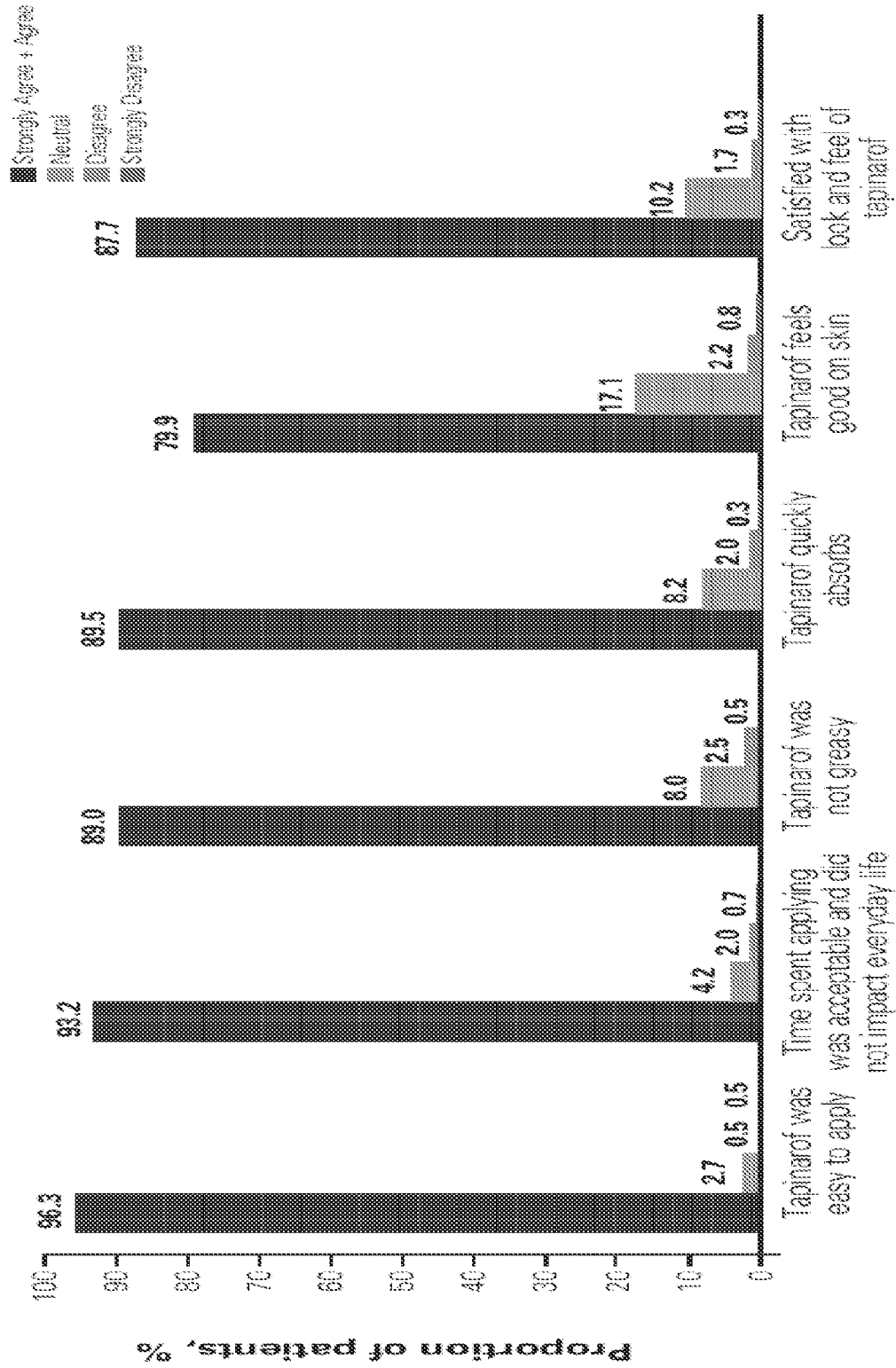


FIG. 15

16/20

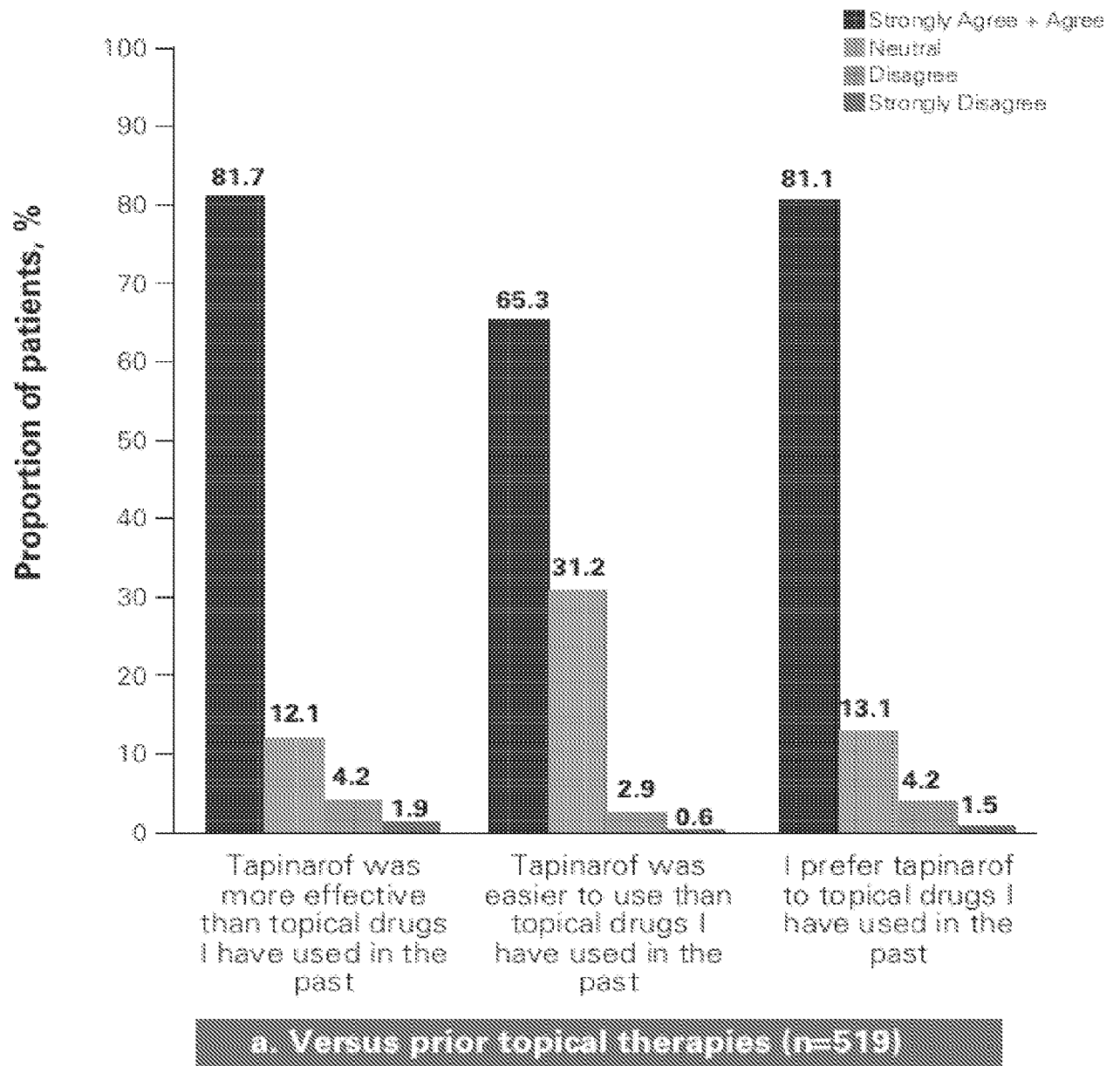


FIG. 16

17/20

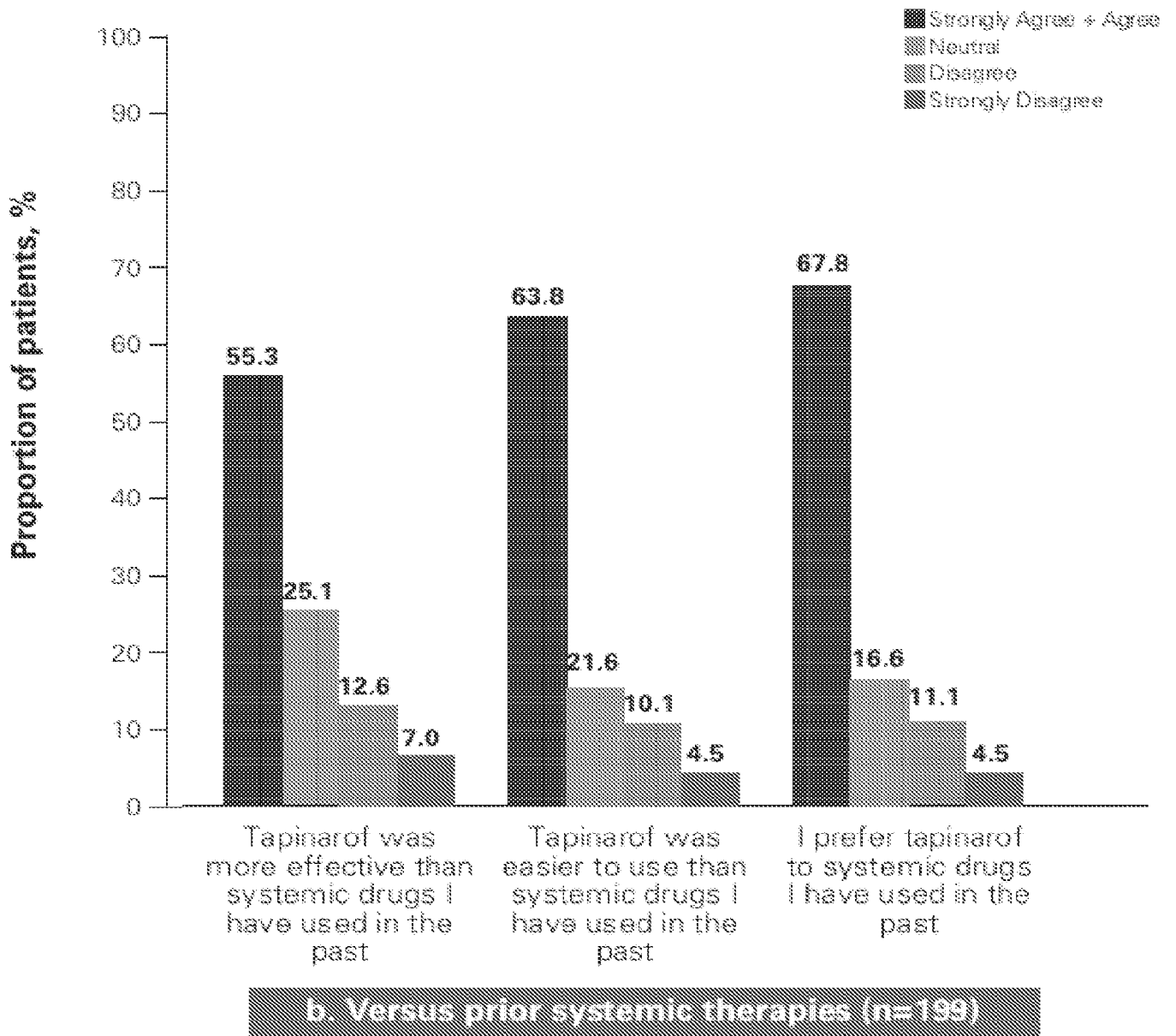


FIG. 17

18/20

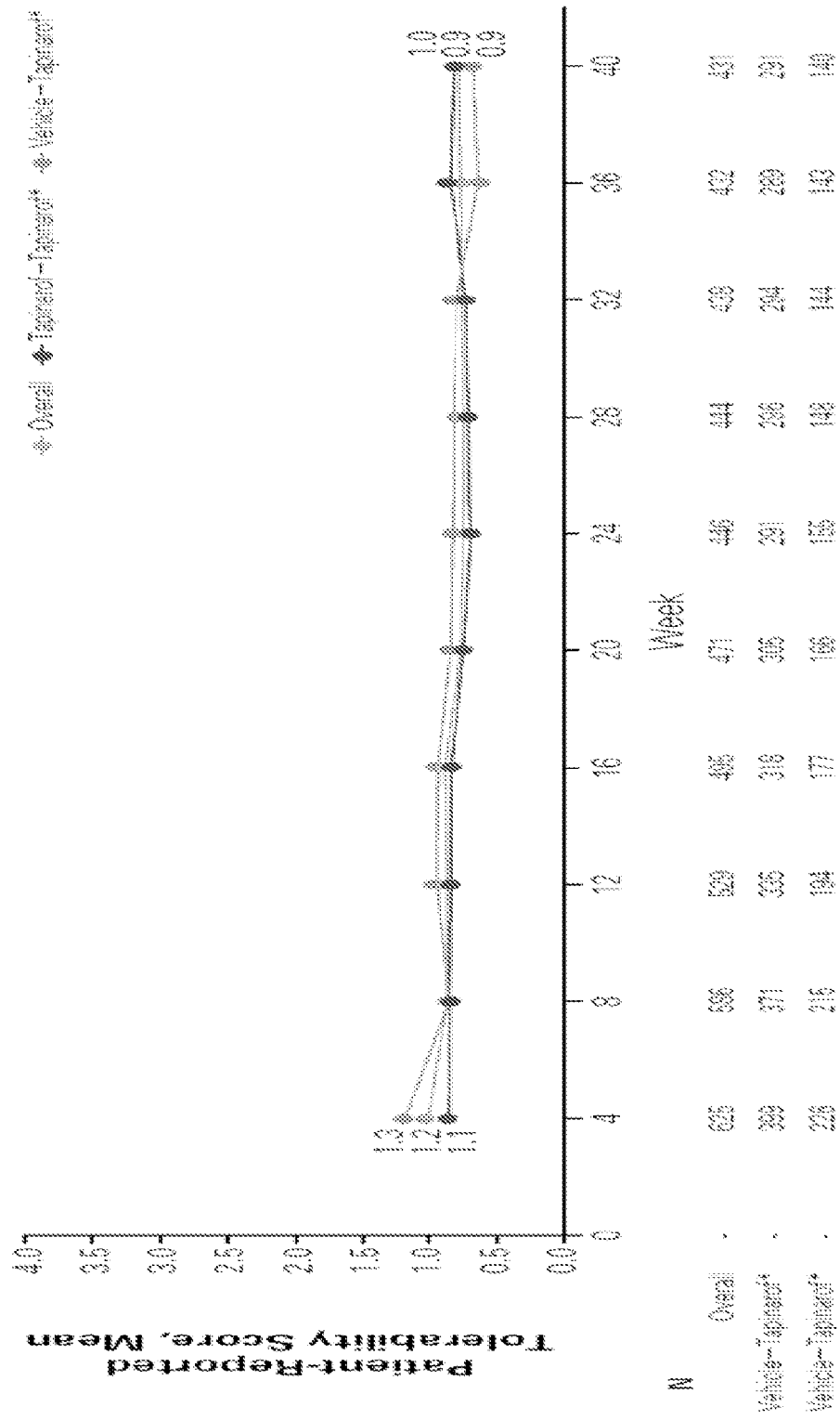


FIG. 18

19/20

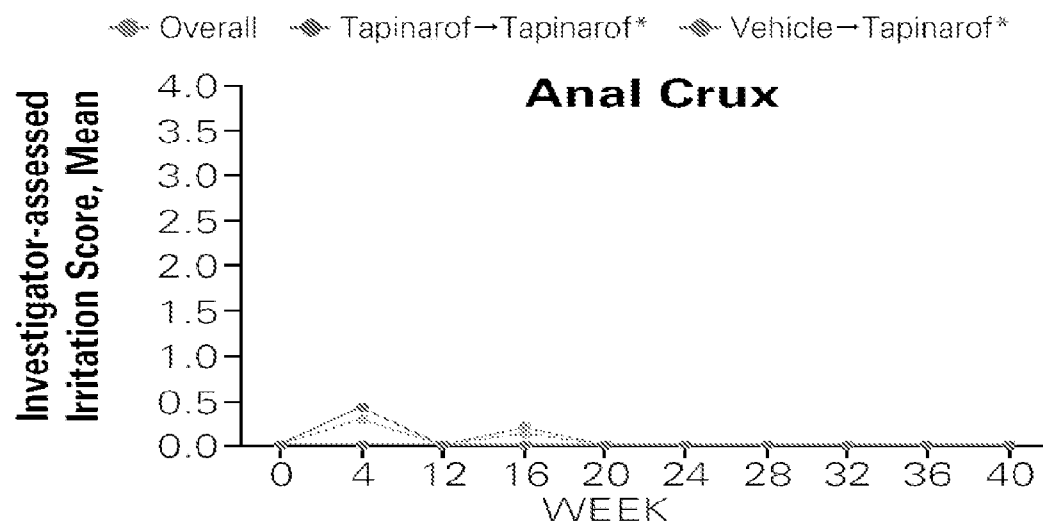


FIG. 19A

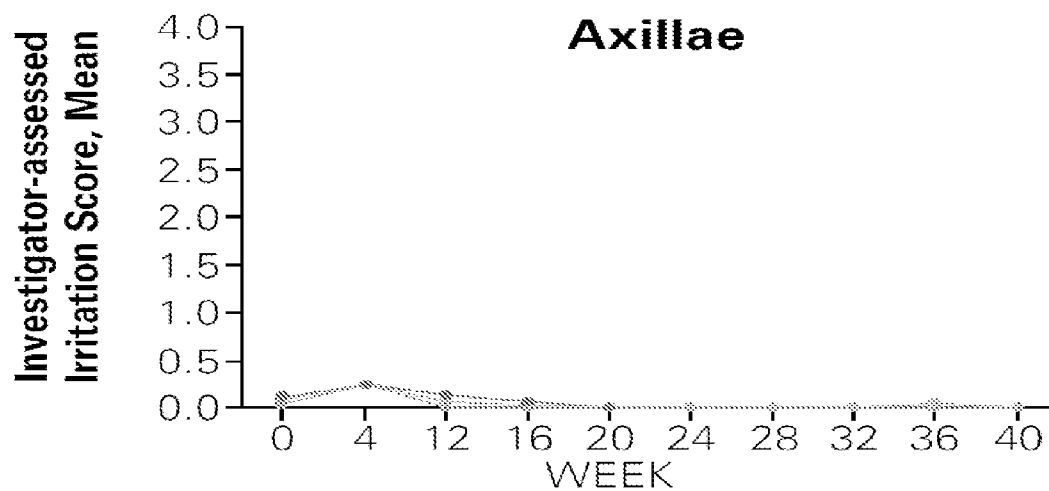


FIG. 19B

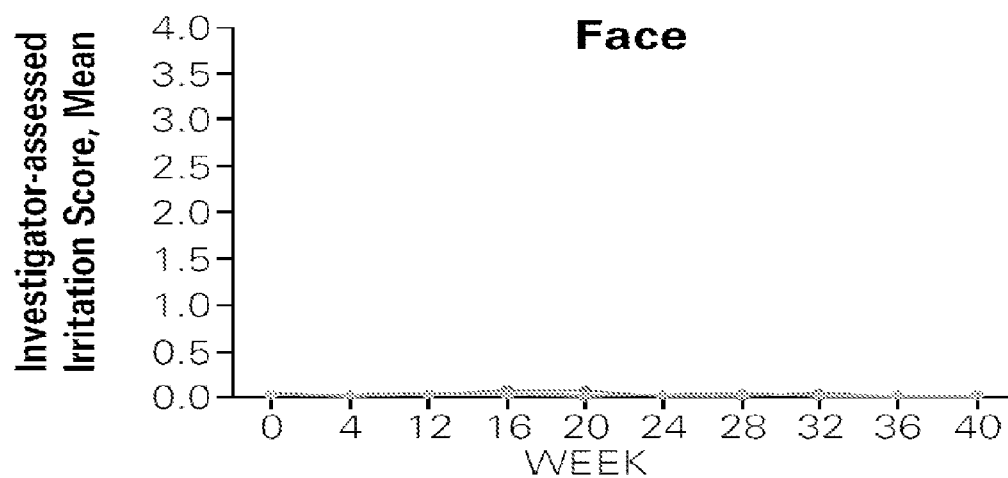
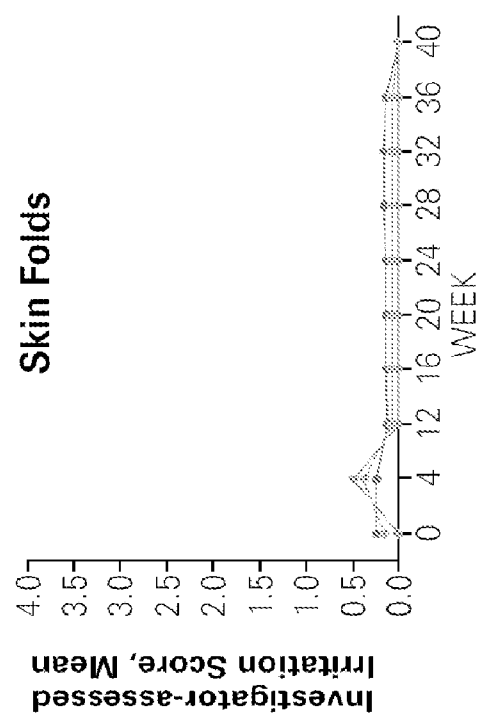
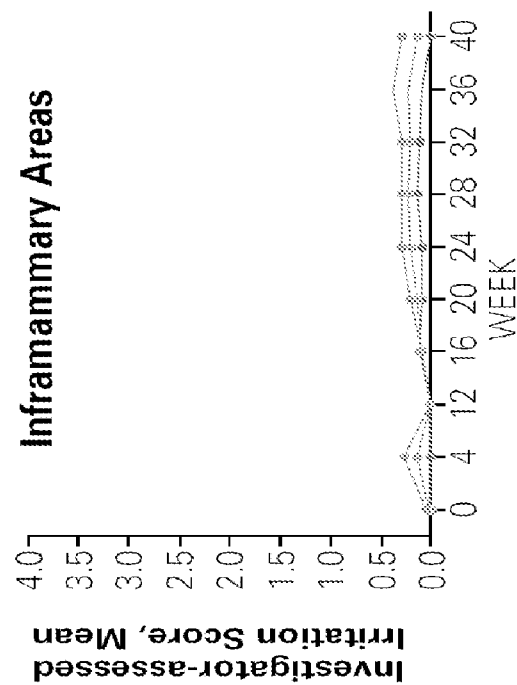
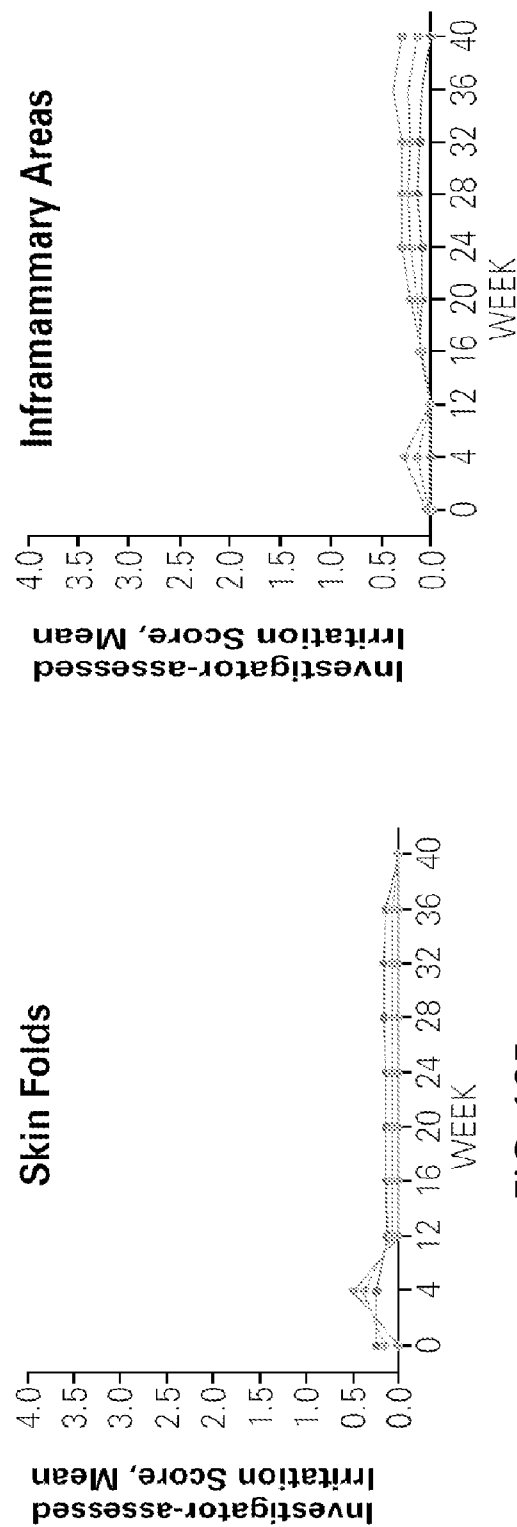
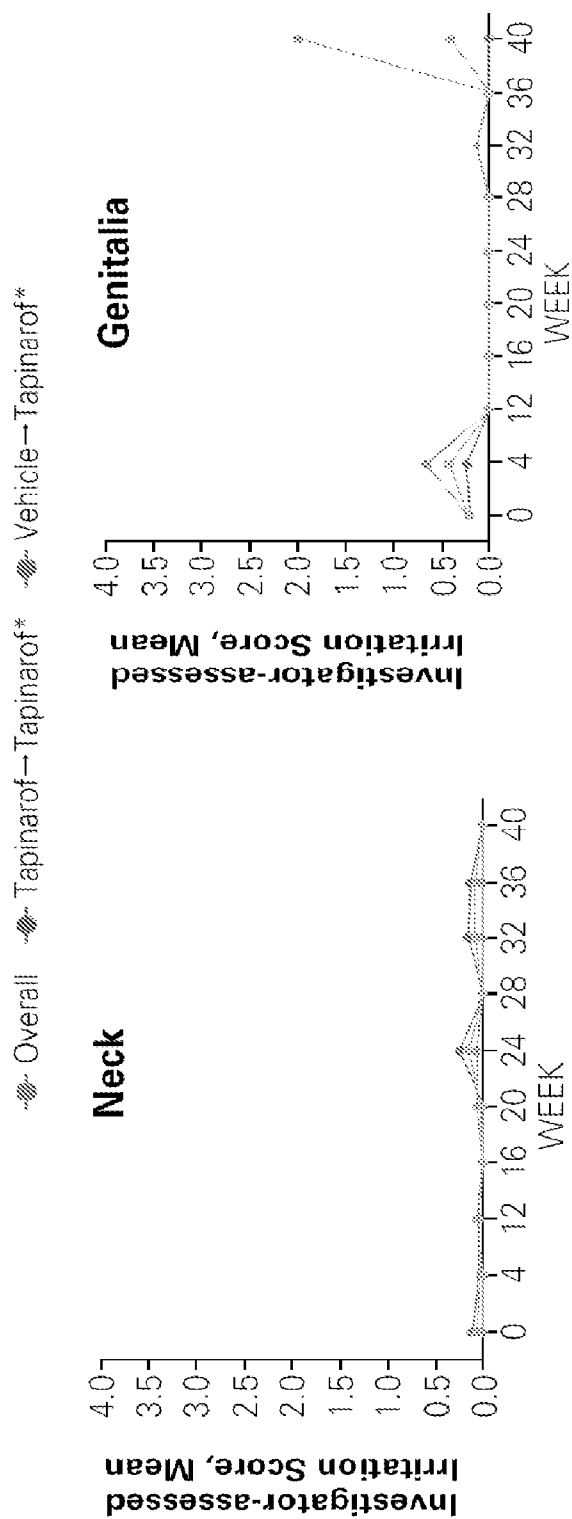


FIG. 19C



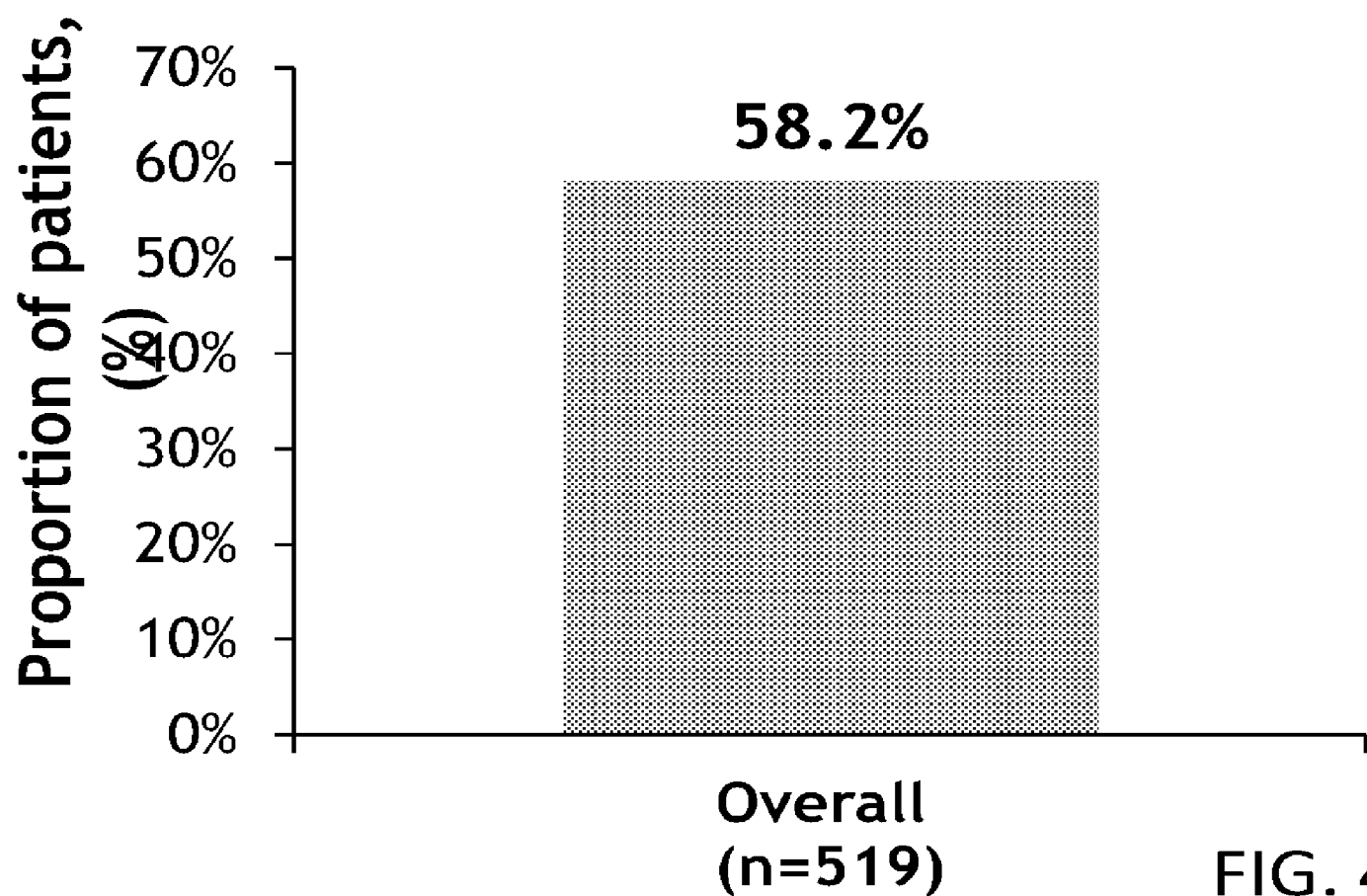
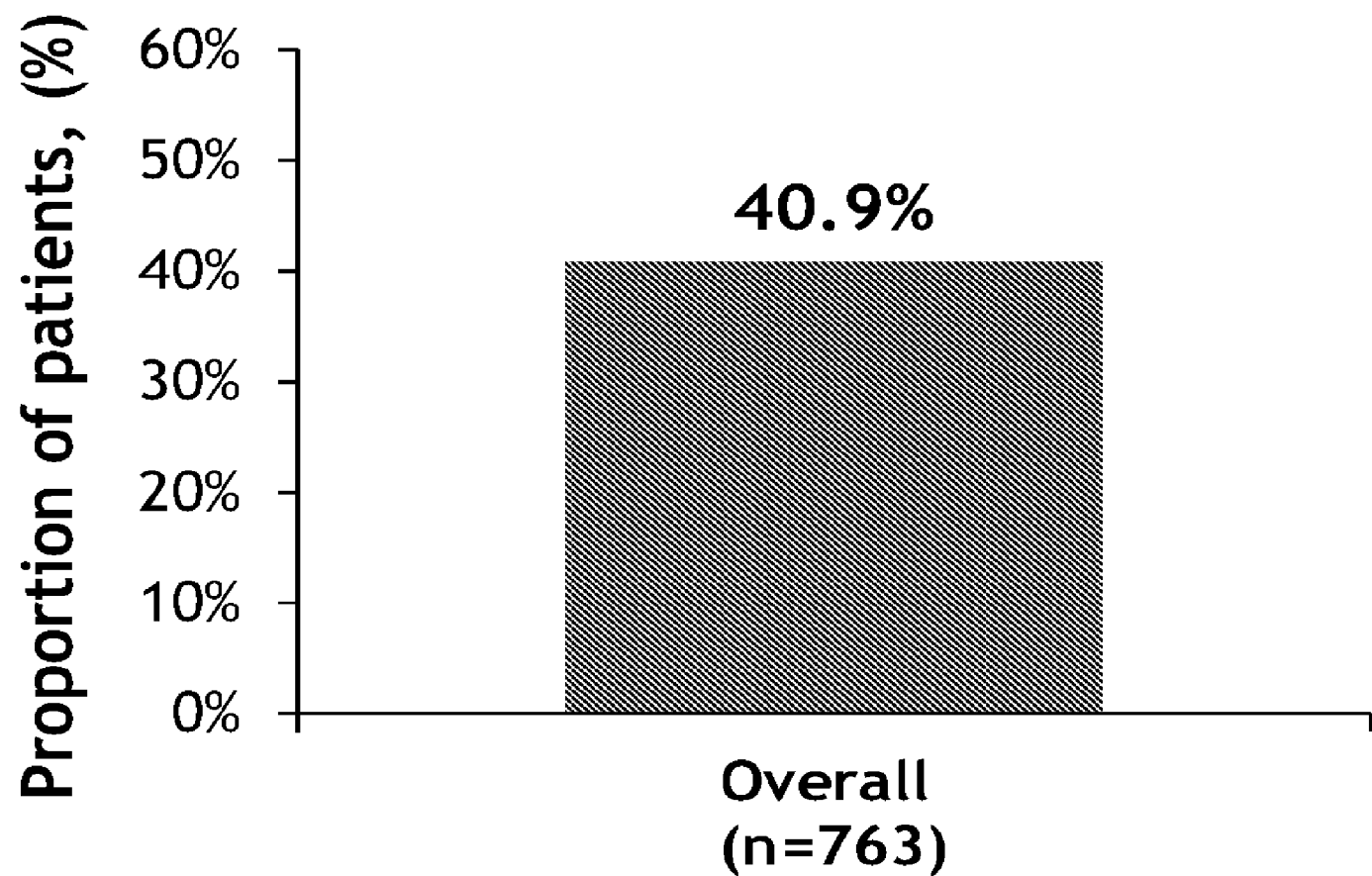


FIG. 4