

METHODS OF TREATING ATOPIC DERMATITIS USING TAPINAROF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claim priority US Provisional patent application 63/490,470 filed March 15, 2023, US Provisional patent application 63/466,979 filed May 16, 2023, US Provisional patent application 63/543,645 filed October 11, 2023, US Provisional patent application 63/618,518 filed January 8, 2024 and US Provisional patent application 63/462,860 filed April 28, 2023, each of which is incorporated by reference in its entirety for any purpose.

FIELD OF THE INVENTION

[0002] The present invention relates to methods of treating atopic dermatitis using tapinarof.

BACKGROUND

[0003] Various treatment options are available for atopic dermatitis, a chronic inflammatory skin condition characterized by pruritic and eczematous lesions. Conventional treatments typically involve the use of topical corticosteroids, calcineurin inhibitors, and emollients to manage symptoms and improve skin barrier function. However, these treatments may be associated with adverse effects such as skin thinning, striae formation, and increased risk of skin infections. Additionally, some patients may experience inadequate response or relapse following discontinuation of treatment, highlighting the need for alternative therapeutic approaches.

[0004] In recent years, there has been growing interest in the development of novel topical agents for the treatment of atopic dermatitis that offer improved efficacy and safety profiles. Tapinarof, a novel aryl hydrocarbon receptor modulator, has shown promising results in preclinical and clinical studies for the treatment of inflammatory skin conditions. Tapinarof exerts its anti-inflammatory effects by modulating the expression of pro-inflammatory cytokines and promoting skin barrier repair, making it a potential candidate for the treatment of atopic dermatitis.

[0005] Despite the advancements in topical therapies for atopic dermatitis, there remains a need for a treatment approach that not only effectively improves disease severity but also minimizes systemic exposure to the active ingredient to reduce the risk of systemic side effects. Current treatment regimens often require prolonged use of medications at high concentrations, leading to concerns about systemic absorption and potential adverse effects. However, none of

these approaches have provided a comprehensive solution that combines the features described in this disclosure.

SUMMARY

[0006] Embodiments of the invention are directed to a method for treating atopic dermatitis in a subject in need thereof, comprising: applying a thin layer of about 1.0% tapinarof topical cream composition to the affected areas of the subject for a period of time of at least 8 weeks; wherein, after the period of time, the subject has: at least a 2-grade improvement in vIGA-AD score from baseline, and an vIGA-AD score of 0; and wherein the plasma concentration of tapinarof in the subject is below 50 pg/mL while applying the 1.0% tapinarof topical cream.

[0007] In certain embodiments, the subject has an improvement in an EASI score of about 75% from baseline during the period of time. In some embodiments, the subject has a reduction in a PP-NRS score ≥ 4 points from baseline during the period of time. In certain embodiments, the subject is at least 12 years old. In some embodiments, the subject is at least 2 years old. In certain embodiments, the subject does not experience an adverse event during the period of time, wherein the adverse event is selected from the group consisting of contact dermatitis, folliculitis, headache, and a combination thereof. In some embodiments, the subject has an affected BSA of about 43%. In certain embodiments, the subject as an affected BSA of up to about 90%.

[0008] Embodiments of the invention are directed to topical compositions and methods for using topical compositions comprising tapinarof to treat mild to moderate atopic dermatitis in adolescents are described herein. Also described is treatment of subjects aged 2-11 years or aged 12-17 years, diagnosed with atopic dermatitis, wherein about $\geq 25\%$ or $\geq 35\%$ of body surface area was affected, and Investigator Global Assessment (IGA) score was greater than or equal to 3.

[0009] In an embodiment, a method for treating atopic dermatitis in a subject from 2-17 years old comprises topically administering a topical composition containing about 1.0% tapinarof to affected areas of the subject once a day for about 4 weeks, wherein after topically administering the topical composition an Investigator Global Assessment (IGA) score of the subject is improved by 2 grades or has improved to a score of 0 or 1, and the adolescent subject has a maximum observed plasma tapinarof concentration ($C_{\max}$) of <50 pg/mL.

BRIEF DESCRIPTION OF DRAWINGS

[0010] FIG. 1A and FIG. 1B each present depictions of the potential mechanism of clinical remittive effect with tapinarof.

[0011] FIG. 2 is a graph showing the change in IGA score by dosing regimen over time in a Phase 2b study of subjects with atopic dermatitis, where treatment success was defined as an IGA score of clear or almost clear with a minimum 2-point improvement.

[0012] FIG. 3 illustrates the trial design of the first portion of the phase 3 ADORING program for tapinarof 1% ("VTAMA") cream (ADORING 1 and ADORING 2).

[0013] FIG. 4 illustrates the trial design of the phase 3 program for tapinarof 1% ("VTAMA") cream, including the open-label, long-term extension study (ADORING 3).

[0014] FIG. 5 is a flow chart illustrating the patient disposition for the ADORING 1 and ADORING 2 studies.

[0015] FIG. 6 shows the primary efficacy results (vIGA-AD score of 0 or 1 and ≥ 2 grade improvement from baseline) from the ADORING 1 and ADORING 2 trials.

[0016] FIG. 7 shows vIGA-AD Score of 0 or 1 and ≥ 2 -grade improvement from baseline at week 8 across multiple statistical analyses in the ADORING 1 trial.

[0017] FIG. 8 shows vIGA-AD Score of 0 or 1 and ≥ 2 -grade improvement from baseline at week 8 across multiple statistical analyses in the ADORING 2 trial.

[0018] FIG. 9 shows the EASI75 improvement of patients in ADORING 1 and ADORING 2 from baseline to week 8.

[0019] FIG. 10 shows the absolute change in %BSA affected in ADORING 1 and ADORING 2 from baseline to week 8.

[0020] FIG. 11 shows the EASI90 improvement of patients in ADORING 1 and ADORING 2 from baseline to week 8.

[0021] FIG. 12 shows the PP-NRS improvement of patients in ADORING 1 and ADORING 2 from baseline to week 8 in patients 12 or older.

[0022] FIG. 13A shows the mean change in daily PP-NRS as a function of time in ADORING 1.

[0023] FIG. 13B shows the mean change in daily PP-NRS as a function of time in ADORING 2.

[0024] FIG. 14 shows photos of a representative target lesion of a pediatric patient treated with VTAMA cream, 1% once daily in the ADORING 1 clinical trial.

[0025] FIG. 15 shows photos of another representative target lesion of a pediatric patient treated with VTAMA cream, 1% once daily in the ADORING 1 clinical trial.

[0026] FIG. 16 shows photos of yet another representative target lesion of a pediatric patient treated with VTAMA cream, 1% once daily in the ADORING 1 clinical trial.

[0027] FIG. 17 shows photos of a representative target lesion of a pediatric patient treated with VTAMA (tapinarof 1%) cream once daily in the ADORING 2 clinical trial.

[0028] FIG. 18 shows photos of another representative target lesion of an adult patient treated with VTAMA (tapinarof 1%) cream once daily in the ADORING 2 clinical trial.

[0029] FIG. 19 shows treatment success (as indicated by vIGA-AD score of 0 or 1 and ≥ 2 -grade improvement from baseline at week 8), by baseline vIGA-AD score (moderate or severe) in the ADORING 1 and ADORING 2 trials.

[0030] FIG. 20 shows treatment success (as indicated by vIGA-AD score of 0 or 1 and ≥ 2 -grade improvement from baseline at week 8), by age group (2-6 years, 7-11 years, 12-17 years, and ≥ 18 years) in the ADORING 1 and ADORING 2 trials.

[0031] FIG. 21 shows treatment success (as indicated by vIGA-AD score of 0 or 1 and ≥ 2 -grade improvement from baseline at week 8), by visit (weeks 0, 1, 2, 4, and 8) in the ADORING 1 and ADORING 2 trials.

[0032] FIG. 22 shows improvement in PP-NRS of ≥ 4 Points at Week 8 for all patients in the ADORING 1 and ADORING 2 trials.

[0033] FIG. 23 shows improvement in PP-NRS of ≥ 4 Points at Week 8 in patients aged < 12 years in the ADORING 1 and ADORING 2 trials.

[0034] FIG. 24 shows PP-NRS response at Week 8 in patients aged ≥ 12 years in the ADORING 1 and ADORING 2 trials.

[0035] FIG. 25A shows the mean change in patient-assessed local tolerability scores as a function of time in ADORING 1.

[0036] FIG. 25B shows the mean change in patient-assessed local tolerability scores as a function of time in ADORING 2.

[0037] FIG. 26A shows the mean change in investigator-assessed local tolerability scores as a function of time in ADORING 1.

[0038] FIG. 26B shows the mean change in investigator-assessed local tolerability scores as a function of time in ADORING 2.

[0039] FIG. 27A shows the mean change in investigator-assessed irritation score on the face as a function of time in the safety populations of ADORING 1 and ADORING 2.

[0040] FIG. 27B shows the mean change in investigator-assessed irritation score on the neck as a function of time in the safety populations of ADORING 1 and ADORING 2.

[0041] FIG. 27C shows the mean change in investigator-assessed irritation score in the inframammary area as a function of time in the safety populations of ADORING 1 and ADORING 2.

[0042] FIG. 27D shows the mean change in investigator-assessed irritation score in the gluteal cleft as a function of time in the safety populations of ADORING 1 and ADORING 2.

[0043] FIG. 27E shows the mean change in investigator-assessed irritation score in the skin folds as a function of time in the safety populations of ADORING 1 and ADORING 2.

[0044] FIG. 27F shows the mean change in investigator-assessed irritation score in the axillae as a function of time in the safety populations of ADORING 1 and ADORING 2.

[0045] FIG. 27G shows the mean change in investigator-assessed irritation score on the genitalia as a function of time in the safety populations of ADORING 1 and ADORING 2.

[0046] FIG. 28 shows photos of a representative target lesion of a 3-year-old patient treated with tapinarof cream, 1% QD in the ADORING 1 clinical trial.

[0047] FIG. 29 shows the intertriginous psoriasis trial design.

[0048] FIG. 30A shows that 82.8% of patients achieved an iPGA response with tapinarof cream at Week 12; a response was seen as early as Week 2 in a phase 4, 12-week, open-label trial of tapinarof cream 1% QD for the treatment of adults with mild to severe plaque psoriasis in intertriginous areas.

[0049] FIG. 30B shows that 65.5% of patients achieved complete disease clearance (iPGA score of 0) with tapinarof cream at Week 12 in a phase 4, 12-week, open-label trial of tapinarof cream 1% QD for the treatment of adults with mild to severe plaque psoriasis in intertriginous areas.

[0050] FIG. 31 shows that tapinarof cream 1% QD demonstrated no irritation over 12 weeks plus improvements from pre-treatment score for all intertriginous areas from baseline.

[0051] FIG. 32 shows complete disease clearance and resolution of itch in a patient with intertriginous plaque psoriasis and pre-existing irreversible striae (due to previous TCS) treated with tapinarof cream 1% QD.

[0052] FIG. 33 shows the mean ($\pm$ standard deviation) tapinarof and tapinarof sulfate concentration versus nominal time (semi-log scale) on day 1 of an open label maximal use study to evaluate the safety, tolerability, and pharmacokinetics of tapinarof cream, 1% in pediatric patients with atopic dermatitis as described herein.

[0053] FIG. 34 shows the mean ($\pm$ standard deviation) tapinarof and tapinarof sulfate concentration versus nominal time by age group (semi-log scale) on day 1 of an open label maximal use study to evaluate the safety, tolerability, and pharmacokinetics of tapinarof cream, 1% in pediatric patients with atopic dermatitis as described herein.

[0054] FIG. 35 shows the proportion of patients by age group with tapinarof concentrations below the quantifiable limit (<50 pg/ml) at day 28 of an open label maximal use study to evaluate the safety, tolerability, and pharmacokinetics of tapinarof cream, 1% in pediatric patients with atopic dermatitis as described herein.

DETAILED DESCRIPTION

[0055] 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.

[0056] 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.

[0057] 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.

[0058] 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.

[0059] 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.

[0060] 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.

[0061] The term “applying a thin layer”, refers to rubbing enough of a composition (e.g., a 1% tapinarof cream composition) into the skin to cover the area requiring application until any residual cream is no longer visible.

[0062] 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.

[0063] 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.

[0064] 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.”

[0065] The term “disorder” is used in this disclosure to mean, and is used interchangeably with, the terms disease, condition, or illness, unless otherwise indicated.

[0066] 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.

[0067] 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.

[0068] 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. The terms “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 adolescent (i.e., 12-17 years old). In some embodiments, the patient or subject is from 2-11 years old.

[0069] 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.

[0070] 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 the 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.

[0071] 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.

[0072] 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.

[0073] 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.

[0074] 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.

[0075] 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.

[0076] *Psoriasis*

[0077] 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.

[0078] 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.

[0079] 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.

[0080] 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.

[0081] 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.

[0082] 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 $\geq$ 2).

[0083] 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. 1A and FIG. 1B (AhR, aryl hydrocarbon receptor; ARNT, aryl hydrocarbon receptor nuclear translocator; FLG, filaggrin; HRNR, homerin; IL, interleukin; IVL, involucrin; LOR, loricrin; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; TAP, tapinarof; Th, T helper.)): 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.

[0084] 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 CD45ROhi, CD45RALow, CD69hi, CD103hi and CD103low.

[0085] 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.

[0086] 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.

[0087] Atopic Dermatitis

[0088] Atopic dermatitis (AD) (also called atopic eczema) is an intensely pruritic, chronic, relapsing, inflammatory skin disease. The characteristic signs and symptoms of AD include sensations of pruritus and burning, xerosis, erythematous papules and plaques, exudation, crusting, and lichenification. Quality of life is affected through sleep deprivation due to the intense and constant itching, as well as the stigma associated with having a visible skin disease. Up to 30% of children may be affected by AD at some point, and 1% to 3% of adults have AD. Currently there is no curative therapy. Stabilizing the disease and reducing the number and severity of flares are the primary goals of treatment. Topical treatments directed at skin inflammation are a key factor in disease management, as is symptomatic relief of itching. Although multiple 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

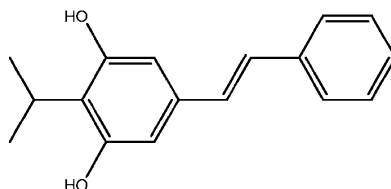
application to a large body surface area (BSA) of $\geq 25\%$ or $\geq 35\%$ without restrictions on duration of treatment.

[0089] The cause of AD is multifactorial, with genetic and environmental factors, deficient skin barrier function, and impaired immune response. The inflammatory component is thought to be mediated primarily by the Th2 type T-cell activation pathway, although in chronic AD skin lesions, a shift towards a Th1-driven pathway has been described. Tapinarof inhibits the secretion of multiple pro-inflammatory cytokines and chemokines (e.g., Th2 cytokines and leukotriene B4), inhibits molecules involved in the adhesion and recruitment of cells involved in the pathogenesis of AD, and activates the aryl hydrocarbon receptor (AhR) and nuclear factor-erythroid 2-related factor-2 (Nrf2) anti-inflammatory pathways.

[0090] Tapinarof is a fully synthetic hydroxylated stilbene and new molecular entity that is a novel anti-inflammatory agent for the topical treatment of AD and plaque psoriasis.

[0091] *COMPOSITIONS*

[0092] 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:



[0093] 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.

[0094] 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.

[0095] In certain embodiments described herein, the topical composition comprises about 0.50% to about 1.0% tapinarof, or a pharmaceutically acceptable salt thereof. In certain embodiments described herein, the topical composition comprises about 0.50% tapinarof, or a pharmaceutically acceptable salt thereof. In certain embodiments described herein, the topical composition comprises about 1.0% tapinarof, or a pharmaceutically acceptable salt thereof.

[0096] 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.

[0097] 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.

[0098] 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.

[0099] In certain embodiments, the topical composition comprises 0.50% tapinarof, or a pharmaceutically acceptable salt thereof, 65.18% 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.

[0100] In embodiments, the topical composition may include pharmaceutically or cosmetically acceptable excipients, additives or other active agents as described herein.

[0101] In embodiments, the topical compositions may further include one or more pharmaceutical and/or cosmetically acceptable excipients selected from the group consisting of diluents, fillers, disintegrants, binders, lubricants, surfactants, hydrophobic vehicles, water soluble vehicles, emulsifiers, buffers, humectants, moisturizers, solubilizers, preservatives, colorants, plastizers, carriers, excipients, or combinations thereof. The person of ordinary skill in the art can refer to various pharmacologic references such as, for example, Modern Pharmaceutics, Banker & Rhodes, Marcel Dekker, Inc. (1979) and Goodman & Gilman's The Pharmaceutical Basis of Therapeutics, 6th Edition, MacMillan Publishing Co, New York (1980) for guidance in determining the amount of such components in the topical compositions and formulations of embodiments.

[0102] In embodiments, the topical compositions may include emollient or lubricating vehicles that help hydrate the skin can also be used. Examples of suitable bases or vehicles for preparing hydrating compositions for use with a subject skin are petrolatum, petrolatum plus volatile silicones, lanolin, cold cream (USP), and hydrophilic ointment (USP).

[0103] In embodiments, the topical compositions may include a second active agent. In embodiments, the second active agent is selected from dupilumab; crisaborole; calcineurin inhibitors, such as tacrolimus and pimecrolimus; antibiotics; hydrocortisone; corticosteroids, such as prednisone; antihistamines, such as cetirizine, fexofenadine, diphenhydramine; and combinations thereof. In embodiments, the second active agent is selected from apremilast (OtezlaTM); adalimumab; secukinumab; guselkumab; ixekizumab; etanercept; infliximab; ustekinumab; golimumab; apremilast; topical corticosteroids (TCS), such as prednisone; vitamin D; vitamin D derivatives, such as calcipotriene or calcitriol; combination of calcipotriene and betamethasone dipropionate (EnstilarTM) anthralin; methotrexate;

cyclosporine; vitamin A; vitamin A derivatives, such as retinoids, tazarotene, or acitretin; calcineurin inhibitors, such as tacrolimus and pimecrolimus; thioguanine; hydroxyurea; salicylic acid; coal tar; and combinations thereof.

[0104] In embodiments, the topical compositions may be formulated in any formulation suitable for topical administration, including, but not limited to, a solution, fluid, emulsion, suspension, solid, semi-solid, jelly, paste, gel, hydrogel, ointment, lotion, emulsion, cream, foam, mousse, liquid, spray, suspension, dispersion, powder, aerosol, or transdermal patch. Formulations described in U.S. Patent Publication Nos. 2016/0338973, 2018/0064656, and 2019/0144367 are incorporated herein by reference in their entirety.

[0105] In embodiments, the topical compositions described herein may be formulated as a liquid. Liquid dosage forms for topical administration may include diluents such as, for example, alcohols, glycols, oils, water, and the like. Such topical compositions may also include wetting agents or emulsifiers. In some embodiments, the topical compositions of embodiments may be formulated as oil-in-water or water-in-oil emulsion. A cream can be a water-in-oil (w/o) emulsion in which an aqueous phase is dispersed in an oil phase, or an oil-in-water (o/w) emulsion in which an oil is dispersed within an aqueous base. An ointment generally refers to a more viscous oil-in-water cream. Traditional ointment bases (i.e., carrier) include hydrocarbons (petrolatum, beeswax, etc.) vegetable oils, fatty alcohols (cholesterol, lanoilin, wool alcohol, stearyl alcohol, etc.) or silicones. Insoluble solids such as starch, zinc oxide, calcium carbonate, or talc can also be used in ointments and creams. Gel forms of the topical compositions described above can be formed by the entrapment of large amounts of aqueous or aqueous-alcoholic liquids in a network of polymers or of colloidal solid particles. Such polymers or colloids (gelling or thickening agents) are typically present at concentrations of less than 10% w/w and include carboxymethyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, methyl cellulose, sodium alginate, alginic acid, pectin, tragacanth, carrageen, agar, clays, aluminum silicate, carbomers, and the like.

[0106] In embodiments, the topical compositions described herein may be formulated as aerosols, in which the topical composition is dissolved in a propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide, or other suitable gas, and a co-solvent such ethanol, acetone, hexadecyl alcohol, and the like and combinations thereof.

[0107] In embodiments, the topical compositions can be in the form of hydrogels. Hydrogels are typically prepared by cross-linking various monomers and/or polymers to

provide a three-dimensional polymer network. Non-limiting examples of polymers include, polyoxyethylene-polypropylene block copolymers, ionic poly saccharides, such as chitosan or sodium alginate, cellulose, and biodegradable polymers, such as poly-lactides (PLA) and poly-glycolides (PGA), butylene succinate (PBS), polyhydroxyalkanoate (PHA), polycaprolactone acid lactone (PCL), polyhydroxybutyrate (PHB), glycolic amyl (PHV), PHB and PHV copolymer (PHBV), and poly lactic acid (PLA)-polyethylene glycol (PEG) copolymers (PLEG).

[0108] In embodiments, the topical compositions disclosed herein can be in the form of transdermal patches. The transdermal patches can be in any conventional form such as, for example, a strip, a gauze, a film, and the like. Patch material may be nonwoven or woven (e.g., gauze dressing). Layers may also be laminated during processing. It may be nonocclusive or occlusive, but the latter is preferred for backing layers. The patch is preferably hermetically sealed for storage (e.g., foil packaging). The patch can be held onto the skin and components of the patch can be held together using various adhesives. For example, the transdermal patch can be in the form of a band-aid type device, or it may be packaged in a small metal or plastic “cup”, which is strapped onto the appropriate site using an adhesive, tape, or an outer fabric or leather strap, similar to that worn as part of a watch. The entire patch may be disposable or may be refillable.

[0109] In embodiments, the topical compositions disclosed herein can be coated on bandages, mixed with bioadhesives, or included in dressings.

[0110] A wide variety of methods may be used for preparing the formulations described herein. Broadly speaking, the formulations may be prepared by combining together the components of the formulation, as described herein, at a temperature and for a time sufficient to provide a pharmaceutically acceptable composition. For example, in some embodiments, the topical compositions components may be dissolved, suspended, dispersed or otherwise mixed in a selected carrier or vehicle, at an effective concentration such that the condition to be treated is relieved or ameliorated.

[0111] 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).

[0112] *METHODS OF USING TOPICAL COMPOSITIONS TO TREAT PSORIASIS*

[0113] 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.

[0114] 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.

[0115] 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.

[0116] 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.

[0117] In certain embodiments the plaque psoriasis is moderate or severe plaque psoriasis.

[0118] 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.

[0119] 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.

[0120] 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.

[0121] 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.

[0122] 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.

[0123] 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.

[0124] 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.

[0125] 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.

[0126] In certain embodiments the plaque psoriasis is moderate or severe plaque psoriasis.

[0127] 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.

[0128] 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.

[0129] 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.

[0130] 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.

[0131] 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.

[0132] 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.

[0133] 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.

[0134] 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.

[0135] In certain embodiments the plaque psoriasis is moderate or severe plaque psoriasis.

[0136] 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.

[0137] 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.

[0138] 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.

[0139] 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.

[0140] 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.

[0141] 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.

[0142] 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.

[0143] 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.

[0144] 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.

[0145] 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.

[0146] 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.

[0147] 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.

[0148] 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.

[0149] 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.

[0150] 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).

[0151] 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.

[0152] 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.

[0153] 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.

[0154] 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.

[0155] 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.

[0156] 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.

[0157] 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.

[0158] 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.

[0159] 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.

[0160] 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.

[0161] 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.

[0162] 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.

[0163] 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

[0164] 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.

[0165] 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.

[0166] 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.

[0167] 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.

[0168] Plaque psoriasis is a chronic disease which typically requires daily treatment for the duration of the subject's life. 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 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.

[0169] 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

[0170] Key features in the pathogenesis of AD include dermal inflammation, epithelial barrier dysfunction, and oxidative stress, which are associated with changes in AhR signaling and reduced nuclear factor erythroid 2-related factor 2 (Nrf2) activity. Type 2 proinflammatory cytokines implicated in AD include interleukin (IL)-4, IL-5, IL-13, and the pruritogenic cytokine, IL-31. Without wishing to be bound by theory, tapinarof reduces inflammation and normalizes skin barrier function by uniquely activating AhR in a ligand-dependent manner, resulting in downregulation of inflammatory Th2 cytokines implicated in AD, modulation of

keratinocyte differentiation and increased expression of the skin-barrier components including proteins (filaggrin, loricrin, and involucrin) and ceramides. Additionally, without wishing to be bound by theory, tapinarof increases cytoprotective antioxidant responses to suppress oxidative stress in AD, through activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway and by direct scavenging of reactive oxygen species in the skin. Tapinarof is a potent agonist of Nrf2 with a pEC50 of 7.6 mol/L (pEC50 defined as the negative logarithm of the EC50) as well as IL-6. Accordingly, tapinarof should normalize pigmentation in patients being treated with topical tapinarof for psoriasis and/or atopic dermatitis as well as vitiligo and other inflammatory skin disorders.

[0171] Embodiments of the invention are directed to a method for treating atopic dermatitis (AD) 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 8 weeks, until the subject has an IGA score of 0;
- b. after the initial period of time, stop treating the subject with tapinarof for a remittive period of time of about 1 month to about 7 months, wherein the remittive period of time is the time wherein the subject maintains an IGA score < 2; and
- c. if, after the remittive period of time, the subject has an IGA score of > 2, 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 an IGA 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 the atopic dermatitis 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 atopic dermatitis; 4) I have confidence in the study drug; 5) The study drug cleared my skin and kept my atopic dermatitis from coming back; 6) If the study drug was available by prescription, I would recommend it to other patients with atopic dermatitis; 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 atopic dermatitis; 14) The study drug is easier to use than other topical drugs I have used to treat my atopic dermatitis; 15) I prefer the study drug to other topical drugs I have used to treat my atopic dermatitis; 16) The study drug is more effective than systemic drugs I have used to treat my atopic dermatitis; 17) The study drug is easier to use than systemic drugs I have used to treat my atopic dermatitis; and 18) I prefer the study drug to systemic drugs I have used to treat my atopic dermatitis.

[0172] Embodiments of the invention are directed to a method for treating atopic dermatitis (AD) in a subject in need thereof, wherein the subject has achieved an IGA 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 an initial period of time of about 8 weeks to 52 weeks, comprising: stopping treatment of the subject with tapinarof for a remittive period of time of about 1 month to about 7 months, wherein the remittive period of time is the time wherein the subject has an IGA score < 2 , and

if, after the remittive period of time, the subject has an IGA score of ≥ 2 , 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 an IGA 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 the atopic dermatitis 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 atopic dermatitis; 4) I have confidence in the study drug; 5) The study drug cleared my skin and kept my atopic dermatitis from coming back; 6) If the study drug was available by prescription, I would recommend it to other patients with atopic dermatitis; 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 atopic dermatitis; 14) The study drug is easier to use than other topical drugs I have used to treat my atopic dermatitis; 15) I prefer the study drug to other topical drugs I have used to treat my atopic dermatitis; 16) The study drug is more effective than systemic drugs I have used to treat my atopic dermatitis; 17) The study drug is easier to use than systemic drugs I have used to treat my atopic dermatitis; and 18) I prefer the study drug to systemic drugs I have used to treat my atopic dermatitis.

Embodiments of the invention are directed to methods of treating atopic dermatitis in a subject from 2-17 years old comprising topically administering to the subject in need thereof a topical composition containing tapinarof as described herein, wherein one or more symptom of atopic dermatitis is improved.

[0173] Embodiments of the invention are directed to methods of treating atopic dermatitis in a subject from 2-17 years old comprising topically administering to the subject in need thereof a topical composition containing tapinarof as described herein, wherein one or more symptom of atopic dermatitis is improved.

[0174] Embodiments of the invention are directed to methods of treating atopic dermatitis in a subject from 2-17 years old comprising topically administering once a day to the subject in need thereof a topical composition containing about 0.5% tapinarof as described herein, wherein one or more symptom of atopic dermatitis is improved.

[0175] Embodiments of the invention are directed to methods of treating atopic dermatitis in a subject from 2-17 years old comprising topically administering once a day to the subject in need thereof a topical composition containing about 1.0% tapinarof as described herein, wherein one or more symptom of atopic dermatitis is improved.

[0176] Embodiments of the invention are directed to methods of treating atopic dermatitis in a subject from 2-17 years old comprising topically administering twice a day to the subject in need thereof a topical composition containing about 0.5% tapinarof as described herein, wherein one or more symptom of atopic dermatitis is improved.

[0177] Embodiments of the invention are directed to methods of treating atopic dermatitis in a subject from 2-17 years old comprising topically administering twice a day to the subject in need thereof a topical composition containing about 1.0% tapinarof as described herein, wherein one or more symptom of atopic dermatitis is improved.

[0178] In embodiments, the improvement is seen in about 4 weeks. Such improvements may be an improvement in the IGA score as described infra.

[0179] 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 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.

[0180] In embodiments described herein, the subject has been diagnosed with atopic dermatitis having a percent body surface area (BSA) affected of greater than or equal to about 25%, or greater than or equal to about 35%. In preferred embodiments, the subject has been diagnosed with atopic dermatitis having a percent body surface area (BSA) affected of about 26% to about 90%. In embodiments, the BSA affected is from about 47% to about 90%, about 50% to about 90%, 55% to about 90%, or about 60% to about 90%. In embodiments described herein, body surface area (BSA) excludes the scalp, palms of the hands and soles of the feet.

[0181] In embodiments described herein, the subject has been diagnosed with atopic dermatitis having an Investigator Global Assessment (IGA) of about 3, or about 4. In embodiments described herein, the subject has been diagnosed with mild to moderate atopic dermatitis having an Investigator Global Assessment (IGA) of greater than or equal to 3.

[0182] 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 4 weeks (i.e., 1 month). In embodiments described herein, the topical composition is administered once daily until the atopic dermatitis is resolved.

[0183] 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), 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, and patient reported outcomes.

[0184] In embodiments described herein, the Investigator's Global Assessment (IGA) is used for assessing the current state/severity of a subject's AD, also referred to as vIGA-ADTM (Validated Investigator Global Assessment for Atopic Dermatitis), a scale developed by Eli

Lilly and Company and atopic dermatitis experts, including International Eczema Council advisors and Industry experts, for use in clinical trials. 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). A score of 0 (Clear) has the following morphological description: no inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting), and post-inflammatory hyperpigmentation and/or hypopigmentation may be present. A score of 1 (Almost Clear) has the following morphological description: barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification, and no oozing or crusting. A score of 2 (Mild) has the following morphological description: slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification, and no oozing or crusting. A score of 3 (Moderate) has the following morphological description: clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification, and oozing and crusting may be present. A score of 4 (Severe) has the following morphological description: marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification, disease is widespread in extent, and oozing or crusting may be present. 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 Investigator Global Assessment (IGA) score improved by about 2 grades. In embodiments described herein, the subject's Investigator Global Assessment (IGA) score improved to a score of about 0 or about 1. In embodiments described herein, the subject's Investigator Global Assessment (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, or week 4. In certain embodiments, the subject achieved a 2-grade improvement by week 1, week 2, week 3, or week 4.

[0185] Embodiments of the invention are directed to a method for treating atopic dermatitis (AD) in a subject in need thereof, wherein the subject has an IGA score of at least 1 point lower than baseline but has not achieved an IGA 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 8 weeks to about 52 weeks, comprising continuing to apply 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 IGA 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 the atopic dermatitis 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 atopic dermatitis; 4) I have confidence in the study drug; 5) The study drug cleared my skin and kept my atopic dermatitis from coming back; 6) If the study drug was available by prescription, I would recommend it to other patients with atopic dermatitis; 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 atopic dermatitis; 14) The study drug is easier to use than other topical drugs I have used to treat my atopic dermatitis; 15) I prefer the study drug to other topical drugs I have used to treat my atopic dermatitis; 16) The study drug is more effective than systemic drugs I have used to treat my atopic dermatitis; 17) The study drug is easier to use than systemic drugs I have used to treat my atopic dermatitis; and 18) I prefer the study drug to systemic drugs I have used to treat my atopic dermatitis.

[0186] In certain embodiments, the atopic dermatitis is moderate or severe atopic dermatitis.

[0187] In some embodiments, the initial period of time is about 8 weeks to about 52 weeks. In certain embodiments the initial period of time is about 8 weeks. In certain embodiments the initial period of time is about 12, 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.

[0188] 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.

[0189] In some embodiments, wherein 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.

[0190] 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.

[0191] 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.

[0192] 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.

[0193] 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.

[0194] 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.

[0195] 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.

[0196] 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.

[0197] 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.

[0198] 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.

[0199] 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.

[0200] 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.

[0201] 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.

[0202] 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.

[0203] 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.

[0204] 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.

[0205] 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.

[0206] 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.

[0207] 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.

[0208] 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.

[0209] 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.

[0210] 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.

[0211] 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.

[0212] 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.

[0213] 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.

[0214] 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.

[0215] 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).

[0216] 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.

[0217] 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.

[0218] 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 the atopic dermatitis 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 atopic dermatitis
- 4) I have confidence in the study drug
- 5) The study drug cleared my skin and kept my atopic dermatitis from coming back
- 6) If the study drug was available by prescription, I would recommend it to other patients with atopic dermatitis
- 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 atopic dermatitis

14) The study drug is easier to use than other topical drugs I have used to treat my atopic dermatitis

15) I prefer the study drug to other topical drugs I have used to treat my atopic dermatitis

16) The study drug is more effective than systemic drugs I have used to treat my atopic dermatitis

17) The study drug is easier to use than systemic drugs I have used to treat my atopic dermatitis

18) I prefer the study drug to systemic drugs I have used to treat my atopic dermatitis

[0219] 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.

[0220] 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.

[0221] 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.

[0222] 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.

[0223] Atopic dermatitis is a chronic disease which typically requires daily treatment for the duration of the subject's life. 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.

[0224] 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.

[0225] 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).

[0226] In some embodiments, different quality of life scales are utilized to assess patient improvement through Patient Reported Outcome (PRO) measures. EQ-5D-5L is a five level scale to define general health levels, for example having no problems, having slight problems, having moderate problems, having severe problems and being unable to do/having extreme problems. Children's Dermatology Life Quality Index (CDLQI) includes physical symptoms, such as itching and sleep loss, as well as psychosocial questions regarding friendships, bullying, school performance, sports participation, and enjoyment of vacation. Dermatology Life Quality Index (DLQI) inquires about skin symptoms, feelings of embarrassment, and how skin disease has affected day-to-day activities, working and social life. Infant's Dermatology Quality of Life (IDQOL) includes questions regarding an infant or young child's difficulties with mood, sleep, bathing, dressing, play, mealtimes, other family activities, and treatment. Dermatitis Family Impact (DFI) is designed to be completed by a caretaker of the child, usually a parent, and consists of 10 questions related to housework, food preparation and feeding, sleep, family leisure activity, shopping, expenditure, fatigue, emotional distress and relationships. The PROMIS Itch-Mood and Sleep Short Form 8a assesses mood and sleep related quality of life impairment from itch (pruritus) in adults (18+), it is universal rather than disease specific

and assesses the impact of itch over the past 7 days and includes 18 items. In embodiments described herein, the subject score in one of more PRO, such as EQ-5D-5L, CDLQI, DLQI, IDQOL, DFI, and/or PROMIS Itch-Mood and Sleep improves.

[0227] 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, or week 4. In embodiments described herein, the subject has sustained improvement of 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 of 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 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.

[0228] 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, or week 4. In embodiments described herein, the subject has sustained improvement of one or more symptoms assessed by the POEM after treatment has ended. In embodiments described herein, the subject has sustained improvement of one or more symptoms assessed by the 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 symptoms assessed by the 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.

[0229] 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, or 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 of 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.

[0230] 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 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 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 composition has ceased. In embodiments described herein, the one or more symptoms remain improved about 2 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved about 3 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved about 4 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved about 8 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved about 12 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved about 16 weeks after administration of the topical composition has ceased. In embodiments described herein, the one or more symptoms remain improved about 20 weeks after administration of the topical composition has ceased.

[0231] In embodiments described herein, the topical composition exhibits low systemic absorption following topical application. In embodiments described herein, the topical composition exhibits no accumulation with repeat dosing. Systemic absorption of tapinarof is measured in plasma. In embodiments described herein, plasma concentration of tapinarof is below the limit of detection (LOD) when measured at 1, 2, 4, 6, 8 and 24 hours following once daily application of the topical composition described herein. In embodiments described herein, plasma concentration of tapinarof is below the limit of detection (LOD) when measured at 1, 2, 4, 6, 8 and 24 hours following twice daily application of the topical composition described herein. In some embodiments, the mean AUC[0-24] is about 23.4 to about 2.2 h*ng/mL. In some embodiments, the mean AUC[0-24] is about 10.5 to about 1.5 h*ng/mL.

[0232] In embodiments described herein, the topical composition is non-stinging.

[0233] In embodiments described herein, the topical composition is more effective than pimecrolimus (Elidel™), tacrolimus (Protopic™), crisaborole (Eucrisa™), or desonide (Verdeso™ or Desonate™).

[0234] In embodiments described herein, the topical composition is administered in an initial dosing regimen followed by a maintenance dosing regimen. In embodiments described herein, the initial dosing regimen is about 1 week to about 4 weeks in duration. In embodiments described herein, the topical composition administered in the initial dosing regimen contains 1% tapinarof. In embodiments described herein, the topical composition administered in the maintenance dosing regimen contains 0.5% tapinarof.

[0235] In embodiments, the method may include the co-administration of additives, other second active agents or enzymes as described herein. In embodiments, co-administration may be at the same time, substantially the same time, before or after administration of the topical compositions described herein.

[0236] In embodiments, the additives may be selected from the group consisting of vitamins, cosmetic peptides, oil control agents, sensation modifying agents, skin lightening agents, hydrating compositions, a sunblock agent, a compound that absorbs or reflects UV photons, other skin care agents, a second active agent and combinations thereof, as described herein.

[0237] In some embodiments, the topical composition can be applied to the skin one, two, three, four, five or more times each day, and applying can be carried out for a period of at least 1 month, 2 months, 3 months, 4 months, 6 months, 8 months or 12 months.

[0238] In such embodiments, the topical composition can be applied to the skin one, two, three, four, five or more times each day, and applying can be carried out for a period of at least 1 month, 2 months, 3 months, 4 months, 6 months, 8 months or 12 months.

[0239] In some embodiments, the topical composition may be administered once, as needed, once daily, twice daily, three times a day, once a week, twice a week, every other week, every other day, or the like for one or more dosing cycles. A dosing cycle may include administration for about 1 week, about 2 weeks, about 3 weeks, or about 4 weeks. After this cycle, a subsequent cycle may begin approximately 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 weeks later. The treatment regimen may include 1, 2, 3, 4, 5, or 6 cycles, each cycle being spaced apart by approximately 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 weeks.

[0240] In some embodiments, a method of treating atopic dermatitis in a subject as set forth in Example 1 is provided. The subject may be 2-11 years old with at least a 35% BSA affected and is topically administered once daily for four weeks the 1% tapinarof composition described herein to achieve one or more of the primary or secondary endpoints disclosed in Example 1, such as an IGA score improved by 2 grades or an IGA a score of 0 or 1. Further baseline characteristics of the subject may be as set forth in Example 1. The Cmax of tapinarof in the blood may be less than 50 pg/mL after four weeks of administration. The TEAEs experienced by the subject may be as set forth in Example 1 and may be less than the expected TEAEs based upon prior clinical use.

[0241] In some embodiments, a method of treating atopic dermatitis in a subject as set forth in Example 1 is provided. The subject may be 12-17 years old with at least a 25% BSA affected and is topically administered once daily for four weeks the 1% tapinarof composition described herein to achieve one or more of the primary or secondary endpoints disclosed in Example 1, such as an IGA score improved by 2 grades or an IGA a score of 0 or 1. Further baseline characteristics of the subject may be as set forth in Example 1. The Cmax of tapinarof in the blood may be less than 50 pg/mL after four weeks of administration. The TEAEs experienced by the subject may be as set forth in Example 1 and may be less than the expected TEAEs based upon prior clinical use.

[0242] METHODS OF USING TOPICAL COMPOSITIONS TO TREAT RADIATION DERMATITIS

[0243] 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.

[0244] 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.

[0245] 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.

[0246] 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.

[0247] 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.

[0248] 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.

[0249] 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.

[0250] 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.

[0251] 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.

[0252] 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).

[0253] 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).

[0254] 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.

[0255] 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.

[0256] 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.

[0257] 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.

[0258] 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.

[0259] 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.

[0260] 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.

[0261] 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.

[0262] 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.

[0263] 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.

[0264] *ADDITIONAL METHODS OF USE*

[0265] 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.

[0266] 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.

[0267] 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.

[0268] 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.

[0269] 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.

[0270] 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.

[0271] 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.

[0272] 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.

[0273] 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.

[0274] 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.

[0275] 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).

[0276] 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).

[0277] 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).

[0278] 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).

[0279] 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).

[0280] 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).

[0281] 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).

[0282] 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).

[0283] 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).

[0284] 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).

[0285] 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.

[0286] 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.

[0287] 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.

[0288] 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.

[0289] 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.

[0290] 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.

[0291] 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.

[0292] 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.

[0293] 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.

[0294] 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).

[0295] 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

[0296] Embodiment 1: A method for treating atopic dermatitis in a subject in need thereof, comprising: applying a thin layer of about 1.0% tapinarof topical cream composition to an affected area of the subject for a period of time of at least 8 weeks; wherein, after the period of time, the subject has: at least a 2-grade improvement in vIGA-AD score from baseline, and an vIGA-AD score of 0; and wherein the plasma concentration of tapinarof in the subject is below 50 pg/mL while applying the 1.0% tapinarof topical cream.

[0297] Embodiment 2: The method of Embodiment 1, wherein the subject has an improvement in an EASI score of about 75% from baseline during the period of time.

[0298] Embodiment 3: The method of Embodiment 1 or 2, wherein the subject has a reduction in a PP-NRS score ≥ 4 points from baseline during the period of time.

[0299] Embodiment 4: The method of any of Embodiments 1-3, wherein the subject is at least 12 years old.

[0300] Embodiment 5: The method of any of Embodiments 1-3, wherein the subject is at least 2 years old.

[0301] Embodiment 6: The method of any of Embodiments 1-5, wherein the subject does not experience an adverse event during the period of time, wherein the adverse event is selected from the group consisting of contact dermatitis, folliculitis, headache, and a combination thereof.

[0302] Embodiment 7: The method of any of Embodiments 1-6, wherein the subject has an affected BSA of about 43%.

[0303] Embodiment 8: The method of any of Embodiments 1-6, wherein the subject as an affected BSA of up to about 90%.

[0304] Embodiment 9: A method for treating atopic dermatitis as described in Example 1 herein.

[0305] Embodiment 10: A method for treating atopic dermatitis as described in the ADORING 2 trial and having one or more of the results described herein.

[0306] 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.

[0307] Embodiment 12: The method of Embodiment 11, wherein the initial period of time is about 16 weeks to about 40 weeks.

[0308] Embodiment 13: The method of Embodiment 11, wherein atopic dermatitis is clear when the Investigator Global Assessment (IGA) score is 0 or 1.

[0309] Embodiment 14: The method of Embodiment 11, wherein further treatment is required if the IGA score is greater than or equal to 2.

[0310] 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.

[0311] Embodiment 16: The method of Embodiment 15, wherein the subsequent period of time is about 8 weeks to about 16 weeks.

[0312] Embodiment 17: The method of Embodiment 12, wherein the initial period of time is about 40 weeks.

[0313] Embodiment 18: The method of Embodiment 17, wherein reassessment of the subject occurs at about 4 months after administration.

[0314] Embodiment 19: The method of Embodiment 18, wherein further treatment is initiated.

[0315] 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.

[0316] 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.

[0317] Embodiment 22: The method of Embodiment 21, wherein the initial period of time is about 16 weeks to about 40 weeks.

[0318] Embodiment 23: The method of Embodiment 21, wherein radiation dermatitis is clear when the Grade Classification score is 1.

[0319] Embodiment 24: The method of Embodiment 21, wherein further treatment is required if the Grade Classification score is greater than or equal to 2.

[0320] 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.

[0321] Embodiment 26: The method of Embodiment 25, wherein the subsequent period of time is about 8 weeks to about 16 weeks.

[0322] Embodiment 27: The method of Embodiment 22, wherein the initial period of time is about 40 weeks.

[0323] Embodiment 28: The method of Embodiment 27, wherein reassessment of the subject occurs at about 4 months after administration.

[0324] Embodiment 29: The method of Embodiment 28, wherein further treatment is initiated.

[0325] 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.

[0326] 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.

[0327] 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.

[0328] Embodiment 33: The method of Embodiment 31, wherein the administration is stopped for about 4 months or indefinitely.

[0329] 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.

[0330] 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.

[0331] Embodiment 36: The method of Embodiment 35, wherein the subject maintains an improved PGA score but does not reach 0.

[0332] 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.

[0333] 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.

[0334] 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.

[0335] Embodiment 40: The method of Embodiment 38, wherein the administration is stopped for about 4 months or indefinitely.

[0336] 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.

[0337] 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.

[0338] Embodiment 43: The method of Embodiment 42, wherein the subject maintains an improved IGA score but does not reach 0.

[0339] 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.

[0340] 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.

[0341] Embodiment 46: The method of Embodiment 45, wherein the subject reaches a National Cancer Institute classification of Grade 1 at 12 weeks.

[0342] Embodiment 47: The method of Embodiment 45, wherein the administration is stopped for an indefinite amount of time.

[0343] 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.

[0344] 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.

[0345] Embodiment 50: The method of Embodiment 49, wherein the subject maintains an improved classification but does not reach Grade 1.

[0346] 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.

[0347] Embodiment 52: A method of treating atopic dermatitis, as described in one or more of FIG. 1A, FIG. 1B, FIG. 2, FIG. 3, FIG. 4, FIG. 5, FIG. 6, FIG. 7, FIG. 8, FIG. 9, FIG. 10, FIG. 11, FIG. 12, FIG. 13A, FIG. 13B, FIG. 14, FIG. 15, FIG. 16, FIG. 17, FIG. 18, FIG. 19, FIG. 20, FIG. 21, FIG. 22, FIG. 23, FIG. 24, FIG. 25A, FIG. 25B, FIG. 26A, FIG. 26B, FIG. 27A, FIG. 27B, FIG. 27C, FIG. 27D, FIG. 27E, FIG. 27F, FIG. 27G, and FIG. 28 included herein.

[0348] Embodiment 53: A method of treating plaque psoriasis, as described in one or more of FIG. 29, FIG. 30A, FIG. 30B, FIG. 31, and FIG. 32 included herein.

[0349] Embodiment 54: The method of any of Embodiments 1-3, wherein the subject is less than 12 years old.

[0350] Embodiment 55: The method of any of Embodiments 1-5 or 54, wherein the subject achieves an LTS score of 0, 1, or 2 during the period of time.

[0351] Embodiment 56: The method of Embodiment 55, wherein the subject achieves an LTS score of 0 or 1 during the period of time.

[0352] Embodiment 57: The method of any of Embodiments 1-8 or 54-56, wherein the subject has a Fitzpatrick skin type selected from the group consisting of type I, type II, type III, type IV, type V, and type VI.

[0353] Embodiment 58: The method of any of Embodiments 1-8 or 54-56, wherein the subject has a race selected from the group consisting of White, Black, Asian, American Indian/Alaska Native, Native Hawaiian/Pacific Islander, and combinations thereof.

[0354] Embodiment 59: The method of any of Embodiments 1-8, wherein the subject has a patient-reported Local Tolerability Score (LTS) < 1.

[0355] Embodiment 60: The method of any of Embodiments 1-8 or 60, wherein the subject does not experience burning, stinging, or local irritation at the affected area.

[0356] Embodiment 61: The method of any of Embodiments 1-8, 60, or 61, wherein the affected area comprises a sensitive area, an intertriginous area, or a combination thereof.

[0357] 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 due 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

[0358] Example 1: A Long-Term, Open-Label, Extension Study to Evaluate the Safety and Efficacy of Tapinarof Cream, 1% for the Treatment of Atopic Dermatitis in Adults

Background

[0359] Atopic dermatitis (AD) (also called atopic eczema) is an intensely pruritic, chronic, relapsing, inflammatory skin disease that commonly presents in early childhood, but also affects adults, and severely impacts the quality of life of patients and their families. The characteristic signs and symptoms of AD include sensations of pruritis and burning, xerosis, erythematous papules and plaques, exudation, crusting, and lichenification. Quality of life is affected through sleep deprivation due to the intense and constant itching, as well as the stigma associated with having a visible skin disease. The cardinal and most burdensome symptom of AD is severe and intense pruritus, which has a profound negative influence on sleep, physical

and mental development, and the overall quality of life of patients, their families, and caregivers. Sleep impairments in children with AD are associated with increased risk of short stature, metabolic syndrome, mental illness, and neurocognitive dysfunction. Up to 30% of children may be affected by AD at some point, and 2% to 10% of adults have AD. Currently there is no curative therapy. Stabilizing the disease and reducing the number and severity of flares are the primary goals of treatment. Topical treatments directed at skin inflammation are a key factor in disease management, as is symptomatic relief of itching. Although multiple 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.

[0360] Tapinarof cream, 1% is a white to off-white, oil-in-water emulsion intended for topical application to AD and psoriatic skin lesions, which has a novel mechanism of action. Tapinarof is a nonsteroidal, small molecule therapeutic aryl hydrocarbon receptor (AhR) modulating agent (TAMA), which likely exerts its therapeutic effects via agonism of AhR, a cytosolic ligand dependent transcription factor. Upon ligand binding, AhR translocates to the nucleus and dimerizes with AhR nuclear translocator (ARNT) forming an AhR ARNT heterodimer. The AhR ARNT heterodimer modulates gene transcription through direct and indirect interaction with DNA. By activation of this AhR signaling pathway, tapinarof has the potential to downregulate the expression of pro inflammatory cytokines, including interleukin (IL)-4, IL-5, IL-6, IL-13, IL 17A and F, IL-31, and eotaxin, and normalize the skin barrier through upregulation of the expression of several skin barrier proteins, including filaggrin, loricrin, hornerin, involucrin, and ceramide lipids. In addition, AhR also activates the antioxidative transcription factor nuclear factor-erythroid 2-related factor-2 (Nrf2), upregulating the expression of antioxidative enzymes. By targeting AhR, tapinarof has a biological profile that differs from that of currently available products, offering patients a truly novel therapeutic treatment option for plaque psoriasis and AD. Tapinarof is a potent agonist of Nrf2 with a pEC50 of 7.6 mol/L (pEC50 defined as the negative logarithm of the EC50) as well as IL-6. Accordingly, tapinarof should normalize pigmentation in patients being treated with topical tapinarof for psoriasis and/or atopic dermatitis as well as vitiligo and other inflammatory skin disorders.

[0361] Two Phase 2b, 12-week, randomized, double-blind, vehicle-controlled, 6 arm, parallel group, dose finding studies with topically applied tapinarof cream were conducted by GlaxoSmithKline (GSK); 1 study each in subjects with AD or psoriasis. These 2 studies

evaluated the safety and efficacy of tapinarof cream (Formulation F) at 2 concentrations (0.5% or 1% weight/weight [w/w]) and 2 application frequencies (once daily [QD] or twice daily [BID]) in 247 adult and adolescent subjects with AD and in 227 adult subjects with plaque psoriasis. In both studies, tapinarof showed a clear therapeutic effect compared with vehicle, with the 1% w/w concentration treatment groups demonstrating a higher proportion of subjects with treatment success compared with the 0.5% w/w concentration groups (applied QD and BID in the AD study). In both indications, the tapinarof 1% dosing groups showed a faster onset of action than the 0.5% dosing groups, and QD application had similar efficacy to BID application. In both Phase 2b studies, tapinarof showed an acceptable safety profile. Treatment-emergent adverse events (TEAEs) were reported with a higher frequency in the tapinarof groups than in the vehicle groups. The most frequent TEAEs ($\geq 5\%$ in any arm or in total) were nasopharyngitis, folliculitis, dermatitis contact, atopic dermatitis, upper respiratory tract infection, headache, vomiting, acne, application site dermatitis, miliaria, dermatitis allergic, and impetigo. The majority of TEAEs were mild or moderate in severity. In each study, the tapinarof 1% QD treatment group had a lower frequency of TEAEs than the tapinarof 1% BID treatment group.

[0362] Tapinarof has been evaluated in two identical Phase 3, 12-week, randomized, double-blind, vehicle-controlled trials in adult subjects with plaque psoriasis. These studies evaluated the safety and efficacy of tapinarof cream, 1% QD versus vehicle cream QD in a combined 1025 subjects randomized 2:1 tapinarof to vehicle. In both trials, tapinarof demonstrated superiority against vehicle on the primary endpoint, a Physician Global Assessment (PGA) score of 0 (clear) or 1 (almost clear) with a 2-point improvement at Week 12. In addition, tapinarof was highly statistically significant compared to vehicle on all secondary endpoints which included proportion of subjects achieving a 75% improvement in the Psoriasis Area and Severity Index, a PGA score of 0 or 1, change in percent body surface area (%BSA), and proportion of subjects achieving a 90% improvement in the Psoriasis Area and Severity Index at Week 12. TEAEs were reported with a higher frequency in the tapinarof group than in the vehicle group. The most frequent TEAEs ($\geq 5\%$ in any arm or in total) were folliculitis, nasopharyngitis, and contact dermatitis. The majority of TEAEs were mild or moderate in intensity.

[0363] Tapinarof has also been evaluated in an open-label, long-term extension (OL-LTE) study in adult subjects with plaque psoriasis. The OL-LTE study in adults with plaque psoriasis evaluated the safety and efficacy of tapinarof cream, 1% QD for 40 weeks in 763 subjects

enrolled from the two identical 12-week studies. While the study remains ongoing at this time, a pre-specified interim analysis of the study tapinarof demonstrated continued and substantial improvement in efficacy endpoints beyond the 12 weeks of treatment observed in the identical Phase 3 studies. A high rate of complete disease clearance was achieved, with a remittive effect of approximately 4 months of disease control off therapy. Tapinarof was well tolerated with long-term use and had a safety profile consistent with previous studies.

ADORING Study Rationale

[0364] Twin pivotal Phase 3 studies (Phase 3 pivotal safety and efficacy study DMVT-505-3101 (ADORING 1) and Phase 3 pivotal safety and efficacy study DMVT-505-3102 (ADORING 2)) were conducted as part of a clinical development program to evaluate the efficacy and safety of tapinarof cream, 1% for the topical treatment of atopic dermatitis (AD) in adults and children ages 2 years and above. The results of this study are intended to support product registration in the United States and Canada.

[0365] A 48-week, Phase 3, OL-LTE study (ADORING 3) will also be conducted as part of a clinical development program to evaluate the long-term safety and continued efficacy of tapinarof cream, 1% for the treatment of AD in children and adults. Subjects who complete one of three parent studies (Phase 3 pivotal safety and efficacy study DMVT-505-3101, Phase 3 pivotal safety and efficacy study DMVT-505-3102, or Phase 2 maximal use pharmacokinetics [PK] study DMVT-505-2104) and meet the predefined criteria will have the option to participate in this study. Additionally, approximately 125 pediatric subjects ages 2 to < 18 years who are not eligible for participation in the Phase 3 pivotal studies will also be enrolled directly into this OL-LTE study.

[0366] *Rationale for Study Design, Dose, and Control Groups.* The Phase 3 pivotal studies (Phase 3 pivotal safety and efficacy study DMVT-505-3101 (ADORING 1), Phase 3 pivotal safety and efficacy study DMVT-505-3102 (ADORING 2), both for the topical treatment of AD) were both 8-week double-blind, vehicle-controlled treatment studies in which subjects were randomized to receive tapinarof cream, 1% or vehicle cream QD for 8 weeks. The studies were conducted at multiple study sites in more than one country to enhance the possibility of inclusion of a wider range of population groups and to increase generalizability of the results. This randomized, double-blind, vehicle-controlled study design minimized the potential for subjective bias related to possible identification of which subjects received active treatment and minimized selection and allocation bias by balancing potential prognostic factors. A

vehicle control group was included to provide a control for comparison and to ensure study sensitivity for characterization of the safety and efficacy profile of tapinarof cream, 1%.

[0367] Tapinarof cream has been investigated for the topical treatment of AD in prior studies at concentrations of up to 8.0% w/w in nonclinical studies and 2.0% w/w in clinical studies at QD and BID dosing frequencies. The 1% concentration applied QD was chosen as the dose and dosing frequency to take forward in the Phase 3 clinical development program based on the data from GSK Phase 2b clinical Study 203121. In that study, applications of tapinarof cream at concentrations of 0.5% and 1% applied QD or BID were evaluated. Treatment success as defined by an Investigator's Global Assessment (IGA) score of clear or almost clear with a minimum 2-point improvement was higher with both tapinarof concentrations than with vehicle at all visits beyond Week 2, as shown in FIG. 2, which shows treatment success (IGA score) by dosing regimen in Study 203121. The groups treated with a 1% concentration showed higher efficacy and resulted in a quicker onset of effect than did the groups treated with a 0.5% concentration. Efficacy responses began as early as Week 2 and continued through Week 12. The proportion subjects with $\geq 75\%$ improvement in Eczema Area Severity Index (EASI) was also higher for the 1% BID (60%) and 1% QD (51%) compared to vehicle (25-26%). Overall, both concentrations demonstrated an acceptable safety profile when applied once or BID with the 1% QD arm having a lower number of reported TEAEs compared to the 1% BID arm (54% vs 70%, respectively). QD application was selected as efficacy was similar between 1% BID and 1% QD regimens and provided a better safety profile. In addition, QD application may improve treatment adherence compared with more frequent dosing administrations.

[0368] The 8-week treatment endpoint for the Phase 3 pivotal studies was selected based on similar response rates between week 8 and week 12 for IGA and EASI endpoints. Treatment success for IGA was 49% at Week 8 and 46% at Week 12 for the 1% QD arm. Similarly, the proportion subjects with $\geq 75\%$ improvement in EASI was 57% at both Week 8 and Week 12. The effect of vehicle continued to increase between these timepoints. Clinical studies in AD have historically shown a notable vehicle response rate that could be attributable to the effects of skin moisturization or to the increased emphasis on proper skin care while participating in a clinical study. An 8-week duration may best show differences between active and vehicle dosing groups, demonstrating the true drug effect.

[0369] Based on the efficacy and safety data from Study 203121, tapinarof cream, 1% QD was chosen as the concentration and dosing frequency to be investigated in the Phase 3 pivotal

studies and intended for registration. The dose selected from adolescent and adult data is likely to be effective and safe in younger pediatric populations based on similarities in skin anatomical and functional maturity, and our current understanding of the mechanism of action. Furthermore, extrapolation of data from the Phase 3 program into this younger population is supported by similarities in disease definition, clinical classification, measures of disease progression, and pathophysiology.

[0370] In GSK study 203121, the safety, efficacy, and plasma concentrations of tapinarof were similar between adults and adolescents. Adolescent subjects had a similar IGA score and %BSA affected at baseline relative to adults. The incidence and type of adverse events (AEs) in the adult and adolescent populations were consistent with that seen in the overall population. In addition, plasma concentrations were similar between adults and adolescents, with both groups having minimal or no absorption.

[0371] Evaluation of the clinical pharmacology of tapinarof across 10 studies demonstrates the skin as the site of drug action, minimal systemic absorption following topical dosing, and no accumulation with repeat QD dosing. The skin of infants would be expected to have similar barrier function to adults. Infants born at 30 and 32 weeks gestational age were found to have a fully functional stratum corneum comparable with that of adults. Another study demonstrated that the way the stratum corneum stores and transports water becomes adult-like after the first year of life.

[0372] Given the low systemic absorption of tapinarof observed in adults and adolescents and the fact the skin barrier function in the age group being evaluated is expected to be similar to that of adults, absorption of tapinarof in pediatric patients was expected to be low and not impacted by BSA:bodyweight ratios. The sponsor has evaluated various relationships between pharmacokinetics (when detectable) and patient factors. An analysis from the psoriasis maximal use study demonstrated no relationship between subjects' %BSA affected and tapinarof exposure. Furthermore, no clinically relevant differences in plasma concentration were observed based on age, sex, race, and %BSA affected in the Phase 3 pivotal trials in patients with psoriasis.

[0373] Potential relationships between tapinarof plasma exposure and measures of efficacy and safety in subjects with psoriasis and AD were explored in an exposure response analysis across Phase 2 and 3 studies. No significant correlations between plasma exposure and adverse events of special interest (AESIs) or efficacy were observed. Thus, the minimal systemic

exposure and lack of any pharmacokinetic/pharmacodynamic relationships further support usage of tapinarof down to 2 years of age.

[0374] As in the three parent studies, the Phase 3 OL-LTE study will be conducted at multiple study sites in more than one country to enhance the possibility of inclusion of a wider range of population groups and to subsequently increase generalizability of the results. Tapinarof cream is intended for long-term, intermittent use in non-life-threatening inflammatory dermatologic conditions. Therefore, the 48-week duration of long-term, intermittent use of tapinarof cream, 1% in this study is expected to be an adequate duration to assess safety and efficacy of repeated treatment courses of tapinarof as recommended in the International Conference on Harmonisation E1A (ICH E1A) guideline on the extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions, which recommends a minimum of 100 subjects treated with the intended clinical dose to be followed for at least one year.

[0375] Phase 3 pivotal study objective: To evaluate the efficacy of tapinarof cream, 1% QD compared with vehicle control in subjects with AD. Endpoint: Proportion of subjects who have a validated Investigator Global Assessment in Atopic Dermatitis (vIGA-AD) score of clear or almost clear (0 or 1) and at least a 2-grade reduction from Baseline at Week 8.

[0376] Phase 3 pivotal study objective: To further characterize the efficacy of tapinarof cream, 1% QD compared with vehicle control over time. Endpoints: Proportion of subjects with $\geq 75\%$ improvement in EASI from Baseline at Week 8; Mean change in %BSA affected from Baseline at Week 8; Proportion of subjects with $\geq 90\%$ improvement in EASI from Baseline at Week 8; Proportion of subjects ≥ 12 years old with a Baseline Peak Pruritus-Numeric Rating Scale (PP-NRS) score ≥ 4 who achieve ≥ 4 -point reduction in the PP-NRS from Baseline at Week 8; Time to achieve a vIGA-AD score of 0 or 1 and at least a 2-grade reduction from Baseline; Proportion of subjects who achieve a vIGA-AD score of clear or almost clear (0 or 1) and at least a 2-grade reduction from Baseline at Weeks 1, 2, and 4; Proportion of subjects with $\geq 50\%$ improvement in EASI from Baseline at each study visit; Proportion of subjects with $\geq 75\%$ improvement in EASI from Baseline at Weeks 1, 2, and 4; Proportion of subjects with $\geq 90\%$ improvement in EASI from Baseline at Weeks 1, 2, and 4; Mean change in %BSA affected from Baseline at Weeks 1, 2, and 4; Mean percent change in %BSA affected from Baseline at each study visit; Mean change and percent change in BSA $\times$ vIGA-AD from Baseline at each study visit; Mean change and percent change in EASI score from Baseline at each study visit; vIGA-AD scores and change from Baseline at each study

visit; Mean change in PP-NRS score from Baseline at each study visit; Proportion of subjects with a Baseline PP-NRS score ≥ 4 who achieve ≥ 4 -point reduction in the PP-NRS from Baseline at each study visit; Proportion of subjects ≥ 12 years old with a Baseline PP-NRS score ≥ 4 who achieve ≥ 4 -point reduction in the PP-NRS from Baseline at Weeks, 1, 2, and 4; Proportion of subjects < 12 years old with a Baseline PP-NRS score ≥ 4 who achieve ≥ 4 -point reduction in the PP-NRS from Baseline at each study visit.

[0377] Phase 3 pivotal study (ADORING 1 and ADORING 2) objective: To evaluate the safety and tolerability of tapinarof cream, 1% QD in subjects with AD. Endpoints: Incidence, frequency, and duration of TEAEs and serious adverse events (SAEs); Change from Baseline in laboratory values; Change from Baseline in ECG parameters; Change from Baseline in vital signs; Mean Investigator-assessed local tolerability scale (LTS) scores by visit (overall and sensitive areas); Mean subject (or caregiver)-assessed LTS scores by visit.

[0378] Phase 3 pivotal study (ADORING 1 and ADORING 2) objective: To describe the effect of tapinarof cream, 1% QD on AD symptom severity and the associated impact on daily activities and attitudes in subjects with AD. Endpoints: Mean change from Baseline in Dermatology Life Quality Index (DLQI), Children's Dermatology Life Quality Index (CDLQI), and Infant's Dermatitis Quality of Life Index (IDQOL) total and individual domain scores at each study visit; Mean change from Baseline in EQ-5D-5L and EQ-5D-Y total and individual domain scores at each study visit; Mean change from Baseline in the total score of the Patient Oriented Eczema Measure (POEM) For Self-Completion (subjects ≥ 12 years old) at each study visit; Mean change from Baseline in the total score of the POEM For Proxy-Completion (by caregiver for subjects < 12 years old) at each study visit; Mean change from Baseline in the total score of the Dermatitis Family Impact (DFI) at each study visit.

[0379] Phase 3 pivotal study (ADORING 1 and ADORING 2) objective: To evaluate plasma concentrations of tapinarof in subjects with AD. Endpoint: Plasma concentration of tapinarof at Weeks 4 and 8.

[0380] Phase 3 OL-LTE study (ADORING 3) objective: To evaluate the safety and tolerability of tapinarof cream, 1% in subjects with AD. Endpoints: Incidence, frequency, and duration of TEAEs and serious adverse events (SAEs); Change from Baseline in laboratory values; Change from Baseline in vital signs; Mean Investigator-assessed local tolerability scale (LTS) scores by visit (overall and sensitive areas); Mean subject (or caregiver)-assessed LTS scores by visit.

[0381] Phase 3 OL-LTE study (ADORING 3) objective: To evaluate the efficacy of tapinarof cream, 1% over an extended period of time in subjects with AD. Endpoints: For subjects entering the study with a validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) score of clear (0): Proportion of subjects who experience vIGA-AD ≥ 2 at least 1 time during the study; Proportion of subjects who never experience vIGA-AD ≥ 2 throughout the study; Time to first worsening (vIGA-AD ≥ 2), defined as days from date of Baseline visit to the date of first occurrence of vIGA-AD ≥ 2 ; Subjects who never experience vIGA-AD ≥ 2 throughout the study will be censored at the date of their last vIGA-AD assessment. For subjects entering the study with a vIGA-AD score ≥ 1 : Proportion of subjects who achieve vIGA-AD = 0 at least 1 time during the study; Proportion of subjects who never achieve vIGA-AD = 0 throughout the study; Time to first achieving a vIGA-AD score of 0, defined as days from date of Baseline visit to the date of first occurrence of vIGA-AD score of 0; Subjects who never achieve vIGA-AD = 0 throughout the study will be censored at the date of their last vIGA-AD assessment. For subjects entering the study with a vIGA-AD score ≥ 2 : Proportion of subjects who achieved vIGA-AD = 0 or 1 at least 1 time during the study; Proportion of subjects who never achieve vIGA-AD = 0 or 1 throughout the study. The following endpoints will be summarized over subjects in the intent-to-treat (ITT) population: Duration (days) of treatment periods, defined as time (days) from each treatment initiation/re-initiation to each subsequent disease clearance (vIGA-AD = 0); Duration (days) of treatment-free intervals, defined as time (days) from each treatment discontinuation (vIGA-AD score of 0) to each subsequent treatment re-initiation (vIGA-AD ≥ 2); vIGA-AD scores and the change from Baseline values by visit (observed case [OC] and last observation carried forward [LOCF]); Absolute value, change and percent change from Baseline in %BSA affected by visit (OC and LOCF); Absolute value, change and percent change from Baseline in BSA*vIGA-AD values by visit (OC and LOCF); Absolute value, change and percent change from Baseline in Eczema Area and Severity Index (EASI) score by visit (OC and LOCF); Proportion of subjects with $\geq 50\%$ improvement in EASI score from Baseline by visit (OC and LOCF); Proportion of subjects with $\geq 75\%$ improvement in EASI score from Baseline by visit (OC and LOCF); Proportion of subjects with $\geq 90\%$ improvement in EASI score from Baseline by visit (OC and LOCF).

[0382] Phase 3 OL-LTE study (ADORING 3) objective: To describe the effect of tapinarof cream, 1% on AD symptom severity and the associated impact on daily activities and attitudes in subjects with AD. Endpoints: Mean change in Peak Pruritus-Numeric Rating Scale (PP-

NRS) score from Baseline at each study visit; Proportion of subjects with a Baseline PP-NRS score ≥ 4 who achieve ≥ 4 -point reduction in the PP-NRS from Baseline at each study visit; Proportion of subjects ≥ 12 years old with a Baseline PP-NRS score ≥ 4 who achieve ≥ 4 -point reduction in the PP-NRS from Baseline at each study visit; Proportion of subjects < 12 years old with a Baseline PP-NRS score ≥ 4 who achieve ≥ 4 -point reduction in the PP-NRS from Baseline at each study visit; Mean change from Baseline in Dermatology Life Quality Index (DLQI), Children's Dermatology Life Quality Index (CDLQI), and Infant's Dermatitis Quality of Life Index (IDQOL) total and individual domain scores at each study visit; Mean change from Baseline in the total score of the Patient Oriented Eczema Measure (POEM) For Self-Completion (for subjects ≥ 12 years old) at each study visit; Mean change from Baseline in the total score of the POEM For Proxy-Completion (by caregiver for subjects < 12 years old) at each study visit; Mean change from Baseline in EQ-5D-5L and EQ-5D-Y total and individual domain scores at each study visit; Mean change from Baseline in the total score of the Dermatitis Family Impact (DFI) at each study visit.

Study Design (ADORING 1 and ADORING 2)

[0383] Each Phase 3 pivotal study was a double-blind, randomized, vehicle-controlled, Phase 3, multicenter study to evaluate the efficacy and safety of topical tapinarof cream, 1% compared with vehicle cream in children and adult subjects with AD.

[0384] Following a 30-day screening period, eligible subjects were randomized at a 2:1 ratio to receive QD treatment with tapinarof cream, 1% or vehicle cream for 8 weeks. Subjects returned to the clinic at Weeks 1, 2, 4, and 8 for efficacy and safety assessments. Additionally, subjects were contacted by phone at Weeks 3 and 6 to assess AEs and concomitant medications, to review study drug administration instructions, and to confirm subject's continued participation in this study.

[0385] Study drug was dispensed and applied during the clinic visits and was administered at home between clinic visits as instructed by site personnel. Subjects or their caregivers were instructed to apply study drug QD to all affected areas, including newly appearing lesions and lesions/areas that improved during the study. Subjects or their caregivers applied sufficient study drug to cover completely each lesion with a thin layer of study drug and recorded the time of study drug application and daily itch score (PP-NRS) in a daily diary provided by the study site. Subjects were allowed, but not required, to treat scalp lesions with study drug; however, efficacy analyses did not include assessment of AD in the scalp. Subjects and/or caregivers were advised to maintain the approximate dosing time chosen at the beginning of

the study for their full study participation. Nonmedicated emollients that do not contain salicylic acid could be used on nonlesional skin but the subject (or caregiver) were instructed to wait at least 30 minutes after applying study drug before applying nonmedicated emollients; emollients should not be applied to lesional skin during treatment. The same emollient was to be used throughout the subject's participation in the study. At the phone contacts at Weeks 3 and 6, subjects or caregivers were reminded to complete their daily diary and bring it with them to the next clinic visit.

[0386] Study drug application instructions were reviewed at all post-randomization clinic visits and during any planned study phone calls. On clinic visit days, subjects and/or caregivers were instructed/reminded on how to apply study drug (except during the final treatment/end-of-study visits). During the clinic visits, subjects or their caregivers applied the daily dose of study drug while on-site under the supervision of site personnel after efficacy and safety assessments have been completed, with the exception of the LTS at some visits (as outlined in the Schedule of Assessments). The time of the dose application and assessments depended on the time of the clinic visit. Therefore, the timing of the clinic visit could have led to a change in the subject's chosen dosing time for that day.

[0387] At the end of the 8 weeks of assessments in this study (ADORING 1 and ADORING 2), subjects had the option to enroll in an Open-Label, Long-Term Extension (OL-LTE) study for an additional 48 weeks. Subjects who complete Visit 6/Week 8 but chose not to participate in the OL-LTE study or who failed to qualify for participation in the OL-LTE study completed a Follow-up Visit (Visit 7/Week 9 visit) approximately 1 week after the end of treatment in this study. Subjects who withdrew from the study before Visit 6/Week 8 completed an Early Termination Visit as their final visit and were not eligible for the OL-LTE study. The subjects who completed the Early Termination Visit did not complete a Follow-Up Visit.

[0388] Study duration for subjects who completed this Phase 3 pivotal study (ADORING 1 and ADORING 2) and who failed to qualify for participation in the OL-LTE study (ADORING 3), or who qualified to participate in the OL-LTE study but elected not to enroll in that study, was approximately 13 weeks in total. Study duration for subjects who completed this Phase 3 study (ADORING 1 and ADORING 2) and were eligible and decided to participate in the OL-LTE study (ADORING 3) was approximately 12 weeks in total.

[0389] Efficacy assessments included vIGA-AD score, %BSA affected, EASI, PP-NRS, DLQI/CDLQI/IDQOL (depending on age), POEM For Self-Completion/POEM For Proxy-Completion (depending on age), EQ-5D-5L/EQ-5D-Y (depending on age), and DFI (if

applicable). Safety assessments included AEs, clinical laboratory tests, physical examination, vital signs, and ECGs (in a subset of subjects), and LTS. PK was assessed in a subset of subjects at Week 4 and Week 8.

Study Design (ADORING 3)

[0390] The Phase 3 OL-LTE study is an open-label, long-term multicenter, study to evaluate the safety and efficacy of topical tapinarof cream, 1% in subjects with AD. Subjects in this study will have either: a) completed treatment with tapinarof or vehicle in one of two Phase 3 pivotal safety and efficacy studies, DMVT-505-3101 or DMVT-505-3102 (ADORING 1 and ADORING 2), and rolled over into this study; b) completed treatment with tapinarof in the Phase 2 maximal use PK study, DMVT-505-2104, and rolled over into this study; or c) enrolled directly into this study. This study will consist of up to 48 weeks of treatment and a 1-week safety follow-up period.

[0391] At the completion of the Week 8 visit of study DMVT-505-3101 or study DMVT-505-3102 (ADORING 1 and ADORING 2) or the Day 28 visit of study DMVT-505-2104 (Baseline [Day 1] in this study), all eligible subjects will be offered enrollment in this OL-LTE study (ADORING 3). Approximately 125 additional pediatric subjects ages 2 to < 18 years who are not eligible for participation in the Phase 3 pivotal studies (DMVT-505-3101 or DMVT-505-3102) will be enrolled directly into this OL-LTE study (ADORING 3). Study visits during the treatment period for all subjects will occur every 4 weeks ($\pm$ 3 days). Unscheduled visits may occur, as needed. Subjects who withdraw from the study before Week 48 will return to the study site for an Early Termination visit. The total duration of subject participation in this study will be approximately 49 weeks for rollover subjects (Baseline to Follow-Up) and approximately 53 weeks for direct-enrolling subjects (Screening to Follow-Up).

[0392] Rollover subjects in this study will begin treatment based on their vIGA-AD score from the final visit in one of the three aforementioned studies (DMVT-505-3101, DMVT-505-3102, or DMVT-505-2104). Subjects entering with a vIGA-AD $\geq$ 1 will receive treatment with tapinarof cream, 1% QD until they achieve a vIGA-AD score of 0, at which time treatment will be discontinued and subjects monitored for maintenance of disease control (i.e., the extent of the remittive effect). If/when disease worsening occurs, as evidenced by a flare to vIGA-AD $\geq$ 2, treatment will then be re-initiated and continued until a vIGA-AD of 0 is achieved. Subjects entering with a vIGA-AD of 0 will have treatment discontinued beginning at the Baseline visit and will be monitored for maintenance of the remittive effect. If/when disease

worsening occurs, as evidenced by a vIGA-AD ≥ 2 , treatment will then be re-initiated and continued until a vIGA-AD of 0 is achieved. This treatment and re-treatment pattern of use will be continued until the end of the study (i.e., subjects may receive study treatment up until the Week 48 visit).

[0393] Subjects enrolling directly into this study will receive treatment QD with tapinarof cream, 1% beginning at Baseline and continue treatment until they achieve a vIGA-AD score of 0, at which time treatment will be discontinued and subjects monitored for maintenance of the remittive effect. If/when disease worsening occurs, as evidenced by a flare to vIGA-AD ≥ 2 , treatment will be re-initiated and continued until a vIGA-AD of 0 is achieved. This regimen of treatment and re-treatment will continue until the end of the study (i.e., subjects may receive study drug up until the Week 48 visit).

[0394] Study drug will be dispensed to subjects or their caregivers, applied during the clinic visits, and applied at home between clinic visits as instructed by site personnel. Subjects or their caregivers will be instructed to apply study drug QD to all affected areas, including newly appearing lesions and lesions/areas that improve during the study until a vIGA-AD of 0 is achieved. Once a vIGA-AD of 0 is achieved, the treatment period ends. If/when disease worsening occurs, and treatment is re-initiated at a vIGA-AD of ≥ 2 , all lesions currently present and any new lesions that occur during the new treatment period should be treated. Subjects or their caregivers will apply sufficient study drug to cover each lesion completely with a thin layer of study drug and will record the time of study drug application and daily itch score (PP-NRS) in a daily diary provided by the study site. Subjects are allowed, but not required, to treat scalp lesions with study drug; however, efficacy analyses will not include assessment of AD on the scalp. At the first clinic visit, if applicable, subjects and/or caregivers will be instructed to maintain the approximate dosing time for the daily application of study drug. At the phone contact at Week 2, subjects or caregivers should be reminded to complete their daily diary and bring it with them to the next clinic visit.

[0395] Study drug application instructions will be reviewed at all post-randomization clinic visits and during any planned study phone calls. On clinic visit days, subjects and/or caregivers will be instructed/reminded on how to apply study drug (except during the final treatment/end-of-study visits). During the clinic visits, subjects or their caregivers will apply the daily dose of study drug while on-site under the supervision of site personnel, after efficacy and safety assessments have been completed (except for LTS at Week 4 through Week 44). The time of

the dose application and assessments will depend on the time of the clinic visit. Therefore, the timing of the clinic visit may lead to a change in the subject's chosen dosing time for that day.

[0396] Safety assessments will include AEs, clinical laboratory tests, physical examination, vital signs, and LTS. Efficacy assessments will include vIGA-AD score, %BSA affected, EASI, PP-NRS, DLQI/CDLQI/IDQOL (depending on age), POEM For Self-Completion/POEM For Proxy-Completion (depending on age), EQ-5D-5L/EQ-5D-Y (depending on age), DFI (if applicable), and the Patient Satisfaction Questionnaire.

Treatment Groups and Duration (ADORING 1, ADORING 2, and ADORING 3)

[0397] Each 8-week, Phase 3 pivotal study was a double-blind, vehicle controlled treatment study in which subjects were randomized in a 2:1 ratio to receive QD treatment with either tapinarof cream, 1% or matching vehicle cream.

[0398] In order to complete the study, a subject was required to complete 8 weeks of study assessments. To be considered a "study completer" in terms of treatment period, a subject was required to complete $\geq 80.0\%$ of the intended doses. The number of intended doses was defined as the Study Day of the subject's Week 8 visit minus 1 (e.g., if the subject's Week 8 visit occurred on Day 57, their number of intended doses was 56). To be eligible for the OL-LTE study, a subject must have been a "study completer." Subjects who completed the study (ADORING 1 and ADORING 2) had the option to enroll in the Phase 3 OL-LTE study of 48 weeks in duration (ADORING 3).

[0399] The end of study (ADORING 1 and ADORING 2) was defined as when the last active subject completed the 8 weeks of assessments in this study and either enrolled in the OL-LTE study OR did not enroll in the OL-LTE study and completed the Week 9 (Follow up) Visit.

[0400] Subjects entering the Phase 3 OL-LTE study (ADORING 3) with a vIGA AD ≥ 1 will receive treatment with tapinarof cream, 1% until they achieve a vIGA AD score of 0, at which time treatment will be discontinued and subjects monitored for remittive effect. If/when disease worsening occurs, as evidenced by a vIGA AD ≥ 2 , treatment will then be re-initiated and continued until a vIGA AD of 0 is achieved. Subjects entering with a vIGA AD of 0 will have treatment discontinued beginning at the Baseline visit and will be monitored for remittive effect. If/when disease worsening occurs, as evidenced by a vIGA AD ≥ 2 , treatment will then be re-initiated and continued until a vIGA AD of 0 is achieved.

[0401] A subject will be considered to have completed the Phase 3 OL-LTE study (ADORING 3) when he/she completes all required procedures/visits for the 48-week treatment

period and the Week 49 (Follow-Up) visit. The end of the study is defined as when the last active subject has completed the Follow-up Visit.

Type and Number of Subjects (ADORING 1, ADORING 2, and ADORING 3)

[0402] Approximately 400 adult and pediatric subjects ages 2 years and above with AD will be enrolled in each Phase 3 pivotal study (ADORING 1 and ADORING 2) at approximately 60 study sites in the US and Canada. A minimum of approximately 15% of subjects will be enrolled into each of the following age groups: 2-6 years, 7-11 years, 12-17 years, 18 years and above. Adults 18 years and above will comprise a maximum of 20% of enrolled subjects.

[0403] Up to 961 pediatric and adult subjects with AD will be enrolled in the Phase 3 OL-LTE study (ADORING 3) at up to approximately 135 study sites in the US and Canada.

Inclusion Criteria (ADORING 1 and ADORING 2)

[0404] Each subject must meet all of the following criteria to be eligible to participate in the Phase 3 pivotal study:

[0405] Male and female subjects ages 2 years and above with clinical diagnosis of AD by Hanifin and Rajka criteria.

[0406] Subjects with AD covering $\geq 5\%$ and $\leq 35\%$ of the BSA. Scalp should be excluded from the BSA calculation to determine eligibility during Screening and at Baseline, and for all efficacy assessments. Subjects with disease only on palms and soles are not eligible.

[0407] A vIGA AD score of > 3 at Screening and Baseline (pre-randomization).

[0408] An EASI score of > 6 at Screening and Baseline (pre-randomization).

[0409] AD present for at least 6 months for ages 6 years old and above or 3 months for ages 2 to 5 years old, confirmed by prior medical documentation and/or according to the subject/caregiver report.

[0410] Female subjects of childbearing potential who are engaging in sexual activity that could lead to pregnancy should use 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 include intrauterine device, hormonal contraceptives, barrier method (e.g., condom or diaphragm), or surgical sterilization of male partner (vasectomy). Subjects who claim abstinence as their method of contraception are allowed provided they agree to use a barrier method (e.g., condom or diaphragm) should they become sexually active from Screening to 4 weeks after the last dose of study drug. Non-child-bearing potential is defined as: premenarchal; pre-menopausal females with a documented bilateral tubal ligation, bilateral

oophorectomy, hysterectomy, or hysteroscopic sterilization; postmenopausal female with a cessation of menses for at least 12 months without an alternative medical cause; a blood sample with follicle stimulating hormone > 40 mIU/mL is confirmatory in questionable cases.

[0411] Female subjects of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline (Day 1).

[0412] Subject, subject's parent(s), or legal representative must be capable of giving written informed consent/assent, which includes compliance with the requirements and restrictions listed in the consent/assent form; written informed consent must be obtained prior to any study related procedures.

Inclusion Criteria (ADORING 3)

[0413] Each subject must meet all of the following criteria to be eligible to participate in the Phase 3 OL-LTE study:

[0414] For Rollover Subjects Only: Met the criteria as a Study Completer in one of three parent studies (Phase 3 pivotal safety and efficacy study DMVT-505-3101, Phase 3 pivotal safety and efficacy study DMVT-505-3102, or Phase 2 maximal use PK study DMVT-505-2104) and was still receiving study drug at the last visit of one of these studies (to meet the criteria as a Study Completer in one of the three parent studies, a subject must have completed $\geq 80\%$ of the intended doses in that study); Female subjects of childbearing potential must have a negative urine pregnancy test at Baseline (Day 1).

[0415] For Direct-Enrolling Subjects Only: Male and female subjects ages 2 years to < 18 years at the time of consent with clinical diagnosis of AD by Hanifin and Rajka criteria; Subjects with a vIGA AD score of ≥ 3 and AD covering $\geq 40\%$ of the BSA at Screening and Baseline (pre-randomization), or subjects with a vIGA AD score of 2 at Screening and Baseline (pre-randomization) regardless of BSA (Scalp should be excluded from the BSA calculation to determine eligibility during Screening and at Baseline, and for all efficacy assessments; Subjects must have screened for the DMVT-505-3101 or DMVT-505-3102 study and failed to meet BSA and/or vIGA ADTM eligibility criteria); Subjects with disease only on palms and soles are not eligible; AD present for at least 6 months for ages 6 years old and above or 3 months for ages 2 to 5 years old, confirmed by prior medical documentation and/or according to the subject/caregiver report; Female subjects of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline (Day 1).

[0416] For All Subjects (Rollover Subjects and Direct-Enrolling Subjects): Female subjects of childbearing potential who are engaging in sexual activity that could lead to

pregnancy should use 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 include intrauterine device, hormonal contraceptives, barrier method (e.g., condom or diaphragm), or surgical sterilization of male partner (vasectomy). Subjects who claim abstinence as their method of contraception are allowed provided they agree to use a barrier method (e.g., condom or diaphragm) should they become sexually active from Baseline to 4 weeks after the last dose of study drug. Non-child-bearing potential is defined as: premenarchal; pre-menopausal females with a documented bilateral tubal ligation, bilateral oophorectomy, hysterectomy, or hysteroscopic sterilization; postmenopausal female with a cessation of menses for at least 12 months without an alternative medical cause; a blood sample with follicle stimulating hormone > 40 mIU/mL is confirmatory in questionable cases; Subject, subject's parent(s), or legal representative must be capable of giving written informed consent/assent, which includes compliance with the requirements and restrictions listed in the consent/assent form; written informed consent must be obtained prior to any study related procedures.

Exclusion Criteria (ADORING 1 and ADORING 2)

[0417] A subject who meets any of the following criteria will be excluded and considered ineligible for participation in the Phase 3 pivotal study:

[0418] Concurrent conditions: Immunocompromised (e.g., lymphoma, acquired immunodeficiency syndrome) or history or evidence of active or latent tuberculosis or human immunodeficiency virus antibody as documented by medical history and/or according to the subject/caregiver report; Chronic or acute systemic infection requiring treatment with antiparasitics, or antiprotozoals, within 4 weeks prior to the Baseline visit; Chronic or acute systemic bacterial infection requiring treatment with systemic antibiotics within one week prior to the Baseline visit; Chronic or acute superficial fungal infection requiring treatment with systemic antifungals within one week prior to the Baseline visit; Acute active bacterial, fungal, or viral (herpes simplex, herpes zoster, chicken pox) skin infection within 1 week prior to the Baseline visit; the condition should be completely resolved one week prior to Baseline Visit; Significant dermatologic or inflammatory condition other than AD that, in the Investigator's opinion, would make it difficult to interpret data or assessments during the study (for example, subjects with an active skin condition such as Kaposi's varicelliform eruption, scabies, molluscum contagiosum, impetigo, psoriasis, severe acne, connective tissue disorder, or Netherton's syndrome, or any other concurrent active disease); Concurrent skin lesions in the treatment area or pruritus due to conditions other than AD that, in the opinion of the

Investigator, would either interfere with study evaluations or affect the safety of the subject; Screening alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\geq 2.0 \times$ the upper limit of normal (ULN); Screening total bilirubin $> 1.5 \times$ ULN; total bilirubin $> 1.5 \times$ ULN is acceptable if bilirubin is fractionated and direct bilirubin $< 35\%$; Current or chronic history of liver disease, known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones), presence of hepatitis B surface antigen (HBsAg), or positive hepatitis C antibody test result, or presence of anti-hepatitis B core antigen (anti-HBc). Subjects having a negative HBsAg and a positive anti-HBc may enroll if they have a positive anti-hepatitis B surface antigen demonstrating natural immunity; Subjects with a history of hepatitis C virus infection who were medically cured and have an undetectable viral load are eligible to enroll; Subjects with a history of stable non-alcoholic fatty liver disease without evidence of active inflammation (elevated ALT/AST $\geq 2.0 \times$ ULN) or cirrhosis are eligible to enroll; Current or a history of cancer within 5 years except for adequately treated cutaneous basal cell carcinoma, squamous cell carcinoma or carcinoma in situ of the cervix (surgical excision or electrodesiccation and curettage); Subjects who would not be considered suitable for topical therapy (e.g., those with extensive disease involvement over a large BSA who would be candidates for systemic therapy); Use of any prohibited medication or procedure within the indicated period before the Baseline visit.

[0419] Prohibited concomitant medications, therapy, etc. during the defined period are as listed below. If a subject requires any of these medications throughout the study period, he/she may be excluded from or discontinued from the study, at the discretion of the Investigator and Medical Monitor.

[0420] From 4 months prior to Baseline until the completion of the Follow-up visit or study discontinuation: DUPIXENT (dupilumab) injection; Any monoclonal antibody product that becomes approved for AD during the course of the trial.

[0421] From 28 days prior to Baseline until the completion of the Follow-up visit or discontinuation: Oral, injectable, and suppository preparations of corticosteroids; Eye drops and nasal preparations are allowed; Inhaled preparations are allowed when used for a stable condition and stable dose for > 28 days before Screening and are continued at the same dose throughout the study. Oral preparations and injections of immunosuppressants (cyclosporine, methotrexate, azathioprine, tacrolimus, Janus kinase inhibitors, etc.); Excessive sun exposure, tanning booth, other ultraviolet light source and phototherapy including psoralen and ultraviolet A therapy or is unwilling to minimize natural and artificial sunlight exposure;

Treatment with antivirals with the exception of short-term treatment for acute upper respiratory viral infections (i.e., influenza) or viral suppressive therapy for a history of recurrent herpes labialis or genital herpes.

[0422] From 14 days prior to Baseline until the completion of the Follow-up visit or discontinuation: EUCRISA (crisaborole) and any other PDE4 inhibitor; Tacrolimus ointment and pimecrolimus cream; Topical corticosteroids that are classified as medium or high potency (e.g., fluocinonide, triamcinolone acetonide) or super-high potency (e.g., clobetasol propionate); Eye drops and nasal preparations are allowed; Coal tar products (on the body); If subject chooses to treat scalp with study drug, then coal tar products are prohibited for use on the scalp; Over the counter or herbal medicines for AD (topical and oral preparations); If subjects are using emollients, they may continue to use the same emollient on nonlesional skin during the study; Emollients containing salicylic acid are prohibited during the study.

[0423] From 7 days prior to Baseline until the completion of the Follow-up visit or discontinuation: Topical corticosteroids that are classified as low potency (e.g., desonide, hydrocortisone); Oral, injectable, or intravenous antibiotics or antifungal medications; Topical doxepin, topical gentamicin, or topical neomycin sulfate; Oral doxepin is allowed for treatment of depression if subject has been on a stable dose (4 weeks) at Screening; Topical products containing urea, except for the treatment of follicular events; Antihistamines/antiallergics (oral, topical and injections): diphenhydramine, chlorpheniramine maleate, hydroxyzine; The following antihistamines are allowed from Screening throughout the treatment period: loratadine, fexofenadine hydrochloride, cetirizine hydrochloride; Subjects are allowed to switch from non-allowed antihistamines to allowed antihistamines during Screening but must be on a stable dose for 7 days prior to Baseline; The subject has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days or 5 half-lives of the investigational product (whichever is longer).

[0424] Additional exclusion criteria are a history of or ongoing serious illness or medical, physical, or psychiatric condition(s) that, in the Investigator's opinion, may interfere with the subject's participation in the study, interpretation of results, or ability to understand and give informed consent; Pregnant females as determined by positive serum (Screening) or urine (Baseline) human chorionic gonadotropin test; Lactating females; History of sensitivity to the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates their participation; Previous

known participation in a clinical study with tapinarof (previously known as GSK2894512 and WBI-1001).

[0425] *Exclusion Criteria (ADORING 3)*

[0426] A subject who meets any of the following criteria will be excluded and considered ineligible for participation in the Phase 3 OL-LTE study:

[0427] For Rollover Subjects Only: Subjects who were not receiving study drug at the time of the last visit in the parent study (DMVT-505-3101, DMVT-505-3102, or DMVT-505-2104); Used a prohibited concomitant product or procedure to treat AD during the parent study; Had an SAE that was related to treatment or experienced an AE that led to permanent discontinuation of treatment in the parent study; Pregnant females as determined by positive urine human chorionic gonadotropin test at Baseline.

[0428] For Direct-Enrolling Subjects Only: Concurrent conditions: Immunocompromised (e.g., lymphoma, acquired immunodeficiency syndrome) or medical history of positive human immunodeficiency virus antibody at Screening; Chronic or acute systemic infection requiring treatment with antiparasitics or antiprotozoals, within 4 weeks prior to the Baseline visit; Chronic or acute systemic bacterial infection requiring treatment with systemic antibiotics within one week prior to the Baseline visit; Chronic or acute superficial fungal infection requiring treatment with systemic antifungals within one week prior to the Baseline visit; Acute active bacterial, fungal, or viral (herpes simplex, herpes zoster, chicken pox) skin infection within 1 week prior to the Baseline visit; the condition should be completely resolved one week prior to Baseline Visit; Significant dermatologic or inflammatory condition other than AD that, in the Investigator's opinion, would make it difficult to interpret data or assessments during the study (for example, subjects with an active skin condition such as Kaposi's varicelliform eruption, scabies, molluscum contagiosum, impetigo, psoriasis, severe acne, connective tissue disorder, or Netherton's syndrome, or any other concurrent active disease); Concurrent skin lesions in the treatment area or pruritus due to conditions other than AD that, in the opinion of the Investigator, would either interfere with study evaluations or affect the safety of the subject; Screening alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\geq 2.0 \times$ the upper limit of normal (ULN); Screening total bilirubin $> 1.5 \times$ ULN; total bilirubin $> 1.5 \times$ ULN is acceptable if bilirubin is fractionated and direct bilirubin $< 35\%$; Current or chronic history of liver disease, known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones), presence of hepatitis B surface antigen (HBsAg), or positive hepatitis C antibody test result, or presence of anti-hepatitis B core antigen (anti-HBc)

(Subjects having a negative HBsAg and a positive anti HBc may enroll if they have a positive anti-hepatitis B surface antigen demonstrating natural immunity. Subjects with a history of hepatitis C virus infection who were medically cured and have an undetectable viral load are eligible to enroll. Subjects with a history of stable non-alcoholic fatty liver disease without evidence of active inflammation (elevated ALT/AST $\geq 2.0 \times$ ULN) or cirrhosis are eligible to enroll.); Current or a history of cancer within 5 years except for adequately treated skin basal cell carcinoma, cutaneous squamous cell carcinoma or carcinoma in situ of the cervix (surgical excision or electrodesiccation and curettage); Pregnant females as determined by positive serum (Screening) or urine (Baseline) human chorionic gonadotropin test; Lactating females; Previous known participation in a clinical study with tapinarof (previously known as GSK2894512 and WBI-1001); Use of any prohibited medication or procedure within the indicated period before the Baseline visit. Prohibited concomitant medications, therapy, etc. during the defined period are as listed below. If a subject requires any of these medications throughout the study period, he/she may be excluded from or discontinued from the study, at the discretion of the Investigator and Medical Monitor.

[0429] From 4 months prior to Baseline: DUPIXENT (dupilumab) injection; Any monoclonal antibody product that becomes approved for AD during the course of the trial.

[0430] From 28 days prior to Baseline: Oral, injectable, and suppository preparations of corticosteroids; Eye drops and nasal preparations are allowed; Inhaled preparations are allowed when used for a stable condition and stable dose for > 28 days before Screening and are continued at the same dose throughout the study; Oral preparations and injections of immunosuppressants (cyclosporine, methotrexate, azathioprine, tacrolimus, Janus kinase [JAK] inhibitors, etc.); Excessive sun exposure, tanning booth, other ultraviolet light source and phototherapy including psoralen and ultraviolet A therapy or is unwilling to minimize natural and artificial sunlight exposure; Treatment with antivirals with the exception of short-term treatment for acute upper respiratory viral infections (i.e., influenza) or viral suppressive therapy for a history of recurrent herpes labialis or genital herpes.

[0431] From 14 days prior to Baseline: EUCRISA® (crisaborole) and any other PDE4 inhibitor; Tacrolimus ointment and pimecrolimus cream; Topical JAK inhibitors; Topical corticosteroids that are classified as medium or high potency (e.g., fluocinonide, triamcinolone acetonide) or super-high potency (e.g., clobetasol propionate). Eye drops and nasal preparations are allowed; Over the counter or herbal medicines for AD (topical and oral preparations). If subjects are using emollients, they may continue to use the same emollient on

nonlesional skin during the study. Emollients containing salicylic acid are prohibited during the study.

[0432] From 7 days prior to Baseline: Topical corticosteroids that are classified as low potency (e.g., desonide, hydrocortisone); Oral, injectable, or intravenous antibiotics or antifungal medications; Topical doxepin, topical gentamicin, or topical neomycin sulfate; Oral doxepin is allowed for treatment of depression if subject has been on a stable dose (4 weeks) at Screening; Topical products containing urea, except for the treatment of follicular events; Antihistamines/antiallergics (oral, topical and injections): diphenhydramine, chlorpheniramine maleate, hydroxyzine; For direct-enrolling subjects, the following antihistamines are allowed from Screening throughout the treatment period: loratadine, fexofenadine hydrochloride, cetirizine hydrochloride. Subjects are allowed to switch from non-allowed antihistamines to allowed antihistamines during Screening but must be on a stable dose for 7 days prior to Baseline.

[0433] The subject has received an investigational product within the following time period prior to the first dosing day in the current study: Minimum of 30 days or 5 half-lives of the investigational product (whichever is longer).

[0434] For All Subjects (Rollover Subjects and Direct-Enrolling Subjects): A history of or ongoing serious illness or medical, physical, or psychiatric condition(s) that, in the Investigator's opinion, may interfere with the subject's participation in the study, interpretation of results, safety of the subject or ability to understand and give informed consent; Known hypersensitivity to tapinarof or excipients.

Study Drug (ADORING 1 and ADORING 2)

[0435] The descriptions of the study drugs, tapinarof cream, 1% and the vehicle cream, are presented in Table 1.

Table 1. Tapinarof and Vehicle Cream.

Study Drug	Tapinarof (DMVT-505, Formulation F)	Vehicle Cream
Physical description	White to off-white cream	White to off-white cream
Unit dose strength/how supplied	1% w/w (10 mg/gram)/30-gram tube	NA/30-gram tube
Route of administration/duration	Topical/8 weeks (or 48 weeks for OL-LTE study)	Topical/8 weeks
Dosing instructions	QD topical application of thin layer to affected areas	QD topical application of thin layer to affected areas
Manufacturer	GlaxoSmithKline (Barnard Castle, UK)	GlaxoSmithKline (Barnard Castle, UK)

NA = not applicable; QD = once daily; w/w = weight/weight

[0436] The excipients included in tapinarof cream and vehicle cream are purified water, medium chain triglycerides, propylene glycol, emulsifying wax, diethylene glycol monoethyl ether, polyoxyl stearyl ether-2, polysorbate 80, polyoxyl stearyl ether-20, benzoic acid, sodium citrate, butylated hydroxytoluene, edetate disodium and citric acid monohydrate.

[0437] Administration of Study Drug (ADORING 1 and ADORING 2)

[0438] Study drug was dispensed to subjects or their caregivers at the clinical site in appropriately labeled tubes. Subjects or caregivers took the tubes home and self-administered study drug (or had caregiver apply if necessary) to affected areas QD, except on clinic visit days when study drug was applied under supervision at the site.

[0439] Subjects of each Phase 3 pivotal study were instructed to apply study drug as follows:

[0440] QD application to affected areas; subjects or their caregivers were advised to choose the application time they preferred and to apply the study drug at that approximate time each day of study participation. Subjects were instructed to avoid dosing around midnight to avoid potentially dosing twice in one calendar day.

[0441] If a subject missed a daily dose, it was recorded as a protocol deviation. The subject was instructed to continue dosing the next day and was instructed not to apply more than once daily to make up for the missed dose on the previous day. If a dose was missed, the missed dose and the reason for the missed dose was recorded in the daily diary as such. Itch rating could still be recorded in the diary even if a daily dose was missed.

[0442] Participants were instructed as follows: Study drug was applied to dry, clean skin; Study drug may be applied to skin around the eye but avoid direct contact with the eye – study drug is not for ophthalmic use; Wash hands after application, unless treating lesions on the

hands; Study drug should be applied to all lesions, including newly appearing lesions and lesions that have improved or resolved during the study. A body diagram identifying locations of lesions may be provided to the subject and/or caregiver; Subjects are allowed, but not required, to treat scalp lesions with study drug; however, efficacy analyses will not include assessment of AD in this area; If there is residual cream visible on the disease-affected lesional skin, then the subject or caregiver should be instructed to continue to lightly rub the cream into the skin until it is no longer visible; If study drug is applied to the subject by another person, that person should thoroughly wash his/her hands after application; When dosing at home subjects or caregiver should record the time of study drug application in the daily diary; Itch rating should also be recorded in the diary; On clinic visit days, study drug should be applied in the clinic under the supervision of site personnel and after safety and efficacy assessments have been completed (except for subject and Investigator LTS at Weeks 1, 2 and 4); The time of the dose and assessments on clinic visit days will depend on the time of the clinic visit. Therefore, the timing of the clinic visit may differ from the subject's chosen dosing time. The intention is to allow flexibility to accommodate subjects' schedules.

[0443] Participants were instructed that nonmedicated emollients that do not contain salicylic acid may be used on nonlesional skin but the subject (or caregiver) should wait at least 30 minutes after applying study drug before applying nonmedicated emollients; emollients should not be applied to lesional skin during treatment. The same emollient should be used throughout the subject's participation in the study. Subjects and/or caregivers will be instructed/reminded on how to apply study drug at each clinic visit (except during the final treatment visit).

[0444] *Administration of Study Drug (ADORING 3)*

[0445] Subjects entering the Phase 3 OL-LTE study with a vIGA-AD ≥ 1 (including all subjects enrolling directly into the study) will receive treatment QD with tapinarof cream, 1% until they achieve a vIGA-AD score of 0, at which time treatment will be discontinued and subjects monitored for maintenance of disease control (i.e. the extent of the remittive effect). If/when disease worsening occurs, as evidenced by a flare to vIGA-AD ≥ 2 , treatment will be re-initiated and continued until a vIGA AD of 0 is achieved. Subjects entering with a vIGA-AD of 0 will have treatment discontinued beginning at the Baseline visit and will be monitored for maintenance of the remittive effect. If/when disease worsening occurs, as evidenced by a flare to vIGA-AD ≥ 2 , treatment will be re-initiated and continued until a vIGA-AD of 0 is achieved. Once a vIGA-AD of 0 is achieved, the treatment period ends. If/when disease worsening occurs, and treatment is re-initiated at a vIGA-AD of ≥ 2 , all lesions currently

present and any new lesions that occur during the new treatment period should be treated. This treatment and re-treatment pattern of use will be continued until the end of the study (i.e., subjects may receive study treatment up until the Week 48 visit).

[0446] Subjects who experience suspected disease worsening between scheduled study visits may contact the study site to arrange an unscheduled visit. Upon confirmation of disease worsening, subjects will restart treatment with study drug.

[0447] If disease worsening is suspected between scheduled study visits, an unscheduled visit may be performed. If disease worsening (i.e., vIGA-AD ≥ 2) is not confirmed, the subject will continue to be assessed at routine, scheduled visits.

[0448] For each confirmed episode of disease worsening (i.e., vIGA-AD ≥ 2) during the study (at either a scheduled or unscheduled visit), a treatment course of tapinarof cream, 1% QD will be initiated and will continue until the subject achieves a vIGA-AD of 0, as assessed at scheduled visits, approximately every 4 weeks beginning at Baseline.

[0449] Subjects of the Phase 3 OL-LTE study will be instructed to apply study drug as follows:

[0450] QD application to affected areas; subjects or their caregivers are advised to choose the application time they prefer and to apply the study drug at that approximate time each day of study participation. Subjects should avoid dosing around midnight to avoid potentially dosing twice in one calendar day.

[0451] If a subject misses a daily dose, it will be recorded as a protocol deviation. The subject should continue dosing the next day and should not apply more than once daily to make up for the missed dose on the previous day. If a dose is missed, the missed dose and the reason for the missed dose should be recorded in the daily diary as such. Itch rating can still be recorded in the diary even if a daily dose was missed.

[0452] Study drug should be applied to dry, clean skin.; Study drug may be applied to skin around the eye but avoid direct contact with the eye – study drug is not for ophthalmic use; Wash hands after application, unless treating lesions on the hands.

[0453] Study drug should be applied to all lesions, including newly appearing lesions and lesions/areas that improve during the study until a vIGA-AD of 0 is achieved. Once a vIGA-AD of 0 is achieved, the treatment period ends. If/when disease worsening occurs, and treatment is re-initiated at a vIGA-AD of ≥ 2 , all lesions currently present and any new lesions that occur during the new treatment period should be treated. A body diagram identifying locations of lesions may be provided to the subject and/or caregiver.

[0454] Subjects are allowed, but not required, to treat scalp lesions with study drug; however, efficacy analyses will not include assessment of AD in this area; If there is residual cream visible on the disease-affected lesional skin, then the subject or caregiver should be instructed to continue to lightly rub the cream into the skin until it is no longer visible; If study drug is applied to the subject by another person, that person should thoroughly wash his/her hands after application; When dosing at home subjects or caregiver should record the time of study drug application in the daily diary. Itch rating should also be recorded in the diary; On clinic visit days, study drug should be applied in the clinic under the supervision of site personnel and after safety and efficacy assessments have been completed (except for subject [or caregiver]- and Investigator-assessed LTS); The time of the dose and assessments on clinic visit days will depend on the time of the clinic visit. Therefore, the timing of the clinic visit may differ from the subject's chosen dosing time. The intention is to allow flexibility to accommodate subjects' schedules.

[0455] Nonmedicated emollients that do not contain salicylic acid may be used on nonlesional skin but the subject (or caregiver) should wait at least 30 minutes after applying study drug before applying nonmedicated emollients; emollients should not be applied to lesional skin during treatment. The same emollient should be used throughout the subject's participation in the study.

Statistical Analysis (ADORING 1 and ADORING 2)

[0456] Enrollment of 400 patients in each trial was estimated to provide a 97.2% power to detect a significant difference (2-sided P value <0.05), assuming 45% of the patients in the tapinarof arms and 25% in the vehicle arms would achieve the primary endpoint. Trial power was calculated using Fisher's exact sample size calculation. Power calculations assumed that 15% of patients receiving tapinarof cream and 30% receiving vehicle cream would be lost to follow-up at Week 8.

[0457] The primary efficacy endpoint and other dichotomous endpoints were analyzed using a Cochran-Mantel-Haenszel test stratified by baseline vIGA-AD and age group. Efficacy endpoints were based on the intention-to-treat population. The primary estimand of interest was focused on the composite estimand (treatment effect measured by the ratio of vIGA-AD response rates at Week 8) in the active treatment versus vehicle-control arms. Subjects who prematurely discontinued treatment due to an AE or lack of efficacy and subjects who used a prohibited medication with significant impact on efficacy evaluations prior to Week 8 were be considered treatment failures.

[0458] Missing data were handled using multiple imputation (MI) in which 100 imputations were generated using the PROC MI procedure of SAS software version 9.4.

Randomization/Treatment Assignment (ADORING 1 and ADORING 2)

[0459] For each double-blind, vehicle-controlled phase of the study (Phase 3 pivotal study), subjects were randomized at a ratio of 2:1 to receive tapinarof cream, 1% or vehicle cream as follows:

Table 2. Randomization in Double-Blind, Vehicle-Controlled Phase

Regimen	Number of Subjects	
	ADORING 1	ADORING 2
Tapinarof cream, 1% QD for 8 weeks	270 Subjects	271 Subjects
Vehicle cream QD for 8 weeks	137 Subjects	135 Subjects

QD = once daily

[0460] Randomization was stratified by Baseline vIGA AD score so that subjects with severe AD (vIGA AD score of 4) were limited to approximately 10% each of the total randomized population, and the majority of the enrolled subjects (approximately 90%) had a vIGA AD score of 3, signifying moderate disease.

[0461] Randomization was also stratified by age so that a minimum of approximately 15% of subjects were enrolled into each of the following age groups: 2-6 years, 7-11 years, 12-17 years, 18 years and above. Adults 18 years and above comprised a maximum of 20% of enrolled subjects.

[0462] The randomization lists were generated using a validated system, which involves a pseudo random number generator so that the resulting treatment was both reproducible and non-predictable. Access to the codes was controlled and documented.

Efficacy Assessments: Phase 3 pivotal studies (ADORING 1 AND ADORING 2)

[0463] To minimize inter-observer variability, investigators and evaluators/raters were trained on each of the required assessments during an investigator meeting, site initiation visit, and/or 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.

[0464] Validated Investigator Global Assessment of Atopic Dermatitis: The vIGA-AD of disease severity was assessed at every clinic visit. The vIGA-AD is a global assessment of the current state of the disease. It is a 5-point morphological assessment of overall disease severity (scalp excluded) and will be determined according to the categories described in Table 3. To be eligible, subjects must have a vIGA-AD score of 3 or 4 at Screening and the Baseline visit (Day 1). Eli Lilly and Company developed the vIGA-AD scale for use in clinical trials.

Table 3. Validated Investigator Global Assessment Scale for Atopic Dermatitis

Score	Category	Definition
0	Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.
1	Almost clear	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2	Mild	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting
3	Moderate	Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4	Severe	Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

[0465] Body Surface Area Affected: The assessment of the %BSA affected is an estimate of the percentage of total involved skin with AD. For the purpose of clinical estimation, the total palmar surface of the subject's palm and digits may be assumed to be approximately equivalent to 1% BSA. The %BSA affected by AD will be evaluated from 0% to approximately 100% (scalp excluded). Percentage BSA is a static assessment made without reference to previous scores.

[0466] Eczema Area and Severity Index: The EASI was assessed at every clinic visit. It quantifies the severity of a subject's AD based on both lesion severity and the %BSA affected. The subject's scalp is excluded from this assessment. The EASI is a composite score ranging from 0 to 72 that takes into account the degree of erythema, edema/papulation, excoriation, and

lichenification (each scored from 0 to 3 separately) for each of four body regions, with adjustment for the %BSA involved for each body region relative to the whole body. The EASI score was calculated in the CRF based on the subject's age, the rating scores for each region, and the number of handprints involved for each region.

[0467] Dermatology Life Quality Index, Children's Dermatology Life Quality Index, and Infant's Dermatitis Quality of Life Index: The IDQOL was used for ages 2 to < 4 years and completed by the caregiver. The CDLQI was used for ages 4 to < 16 years and completed by the subject with the help of the caregiver, as necessary. The DLQI was used for ages 16 years and above and completed by the subject. A subject continued to use the same questionnaire throughout the study, regardless of a change in age during their participation. The DLQI, CDLQI, and IDQOL are simple dermatology-specific 10 question validated questionnaires to assess the impact of the disease on a subject's quality of life for adults, children, and infants, respectively (Cardiff University, Department of Dermatology, Quality of Life Questionnaires). 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).

[0468] Patient Oriented Eczema Measures For Self-Completion and For Proxy-Completion: The POEM For Self-Completion and POEM For Proxy-Completion are tools used for monitoring AD severity. They focus on the illness as experienced by the patients. For subjects ages 2 to < 12 years, the POEM For Proxy-Completion was completed by the caregiver. For subjects ages ≥ 12 years, the POEM For Self-Completion was completed by the subject.

[0469] Peak Pruritus Numeric Rating Scale: The PP-NRS is a scale used to quickly assess itch/pruritus severity over a 24-hour period. The subject or caregiver utilized the scale to assess peak pruritus QD and recorded the results in their daily diaries. The itch rating could be done before or after study drug administration since it should reflect the past 24 hours. On clinic visit days, the PP-NRS was assessed in the clinic. For subjects ages 2 to < 12 years, the PP-NRS was completed by the caregiver. For subjects ages ≥ 12 years, the PP-NRS was completed by the subject.

[0470] EQ-5D-5L and EQ-5D-Y: The EQ-5D-5L was introduced by the EuroQol Group in 2009 to improve the instrument's sensitivity and to reduce ceiling effects, as compared to the

EQ-5D-3L. The EQ-5D-5L essentially consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale. The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The subject is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state. The EQ visual analogue scale records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The visual analogue scale can be used as a quantitative measure of health outcome that reflects the patient's own judgement. The EQ-5D-5L was used in subjects ≥ 16 years and completed by the subject. The child-friendly EQ-5D version (EQ-5D-Y) was introduced by the EuroQol Group in 2009 as a more comprehensible instrument suitable for children and adolescents. The EQ-5D-Y is based on the EQ-5D-3L and essentially consist of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale. The EQ-5D-Y descriptive system comprises the following five dimensions: mobility, looking after myself, doing usual activities, having pain or discomfort and feeling worried, sad or unhappy. Each dimension has 3 levels: no problems, some problems and a lot of problems. The younger patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the younger patient's health state. The EQ visual analogue scale records the younger patient's self-rated health on a vertical visual analogue scale where the endpoints are labelled "The best health you can imagine" and "The worst health you can imagine". The visual analogue scale can be used as a quantitative measure of health outcome that reflects the younger patient's own judgement. The EQ-5D-Y was used in subjects ≥ 8 to < 16 years and completed by the subject.

[0471] Dermatitis Family Impact Questionnaire: The DFI is a questionnaire that measures how much having a child with AD affects the quality of life of other members of the family. It is a 10-question tool completed by the caregiver age 16 or over who has a pediatric subject < 16 years old in the study. The same caregiver was used to complete each questionnaire.

[0472] Optional Clinical Photography: Clinical photography could be performed in a subgroup of subjects at selected study sites. Informed consent/assent and photographic release was required. The photographs could not be referred to by the Investigator at any subsequent study visit for the purposes of grading. Photographs were taken of a representative area of the subject's disease area at the time points specified in the Schedule of Assessments. Photographs of the selected skin area were taken in a standardized fashion (i.e., same camera, angle, background, distance).

[0473] *Efficacy Assessments: Phase 3 OL-LTE study (ADORING 3)*

[0474] To minimize inter observer variability, Investigators and/or evaluators/raters will be trained on each of the required assessments during an Investigator meeting, site initiation visit, and/or utilizing online assessments before enrolling subjects at their study site. Only trained evaluators/raters are permitted to perform the efficacy assessments. To the fullest extent possible, the same Investigator (or designated evaluator/rater) will perform all efficacy assessments for an individual subject throughout the study. If it is not possible for the same evaluator/rater to continue performing assessments, it is recommended that the primary and subsequent evaluator/rater both examine and discuss their respective scoring during at least 1 visit.

[0475] Validated Investigator Global Assessment of Atopic Dermatitis: The vIGA-AD of disease severity will be assessed at every clinic visit. The vIGA-AD is a global assessment of the current state of the disease. It is a 5-point morphological assessment of overall disease severity (scalp excluded) and will be determined according to the categories described in Table 3 above. Eli Lilly and Company developed the vIGA-AD scale for use in clinical trials.

[0476] Body Surface Area Affected: The assessment of the %BSA affected is an estimate of the percentage of total involved skin with AD. For the purpose of clinical estimation, the total palmar surface of the subject's palm and digits may be assumed to be approximately equivalent to 1% BSA. The %BSA affected by AD will be evaluated from 0% to approximately 100% (scalp excluded). Percentage BSA is a static assessment made without reference to previous scores.

[0477] Eczema Area and Severity Index: The EASI will be assessed at every clinic visit. It quantifies the severity of a subject's AD based on both lesion severity and the %BSA affected. The subject's scalp is excluded from this assessment. The EASI is a composite score ranging from 0 to 72 that takes into account the degree of erythema, edema/papulation, excoriation, and lichenification (each scored from 0 to 3 separately) for each of four body regions, with

adjustment for the %BSA involved for each body region relative to the whole body. The EASI score will be calculated in the CRF based on the subject's age, the rating scores for each region, and the number of handprints involved for each region.

[0478] Dermatology Life Quality Index, Children's Dermatology Life Quality Index, and Infant's Dermatitis Quality of Life Index: The IDQOL will be used for ages 2 to < 4 years and completed by the caregiver. The CDLQI will be used for ages 4 to < 16 years and completed by the subject with the help of the caregiver, as necessary. The DLQI will be used for ages 16 years and above and completed by the subject. For subjects rolling over from DMVT-505-3101 or DMVT-505-3102, the DLQI, CDLQI, or IDQOL completed at the final visit of the parent study will be used as the Baseline value for this study. For subjects rolling over from DMVT-505-2104 or subjects enrolling directly into DMVT-505-3103, the DLQI, CDLQI, or IDQOL should be completed pre-dose at Baseline. The DLQI, CDLQI, and IDQOL are simple dermatology-specific 10-question validated questionnaires to assess the impact of the disease on a subject's quality of life for adults, children, and infants, respectively (Cardiff University, Department of Dermatology, Quality of Life Questionnaires). 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).

[0479] Patient Oriented Eczema Measures For Self-Completion and For Proxy Completion: The POEM For Self-Completion and POEM For Proxy-Completion are tools used for monitoring AD severity. They focus on the illness as experienced by the patients. For subjects ages 2 to < 12 years, the POEM For Proxy-Completion will be completed by the caregiver. For subjects ages ≥ 12 years, the POEM For Self-Completion will be completed by the subject. For subjects rolling over from DMVT-505-3101 or DMVT-505-3102, the POEM For Self-Completion or POEM For Proxy Completion completed at the final visit of the parent study will be used as the Baseline value for this study. For subjects rolling over from DMVT-505-2104 or subjects enrolling directly into DMVT-505-3103, the POEM For Self-Completion or POEM For Proxy Completion should be completed pre-dose at Baseline.

[0480] Peak Pruritus-Numeric Rating Scale: The PP-NRS is a scale used to quickly assess itch/pruritus severity over a 24-hour period. The subject or caregiver will utilize the scale to

assess peak pruritus QD and record the results in their daily diaries. The itch rating can be done before or after study drug administration since it should reflect the past 24 hours. On clinic visit days, the PP-NRS will be assessed in the clinic. PP-NRS should be completed every day, even if subjects are not actively applying study drug. For subjects ages 2 to < 12 years, the PP-NRS will be completed by the caregiver. For subjects ages ≥ 12 years, the PP-NRS will be completed by the subject.

[0481] EQ-5D-5L and EQ-5D-Y: The EQ-5D-5L was introduced by the EuroQol Group in 2009 to improve the instrument's sensitivity and to reduce ceiling effects, as compared to the EQ-5D-3L. The EQ-5D-5L essentially consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale. The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The subject is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state. The EQ visual analogue scale records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The visual analogue scale can be used as a quantitative measure of health outcome that reflects the patient's own judgement. The full version of EQ-5D-5L is available through the EuroQol Group. The EQ-5D-5L will be used in subjects ≥ 16 years and completed by the subject. The child-friendly EQ-5D version (EQ-5D-Y) was introduced by the EuroQol Group in 2009 as a more comprehensible instrument suitable for children and adolescents. The EQ-5D-Y is based on the EQ-5D-3L and essentially consist of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale. The EQ-5D-Y descriptive system comprises the following five dimensions: mobility, looking after myself, doing usual activities, having pain or discomfort and feeling worried, sad or unhappy. Each dimension has 3 levels: no problems, some problems and a lot of problems. The younger patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the younger patient's health state. The EQ visual analogue scale records the younger patient's self-rated health on a vertical visual analogue scale where the endpoints are labelled "The best

health you can imagine” and “The worst health you can imagine”. The visual analogue scale can be used as a quantitative measure of health outcome that reflects the younger patient’s own judgement. The EQ-5D-Y will be used in subjects ≥ 8 to < 16 years and completed by the subject. For subjects rolling over from DMVT-505-3101 or DMVT-505-3102, the EQ-5D-5L or EQ-5D-Y completed at the final visit of the parent study will be used as the Baseline value for this study. For subjects rolling over from DMVT-505-2104 or subjects enrolling directly into DMVT-505-3103, the EQ-5D-5L or EQ-5D-Y should be completed pre-dose at Baseline.

[0482] Dermatitis Family Impact Questionnaire: The DFI is a questionnaire that measures how much having a child with AD affects the quality of life of other members of the family. It is a 10-question tool that will be completed by the caregiver age 16 or over who has a pediatric subject < 16 years old in the study. The same caregiver should be used to complete each questionnaire. For subjects rolling over from DMVT-505-3101 or DMVT-505-3102, the DFI completed at the final visit of the parent study will be used as the Baseline value for this study. For subjects rolling over from DMVT-505-2104 or subjects enrolling directly into DMVT-505-3103, the DFI should be completed pre-dose at Baseline.

[0483] Patient Satisfaction Questionnaire: For subjects ages 2 to < 16 years, the Patient Satisfaction Questionnaire will be completed by the caregiver at the end of treatment (Week 48) or the Early Termination visit. For subjects ages ≥ 16 years, the Patient Satisfaction Questionnaire will be completed by the subject at the end of treatment (Week 48) or the Early Termination visit.

[0484] Optional Clinical Photography

[0485] Clinical photography may be performed in a subgroup of subjects at selected study sites. Informed consent/assent and photographic release will be required. The photographs may not be referred to by the Investigator at any subsequent study visit for the purposes of grading. Photographs will be taken of a representative area of the subject’s disease area at the time points specified in the Schedule of Assessments. Photographs of the selected skin area will be taken in a standardized fashion (i.e., same camera, angle, background, distance).

[0486] ADORING 3 will confirm if the durability (lack of tachyphylaxis), and potential to achieve complete clearance with disease control maintained while off therapy (i.e. a “remittive” effect), observed with tapinarof cream 1% QD in the phase 3 PSOARING psoriasis long-term extension trial will be replicated in patients with AD. ADORING 3 will also provide further evidence regarding potential long-term use of tapinarof cream 1% QD in patients down to 2 years of age with AD of any severity including mild, to achieve consistent efficacy when used

as needed, based on individual patient responses. A remittive effect, as demonstrated in the treatment of psoriasis with tapinarof, could offer the opportunity for treatment that can be stopped and restarted, as needed, without concerns regarding rebound phenomena. ADORING 3 will also provide further evidence regarding potential long-term use of tapinarof cream 1% QD in patients down to 2 years of age with AD of any severity, including mild, to achieve consistent efficacy when used as needed, based on individual patient responses.

Trial Design and Baseline Demographics (ADORING 1 and ADORING 2)

[0487] FIG. 3 illustrates the trial design of the first portion of the phase 3 ADORING program for tapinarof 1% (“VTAMA”) cream (ADORING 1 and ADORING 2). FIG. 4 illustrates the trial design of the phase 3 program for tapinarof 1% (“VTAMA”) cream, including the open-label, long-term extension study (ADORING 3). Approximately 800 patients as young as 2 years of age with atopic dermatitis were enrolled in two identical trials (ADORING 1 and ADORING 2), which will be followed by a long-term, open-label extension (LT-OLE, ADORING 3). A minimum of ~15% of patients were enrolled into the following age groups: 2-6 years, 7-11 years, 12-17 years, and ≥ 18 years. Adults (≥ 18 years) comprised a maximum of approximately 20% of enrolled patients. Patients with a vIGA-AD score of 4 (severe) represented a minimum of ~10% of the total randomized population; the remainder will have a vIGA-AD TM score of 3 (moderate). Patients electing not to participate in ADORING 3 attended a follow up visit 1 week after completion of the treatment period in ADORING 1 or 2.

[0488] ADORING 1 was conducted at 67 sites from September 1, 2021 to April 7, 2023; ADORING 2 was conducted at 62 sites from September 23, 2021 to February 8, 2023. All sites were located in the US or Canada. In total, 602 and 540 patients underwent screening and 407 and 406 were randomized in ADORING 1 and 2, respectively (Supplementary Figure S1). On completion of ADORING 1 or 2, 91% of eligible patients elected to enroll into the long-term extension trial, ADORING 3. Demographic and disease characteristics were balanced across arms of each trial at baseline with no systematic differences that could influence the outcomes of interest (Table 1). Overall, 80% of patients were pediatric (<18 years). At baseline, 89.9% and 84.0% of patients in ADORING 1 and 2 had a vIGA-AD score of 3 (moderate), respectively.

[0489] Table 4 shows the baseline demographics and disease characteristics for the ADORING 1 and ADORING 2 study participants. (BMI, body mass index; BSA, body surface area; EASI, Eczema Area and Severity Index; ITT, intention to treat; PP-NRS, peak pruritus

numeric rating scale; QD, once daily; SD, standard deviation; vIGA AD, Validated Investigator Global Assessment for Atopic Dermatitis). Baseline disease characteristics reflected moderate to severe patient population, age 2-81 years, and mean PP-NRS of 6.7-6.8.

Table 4. Baseline demographics and disease characteristics for ADORING 1 and ADORING 2

	ADORING 1			ADORING 2		
Patients, n (%)	Tapinarof 1% QD (n=270)	Vehicle QD (n=137)	Overall (n=407)	Tapinarof 1% QD (n=271)	Vehicle QD (n=135)	Overall (n=406)
Age, mean (SD)	15.6 (16.62)	15.6 (16.49)	15.6 (16.56)	16.4 (16.24)	16.7 (16.05)	16.5 (16.16)
Age group, n (%)						
2–6 years	76 (28.1)	39 (28.5)	115 (28.3)	65 (24.0)	32 (23.7)	97 (23.9)
7–11 years	75 (27.8)	37 (27.0)	112 (27.5)	64 (23.6)	32 (23.7)	96 (23.6)
12–17 years	67 (24.8)	34 (24.8)	101 (24.8)	89 (32.8)	44 (32.6)	133 (32.8)
≥18 years	52 (19.3)	27 (19.7)	79 (19.4)	53 (19.6)	27 (20.0)	80 (19.7)
Male, n (%)	130 (48.1)	66 (48.2)	196 (48.2)	117 (43.2)	58 (43.0)	175 (43.1)
Weight, kg, mean (SD)	46.69 (27.251)	47.69 (27.725)	47.03 (27.381)	51.52 (29.148)	54.03 (32.005)	52.36 (30.112)
BMI, kg/m ² , mean (SD)	21.38 (6.307)	22.06 (6.557)	21.61 (6.392)	22.65 (7.460)	23.25 (8.257)	22.85 (7.729)
Fitzpatrick skin type (n, %)						
I	9 (3.3)	7 (5.1)		11 (4.1)	4 (3.0)	
II	66 (24.4)	22 (16.1)		52 (19.2)	28 (20.7)	
III	60 (22.2)	31 (22.6)		50 (18.5)	33 (24.4)	
IV	67 (24.8)	30 (21.9)		71 (26.2)	31 (23.0)	
V	44 (16.3)	40 (29.2)		63 (23.2)	27 (20.0)	
VI	24 (8.9)	7 (5.1)		24 (8.9)	12 (8.9)	
Race/ethnic group [†] (n, %)						
White	152 (56.3)	79 (57.7)		124 (45.8)	58 (43.0)	
Black	70 (25.9)	38 (27.7)		95 (35.1)	47 (34.8)	
Asian	26 (9.6)	10 (7.3)		39 (14.4)	23 (17.0)	
American Indian/Alaska Native	2 (0.7)	0 (0.0)		0 (0.0)	2 (1.5)	
Native Hawaiian/Pacific Islander	0 (0.0)	0 (0.0)		1 (0.4)	0 (0.0)	
Multiple races	14 (5.2)	5 (3.6)		6 (2.2)	2 (1.5)	
Not reported	6 (2.2)	5 (3.6)		6 (2.2)	3 (2.2)	
vIGA-AD, n (%)						
3 – Moderate	244 (90.4)	122 (89.1)	366 (89.9)	228 (84.1)	113 (83.7)	341 (84.0)

	ADORING 1			ADORING 2		
Patients, n (%)	Tapinarof 1% QD (n=270)	Vehicle QD (n=137)	Overall (n=407)	Tapinarof 1% QD (n=271)	Vehicle QD (n=135)	Overall (n=406)
4 – Severe	26 (9.6)	15 (10.9)	41 (10.1)	43 (15.9)	22 (16.3)	65 (16.0)
Local tolerability scores, mean (SD)						
Patient-assessed burning/stinging	1.3 (1.4)	1.1 (1.3)		1.0 (1.3)	1.1 (1.3)	
Patient-assessed itching	1.9 (1.5)	1.7 (1.5)		1.6 (1.6)	1.5 (1.5)	
Investigator- assessed irritation (dryness, erythema, and peeling)	0.5 (0.9)	0.6 (1.0)		0.3 (0.8)	0.3 (0.9)	
EASI, mean (SD)	12.24 (5.007)	12.86 (5.633)	12.45 (5.228)	13.45 (5.615)	13.09 (4.689)	13.33 (5.322)
BSA affected (%), mean (SD)	16.45 (8.666)	17.71 (9.500)	16.87 (8.964)	17.13 (8.743)	15.84 (7.888)	16.70 (8.480)
PP-NRS (all), mean (SD)	6.8 (2.33)	6.5 (2.39)	6.7 (2.35)	6.7 (2.37)	6.9 (2.09)	6.8 (2.28)
PP-NRS (≥12 years), mean (SD)	6.5 (2.40)	6.3 (2.31)	6.4 (2.36)	6.3 (2.36)	6.5 (2.21)	6.4 (2.31)
PP-NRS (<12 years), mean (SD)	7.0 (2.25)	6.6 (2.46)	6.9 (2.33)	7.1 (2.32)	7.4 (1.82)	7.2 (2.17)

Percentages may not total 100 because of rounding. [†]Race and ethnic group were reported by the patient. [‡]vIGA-AD score is assessed on a scale from 0 to 4, with higher scores indicating more severe atopic dermatitis. Full definitions and morphological feature of the vIGA-AD scale scores are listed in the Supplementary Materials Table S1. [§]EASI score ranges from 0 to 72 with higher scores indicating more severe atopic dermatitis and assesses the degree of erythema, edema/papulation, excoriation, and lichenification (each scored from 0 to 3 separately) for each of four body regions, with adjustment for the %BSA involved for each body region relative to the whole body. The PP-NRS is a well-defined and reliable patient-reported outcome measure for evaluating the intensity of pruritus in the previous 24 hours on a scale of 0 to 10 (with 0 being “no itch” and 10 being “worst itch imaginable”). The PP-NRS is validated for use in patients aged ≥12 years with moderate to severe AD. BMI, body mass index; BSA, body surface area; EASI, Eczema Area and Severity Index; PP-NRS, Peak Pruritus-Numerical Rating Scale; QD, once daily; SD, standard deviation; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis.

[0490] FIG. 5 is a flow chart illustrating the patient disposition for the ADORING 1 and ADORING 2 studies. There was very consistent patient disposition across 122 clinical trial sites in North America. Table 5 below shows the primary endpoint multiple imputations (MI) estimand for the ADORING 1 and ADORING 2 studies.

Table 5. ADORING 1 & 2 Primary Endpoint MI Estimand

Estimand Attribute	Description
Population	Intention-to-treat
Treatment	VTAMA cream, 1% compared with vehicle
Variable of interest (Endpoint)	Proportion of patients who achieve vIGA-AD score of clear (0) or almost clear (1) and at least a 2-grade reduction from baseline at Week 8
Intercurrent event handling	The following patients will be considered <u>treatment failures</u> as of the start of the intercurrent event: • Patients who prematurely discontinue treatment due to AEs • Patients who prematurely discontinue treatment due to lack of efficacy • Patients who use a prohibited medication with significant impact on efficacy evaluations prior to Week 8 Investigator assessments will only include data collected at in-person visits
Summary measure	Ratio of response rates at Week 8

AE, adverse event; MI, multiple imputations; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis.

[0491] Table 6 below shows the patient disposition in the intention-to-treat population, indicating high rates of trial completion and a 91% rollover rate to the LT-OLE (ADORING 3) trial. There were very low trial discontinuation rates due to adverse events (AEs), which were higher with vehicle versus tapinarof treatment groups.

Table 6. ADORING 1 AND 2: Patient Disposition ITT Population

	ADORING 1			ADORING 2		
Patients, n (%)	VTAMA 1% QD (n=270)	Vehicle QD (n=137)	Overall (n=407)	VTAMA 1% QD (n=271)	Vehicle QD (n=135)	Overall (n=406)
Randomized	270	137	407	271	135	406
Discontinued trial	32 (11.9)	27 (19.7)	59 (14.5)	36 (13.3)	29 (21.5)	65 (16.0)

Withdrawal by parent/guardian	7 (2.6)	12 (8.8)	19 (4.7)	9 (3.3)	12 (8.9)	21 (5.2)
Lost to follow-up	13 (4.8)	6 (4.4)	19 (4.7)	15 (5.5)	4 (3.0)	19 (4.7)
Adverse event	5 (1.9)	5 (3.6)	10 (2.5)	4 (1.5)	4 (3.0)	8 (2.0)
Completed treatment	245 (90.7)	112 (81.8)	357 (87.7)	239 (88.2)	105 (77.8)	344 (84.7)
Completed trial	238 (88.1)	110 (80.3)	348 (85.5)	235 (86.7)	106 (78.5)	341 (84.0)
Enrolled in LTE among patients who completed trial	214 (89.9)	95 (86.4)	309 (88.8)	217 (92.3)	98 (92.5)	315 (92.4)

AE, adverse event; ITT, intention-to-treat; LTE, long-term extension; QD, once daily.

[0492] *Baseline Demographics (ADORING 3).* Patients enrolled in ADORING 3 represent a large (n=728), diverse AD population, comprising a high proportion (91%) of eligible patients from the pivotal ADORING trials, 28 patients from a 4-week maximal usage pharmacokinetic trial, and an additional 76 tapinarof-naïve patients aged 2-17 years with mild, or severe and/or extensive AD, who were ineligible for preceding trials. Patients in ADORING 3 were evenly distributed by age: 26.6% were aged 2-6 years; 27.1%, 7-11 years; 29.3%, 12-17 years; and 17.0% were adults. Overall, 46.6% of patients were male, 52.6% White, 11.1% Asian, 30.1% Black/African American, and 6.1% other race categories.

[0493] Patients with AD present different phenotypes and treatment responses. The diverse population enrolled in ADORING 3 is representative across the broad spectrum of disease severity, body surface area affected ($\leq 95\%$), and patient demographics. The high proportion of patients electing to rollover from previous trials suggests a positive treatment experience with tapinarof cream 1% QD. No new safety signals were reported with long-term treatment in this interim analysis.

[0494] *Results (ADORING 1 and ADORING 2).* At Week 8, significantly more patients treated with tapinarof than vehicle achieved the primary efficacy endpoint of a vIGA-AD response, with high statistical significance in favor of tapinarof in both trials: 45.4% in the tapinarof arm compared with 13.9% with vehicle in ADORING 1 ($P<0.0001$), and 46.4%

versus 18.0% in ADORING 2 ($P < 0.0001$). FIG. 6 shows the primary efficacy results from the ADORING 1 and ADORING 2 trials. The results demonstrate robust and consistent efficacy, as demonstrated by the magnitude of vIGA-AD treatment success (vIGA-AD score of 0 or 1 and ≥ 2 grade improvement from baseline). P value based upon Cochran Mantel Haenszel analysis stratified by baseline vIGA-AD score and age group. ITT, intention-to-treat; MI, multiple imputation; QD, once daily; SEM, standard error of mean; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis.

[0495] FIG. 7 shows vIGA-AD Score of 0 or 1 and ≥ 2 -grade improvement from baseline at week 8 across multiple statistical analyses in the ADORING 1 trial. The results shown in FIG. 7 indicate a highly statistically significant performance of VTAMA cream in the ADORING 1 trial, regardless of the statistical method used (i.e., a large and consistent treatment effect observed across all statistical analyses). P value based upon Cochran-Mantel-Haenszel analysis stratified by baseline vIGA-AD™ score and age group. LOCF, last observation carried forward; MI, multiple imputation; OC, observed cases; QD, once daily; SEM, standard error of mean; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis.

[0496] FIG. 8 shows vIGA-AD Score of 0 or 1 and ≥ 2 -grade improvement from baseline at week 8 across multiple statistical analyses in the ADORING 2 trial. The results shown in FIG. 8 indicate a highly statistically significant performance of VTAMA cream in the ADORING 2 trial, regardless of the statistical method used (i.e., a large and consistent treatment effect observed across all statistical analyses). P value based upon Cochran-Mantel-Haenszel analysis stratified by baseline vIGA-AD™ score and age group. LOCF, last observation carried forward; MI, multiple imputation; OC, observed cases; QD, once daily; SEM, standard error of mean; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis.

[0497] The secondary efficacy endpoints of the ADORING 1 and ADORING 2 trials were pre-defined and sequentially evaluated in the following order: Proportion of patients with $\geq 75\%$ improvement in EASI from Baseline at Week 8; Mean change in %BSA affected from Baseline at Week 8; Proportion of patients with $\geq 90\%$ improvement in EASI from Baseline at Week 8; and Proportion of patients aged ≥ 12 years old with a Baseline PP-NRS score ≥ 4 who achieved ≥ 4 -point reduction in PP-NRS from Baseline at Week 8. It was determined in advance that hypothesis testing would stop if statistical significance in favor of VTAMA was not observed (i.e., 2-sided $P \geq 0.05$). BSA, body surface area; EASI, Eczema Area and Severity Index score; PP-NRS, Peak Pruritus-Numerical Rating Scale.

[0498] At Week 8, highly statistically significant differences in favor of tapinarof were also demonstrated in both trials for the key secondary efficacy endpoint of EASI75 response: 55.8% of tapinarof-treated patients versus 22.9% for vehicle in ADORING 1 ($P<0.0001$); and 59.1% vs 21.2%, in ADORING 2 ($P<0.0001$) (Supplementary Figure S2A). FIG. 9 shows the EASI75 improvement of patients in ADORING 1 and ADORING 2 from baseline to week 8. Across both trials, greater than 55% of patients treated with VTAMA cream achieved at least 75% improvement in eczema severity by Week 8.

[0499] FIG. 10 shows the absolute change in %BSA affected in ADORING 1 and ADORING 2 from baseline to week 8. Patients treated with VTAMA in both trials demonstrated marked and consistent reduction in %BSA affected.

[0500] FIG. 11 shows the EASI90 improvement of patients in ADORING 1 and ADORING 2 from baseline to week 8. Across both trials, 30% of patients treated with VTAMA cream achieved at least 90% improvement in eczema severity by Week 8.

[0501] FIG. 12 shows the PP-NRS improvement of patients in ADORING 1 and ADORING 2 from baseline to week 8 in patients 12 or older. Up to 56% of patients treated with VTAMA cream achieved clinically meaningful ≥ 4 point reduction in itch at Week 8 (patients aged ≥ 12 years).

[0502] Table 7 below shows a statistical summary of the primary and secondary endpoints of the ADORING 1 and ADORING 2 trials. All primary and secondary endpoints were met with high significance, and a consistent and predictable response was demonstrated regardless of the efficacy measure observed. There were highly statistically significant reductions in mean weekly PP-NRS scores as early as Week 1, the first trial visit, for patients treated with tapinarof vs vehicle (-2.0 vs -1.2 [$P<0.0001$]) and (-2.0 vs -1.3 [$P=0.0010$]) in ADORING 1 and ADORING 2, respectively. Significantly greater reductions in mean weekly PP-NRS scores with tapinarof vs vehicle were seen for all visits to Week 8 (-4.1 vs -2.6 and -4.1 vs -2.4 [both $P<0.0001$]) for both trials. For daily evaluations of itch from baseline, statistically significantly greater reductions in mean (SD) PP-NRS scores after initial application of tapinarof vs vehicle were observed as early as Day 1 in ADORING 1 (-1.2 [2.2] vs 0.9 [2.0]) and Day 4 in ADORING 2 (-2.2 [2.3] vs -1.6 [2.3]). Improvements with tapinarof in mean (SD) daily PP-NRS scores continued during the first 2 weeks (Day 14; -3.0 [2.8] vs -2.0 [2.2] and -2.9 [2.7] vs -1.8 [2.6]) and through Week 8 of both trials. FIG. 13A and FIG. 13B show the mean change in daily PP-NRS as a function of time in ADORING 1 and ADORING 2, respectively, demonstrating the rapid reduction in pruritus with tapinarof cream 1% QD as early as 24 hours

after first application (PP-NRS=Peak Pruritus Numerical Rating Scale; QD=once daily). As these data show, improvements in itch with tapinarof cream increased through Week 8 in both trials in adults and children down to 2 years with moderate to severe AD.

Table 7. ADORING 1 and ADORING 2: Primary and Secondary Endpoint Statistical Summary

	ADORING 1		ADORING 2	
	Relative Risk or LSM Difference* (95% CI)	P value	Relative Risk or LSM Difference* (95% CI)	P value
Primary endpoint – Week 8				
vIGA-AD treatment success	2.60 (1.66, 4.09)	<0.0001	2.27 (1.54, 3.32)	<0.0001
Secondary endpoints – Week 8				
EASI75	2.17 (1.57, 3.00)	<0.0001	2.14 (1.53, 3.00)	<0.0001
%BSA change from Baseline	-6.17 (-7.69, - 4.66)	<0.0001	-6.60 (-8.17, - 5.02)	<0.0001
EASI90	3.74 (1.98, 7.09)	<0.0001	2.34 (1.39, 3.94)	0.0013
PP-NRS ≥12 years [†]	1.54 (1.03, 2.31)	0.0366	2.17 (1.34, 3.50)	0.0015

*Relative risk for all endpoints except %BSA. [†]Patients had baseline PP-NRS ≥4. ITT, MI Estimand. BSA, body surface area; CI, confidence interval; EASI75, >75% improvement in Eczema Area and Severity Score from baseline; EASI90, ≥90% improvement in Eczema Area and Severity Index score from baseline; ITT, intention-to-treat; LSM, least squares mean; MI, multiple imputation; PP-NRS, Peak Pruritus-Numerical Rating Scale; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis.

[0503] FIG. 14 shows photos of a representative target lesion of a pediatric patient treated with VTAMA cream, 1% once daily in the ADORING 1 clinical trial. The photos and accompanying scores indicate a rapid response to VTAMA treatment in a pediatric patient achieving regulatory endpoint by Week 4. AD, atopic dermatitis; EASI, Eczema Area and Severity Index; POEM, Patient Oriented Eczema Measure; PP-NRS, Peak Pruritus-Numeric Rating Scale; QD, once daily; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis. Patient number 1028-007, 3-year-old male.

[0504] FIG. 15 shows photos of another representative target lesion of a pediatric patient treated with VTAMA cream, 1% once daily in the ADORING 1 clinical trial. The photos and

accompanying scores indicate a rapid response to VTAMA treatment in a pediatric patient achieving regulatory endpoint by Week 4. AD, atopic dermatitis; EASI, Eczema Area and Severity Index; POEM, Patient Oriented Eczema Measure; PP-NRS, Peak Pruritus-Numeric Rating Scale; QD, once daily; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis. Patient number 1028-003, 3-year-old female.

[0505] FIG. 16 shows photos of yet another representative target lesion of a pediatric patient treated with VTAMA cream, 1% once daily in the ADORING 1 clinical trial. The photos and accompanying scores indicate a rapid response to VTAMA treatment in a pediatric patient achieving regulatory endpoint by Week 2. AD, atopic dermatitis; EASI, Eczema Area and Severity Index; POEM, Patient Oriented Eczema Measure; PP-NRS, Peak Pruritus-Numeric Rating Scale; QD, once daily; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis. Patient number 1028-021, 5-year-old male.

[0506] FIG. 17 shows photos of a representative target lesion of a pediatric patient treated with VTAMA (tapinarof 1%) cream once daily in the ADORING 2 clinical trial. There was a rapid response to treatment in this pediatric patient, with the patient achieving the regulatory endpoint by week 2. Rapid resolution of erythema and lichenification of the target lesion in the popliteal fossa was observed. Alongside the visible improvement in this intertriginous skin area, overall disease burden was rapidly and significantly improved as reflected by improvements vIGA-AD, EASI, and PP-NRS as early as Week 2. The posterior view of the knee shows a marked and rapid clinical response in this intertriginous area of skin, with visible improvements in signs of disease as early as Week 2. By Week 4 there are no visible signs of erythema, induration or oozing after which no signs of disease or post-inflammatory pigmentation changes are visible through Week 8. The improvements in the target lesion correspond to global assessments of disease activity assessed on the vIGA-AD and EASI, which show the patient achieved the primary efficacy endpoint of a vIGA-AD response as early as Week 2, and an itch-free state reported at Week 8 (a PP-NRS score of less than 2). AD, atopic dermatitis; CDLQI, Children's Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; PP-NRS, Peak Pruritus-Numeric Rating Scale; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis. Subject number 2903-004, 8-year-old male.

[0507] FIG. 18 shows photos of another representative target lesion of an adult patient treated with VTAMA (tapinarof 1%) cream once daily in the ADORING 2 clinical trial. There was a rapid response to treatment in this patient, with the patient achieving the regulatory endpoint

by week 2. DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; PP-NRS, Peak Pruritus-Numerical Rating Scale; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis. Patient number 2005-001, 67-year-old male.

[0508] FIG. 19 shows treatment success (as indicated by vIGA-AD score of 0 or 1 and ≥ 2 -grade improvement from baseline at week 8), by baseline vIGA-AD score (moderate or severe) in the ADORING 1 and ADORING 2 trials. The results shown in FIG. 18 indicate that VTAMA is highly effective regardless of baseline disease severity. *vIGA-AD score of 0 or 1 and ≥ 2 -grade improvement from baseline. †Non-estimand. BL, baseline; ITT, intention-to-treat; MI, multiple imputations; QD, once daily; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis.

[0509] FIG. 20 shows treatment success (as indicated by vIGA-AD score of 0 or 1 and ≥ 2 -grade improvement from baseline at week 8), by age group (2-6 years, 7-11 years, 12-17 years, and ≥ 18 years) in the ADORING 1 and ADORING 2 trials. The results shown in FIG. 19 indicate that VTAMA shows consistent and predictable performance across all age groups studied. vIGA-AD score of 0 or 1 and ≥ 2 -grade improvement from baseline. †Non-estimand. BL, baseline; ITT, intention-to-treat; MI, multiple imputations; QD, once daily; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis.

[0510] FIG. 21 shows treatment success (as indicated by vIGA-AD score of 0 or 1 and ≥ 2 -grade improvement from baseline at week 8), by visit (weeks 0, 1, 2, 4, and 8) in the ADORING 1 and ADORING 2 trials. The results shown in FIG. 20 indicate that VTAMA treatment success has rapid onset, early separation from vehicle, and continued improvement over time. vIGA-AD score of 0 or 1 and ≥ 2 -grade improvement from baseline. †Estimand. Error bars are standard error of mean. *P values* based on Cochran-Mantel-Haenszel analysis stratified by baseline vIGA-AD score. MI, multiple imputation; QD, once daily; SE, standard error; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis.

[0511] Greater improvements in itch were reported in the tapinarof than vehicle groups in both trials with a statistically significant improvement in the secondary efficacy endpoint of PP-NRS response in the tapinarof arms compared with vehicle in patients aged 12 or older: 55.8% vs 34.2% in ADORING 1 ($P=0.0366$); and 52.8% vs 24.1% in ADORING 2 ($P=0.0015$). Similar and statistically superior PP-NRS responses were reported in patients aged less than 12 years (60.7% vs 28.0% [$P=0.0001$] in ADORING 1; and 60.0% vs 40.8% [$P=0.0414$] in ADORING 2) and in patients overall (61.1% vs 34.0% [$P=0.0001$] in ADORING 1; and 57.4% vs 33.0% [$P=0.0001$] in ADORING 2).

[0512] FIG. 22 shows improvement in PP-NRS of ≥ 4 Points at Week 8 for all patients in the ADORING 1 and ADORING 2 trials. The results shown in FIG. 21 indicate that VTAMA achieves highly statistically significant and clinically meaningful ≥ 4 -point reduction in itch at Week 8. *Patients with baseline PP-NRS score ≥ 4 who achieve ≥ 4 -point reduction in the PP-NRS from baseline. *P value* based upon Cochran-Mantel-Haenszel analysis stratified by baseline vIGA-AD score and age group. ITT, intention-to-treat; MI, multiple imputation; OC, observed cases; PP-NRS, Peak Pruritus Numerical Rating Scale; QD, once daily; SE, standard error; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis.

[0513] FIG. 23 shows improvement in PP-NRS of ≥ 4 Points at Week 8 in patients aged <12 years in the ADORING 1 and ADORING 2 trials. The results shown in FIG. 22 indicate that VTAMA achieves clinically meaningful ≥ 4 -point reduction in itch, even in the youngest patients studied. *Patients with baseline PP-NRS score ≥ 4 who achieve ≥ 4 -point reduction in the PP-NRS from baseline. *P value* based upon Cochran-Mantel-Haenszel analysis stratified by baseline vIGA-AD score and age group. ITT, intention-to-treat; MI, multiple imputation; OC, observed cases; PP-NRS, Peak Pruritus Numerical Rating Scale; QD, once daily; SE, standard error; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis.

[0514] FIG. 24 shows PP-NRS response at Week 8 in patients aged ≥ 12 years in the ADORING 1 and ADORING 2 trials. PP-NRS response is defined as at least a 4-point reduction in the average weekly PP-NRS total score from baseline.

[0515] Tapinarof was well tolerated with patients reporting none (LTS=0) or slight (LTS=1) local burning/stinging or itching across all visits (mean LTS: 0.4-1.2 and 0.2-1.1 in ADORING 1 and 2, respectively). Investigator-assessed mean Local Tolerability Scale (LTS) scores across tapinarof and vehicle groups also showed no irritation for all visits (0.2-0.3 and 0.1-0.2 in ADORING 1 and 2), including for sensitive skin and intertriginous areas (mean sensitive/intertriginous LTS scores 0-1.0 and 0-0.5 in ADORING 1 and 2, for all visits). As described herein, local tolerability in ADORING 1 and ADORING 2 was evaluated using patient/caregiver-reported and investigator-assessed scores, measured on 5-point scales at baseline before first application of trial treatment, and within 2 hours after application of trial treatment at Weeks 1, 2, 4, and 8. Patient/caregiver-reported tolerability scores assessed the presence and degree of burning/stinging and of itching at the application sites, from (0) none to (1) slight (awareness but no discomfort), (2) mild (noticeable discomfort that causes intermittent awareness), (3) moderate (noticeable discomfort with intermittent awareness; occasionally interferes with daily activities), or (4) strong/severe (continuous discomfort that

interferes with daily activities). The scores represent an “average” of evaluations across all application sites. Investigator-assessed tolerability scores were assessed using the Local Tolerability Scale (LTS). This evaluated the presence and overall degree of irritation across application sites (including dryness, erythema, and peeling), from (0) no irritation to (1) mild, (2) moderate, (3) severe, or (4) very severe. Investigators also used the LTS separately to assess irritation for patients treating sensitive and intertriginous skin areas.

[0516] As shown in Table 4 above, mean baseline local tolerability scores in ADORING 1 and ADORING 2, assessed prior to the first application of trial treatment, were similar across groups: patient-reported overall scores, 1.0–1.9; investigator-assessed overall LTS scores, 0.3–0.6. Tapinarof cream was well tolerated, with patients/caregivers reporting no or minimal local tolerability scores for burning/stinging and for itching. Scores improved from pre-treatment baseline values.

[0517] Most patients/caregivers reported no or minimal burning/stinging with tapinarof across all time points (tolerability scores <1). At Week 8, mean local tolerability scores for tapinarof cream versus vehicle were 0.2–0.4 vs 0.7–0.8 for burning/stinging, and 0.6–0.8 vs 1.1–1.1 for itching, respectively, across ADORING 1 and ADORING 2. In both trials, there was no or minimal patient-assessed burning/stinging, with improvement versus pre-treatment baseline with tapinarof cream 1% QD. FIG. 25A and FIG. 25B show the mean change in patient-assessed irritation score as a function of time in the safety populations of ADORING 1 and ADORING 2, respectively. Local tolerability scores (burning/stinging) were reported at baseline prior to first application, and within 2 hours post-dose at subsequent weeks.

[0518] Similarly, investigators assessed most patients as having no or minimal local irritation (LTS scores <1) for dryness/erythema/peeling, with improvements compared with pre-treatment baseline. At Week 8, mean local investigator-assessed LTS scores with tapinarof versus vehicle were 0.1–0.2 vs 0.2–0.2, respectively, across ADORING 1 and ADORING 2. In both trials, there was no or minimal irritation (investigator-assessed), with improvement versus pre-treatment baseline with tapinarof cream 1% QD. FIG. 26A and FIG. 26B show the mean change in investigator-assessed irritation score as a function of time in the safety populations of ADORING 1 and ADORING 2, respectively. Local tolerability scores (dryness/erythema/peeling) were reported at baseline prior to first application, and within 2 hours post-dose at subsequent weeks.

[0519] Tapinarof cream 1% QD demonstrated no to minimal irritation in sensitive skin areas, with improvement versus pre-treatment baseline scores. Across sensitive and intertriginous

areas, tapinarof cream was well tolerated, with investigator-assessed LTS scores of <0.5 (no irritation) across all evaluations. At Week 8, mean LTS scores for tapinarof versus vehicle were 0–0.3 vs 0–0.5, respectively, across ADORING 1 and ADORING 2. FIG. 27A shows the mean change in investigator-assessed irritation score on the face as a function of time in the safety populations of ADORING 1 and ADORING 2; FIG. 27B shows the mean change in investigator-assessed irritation score on the neck as a function of time in the safety populations of ADORING 1 and ADORING 2; FIG. 27C shows the mean change in investigator-assessed irritation score in the inframammary area as a function of time in the safety populations of ADORING 1 and ADORING 2; FIG. 27D shows the mean change in investigator-assessed irritation score in the gluteal cleft as a function of time in the safety populations of ADORING 1 and ADORING 2; FIG. 27E shows the mean change in investigator-assessed irritation score in the skin folds as a function of time in the safety populations of ADORING 1 and ADORING 2; FIG. 27F shows the mean change in investigator-assessed irritation score in the axillae as a function of time in the safety populations of ADORING 1 and ADORING 2; and FIG. 27G shows the mean change in investigator-assessed irritation score on the genitalia as a function of time in the safety populations of ADORING 1 and ADORING 2; (*combined n for treatment groups and trials for patients at baseline; n had different values across visits). Local tolerability scores at baseline were measured prior to first treatment application, and within 2 hours post-application at subsequent weeks.

[0520] FIG. 28 shows photos of a representative target lesion of a 3-year-old patient treated with tapinarof cream, 1% QD in the ADORING 1 clinical trial (*(burning/stinging)/itching LTS scores; AD, atopic dermatitis; EASI, Eczema Area and Severity Index; Inv LTS, investigator Local Tolerability Scale; PP-NRS, Peak Pruritus Numerical Rating Scale; QD, once daily; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis). The patient was a white patient with Hispanic ethnicity and Fitzpatrick Skin Type IV. The patient had severe disease (vIGA-AD=4) at baseline affecting the sensitive neck area, and achieved almost clear skin (vIGA-AD=1) by Week 8. The patient had excellent local tolerability scale scores assessed by the caregiver (burning/stinging=0) and investigator (overall score=0) from baseline to week 8. The patient achieved the primary efficacy endpoint by week 8 with excellent tolerability of tapinarof cream 1% QD.

[0521] Tapinarof cream 1% QD thus demonstrated favorable local tolerability, including on sensitive and intertriginous skin, in adults and children down to 2 years of age with AD, as reported by patients/caregivers and when assessed by investigators. Local tolerability scores,

which were low pre-treatment, improved over time with tapinarof, potentially due to skin barrier repair and improvements in AD during the ADORING 1 and ADORING 2 trials. Tapinarof is therefore a highly effective, well-tolerated, non-steroidal topical treatment option for patients down to 2 years of age with AD, with the potential to be used without restrictions on duration of use, extent of body surface area treated, or sites of application, including the face and other sensitive skin areas.

[0522] Of 407 and 406 randomized patients in ADORING 1 and ADORING 2, respectively, 8.8-15.3% were Asian, 26.5-35.0% were Black, 44.8-56.8% were White, and 4.9-7.9% were Other groups (including American Indian or Alaska Native, and Native Hawaiian or Pacific Islander). Patients with Fitzpatrick skin types IV, V, and VI represented 23.8% and 25.1%, 20.6% and 22.2%, and 7.6% and 8.9%, respectively, of patients in the trials. Across trials, vIGA-AD responses for tapinarof versus vehicle were: Asian, 39.5-48.9% vs 3.7-18.5%; Black, 43.1-47.0% vs 17.5-24.1%; White, 49.4-52.1% vs 12.2-14.5%; and Other, 26.0-44.8% vs 0.0-40.2%. EASI75 responses for tapinarof versus vehicle were: Asian, 47.6-76.6% vs 17.7-20.2%; Black, 48.9-55.3% vs 25.7-30.0%; White, 61.4-67.8% vs 19.6-20.7%; and Other, 38.3-63.3% vs 0.0-40.6%. Tapinarof cream 1% QD was consistently efficacious among patients with skin of color, who were highly represented in these trials.

[0523] Baseline Dermatology Life Quality Index (DLQI), Children's Dermatology Life Quality Index (CDLQI), and Infants' Dermatitis Quality of Life Index (IDQOL) scores (ranges) were similar, 8.6-10.1, 8.6-9.7, and 10.0-11.6, respectively, across treatment groups and trials. Baseline Patient Oriented Eczema Measure (POEM) scores were 16.4-17.4 (≥ 12 years) and 16.4-17.4 (< 12 years). Tapinarof improved QoL versus vehicle across all endpoints: DLQI, -6.2 vs -3.5 ($P=0.0031$) and -5.5 vs -3.5 ($P=0.0028$); Children's Dermatology Life Quality Index CDLQI, -5.2 vs -3.8 ($P=0.0043$) and -6.8 vs -4.1 ($P<0.0001$); IDQOL, -7.3 vs -2.6 ($P<0.0001$) and -6.9 vs -5.4 ($P=0.4364$), in ADORING 1 and 2. Notably, CDLQI sleep subdomain scores significantly improved with tapinarof versus vehicle. AD severity (POEM) improved with tapinarof versus vehicle: ≥ 12 years, -9.4 vs -5.3 ($P<0.0001$), and -10.6 vs -3.6 ($P<0.0001$); < 12 years, -11.4 vs -5.7 ($P<0.0001$), and -10.8 vs -7.3 ($P=0.0005$). Tapinarof cream significantly improved PROs, including sleep, versus vehicle in patients with moderate to severe AD irrespective of age.

[0524] *Adverse Events (ADORING 1 and ADORING 2).* Tapinarof ("VTAMA") 1% QD demonstrated an excellent safety profile in AD patients down to age 2 years. Across both trials, there were very low rates of treatment and trial discontinuation due to adverse events. Trial and

treatment discontinuation were greater in the vehicle-treated group than in the VTAMA-treated group in both trials. In ADORING 2, there was no study discontinuation due to adverse events of special interest. Adverse events of special interest included contact dermatitis (1.1% VTAMA vs. 1.5% vehicle) and folliculitis (8.9% VTAMA vs. 1.5% vehicle). Study and treatment discontinuation rate were greater in vehicle treated group than VTAMA treated group. There was a 92.4% rollover rate into the open label, long term extension study. AEs in general were well balanced between vehicle and treatment arms, with no AE other than folliculitis occurring in greater than 3% of patients in either arm.

[0525] There were no serious treatment-related TEAEs reported in either trial. The most common treatment-related TEAEs ($\geq 5\%$ in any arm) were folliculitis, headache, and nasopharyngitis. Most TEAEs were mild or moderate in intensity, associated with low rates of discontinuation, and trial discontinuation rates due to AEs were lower with tapinarof compared with vehicle (ADORING 1: 1.9% vs 3.6%; ADORING 2: 1.5% vs 3.0%, respectively).

[0526] Rates of contact dermatitis were lower for patients receiving tapinarof than vehicle in both trials: 1.5% vs 2.2% (ADORING 1) and 1.1% vs 1.5% (ADORING 2). Events of contact dermatitis were all mild or moderate, with no grade 3 (severe) events and few trial or treatment discontinuations due to contact dermatitis (0.7% vs 1.5% and 0.0% vs 0.8%).

[0527] Follicular events were reported in 10.0% of patients receiving tapinarof and 0.7% receiving vehicle in ADORING 1, and 8.9% versus 1.5% in ADORING 2. The majority of follicular events in the tapinarof groups were mild in severity (77.8%; n=21/270 and 83.3%; n=20/271), with no severe (grade 3) events; low rates of both trial or treatment discontinuation associated with follicular events across tapinarof and vehicle groups were observed in each trial (0.4% vs 0.0% and 0.0% vs 0.0%).

[0528] Headache was reported in 7.0% of the patients receiving tapinarof and 2.2% receiving vehicle in ADORING 1; and by 1.5% and 0.0% patients, respectively, in ADORING 2. Headache was generally transient and self-limited and mild or moderate except for one report of severe headache with tapinarof in ADORING 1 in a patient who did not discontinue the trial due to the AE. Trial and treatment discontinuations due to headache were also low across arms of both trials (0.4% vs 0.7% and 0.0% vs 0.0%).

[0529] There were no clinically relevant changes or differences in laboratory test and vital signs. Table 8 below shows a summary of TEAEs in the ADORING 1 and ADORING 2 trials.

Table 8. ADORING 1 and ADORING 2: Summary of TEAEs – Safety Population

	ADORING 1		ADORING 2	
Patients, n (%)	VTAMA 1% QD (n=270)	Vehicle QD (n=137)	VTAMA 1% QD (n=271)	Vehicle QD (n=133)
TEAE	118 (43.7)	33 (24.1)	95 (35.1)	24 (18.0)
AESI (treatment emergent)				
Contact dermatitis	4 (1.5)	3 (2.2)	3 (1.1)	2 (1.5)
Follicular event	27 (10.0)	1 (0.7)	24 (8.9)	2 (1.5)
Headache	19 (7.0)	3 (2.2)	4 (1.5)	0
Treatment-related TEAE	34 (12.6)	9 (6.6)	32 (11.8)	9 (6.8)
TEAE leading to treatment discontinuation	6 (2.2)	6 (4.4)	4 (1.5)	5 (3.8)
TEAE leading to trial discontinuation	5 (1.9)	5 (3.6)	4 (1.5)	4 (3.0)
Serious TEAE, non-fatal	3 (1.1)	0	2 (0.7)	0
Serious TEAE, all	3 (1.1)	0	2 (0.7)	0
Death	0	0	0	0
Treatment-related serious TEAE	0	0	0	0
Serious TEAE leading to trial drug discontinuation	0	0	1 (0.4)	0
Serious TEAE leading to trial discontinuation	0	0	1 (0.4)	0
TEAE (COVID-19)	7 (2.6)	5 (3.6)	6 (2.2)	0

Follicular event includes folliculitis, application site folliculitis, follicular eczema, and keratosis pilaris. AD, atopic dermatitis; AE, adverse event; AESI, adverse event of special interest; COVID-19, coronavirus disease 2019; QD, once daily; TEAE, treatment-emergent adverse event

[0530] Table 9 below summarizes treatment-emergent adverse events (TEAEs) having an occurrence of $\geq 1\%$ in the safety population of ADORING 1 and ADORING 2. The data in Table 9 indicate an excellent safety profile for VTAMA in AD patients down to 2 years of age. Low rates of contact dermatitis were observed for both VTAMA and vehicle. A favorable safety profile was exhibited across a large and diverse population of AD patients.

Table 9. ADORING 1 and ADORING 2: Summary of TEAEs System Organ Class and Preferred Term ($\geq 1\%$) – Safety Population

	ADORING 1		ADORING 2	
Patients with any TEAE, n (%)	VTAMA 1% QD (n=270)	Vehicle QD (n=137)	VTAMA 1% QD (n=271)	Vehicle QD (n=133)
Folliculitis	22 (8.1)	1 (0.7)	22 (8.1)	2 (1.5)

Upper respiratory tract infection	13 (4.8)	0	8 (3.0)	2 (1.5)
COVID-19	7 (2.6)	5 (3.6)	6 (2.2)	0
Asthma	6 (2.2)	1 (0.7)	4 (1.5)	0
Headache	19 (7.0)	3 (2.2)	4 (1.5)	0
Nasopharyngitis	13 (4.8)	7 (5.1)	4 (1.5)	1 (0.8)
Pyrexia	5 (1.9)	3 (2.2)	4 (1.5)	2 (1.5)
Ear infection	0	0	3 (1.1)	0
Dermatitis contact	4 (1.5)	3 (2.2)	3 (1.1)	2 (1.5)
Oropharyngeal pain	0	0	3 (1.1)	1 (0.8)
Eczema	0	1 (0.7)	1 (0.4)	2 (1.5)
Dermatitis atopic	1 (0.4)	3 (2.2)	0	2 (1.5)
Vomiting	10 (3.7)	1 (0.7)	0	1 (0.8)
Abdominal pain	4 (1.5)	0	0	0
Diarrhoea	3 (1.1)	1 (0.7)	0	1 (0.8)
Application site pain	3 (1.1)	0	2 (0.7)	1 (0.8)
Influenza	6 (2.2)	1 (0.7)	2 (0.7)	0
Application site folliculitis	3 (1.1)	0	0	0
Gastroenteritis viral	3 (1.1)	0	0	1 (0.8)
Pharyngitis streptococcal	3 (1.1)	0	2 (0.7)	0
Sinusitis	3 (1.1)	0	2 (0.7)	0
Pain in extremity	4 (1.5)	0	2 (0.7)	0
Myalgia	3 (1.1)	0	0	0
Skin papilloma	3 (1.1)	0	2 (0.7)	0
Cough	4 (1.5)	1 (0.7)	1 (0.4)	1 (0.8)
Nasal congestion	3 (1.1)	0	1 (0.4)	0
Urticaria	4 (1.5)	0	0	0
Pruritus	3 (1.1)	0	0	0

MedDRA preferred terms. AD, atopic dermatitis; AE, adverse event; COVID-19, coronavirus disease 2019; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event; QD, once daily.

[0531] Table 10 below summarizes treatment-emergent adverse events (TEAEs) having an occurrence of ≥ 6 subjects in the safety population of ADORING 1 and ADORING 2. The data in Table 10 indicate an excellent safety profile for VTAMA in AD patients down to 2 years of age. Low rates of contact dermatitis were observed for both VTAMA and vehicle. A favorable safety profile was exhibited across a large and diverse population of AD patients.

Table 10. ADORING 1 and ADORING 2: Summary of TEAEs System Organ Class and Preferred Term (≥ 6 subjects) – Safety Population

	ADORING 1		ADORING 2	
Patients with any TEAE, n (%)	VTAMA 1% QD (n=270)	Vehicle QD (n=137)	VTAMA 1% QD (n=271)	Vehicle QD (n=133)
Folliculitis	22 (8.1)	1 (0.7)	22 (8.1)	2 (1.5)
Upper respiratory tract infection	13 (4.8)	0	8 (3.0)	2 (1.5)
COVID-19	7 (2.6)	5 (3.6)	6 (2.2)	0
Asthma	6 (2.2)	1 (0.7)	4 (1.5)	0
Headache	19 (7.0)	3 (2.2)	4 (1.5)	0
Nasopharyngitis	13 (4.8)	7 (5.1)	4 (1.5)	1 (0.8)
Pyrexia	5 (1.9)	3 (2.2)	4 (1.5)	2 (1.5)
Dermatitis contact	4 (1.5)	3 (2.2)	3 (1.1)	2 (1.5)
Pain in extremity	4 (1.5)	0	2 (0.7)	0
Vomiting	10 (3.7)	1 (0.7)	0	1 (0.8)
Influenza	6 (2.2)	1 (0.7)	2 (0.7)	0

MedDRA preferred terms. AD, atopic dermatitis; AE, adverse event; COVID-19, coronavirus disease 2019; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event; QD, once daily.

[0532] Table 11 below shows the incidence of contact dermatitis, an adverse event of special interest (AESI), in the ADORING 1 and ADORING 2 trials. The data in Table 11 indicate a very low incidence of contact dermatitis in an at-risk AD population. The majority of contact dermatitis cases were mild, with no severe cases reported. There were very low trial discontinuations due to contact dermatitis in both VTAMA and vehicle groups.

Table 11. ADORING 1 and ADORING 2: AESI Contact Dermatitis

	ADORING 1		ADORING 2	
Patients, n (%)	VTAMA 1% QD (n=270)	Vehicle QD (n=137)	VTAMA 1% QD (n=271)	Vehicle QD (n=133)
Treatment-emergent contact dermatitis	4 (1.5)	3 (2.2)	3 (1.1)	2 (1.5)
Treatment discontinuation due to contact dermatitis	2 (0.7)	2 (1.5)	0	1 (0.8)

Trial discontinuation due to contact dermatitis	2 (0.7)	2 (1.5)	0	1 (0.8)
Among patients with AE of contact dermatitis				
Treatment-related contact dermatitis	3 (75)	2 (67)	0	1 (50)
Severity				
Mild – grade 1	3 (75)	1 (33)	2 (67)	2 (100)
Moderate – grade 2	1 (25)	2 (67)	1 (33)	0
Severe – grade 3	0	0	0	0
Time to onset, days – median (range)	14 (7, 29)	9 (3, 13)	10 (1, 26)	24.5 (3, 46)
At application site	3 (75)	3 (100)	2 (67)	2 (100)

AD, atopic dermatitis; AE, adverse event; AESI, adverse event of special interest; QD, once daily.

[0533] Table 12 below shows the incidence of follicular events, an adverse event of special interest (AESI), in the ADORING 1 and ADORING 2 trials. Follicular events were generally mild and were not associated with treatment discontinuation. The majority of follicular events were mild, with no severe cases reported. There was only one subject with treatment and trial discontinuation due to a follicular event in the VTAMA-treated group.

Table 12. ADORING 1 and ADORING 2: AESI Follicular Event*

	ADORING 1		ADORING 2	
Patients, n (%)	VTAMA 1% QD (n=270)	Vehicle QD (n=137)	VTAMA 1% QD (n=271)	Vehicle QD (n=133)
Treatment-emergent follicular event	27 (10.0)	1 (0.7)	24 (8.9)	2 (1.5)
Treatment discontinuation due to follicular event	1 (0.4)	0	0	0
Trial discontinuation due to follicular event	1 (0.4)	0	0	0
Among patients with AE of follicular event				
Treatment-related follicular event	22 (82)	1 (100)	23 (95.8)	2 (100)
Severity				
Mild – grade 1	21 (78)	1 (100)	20 (83.3)	2 (100)
Moderate – grade 2	6 (22)	0	4 (16.7)	0

Severe – grade 3	0	0	0	0
Time to onset, days - median (range)	12 (1, 65)	14 (14, 14)	12.5 (2, 54)	9 (7, 11)
At application site	24 (89)	1 (100)	24 (100)	2 (100)

*Follicular event includes folliculitis, application site folliculitis, follicular eczema, and keratosis pilaris. AE, adverse event; AESI, adverse event of special interest; QD, once daily

[0534] Table 13 below shows the incidence of headache, an adverse event of special interest (AESI), in the ADORING 1 and ADORING 2 trials. The clinical relevance of headache is low. The majority of headache AEs were mild or moderate, with low incidence of treatment discontinuation.

Table 13. ADORING 1 and ADORING 2: AESI Headache

	ADORING 1		ADORING 2	
Patients, n (%)	VTAMA 1% QD (n=270)	Vehicle QD (n=137)	VTAMA 1% QD (n=271)	Vehicle QD (n=133)
Treatment-emergent headache	19 (7.0)	3 (2.2)	4 (1.5)	0
Treatment discontinuation due to headache	1 (0.4)	1 (0.7)	0	0
Trial discontinuation due to headache	1 (0.4)	1 (0.7)	0	0
Among patients with AE of headache				
Treatment-related headache	8 (42)	3 (100)	0	0
Severity				
Mild – grade 1	12 (63)	2 (67)	4 (100)	0
Moderate – grade 2	6 (32)	1 (33)	0	0
Severe – grade 3	1 (5)	0	0	0
Time to onset, days - median (range)	1 (1, 75)	8 (1, 18)	1.5 (1, 4)	-

AE, adverse event; AESI, adverse event of special interest; QD, once daily.

[0535] No treatment-related serious adverse events (SAEs) occurred in the ADORING 1 and ADORING 2 trials, and the majority of patients continued in the trials. 5 SAEs were reported in the VTAMA treatment group, and none in the vehicle group. There was no pattern with regard to system organ class. In ADORING 1 there was: (1) Abdominal pain - 7 year old female hospitalized for 2 days, etiology of pain not identified, completed study; (2)

Anaphylactic shock - 14 year old female with known allergies, treated for anaphylaxis, completed study; (3) Septic arthritis of the neck - 69 year old female with septic arthritis of the neck on day 3, drug interrupted on day 33, patient withdrew consent day 43. In ADORING 2 there was: (4) Ischemic colitis - 79 year old male with 90% mesenteric stenosis diagnosed day 35, completed study; (5) Psychogenic seizure - 9 year old female hospitalized for 1 day (day 15), continued treatment without recurrent event, and then discontinued due to AE on day 26. 3 of 5 patients elected to remain in the study and continue therapy without sequelae or recurrence. There were no deaths in the trials.

[0536] Table 14 below summarizes the adverse events in the safety populations of the ADORING 1 and ADORING 2 trials.

Characteristic	ADORING 1		ADORING 2	
	Tapinarof 1% QD (n=270)	Vehicle QD (n=137)	Tapinarof 1% QD (n=271)	Vehicle QD (n=135)
Any adverse event	123 (45.6)	35 (25.5)	100 (36.9)	28 (21.1)
Serious adverse event [†]	3 (1.1)	0 (0.0)	2 (0.7)	0 (0.0)
TEAE leading to trial discontinuation	5 (1.9)	5 (3.6)	4 (1.5)	4 (3.0)
Treatment-related TEAEs				
Any	34 (12.6)	9 (6.6)	32 (11.8)	9 (6.8)
Serious	0	0	0	0
Adverse events of special interest [‡]				
Contact dermatitis	4 (1.5)	3 (2.2)	3 (1.1)	2 (1.5)
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Led to trial discontinuation	2 (0.7)	2 (1.5)	0 (0.0)	1 (0.8)
Follicular event	27 (10.0)	1 (0.7)	24 (8.9)	2 (1.5)
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Led to trial discontinuation	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	19 (7.0)	3 (2.2)	4 (1.5)	0 (0.0)
Grade 3	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)
Led to trial discontinuation	1 (0.4)	1 (0.7)	0 (0.0)	0 (0.0)
Any TEAE (≥5%)				
Folliculitis	22 (8.1)	1 (0.7)	22 (8.1)	2 (1.5)
Headache	19 (7.0)	3 (2.2)	4 (1.5)	0
Nasopharyngitis	13 (4.8)	7 (5.1)	4 (1.5)	1 (0.8)

*Each patient with an adverse event was counted only once for each MedDRA preferred term. Severity was based on the Common Terminology Criteria for Adverse Events (version 5.0) where Grade 1=Mild; Grade 2=Moderate; Grade 3=Severe or medically significant but not immediately life-threatening; Grade 4=Life-threatening consequences; Grade 5=Death related

to AE. [†]No serious adverse events were considered by the investigators to be related to tapinarof 1% cream. [‡]No adverse events of special interest were graded 4 or 5 (considered either life-threatening or related to death). COVID-19, coronavirus disease 2019; MedDRA; Medical Dictionary for Regulatory Activities; QD, once daily; TEAE, treatment-emergent adverse events.

[0537] In the ADORING trials, children as young as two years old received tapinarof (VTAMA) cream 1% at the same dose and frequency as is currently approved for adults with plaque psoriasis. The maximal usage study utilized a 1% dose of tapinarof cream. In ADORING 2, subjects were as young as 2 years old with up to 90% body surface area (BSA) affected and a mean BSA of 43%. The results demonstrated a consistent PK profile and reliable performance regardless of age and disease state. Minimal to no systemic exposure was confirmed under maximal use conditions in subjects with up to 90% body surface area affected. The 1% tapinarof cream had a highly favorable safety profile in subjects with high disease burden (including a low incidence of AEs and well tolerated even in sensitive areas; no contact dermatitis; and only 1 case of mild folliculitis).

Conclusions (ADORING 1 and ADORING 2)

[0538] In ADORING 1 and ADORING 2, a highly favorable efficacy and safety profile for VTAMA was demonstrated in moderate to severe AD patients down to 2 years of age. In terms of efficacy, clinically relevant, meaningful, and statistically significant results were achieved on primary and all secondary endpoints; sensitivity analyses supported the robustness of the primary endpoint; consistent and clinically meaningful primary endpoint vIGA-AD success was achieved across all age groups and both moderate and severe disease; and there was marked improvement in itch with majority of VTAMA-treated patients achieving the clinically relevant gold standard of ≥ 4 -point reduction from baseline. In terms of safety, VTAMA demonstrated an excellent safety profile in AD patients down to 2 years of age; a very low trial and treatment discontinuation due to AEs; and $<1\%$ trial or treatment discontinuations of VTAMA due to AESIs.

[0539] In ADORING 1 (N=407), VTAMA met the primary endpoint of the trial and demonstrated highly statistically significant improvement in the Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-ADTM) score of clear (0) or almost clear (1) with at least a 2-grade improvement from baseline at Week 8 ($P<0.0001$). 45.4% of subjects receiving VTAMA achieved the primary endpoint of vIGA-ADTM response of clear (0) or almost clear (1) with at least a 2-grade improvement from baseline at Week 8, versus 13.9% on vehicle ($P<0.0001$).

[0540] Additionally, VTAMA demonstrated highly statistically significant improvement in the proportion of subjects with $\geq 75\%$ improvement in the Eczema Area and Severity Index (EASI75) from baseline at Week 8 ($P<0.0001$), a key secondary endpoint. All secondary endpoints were met with statistical significance, including 55.8% of subjects treated with VTAMA who achieved the key secondary endpoint of EASI75 at Week 8 ($P<0.0001$). Subjects 12 years and older receiving VTAMA also experienced a statistically significant improvement in itch with a ≥ 4 -point reduction in the patient reported Peak Pruritus Numeric Rating Scale (PP-NRS) ($P=0.0366$), another key secondary endpoint. 61.1% of subjects, with a baseline PP-NRS score ≥ 4 , achieved a ≥ 4 -point reduction in the PP-NRS at Week 8 ($P<0.0001$).

[0541] In ADORING 2, tapinarof 1% cream demonstrated highly statistically significant improvement in Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) score of clear (0) or almost clear (1) from baseline at Week 8 (46.4% vs 18.0%; $P<0.0001$); as well as highly statistically significant improvement in EASI-75 from baseline at week 8 (59.1% vs 21.2%; $P<0.0001$). Subjects ≥ 12 years old receiving VTAMA cream experienced a highly statistically significant itch improvement of ≥ 4 points on the PP-NRS (52.8% vs 24.1%; $P=0.0015$), another key secondary endpoint in the study due to its prevalence among AD sufferers. Tapinarof 1% cream was safe and well tolerated in this population including children as young as 2 years. Adverse events in ADORING 2 were primarily mild which resulted in a low discontinuation rate (1.5% tapinarof vs. 3.0% vehicle). Tapinarof cream 1% QD was well tolerated, displaying a very high 92.4% rollover rate into the long-term extension study. Both adult and pediatric AD subjects receiving VTAMA cream, 1% did so at the same dose and dose regimen as already approved for adults with plaque psoriasis.

[0542] 91% of subjects from ADORING 1 and ADORING 2 elected to enroll into the Phase 3 ADORING 3 open-label, long-term safety study.

[0543] Table 15 below shows a summary of primary and secondary endpoints from ADORING 1 and ADORING 2.

Table 15. ADORING 1 and ADORING 2 Phase 3 Trials – Primary and Key Secondary Endpoints

Endpoint	ADORING 1 Week 8			ADORING 2 Week 8		
	VTAMA 1% QD	Vehicle QD	P Value	VTAMA 1% QD	Vehicle QD	P Value

vIGA-AD success ¹	45.4%	13.9%	<0.0001	46.4%	18.0%	<0.0001
EASI75 ²	55.8%	22.9%	<0.0001	59.1%	21.2%	<0.0001
≥4-point reduction in PP-NRS ³	55.8%	34.2%	0.0366	52.8%	24.1%	0.0015

¹Primary Endpoint: Proportion of subjects who achieved a vIGA-AD score of clear (0) or almost clear (1) with at least a 2-grade improvement from baseline at Week 8.

²Secondary Endpoint: Proportion of subjects with ≥75% improvement in EASI from baseline at Week 8.

³Secondary Endpoint: Proportion of subjects ≥12 years old with a baseline PP-NRS score ≥4 who achieved ≥4-point reduction in the PP-NRS from baseline at Week 8.

[0544] Importantly, when PP-NRS was assessed across the entire VTAMA treated population, 61.1% (P<0.0001) experienced a statistically significant improvement in itch, a highly prevalent symptom among AD sufferers.

[0545] Both adult and pediatric AD subjects down to 2 years of age receiving VTAMA in the ADORING trials did so at the same dose and dose regimen as currently approved for adults with plaque psoriasis. VTAMA may offer simplicity and efficacy of treatment to patients and physicians. Tapinarof cream 1% QD may fill a gap in the current treatment armamentarium for a highly effective, non-steroidal topical that can be used down to 2 years of age without restrictions on duration of use, or extent and sites of application.

[0546] *Results of Pre-Planned Interim Analysis of Data from ADORING 1, ADORING 2, Maximal Usage PK, and ADORING 3*

[0547] A pre-planned interim analysis, which included an integrated evaluation of data, was performed that included ADORING 1, ADORING 2, Maximal Usage Pharmacokinetics (PK), and ADORING 3 (including 76 pediatric subjects were directly enrolled into ADORING 3 who did not meet the criteria for one of the previous studies (disease too mild or too severe), as described herein). The interim analysis efficacy data showed that 92.3% of subjects have achieved at least a 1-grade improvement in vIGA score, and a vIGA-AD score of 0 (clear) or 1 (almost clear) plus at least a 2-grade improvement from baseline was observed in up to 73% (519/711) of subjects. Additional improvement in EASI75 was observed, with up to 80.7% (574/711) of subjects observed to have at least a 75% reduction in disease burden. 51% (373/728) of subjects in ADORING 3 have achieved complete disease clearance (vIGA-AD score of 0). 77.9% (218/280) of subjects achieved a ≥4-point reduction in the patient-reported Peak Pruritus Numeric Rating Scale (PP-NRS).

[0548] In this planned interim analyses of the ADORING program, VTAMA cream achieved an EASI75 in almost 81% of the population, and an impressive 51% of subjects,

including both adults and children as young as 2 years old, achieved complete disease clearance with a vIGA-AD score of 0. Additionally, the safety data are consistent with the previously reported data from ADORING 1 and 2, further supporting VTAMA cream's clinical profile and its ability to achieve long-term disease control.

[0549] The ADORING 3 interim analysis safety data showed that VTAMA cream, 1% was well-tolerated across all anatomic locations by both subjects and investigators. No new safety signals were observed over 56 weeks; consistent safety and tolerability were observed for all ages, anatomic locations, and durations of treatment. The discontinuation rate due to adverse events (AEs) was 2.6%. The AE profile of VTAMA cream, 1% reported in the extension study was consistent with the AE profile observed in the previous ADORING 1 and ADORING 2 trials, with the majority of AEs mild to moderate in nature. The most commonly reported AEs in ADORING 3 were folliculitis, nasopharyngitis, and upper respiratory tract infection. There were no treatment-related serious adverse events (SAEs) reported.

[0550] The ADORING 3 study design provided that when subjects achieved complete disease clearance, all treatment was withdrawn and subjects were followed until disease recurred, defined as a vIGA-AD $\geq$ 2. Subjects were able to be off all therapy for an extended period prior to disease recurrence—a “remittive effect”—potentially giving them the ability to safely manage and have control over their disease on a long-term basis without the need for daily or intermittent use of a prescription product. These results indicate that tapinarof 1% cream, as described herein, may have disease-modifying effects and may solve a significant unmet need as a steroid-free, topical treatment option for both adults and children as young as 2 years old suffering from atopic dermatitis. VTAMA's efficacy and safety profile is combined with its ability to rapidly reduce itch, the most common symptom of atopic dermatitis. Atopic dermatitis is an extremely burdensome disease, especially for pediatric patients, the most frequently affected patient population. The interim integrated data has demonstrated an excellent safety and tolerability profile and effective long-term disease control in pediatric patients in the ADORING studies.

[0551] Example 2: Efficacy of Tapinarof Cream 1% Once Daily for the Treatment of Mild to Severe Intertriginous Plaque Psoriasis

[0552] *Background.* Topical agents are the mainstay of treatment in patients with mild to moderate psoriasis. Although efficacious, topical corticosteroids (TCSs) are associated with extrinsic adverse events (AEs), including acne, rosacea, perioral dermatitis, facial erythema,

hirsutism, ecchymosis, withdrawal phenomena, and irreversible skin thinning and atrophy, striae and telangiectasia. TCSs are also reported to increase the risk of systemic AEs, including hypothalamic-pituitary-adrenal axis suppression in children, and fractures. Because of the risks associated with TCSs, treatment is often applied intermittently. Furthermore, multiple TCSs with differing potencies may be required to treat psoriasis in different locations on the body, especially sensitive areas. Plaque psoriasis commonly affects intertriginous areas; this is also called inverse psoriasis. Affected areas, such as the groin or genitals, are prone to AEs due to the presence of thin skin and direct occlusion, potentially increasing the likelihood of treatment absorption. There remains a need, therefore, for efficacious non-steroidal topical therapies for psoriasis that have minimal systemic absorption, no risk of irreversible AEs, and can be used without restrictions relating to duration or extent of use, or site of application, including in intertriginous areas. Tapinarof cream 1% (VTAMA) is a non-steroidal, topical aryl hydrocarbon receptor agonist approved for the treatment of plaque psoriasis in adults, with no warnings, contraindications, drug-drug interactions, or restrictions on location, extent, or duration of use. In the phase 3 PSOARING trial program (N=1,025), tapinarof cream 1% once daily (QD) was efficacious and well tolerated for the treatment of plaque psoriasis for up to 52 weeks, including in intertriginous and sensitive skin areas. 227 patients with psoriasis in intertriginous area, including axillae, gluteal cleft, inframammary areas, genitalia, and skin folds, reported favorable tolerability with tapinarof use. Efficacy data specific to intertriginous areas were not captured in the phase 3 PSOARING trial program.

[0553] *Objective.* To investigate the real-world efficacy and safety from the phase 4, 12-week, open-label trial of tapinarof cream 1% QD for the treatment of adults with mild to severe plaque psoriasis in intertriginous areas.

[0554] In this phase 4, open-label multicenter trial, adults with mild to severe plaque psoriasis in intertriginous areas received tapinarof cream 1% QD for 12 weeks, followed by 1 week of follow up. FIG. 29 shows the intertriginous psoriasis trial design (iPGA, intertriginous Physician Global Assessment; QD, once daily).

[0555] The primary efficacy endpoint was intertriginous Physician Global Assessment (iPGA) response at Week 12, defined as the proportion of patients with an iPGA score of clear (0) or almost clear (1) and ≥ 2 -grade improvement from baseline at Week 12. Additional efficacy endpoints included time to achieve an iPGA response, and achievement of complete disease clearance (iPGA score of 0) by visit. Patient-reported outcomes (PROs) included Peak Pruritus-Numerical Rating Scale (PP-NRS) score for intertriginous areas; ≥ 4 -point reduction

in PP-NRS score; Dermatology Life Quality Index (DLQI) score; and responses to a Patient Satisfaction Questionnaire (PSQ). A Static Physician’s Global Assessment of Genitalia (sPGA-G) response was defined as the proportion of patients with a baseline score ≥ 2 , who achieve a score of clear (0) or minimal (1) with a ≥ 2 -grade improvement from baseline. Local tolerability was evaluated using investigator-assessed Local Tolerability Scale (LTS) and LTS-external genitalia scores by visit. The LTS is evaluated on a 5-point scale of 0 (no irritation) to 4 (very severe) for dryness, erythema, and peeling. Change in Peak Pruritus Numerical Rating Scale (PP-NRS) score for intertriginous areas was assessed by visit (Weeks 1, 2, 4, 6, 8, and 12). The PP-NRS is evaluated on an 11-point scale, where 0 indicates “no itch” and 10 indicates “worst imaginable itch” within the last 24 hours. Safety assessments included incidence, frequency, and duration of treatment-emergent adverse events (TEAEs).

[0556] *Results.* Overall, 34 patients were enrolled at seven sites in the US and Canada. Table 16 below shows the baseline demographics and disease characteristics of the enrolled patients. 85.3% of patients (n=29/34) completed treatment; 82.4% of patients (n=28/34) completed the trial (Week 13). Patients’ mean age was 54.1 years, and 58.8% were male. 29.4%, 64.7%, and 5.9% had an iPGA score of 2 (mild), 3 (moderate), and 4 (severe), respectively; 11.8% had psoriasis affecting genitalia.

Table 16. Baseline Demographics and Disease Characteristics

	Tapinarof 1% QD (N=34)
Age, years, mean (SD)	54.1 (15.9)
Male, n (%)	20 (58.8)
iPGA, n (%)	
2 – Mild	10 (29.4)
3 – Moderate	22 (64.7)
4 – Severe	2 (5.9)
sPGA-G, n (%)	
1 – Minimal	1 (25.0)
2 – Mild	1 (25.0)
3 – Moderate	2 (50.0)

iPGA, intertriginous Physician Global Assessment; QD, once daily; SD, standard deviation; sPGA-G, Static Physician’s Global Assessment of Genitalia.

[0557] Achievement of an iPGA Response, sPGA-G Response, and Complete Disease Clearance (iPGA Score=0)

[0558] At Week 12, 82.8% (24/29) achieved an iPGA response) and 65.5% (19/29) achieved complete disease clearance. There was rapid onset of efficacy with tapinarof treatment, with both iPGA response and complete disease clearance achieved as early as Week 2. Median time to an iPGA response was approximately 6 weeks. Most TEAEs were mild or moderate, consistent with previous trials; only one patient discontinued due to an adverse event (contact dermatitis). Tapinarof was well tolerated with the majority of patients having no irritation (LTS score=0) at intertriginous areas including genitalia specifically.

[0559] FIG. 30A shows that 82.8% of patients (n=24/29) achieved an iPGA response with tapinarof cream at Week 12; a response was seen as early as Week 2. Median time to achieve an iPGA response was approximately 6 weeks (45 days). FIG. 30B shows that 65.5% of patients achieved complete disease clearance (iPGA score of 0 [clear]) with tapinarof cream at Week 12, and achievement was observed as early as Week 2 with a median time to iPGA=0 of approximately 8 weeks (58 days). Efficacy was maintained to Week 13, after tapinarof treatment was completed at Week 12. 100% (n=3/3) of patients with intertriginous psoriasis in the genital area achieved an sPGA-G response at Week 4 and maintained through Week 12 (n=2/2). sPGA-G response was demonstrated as early as Week 2. (95% CI calculated using Clopper Pearson method. *iPGA score of clear (0) or almost clear (1) and ≥ 2 -grade improvement from baseline at Week 12. CI, confidence interval; iPGA, intertriginous Physician Global Assessment; QD, once daily.)

[0560] FIG. 31 shows that tapinarof cream 1% QD demonstrated no irritation over 12 weeks plus improvements from pre-treatment score for all intertriginous areas from baseline. (Week 0 is baseline, pre-treatment. Negative LTS scores indicate improvement. *For all intertriginous areas. The LTS score is evaluated on a 5-point scale between 0 (no irritation), (1) mild, (2) moderate, (3) severe, and 4 (very severe) for dryness, erythema, and peeling. Intention-to-treat population. LTS, local tolerability scale; QD, once daily; SD, standard deviation.) Tapinarof cream was very well tolerated throughout the trial, and improvements from pre-treatment baseline scores were observed. The majority of patients had no irritation (LTS=0) at all visits for all intertriginous areas. Additionally, for genitalia specifically, no irritation (LTS=0) was observed for most patients at all visits through Week 12.

[0561] FIG. 32 shows complete disease clearance and resolution of itch in a patient with intertriginous plaque psoriasis and pre-existing irreversible striae (due to previous TCS) treated

with tapinarof cream 1% QD. (iPGA is a global efficacy assessment for psoriasis in all intertriginous areas. Example of one representative target lesion in a tapinarof-treated patient from the phase 4 intertriginous plaque psoriasis clinical trial. iPGA, intertriginous Physician Global Assessment; PP-NRS, Peak Pruritus Numerical Rating Scale; QD, once daily.) The patient shown in this figure had a 23-year history of plaque psoriasis and severe psoriasis (iPGA=4) affecting the inguinal area at baseline. Due to previous TCS use, they also had pre-existing irreversible striae in the intertriginous skin. At Week 12, complete disease clearance (iPGA=0) was achieved. Severe itch was reported by the patient at baseline (PP-NRS=8); reduction in itch surpassed the minimal clinically important ≥ 4 -point improvement by Week 4, and continued to improve to a PP-NRS score of 0 (an itch-free state) at Week 12.

[0562] 34 patients with baseline mean intertriginous PP-NRS and total DLQI scores of 5.9 and 9.0, respectively, demonstrating significant itch and burden on the Health-Related Quality of Life Scale (HRQoL) received tapinarof cream 1% QD. Improvement in mean PP-NRS score was demonstrated at Week 1, the earliest assessment (-1.1), and continued through Week 12 (-3.8). At Week 12, 75% (15/20) achieved ≥ 4 -point reduction in PP-NRS score. Improvement in mean DLQI score from baseline was observed as early as Week 1 (-2.4). By Week 2, the mean DLQI minimal clinically important difference of -4.0 was exceeded (-4.1), improving to mean difference of -6.3 at Week 12. Most patients agreed/strongly agreed with PSQ questions assessing satisfaction with application ease (100%), cosmetic elegance (90.3%), efficacy (80.6%), confidence in tapinarof (80.7%), and application time not impacting everyday life (90.3%). Compared with other topical drugs previously used to treat psoriasis, the majority agreed or strongly agreed that tapinarof was more effective (85.8%) and was preferred (85.7%).

[0563] Safety: Most TEAEs were mild or moderate, and consistent with previous trials. No atrophy, striae, telangiectasia, acne, rosacea, perioral dermatitis, facial erythema, hirsutism, skin thinning, ecchymosis, or withdrawal phenomena were reported in this phase 4 trial. Only one patient discontinued from the trial due to an AE (contact dermatitis).

[0564] *Conclusions.* Tapinarof cream 1% QD demonstrated rapid onset of clinically meaningful efficacy as early as Week 2 in patients with mild to severe plaque psoriasis, including in intertriginous areas and genitalia. The primary endpoint of an iPGA response and the exploratory endpoint to achieve completely clear intertriginous skin were achieved by 82.8% and 65.5% of patients, respectively, at Week 12, and were maintained at Week 13, after treatment discontinuation. Tapinarof was well tolerated; TEAEs were consistent with those

seen in previous trials, and only one patient discontinued from the trial due to an AE. Tapinarof cream 1% QD is a highly effective, non-steroidal topical treatment option for patients with mild to severe plaque psoriasis, with no restrictions on extent, duration, or location of use, including in sensitive and intertriginous areas.

[0565] In patients with intertriginous plaque psoriasis, tapinarof cream 1% QD demonstrated rapid and clinically meaningful improvements in patient reported pruritus and HRQoL, as early as Week 1 which continued improvement through Week 12. Patients also reported high rates of satisfaction and positive perceptions of tapinarof, which were consistent with previously reported phase 3 trials.

[0566] Example 3 – Open Label Maximal Use Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Tapinarof Cream, 1% in Pediatric Patients with Atopic Dermatitis

[0567] This Phase 2a maximal use study was conducted as part of a clinical development program to evaluate the safety and systemic exposure of tapinarof cream, 1% for the topical treatment of AD in subjects ages 2 to 17 years. Maximal use trials enrolled subjects with the disease under study and who generally have more severe disease or with a large BSA of affected skin who might be more susceptible to systemic AEs. The purpose of these studies was to evaluate systemic exposure under conditions that would maximize the potential for drug absorption with the intended use of the product.

[0568] Table 17 below shows the objectives and endpoints of the study.

Table 17. Objectives and endpoints

Objectives	Associated Endpoint
Primary	
To evaluate the safety and tolerability of tapinarof cream, 1% QD in pediatric subjects ages 2 to 17 years old with extensive AD	- Incidence, frequency and duration of TEAEs and serious adverse events (SAEs) - Change from Baseline in laboratory values - Change from Baseline in vital signs - Mean Investigator-assessed local tolerability scores (LTS) scores by visit (overall and sensitive areas)
To evaluate the PK of tapinarof cream, 1% QD in pediatric subjects ages 2 to 17 years old with extensive AD	- Tapinarof plasma PK parameters on Day 1, if data permit, including: - area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration (AUC_{0-last}) - maximum plasma concentration (C_{max}) - time to maximum plasma concentration (t_{max}) - time of last quantifiable concentration (t_{last}) - Tapinarof plasma concentration on Day 28
Secondary	

To assess the efficacy of tapinarof cream, 1% QD in pediatric subjects ages 2 to 17 years old with extensive AD	- Change in Validated Investigator Global Assessment in Atopic Dermatitis (vIGA-AD™) score from Baseline at each study visit - Proportion of subjects who have a vIGA-AD™ score of clear or almost clear (0 or 1) at each study visit - Proportion of subjects with $\geq 50\%$ improvement in EASI score from Baseline at each study visit - Proportion of subjects with $\geq 75\%$ improvement in EASI score from Baseline at each study visit - Proportion of subjects with $\geq 90\%$ improvement in EASI score from Baseline at each study visit - Mean change and percent change in EASI score from Baseline at each study visit - Mean change and percent change in %BSA affected from Baseline at each study visit - Mean change and percent change in BSA x vIGA-AD™ values from Baseline at each study visit - Proportion of subjects with a Baseline PP-NRS score ≥ 4 who achieve ≥ 4-point reduction in the PP NRS from Baseline at each study visit - Proportion of subjects ≥ 12 years old with a Baseline PP-NRS score ≥ 4 who achieve a ≥ 4-point reduction in PP-NRS score from Baseline at each study visit - Proportion of subjects 2 to < 12 years old with a Baseline PP-NRS score ≥ 4 who achieve a ≥ 4-point reduction in PP-NRS score from Baseline at each study visit - Mean change in PP-NRS score from Baseline to Day 28 by age group
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[0569] *Study Design.* This was a Phase 2a, multicenter, open-label, safety, tolerability and PK study in pediatric subjects with AD. The study consisted of three phases: Screening (up to 30 days), Treatment (27 days), and Follow-up (approximately 7 days).

[0570] At Day 1 (Baseline), eligible subjects and/or their caregiver(s) were instructed on how to apply tapinarof cream, 1% while under the supervision of site personnel in the clinic and had collection of PK samples to assess systemic absorption. During the treatment period, subjects and/or their caregiver(s) applied tapinarof cream, 1% to affected areas once a day for 27 days, including newly appearing lesions and lesions/areas that improve during the study. Subjects or caregivers applied sufficient study drug to cover completely each lesion with a thin layer of study drug and recorded the time of study drug application and daily itch score (Peak Pruritus-Numeric Rating Scale [PP-NRS]) in a daily diary provided by the study site. (Note that subjects were allowed, but not required, to treat scalp lesions with study drug; however, efficacy analyses did not include assessment of AD in this area.) Subjects returned to the clinic

on Days 8 and 28 for study assessments. On clinic visit days, subjects and/or their caregiver(s) applied study drug under the supervision of site personnel and were instructed/reminded on how to apply study drug (except during the final treatment/end-of-study visits). Additionally, subjects were contacted by phone at Day 15 to assess AEs and concomitant medications, to review study drug administration instructions, confirm subject's continued participation in this study, and reminded to complete their daily diary and bring it with them to the next clinic visit.

[0571] Study drug was dispensed and applied to subjects during the clinic visits and was administered at home between clinic visits as instructed by site personnel. Subjects and/or caregivers were advised to maintain the approximate dosing time chosen at the beginning of the study for their full study participation.

[0572] Nonmedicated emollients that do not contain salicylic acid may be used on nonlesional skin; emollients should not be applied to lesional skin during treatment. The same emollient was used throughout the subject's participation in the study.

[0573] Study drug application instructions were reviewed at all post-baseline clinic visits and during the planned study phone call. The time of the dose application and assessments depended on the time of the clinic visit. Therefore, the timing of the clinic visit could lead to a change in the subject's chosen dosing time for that day.

[0574] On Day 28 of this study, a final PK sample was collected and subjects had the option to enroll in a separate open-label long-term safety study for an additional 48 weeks. Subjects who chose not to participate in the open-label long-term safety study or who failed to qualify for participation in the open-label long-term safety study completed a Follow-up Visit (Day 35) approximately 7 days after the end of treatment in this study. Subjects who withdraw from the study before Day 28 completed an Early Termination Visit as their final visit and were not eligible for the open-label long-term study. Subjects that complete an Early Termination visit did not complete a Follow-up visit.

[0575] Study duration for subjects who completed this study and who failed to qualify for participation in the open-label long-term safety study, or who qualified to participate in the open-label long-term safety study but elected not to enroll in that study was approximately 9 weeks in total. Study duration for subjects who completed this study and were eligible and decided to participate in the open-label long-term safety study was approximately 8 weeks in total.

[0576] Efficacy assessments included v-IGA-ADTM score, %BSA affected, EASI, and PP-NRS. Safety assessments included AEs, clinical laboratory tests, physical examination, vital signs, and LTS.

[0577] Pharmacokinetics were assessed at Days 1 and 28. The screening blood sample was used for baseline PK if the subject was enrolled. Blood samples for PK were not collected from any anatomic site where study drug had been applied in order to minimize potential contamination.

[0578] All subjects received tapinarof cream, 1% QD for 27 days, at an appropriate dose in accordance with the size of the affected area. Subjects or their caregivers were instructed to apply a thin layer to the affected areas.

[0579] Study Population

[0580] Type and Number of Subjects

[0581] Approximately 36 subjects ages 2 to 17 years old were enrolled in the study with approximately 12 subjects, and a minimum of 10 subjects, enrolled into each of the three following age cohorts: 2-6 years old, 7-11 years old, 12-17 years old. Subjects across the age range were enrolled simultaneously.

[0582] Protocol violations from inclusion and exclusion criteria were prohibited because ineligible study subjects could potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol was essential.

[0583] Inclusion Criteria

[0584] Each subject had to meet all of the following criteria to be eligible to participate in the study:

[0585] Male and female subjects ages 2 to 17 years with a clinical diagnosis of AD by Hanifin and Rajka criteria.

[0586] Subjects with AD covering $\geq 25\%$ of the BSA for subjects ages 12-17 years old, or $\geq 35\%$ of the BSA for subjects ages 2-11 years old, suitable for topical therapy. Scalp was excluded from the BSA calculation to determine eligibility during Screening and at Baseline, and for all efficacy assessments.

[0587] A vIGA-AD™ score of 3 or greater at Screening and Baseline (pre-dosing).

[0588] AD present for at least 6 months for subjects ages 6-17 years old or 3 months for subjects ages 2 to 5 years old, confirmed by prior medical documentation and/or according to the subject and/or caregiver(s).

[0589] Female subjects of childbearing potential who were engaging in sexual activity that could lead to pregnancy used one of the following acceptable birth control methods while on study and for 4 weeks after the last exposure to study drug.

[0590] Acceptable contraception methods included intrauterine device, hormonal contraceptives, barrier method (e.g., condom or diaphragm), or surgical sterilization of male partner (vasectomy)

[0591] Subjects who claimed abstinence as their method of contraception were allowed provided they agreed to use a barrier method (e.g., condom or diaphragm) if they became sexually active from Screening to 4 weeks after the last dose of study drug

[0592] Non-child-bearing potential was defined as: premenarchal pre-menopausal females with a documented bilateral tubal ligation, bilateral oophorectomy, hysterectomy, or hysteroscopic sterilization.

[0593] Female subjects of childbearing potential had a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline (Day 1).

[0594] Subject, subject's parent(s), or legal representative must have been capable of giving written informed consent, which included compliance with the requirements and restrictions listed in the consent/assent form; written informed consent must have been obtained prior to any study related procedures.

[0595] Assessments Completed by Investigator:

[0596] Validated Investigator Global Assessment

[0597] The vIGA-AD™ of disease severity was assessed at every clinic visit. The vIGA-AD™ is a global assessment of the current state of the disease. It is a 5-point morphological assessment of overall disease severity and is determined according to the categories described in Table 18 below. To be eligible, subjects must have had a vIGA-AD™ score of at least 3 or 4 at Screening and the Baseline visit (Day 1). Eli Lilly and Company (Lilly) developed the vIGA-AD™ scale for use in clinical trials. For more information on the vIGA-AD™ please refer to the website <http://www.eczemacouncil.org/research/investigator-global-assessment-scale/>, which is incorporated herein by reference.

Table 18. Validated Investigator Global Assessment Scale for Atopic Dermatitis

Score	Category	Definition
0	Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.

1	Almost clear	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2	Mild	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting
3	Moderate	Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4	Severe	Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

[0598] *Body Surface Area Affected.* The assessment of the %BSA affected is an estimate of the percentage of total involved skin with AD. 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 AD was evaluated from 0% to approximately 100% [scalp excluded]. Percentage BSA is a static assessment made without reference to previous scores.

[0599] *Eczema Area and Severity Index.* The EASI was assessed at every clinic visit beginning with the Baseline visit. It quantified the severity of a subject's AD based on both lesion severity and the %BSA affected. The EASI is a composite score ranging from 0 to 72 that takes into account the degree of erythema, edema/papulation, excoriation, and lichenification (each scored from 0 to 3 separately) for each of four body regions, with adjustment for % BSA involved for each body region relative to the whole body. The EASI score was calculated in the CRF based on the subject's age, the rating scores for each region, and the number of handprints involved for each region.

[0600] *Assessments Completed by Subject:*

[0601] *Peak Pruritus Numeric Rating Scale.* The PP NRS is a scale used to quickly assess itch/pruritus severity over a 24-hour period. The subject or caregiver utilized the scale to assess peak pruritus QD and record the results in their daily diaries. The itch rating could be done before or after study drug administration since it reflected the past 24 hours. On clinic visit days, the PP-NRS was assessed in the clinic and not recorded in the diary. For subjects ages 2 to < 12 years, the PP-NRS was completed by the parent or caregiver. For subjects ages $\geq$ 12 years, the PP-NRS was completed by the subject. An example of the PP-NRS includes the question, "On a scale of 0 to 10, with 0 being 'no itch' and 10 being 'worst itch imaginable,' how would you rate your itch at the worst moment during the previous 24 hours?"

[0602] *Safety Assessments:*

[0603] *Adverse Events* All AEs and SAEs were collected from the time the subject signed the Informed Consent Form (ICF) until the final visit/contact with the subject. In prior clinical studies, contact dermatitis, folliculitis, and headache were identified as AEs of particular clinical importance; they were also reported as adverse events of special interest (AESIs) in this study. In each case study drug could be continued or discontinued, based on Investigator judgment, and could be restarted when the event resolved. In addition, the following information was collected for each of these AESIs:

[0604] Contact Dermatitis: The study site collected location, time to onset, duration, size, associated symptoms (itching, burning, pain), severity (mild, moderate, severe), concomitant medications used to treat, action taken with study drug, and photograph the affected site (if possible). If the subject contacted the study site to report significant skin irritation at or near the site of study drug application between study visits, the subject was brought in for an unscheduled visit, if possible.

[0605] Headache: The study site collected time to onset, duration, severity (mild, moderate, severe), location (e.g., frontal, temporal, occipital, diffuse).

[0606] Follicular Event: The study site collected the location, duration, size, associated signs and symptoms (itching, burning, pain erythema), severity (mild, moderate, severe), describe morphology [scale (keratotic/cornified) or no scale (non-keratotic/non-cornified)], time to onset, and photograph the affected site (if possible). In particular, the term ‘folliculitis’ may not correctly describe the morphology of the observed local follicular events as these appear to have been more consistent with a keratoses pilaris-like follicular based papule. Tapinarof upregulates components of the stratum corneum, including involucrin, hornerin, and filaggrin and increased cornification at, and subsequent mechanical occlusion of, the follicular ostia has been suggested to be a potentially on target mechanism by which these lesions may develop in some individuals treated with tapinarof cream. Additional morphologic description may help to more fully and appropriately characterize these follicular events. Possible descriptors include, but are not limited to:

[0607] Folliculitis

[0608] Non-inflammatory

[0609] Inflammatory

[0610] Milia

[0611] Non-inflammatory

[0612] Inflammatory

[0613] Keratosis pilaris

[0614] Non-inflammatory

[0615] Inflammatory

[0616] *Investigator Assessed Local Tolerability Scale.* At each specified study visit, the Investigator (or qualified evaluator) assessed the presence and overall degree of irritation at the application sites according to a 5-point LTS. The score ideally represented an “average” across all application sites. To the fullest extent possible, the same Investigator (or designated evaluator) performed all tolerability assessments for an individual subject throughout the study. If the subject was applying study drug to “sensitive areas,” a separate LTS was used to assess the degree of irritation for each of these areas where study drug was being applied. The sensitive areas that were assessed were face, neck, skin folds, axilla, inframammary, anal crux, and genitalia. The LTS was completed pre-dose at Baseline/Day 1, Day 8, and Day 28 when other assessments are completed. Other than at the Baseline visit, the Investigator-assessed LTS was only completed when the subject was currently receiving study drug (i.e., had applied at least one application in the last 48 hours).

[0617] *Results*

[0618] *Pharmacokinetic Analyses*

[0619] *Pharmacokinetic Concentrations* Thirty-six subjects (12 in each age group) were included in the PK population. The Screening sample from an 8-year-old subject (Subject 4003-005) for tapinarof failed to meet the assay acceptance criteria; the primary sample lacked the required volume for reanalysis as did the backup sample. However, the Screening sample for tapinarof sulfate (metabolite) was successfully analyzed. The additional sample collections from Subject 4003-005 were unable to be drawn, resulting in no concentration results for either tapinarof or tapinarof sulfate for Day 1. As a result, the tapinarof concentration over time profiles presented below represent 35 of the 36 subjects in the PK population.

[0620] Table 19 below summarizes the baseline demographics and disease characteristics for enrolled patients. There were equal proportions (33.3% [12/36]) in the three age groups. Most patients (77.8%) across the three groups had a vIGA-ADTM score of 3 (moderate). Overall mean (SD) EASI score was 23.8 (9.2), with a range of 8.2–49.6 indicating moderate to severe AD. Overall mean (SD) %BSA affected was 42.8% (15.1%), with a range of 26–90%.

Table 19. Baseline Patient Demographics and Disease Characteristics

	Tapinarof cream 1% QD			
	2–6 years (n=12)	7–11 years (n=12)	12–17 years (n=12)	Overall (N=36)
Age, years, mean (SD)	3.7 (1.4)	8.2 (1.4)	14.8 (1.8)	8.9 (4.9)
Male, n (%)	9 (75.0)	7 (58.3)	8 (66.7)	24 (66.7)
vIGA-AD™ of 3 (moderate), n (%)	8 (66.7)	9 (75.0)	11 (91.7)	28 (77.8)
vIGA-AD™ of 4 (severe), n (%)	4 (33.3)	3 (25.0)	1 (8.3)	8 (22.2)
EASI, mean (SD)	30.2 (8.6)	21.0 (10.0)	20.3 (5.5)	23.8 (9.2)
BSA affected, %, mean (SD)	52.4 (19.1)	42.0 (10.0)	33.9 (8.6)	42.8 (15.1)

[0621] The tapinarof and tapinarof sulfate concentrations over time profiles on Day 1 using a semi-log scale is provided in FIG. 33. On Day 1, mean tapinarof concentrations were highest 1 hour post application then decreased over the 5-hour sampling period. Concentrations of the metabolite (tapinarof sulfate) were BQL (< 10 pg/mL) at all time points. The tapinarof and tapinarof sulfate concentrations-over-time profiles on Day 1 by age group using a semi-log scale are provided in FIG. 34.

[0622] A summary of tapinarof concentrations by day and sample time is provided in Table 20 below.

Table 20. Summary of Tapinarof Concentrations by Day and Time (Pharmacokinetic Population)

Time Point		2-6 years (N = 12)	7-11 years (N = 12)	12-17 years (N = 12)	Total (N = 36)
Screening	n	12	11	12	35
	Mean (SD)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
	CV (%)	-	-	-	-
	Median	0.00	0.00	0.00	0.00

	Min, Max	0.00, 0.00	0.00, 0.00	0.00, 0.00	0.00, 0.00
	Geometric Mean	0.00	0.00	0.00	0.00
	Geometric Mean CV (%) ^a	-	-	-	-
Day 1: 1 h postdose	n	12	11	12	35
	Mean (SD)	1790 (2480)	1270 (1680)	1070 (1810)	1380 (1990)
	CV (%)	138	132	169	144
	Median	1120	696	325	616
	Min, Max	53.2, 8870	74.8, 5660	0.00, 5080	0.00, 8870
	Geometric Mean	751	625	0.00	0.00
	Geometric Mean CV (%) ^a	300	207	315	257
Day 1: 3 h postdose	n	11	11	12	34
	Mean (SD)	1110 (911)	1730 (2450)	650 (1120)	1150 (1640)
	CV (%)	82.1	141	172	143
	Median	909	573	210	474
	Min, Max	80.5, 3040	116, 8190	0.00, 4010	0.00, 8190
	Geometric Mean	688	757	0.00	0.00
	Geometric Mean CV (%) ^a	179	235	158	193
Day 1: 5 h postdose	n	11	9	12	32
	Mean (SD)	2140 (6220)	568 (637)	339 (534)	1020 (3660)
	CV (%)	291	112	158	358
	Median	235	197	111	205
	Min, Max	0.00, 20900	0.00, 1590	0.00, 1760	0.00, 20900
	Geometric Mean	0.00	0.00	0.00	0.00
	Geometric Mean CV (%) ^a	295	198	174	207
Day 28: predose	n	10	8	11	29
	Mean (SD)	45.7 (107)	88.8 (130)	125 (413)	87.5 (265)
	CV (%)	234	146	332	302
	Median	0.00	28.1	0.00	0.00
	Min, Max	0.00, 328	0.00, 358	0.00, 1370	0.00, 1370
	Geometric Mean	0.00	0.00	0.00	0.00
	Geometric Mean CV (%) ^a	73.9	97.6	-	142

a. Geometric mean CV (%) was calculated as $[\exp(\text{SD}^2) - 1]^{\frac{1}{2}} \times 100$, where SD is the SD of the natural log transformed data.

Note: BQL = concentrations < 50 pg/mL. BQL values were set to zero for summary statistics. Data reported as pg/mL. BQL = below the quantification limit; CV = coefficient of variation; h = hour; Max = maximum; Min = minimum; SD = standard deviation.

[0623] The highest concentration of tapinarof observed was 20,900 pg/mL, which occurred 5 hours postdose on Day 1 in a 2-year old subject. The Day 1 one-hour and 3-hour postdose values for this subject were 1440 and 1380 pg/mL, respectively. No subject had measurable concentrations of tapinarof sulfate at any time point.

[0624] A summary of number and percent of BQL concentrations for tapinarof and tapinarof sulfate samples is provided in Table 21 below.

Table 21. Summary of Subjects with Concentrations Below the Limit of Quantification (Pharmacokinetic Population)

Time Point		2-6 years (N = 12)	7-11 years (N = 12)	12-17 years (N = 12)	Total (N = 36)
Screening	Tapinarof				
	Total Samples Collected	12	11	12	35
	Number and Percent of BQL	12 (100.0)	11 (100.0)	12 (100.0)	35 (100.0)
	Tapinarof Sulfate				
	Total Samples Collected	12	12	12	36
	Number and Percent of BQL	12 (100.0)	12 (100.0)	12 (100.0)	36 (100.0)
Day 1 (1 h postdose)	Tapinarof				
	Total Samples Collected	12	11	12	35
	Number and Percent of BQL	0 (0.0)	0 (0.0)	2 (16.7)	2 (5.7)
	Tapinarof Sulfate				

	Total Samples Collected	10	11	12	33
	Number and Percent of BQL	10 (100.0)	11 (100.0)	12 (100.0)	33 (100.0)
Day 1 (3 h postdose)	Tapinarof				
	Total Samples Collected	11	11	12	34
	Number and Percent of BQL	0 (0.0)	0 (0.0)	1 (8.3)	1 (2.9)
	Tapinarof Sulfate				
	Total Samples Collected	11	11	12	34
Day 1 (5 h postdose)	Tapinarof				
	Total Samples Collected	11	9	12	32
	Number and Percent of BQL	1 (9.1)	1 (11.1)	5 (41.7)	7 (21.9)
	Tapinarof Sulfate				
	Total Samples Collected	10	10	12	32
Day 28 (predose)	Tapinarof				
	Total Samples Collected	10	8	11	29
	Number and Percent of BQL	8 (80.0)	4 (50.0)	10 (90.9)	22 (75.9)
	Tapinarof Sulfate				
	Total Samples Collected	10	10	11	31

	Number and Percent of BQL	10 (100.0)	10 (100.0)	11 (100.0)	31 (100.0)
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Note: tapinarof BQL = < 50 pg/mL; tapinarof sulfate BQL = < 10 pg/mL

BQL = below the quantification limit; h = hour

[0625] On Day 1, 10 of 101 tapinarof postdose samples (9.9%) were BQL. For predose samples collected on Day 28, 22 of 29 samples (75.9%) were BQL (Table 14.3.4.2.2). Overall, 24.6% of on-treatment samples were BQL. The 12-to-17-year age group consistently had a greater number of BQL samples throughout Day 1 and on Day 28. FIG. 35 shows the proportion of patients by age group with tapinarof concentrations below the quantifiable limit (<50 pg/ml) at day 28.

[0626] The PK parameters for tapinarof were estimated using available tapinarof concentration data and are provided in Table 22 below.

Table 22. Summary Statistics of Pharmacokinetic Parameter Estimates for Tapinarof on Day 1 (Pharmacokinetic Population)

PK Parameter		2-6 years (N = 12)	7-11 years (N = 12)	12-17 years (N = 12)	Total (N = 36)
C _{max} (pg/mL)	n	12	11	12	35
	Mean (SD)	3830 (5860)	2220 (2510)	1250 (1770)	2440 (3900)
	CV (%)	153	113	141	159
	Median	1790	102 0	555	942
	Min, Max	119, 20900	383, 8190	0, 5080	0, 20900
	Geometric Mean	1620	135 0	0	0
	Geometric Mean CV (%) ^a	269	136	212	212
T _{max} (h)	n	12	11	11	34
	Mean (SD)	2.45 (1.17)	2.04 (1.02)	2.61 (1.39)	2.37 (1.19)
	CV (%)	47.8	50.3	53.4	50.4
	Median	2.90	2.00	3.00	2.90
	Min, Max	1.00, 4.70	1.00, 3.30	1.00, 5.00	1.00, 5.00
C _τ (pg/mL)	n	12	11	11	34
	Mean (SD)	2720 (6240)	705 (687)	430 (509)	1330 (3780)
	CV (%)	230	97.5	118	285
	Median	288	443	206	233

Tlast (h)	Min, Max	92.9, 20900	69.2, 1920	50.1, 1760	50.1, 20900
	Geometric Mean	482	394	265	372
	Geometric Mean CV (%) ^a	378	185	130	215
	n	12	11	11	34
	Mean (SD)	4.48 (1.31)	4.44 (0.948)	4.20 (0.969)	4.38 (1.07)
	CV (%)	29.2	21.4	23.1	24.4
	Median	5.00	5.00	4.60	5.00
	Min, Max	1.00, 5.30	2.90, 5.10	3.00, 5.10	1.00, 5.30
AUC(0-t) (pg.h/mL)	Geometric Mean	4.15	4.33	4.09	4.19
	Geometric Mean CV (%) ^a	51.8	24.7	25.2	35.1
	n	12	11	11	34
	Mean (SD)	5520 (6180)	5240 (5910)	3250 (4790)	4690 (5600)
	CV (%)	112	113	148	119
	Median	4150	2680	1350	2770
	Min, Max	394, 23500	740, 17400	177, 15200	177, 23500
	Geometric Mean	3220	3040	1270	2340
	Geometric Mean CV (%) ^a	180	151	280	210

a. Geometric mean CV (%) was calculated as $[\exp(\text{SD}^2) - 1]^{\frac{1}{2}} \times 100$, where SD is the SD of the natural log transformed data.

Note: Actual sampling times were used. BQL concentrations < 50 pg/mL. BQL concentration values before Tmax were set to zero. Cmax set to zero for subjects with BQL values for the entire sampling period. BQL concentration values that occurred after a measurable concentration and followed by a value above the LLOQ were set to missing. BQL concentration values that occurred at the end of the collection interval (after the last quantifiable concentration) were set to missing. Missing values were not replaced. AUC(0-t) = area under the plasma concentration-time curve from time zero to the last quantifiable concentration; BQL = below the quantification limit; Cτ = last quantifiable concentration; Cmax = maximum observed plasma concentration; CV = coefficient of variation; h = hour; LLOQ = lower limit of quantification; Max = maximum; Min = minimum; PK = pharmacokinetic; SD = standard deviation; Tlast = time to last quantifiable concentration; Tmax = time to maximum observed plasma concentration

[0627] Cmax for tapinarof was reported for all subjects (n = 35). Cmax for Subject 4009-007 was set to zero since all samples on Day 1 were BQL; Tmax, Cτ, Tlast, and AUC(0-t), were not estimable for this subject. Tapinarof exposure (AUC(0-t) and Cmax) decreased with

increasing age group; the highest exposure was observed in the 2-to-6-year age group although there was overlap in individual PK parameters across age groups.

Efficacy

[0628] Clinical improvement in pediatric subjects with extensive AD was demonstrated with 4 weeks treatment of tapinarof cream, 1% QD. Key results are shown in Table 23 below; statistical analyses were not performed on efficacy assessments. Overall, treatment with tapinarof cream, 1% resulted in improvement in all measures of efficacy at Week 4.

Table 23. Key Results for Efficacy Assessments (Safety Population)

Efficacy Assessment	Efficacy Endpoint at Week 4	Years of Age			Total (N = 36)
		2-6 (N = 12)	7-11 (N = 12)	12-17 (N = 12)	
vIGA-AD	n	11	10	11	32
	Proportion of subjects with a vIGA-AD score of clear (0) or almost clear (1) and at least a 2-grade reduction from Baseline, n (%)	3 (27.3)	5 (50.0)	0	8 (25.0)
	Change from baseline, n (%)				
	+3 = worsened by 3	0	0	0	0
	+2 = worsened by 2	0	0	0	0
	+1 = worsened by 1	0	0	0	0
	No change	2 (18.2)	3 (30.0)	3 (27.3)	8 (25.0)
	-1 = improved by 1	4 (36.4)	2 (20.0)	8 (72.7)	14 (43.8)
EASI	-2 = improved by 2	5 (45.5)	3 (30.0)	0	8 (25.0)
	-3 = improved by 3	0	2 (20.0)	0	2 (6.3)
	n	11	10	11	32
	Proportion of subjects with EASI50 from Baseline, n (%)	10 (90.9)	7 (70.0)	3 (27.3)	20 (62.5)
	Proportion of subjects with EASI75 from Baseline, n (%)	3 (27.3)	3 (30.0)	1 (9.1)	7 (21.9)
%BSA	Proportion of subjects with EASI90 from Baseline, n (%)	1 (9.1)	2 (20.0)	1 (9.1)	4 (12.5)
	Mean percent change in EASI score from Baseline	-69.35	-61.73	-29.83	-53.38
	n	11	10	11	32
	Mean percent change in %BSA affected from Baseline	-66.65	-56.89	-25.34	-49.40
PP-NRS	n	12	9	11	32
	Proportion of subjects with a Baseline PP-NRS score ≥ 4 who achieved ≥ 4 -point reduction in average weekly PP-NRS score from Baseline, n (%)	7 (58.3)	5 (55.6)	2 (18.2)	14 (43.8)
	n	12	10	11	33

	Mean change from baseline in average weekly PP-NRS score	-4.974	-4.700	-2.766	-4.155
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%BSA = percent of total body surface area; EASI = Eczema Area and Severity Index; EASI50, EASI75, EASI90 = $\geq 50\%$, $\geq 75\%$, $\geq 90\%$ improvement from Baseline in EASI score; PP-NRS = Peak Pruritis-Numeric Rating Scale; vIGA-AD = validated Investigator Global Assessment Scale for Atopic Dermatitis

[0629] vIGA-AD scores by visit, by age group, and overall are provided in Table 24 below.

Table 24. Summary of Validated Investigator Global Assessments for Atopic Dermatitis Scores and Change from Baseline at Week 4 – Observed Cases (Safety Population)

vIGA-AD Score, n (%)	2-6 years (N = 12)	7-11 years (N = 12)	12-17 years (N = 12)	Total (N = 36)
Baseline				
n	12	12	12	36
0 - Clear	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1 - Almost clear	0 (0.0)	0 (0.0))	0 (0.0)	0 (0.0)
2 - Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3 - Moderate	8 (66.7)	9 (75.0)	11 (91.7)	28 (77.8)
4 - Severe	4 (33.3)	3 (25.0)	1 (8.3)	8 (22.2)
Week 1				
n	12	10	12	34
0 - Clear	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1 - Almost clear	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2 - Mild	4 (33.3)	4 (40.0)	1 (8.3)	9 (26.5)
3 – Moderate	8 (66.7)	4 (40.0)	10 (83.3)	22 (64.7)
4 - Severe	0 (0.0)	2 (20.0)	1 (8.3)	3 (
vIGA-AD Score, n (%)				
n	12	10	12	34
vIGA-AD Score of Clear (0) or Almost Clear (1) and at least a 2-grade	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

reduction from Baseline				
Failure to Achieve a vIGA-AD Score of Clear (0) or Almost Clear (1) and at least a 2-grade reduction from Baseline	12 (100.0)	10 (100.0)	12 (100.0)	34 (100.0)
Week 4				
n	11	10	11	32
0 - Clear	0 (0.0)	1 (10.0)	0 (0.0)	1 (3.1)
1 - Almost clear	3 (27.3)	4 (40.0)	0 (0.0)	7 (21.9)
2 - Mild	5 (45.5)	1 (10.0)	7 (63.6)	13 (40.6)
3 - Moderate	3 (27.3)	4 (40.0)	4 (36.4)	11 (34.4)
4 - Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
vIGA-AD Score, n (%)				
n	11	10	11	32
vIGA-AD Score of Clear (0) or Almost Clear (1) and at least a 2-grade reduction from Baseline	3 (27.3)	5 (50.0)	0 (0.0)	8 (25.0)
Failure to Achieve a vIGA-AD Score of Clear (0) or Almost Clear (1) and at least a 2-grade reduction from Baseline	8 (72.7)	5 (50.0)	11 (100.0)	24 (75.0)
Change from baseline, n (%)				
0 = no change				
-1 = improved by 1	2 (18.2)	3 (60.0)	3 (27.3)	8 (25.0)
-2 = improved by 2	4 (36.4)	2 (20.0)	8 (72.7)	14 (43.8)
-3 = improved by 3	5 (45.5)	3 (30.0)	0	8 (25.0)
	0	2 (20.0)	0	2 (6.3)

vIGA-AD = validated Investigator Global Assessment Scale for Atopic Dermatitis

[0630] All subjects began the study with either moderate (77.8%) or severe (22.2%) disease based on their vIGA-AD scores. At Week 1, 26.5% of subjects improved to mild; by Week 4, the majority of subjects (65.6%) improved to either mild (40.6%), almost clear (21.9%), or clear (3.1%) disease. In the 2-to-6-year and the 7-to-11-year age groups, 27.3% and 40.0% of subjects, respectively, improved to almost clear (1), and 1 subject (10.0%) in the 7-to-11-year age group improved to completely clear at Week 4.

[0631] Overall, 8 subjects (25.0%) achieved a vIGA-AD score of clear (0) or almost clear (1) with at least a 2-grade improvement by Week 4. Ten subjects (31.3%) had a ≥ 2 -grade improvement, and 24 subjects (75.0%) had a ≥ 1 -grade improvement in vIGA-AD score at Week 4. There was no worsening in disease as measured by vIGA-AD scores at Week 4 in any age group.

[0632] EASI scores by visit, by age group, and overall are provided in Table 25 below.

Table 25. Summary of Eczema Area and Severity Index Total Scores, Improvement from Baseline by Visit – Observed Cases (Safety Population)

EASI Total Score, n (%)	2-6 years (N = 12)	7-11 years (N = 12)	12-17 years (N = 12)	Total (N = 36)
Week 1				
<i>EASI50</i>				
n	12	10	12	34
Achieving $\geq 50\%$ Improvement from Baseline in EASI Score	4 (33.3)	4 (40.0)	0 (0.0)	8 (23.5)
Failure to Achieve $\geq 50\%$ Improvement from Baseline in EASI Score	8 (66.7)	6 (60.0)	12 (100.0)	26 (76.5)
<i>EASI75</i>				
n	12	10	12	34
Achieving $\geq 75\%$ Improvement from Baseline in EASI Score	1 (8.3)	1 (10.0)	0 (0.0)	2 (5.9)
Failure to Achieve $\geq 75\%$ Improvement from Baseline in EASI Score	11 (91.7)	9 (90.0)	12 (100.0)	32 (94.1)
<i>EASI90</i>				
n	12	10	12	34
Achieving $\geq 90\%$ Improvement from Baseline in EASI Score	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Failure to Achieve $\geq 90\%$ Improvement from Baseline in EASI Score	12 (100.0)	10 (100.0)	12 (100.0)	34 (100.0)
Week 4				
<i>EASI50</i>				
n	11	10	11	32
Achieving $\geq 50\%$ Improvement from Baseline in EASI Score	10 (90.9)	7 (70.0)	3 (27.3)	20 (62.5)
Failure to Achieve $\geq 50\%$ Improvement from Baseline in EASI Score	1 (9.1)	3 (30.0)	8 (72.7)	12 (37.5)
<i>EASI75</i>				
n	11	10	11	32
Achieving $\geq 75\%$ Improvement from Baseline in EASI Score	3 (27.3)	3 (30.0)	1 (9.1)	7 (21.9)
Failure to Achieve $\geq 75\%$ Improvement from Baseline in EASI Score	8 (72.7)	7 (70.0)	10 (90.9)	25 (78.1)
<i>EASI90</i>				
n	11	10	11	32
Achieving $\geq 90\%$ Improvement from Baseline in EASI Score	1 (9.1)	2 (20.0)	1 (9.1)	4 (12.5)
Failure to Achieve $\geq 90\%$ Improvement from Baseline in EASI Score	10 (90.9)	8 (80.0)	10 (90.9)	28 (87.5)

EASI = Eczema Area and Severity Index; EASI50, EASI75, EASI90 = $\geq 50\%$, $\geq 75\%$, $\geq 90\%$ improvement from Baseline in EASI score

[0633] The percentage of subjects in each age group and overall achieving EASI50, EASI75, and EASI90 increased from Week 1 to Week 4, with 90.9% of subjects aged 2 to 6 years old and 70.0% of subjects aged 7 to 11 years old achieving EASI50 by Week 4. Overall, 7 subjects (21.9%) achieved EASI75 and 4 subjects (12.5%) achieved EASI90 at Week 4.

[0634] EASI total scores, change from baseline at Week 4, and percent change from baseline at Week 4 are provided in Table 26 below.

Table 26. Summary of Eczema Area and Severity Index (EASI) Total Scores, Change from Baseline at Week 4, and Percent Change from Baseline at Week 4 - Observed Cases (Safety Population)

EASI Total Score Baseline	2-6 years (N = 12)	7-11 years (N = 12)	12-17 years (N = 12)	Total (N = 36)
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n	12	12	12	36
Mean (SD)	30.16 (8.588)	21.01 (10.043)	20.26 (5.505)	23.81 (9.233)
Median	28.20	19.70	18.50	20.90
Min, Max	19.4, 46.3	8.2, 49.6	12.8, 31.3	8.2, 49.6
Week 4				
n	11	10	11	32
Mean (SD)	9.25 (5.851)	7.82 (6.424)	13.07 (11.141)	10.12 (8.255)
Median	9.40	7.05	11.30	9.40
Min, Max	2.0, 22.4	0.0, 21.2	0.8, 44.0	0.0, 44.0
<i>Change from Baseline</i>				
n	11	10	11	32
Mean (SD)	-19.45 (4.689)	-10.47 (4.541)	-6.41 (12.492)	-12.16 (9.742)
Median	-18.80	-10.95	-7.40	-13.55
Min, Max	-28.1, -14.0	-17.0, -2.5	-30.5, 22.4	-30.5, 22.4
<i>Percent Change from Baseline</i>				
n	11	10	11	32
Mean (SD)	-69.35 (13.981)	-61.73 (28.369)	-29.83 (51.733)	-53.38 (38.337)
Median	-66.90	-65.05	-38.95	-62.16
Min, Max	-92.9, -41.7	-100.0, -10.5	-97.4, 103.7	-100.0, 103.7

Note: Change from baseline computed as postbaseline value – baseline value. Percent change from baseline computed as (postbaseline value – baseline value) / baseline value × 100.

EASI = Eczema Area and Severity Index; Max = maximum; Min = minimum; SD = standard deviation

[0635] All age groups saw improvements in EASI scores at Week 4, with the greatest mean (SD) improvement observed in the 2-to-6-year age group (change from baseline: -19.45 [4.689]; percent change from baseline: -69.35 [13.981]), and the overall mean (SD) change from baseline EASI scores and percent change from baseline EASI scores were -12.16 (9.742) and -53.38 (38.337), respectively.

[0636] %BSA affected, change from baseline at Week 4, and percent change from baseline at Week 4 are provided in Table 27 below.

Table 27. Summary of Percent Body Surface Area Affected, Change from Baseline at Week 4, and Percent Change from Baseline at Week 4 - Observed Cases (Safety Population)

%BSA Affected	2-6 years (N = 12)	7-11 years (N = 12)	12-17 years (N = 12)	Total (N = 36)
Baseline				
n	12	12	12	36
Mean (SD)	52.42 (19.148)	42.00 (10.027)	33.92 (8.557)	42.78 (15.127)
Median	42.00	38.50	30.00	38.50

Min, Max	36.0, 90.0	35.0, 72.0	26.0, 54.5	26.0, 90.0
Week 4				
n	11	10	11	32
Mean (SD)	18.05 (15.400)	16.81 (11.118)	24.32 (21.468)	19.82 (16.501)
Median	14.00	15.00	20.00	15.75
Min, Max	1.5, 55.0	0.0, 36.0	2.0, 85.0	0.0, 85.0
<i>Change from Baseline</i>				
n	11	10	11	32
Mean (SD)	-31.59 (12.593)	-22.59 (11.789)	-9.14 (23.021)	-21.06 (18.789)
Median	-32.00	-22.50	-11.50	-21.75
Min, Max	-58.0, -9.0	-39.0, -1.0	-52.5, 47.0	-58.0, 47.0
<i>Percent Change from Baseline</i>				
n	11	10	11	32
Mean (SD)	-66.65 (22.140)	-56.89 (29.272)	-25.34 (54.830)	-49.40 (41.300)
Median	-64.44	-60.82	-28.57	-59.43
Min, Max	-96.3, -14.1	-100.0, -2.7	-96.3, 123.7	-100.0, 123.7

Note: Change from baseline computed as postbaseline value – baseline value. Percent change from baseline computed as (postbaseline value – baseline value) / baseline value × 100. Max = maximum; Min = minimum; %BSA = percent body surface area; SD = standard deviation

[0637] The majority of subjects (> 95%; 31 of 32 subjects) experienced improvements in %BSA affected at Week 4, and similar to the results for EASI scores at Week 4, all age groups saw improvements in %BSA affected by disease at Week 4, with the greatest mean (SD) improvement observed in the 2-to-6-year age group (change from baseline: -31.59 [12.593]; percent change from baseline: -66.65 [22.140]). The overall mean (SD) change from baseline in %BSA affected and percent change from baseline in %BSA affected were -21.06 (18.789) and -49.40 (41.300), respectively. The overall mean change from baseline (range) and mean percent change from baseline (range) at Week 4 for %BSA × vIGA-AD were -85.15 (-296.0–103.0) and -62.77 (-100.0–67.8), respectively.

[0638] PP-NRS scores by visit for subjects with a Baseline PP-NRS score ≥ 4 who achieved a ≥ 4 -point reduction in the average weekly PP-NRS score from Baseline are provided in Table 28 below for subjects aged 2 to 17 years (depicted for each age group).

Table 28. Summary of Proportion of Subjects with a Baseline PP-NRS Score ≥ 4 Who Achieved ≥ 4 -Point Reduction in the Average Weekly PP-NRS Score from Baseline by Visit - Observed Cases (Safety Population, Subjects with Baseline PP-NRS Score ≥ 4)

PP-NRS, n (%)	2-6 years (N = 12)	7-11 years (N = 11)	12-17 years (N = 12)	Total (N = 35)
Week 1				
n	12	9	11	32
Achieved ≥ 4 -Point Reduction from Baseline in the Average Weekly PP-NRS Score	4 (33.3)	1 (11.1)	1 (9.1)	6 (18.8)
Failure to Achieve a ≥ 4 -point Reduction from Baseline in the Average Weekly PP-NRS Score	8 (66.7)	8 (88.9)	10 (90.9)	26 (81.3)
Week 4				
n	12	9	11	32
Achieved ≥ 4 -Point Reduction from Baseline in the Average Weekly PP-NRS Score	7 (58.3)	5 (55.6)	2 (18.2)	14 (43.8)
Failure to Achieve a ≥ 4 -point Reduction from Baseline in the Average Weekly PP-NRS Score	5 (41.7)	4 (44.4)	9 (81.8)	18 (56.3)

Note: Proxy-completion by caregiver for subjects < 12 years old. Self-completion for subjects ≥ 12 years old.

PP-NRS = Peak-Pruritus Numeric Rating Scale

[0639] Overall, 43.8% of subjects with a Baseline PP-NRS score ≥ 4 achieved a ≥ 4 -point reduction from Baseline in the average weekly PP-NRS score by Week 4. Proportions for the 2-to-6-year and the 7-to-11-year age groups were higher than for the 12-to-17-year age group.

Adverse Events

[0640] A summary of TEAEs is provided in Table 29 below.

Table 29. Overall Summary of Treatment-Emergent Adverse Events (Safety Population)

Adverse Event Category	2-6 years (N = 12)	7-11 years (N = 12)	12-17 years (N = 12)	Total (N = 36)
Any AE, n (%) m	2 (16.7) 3	4 (33.3) 7	2 (16.7) 3	8 (22.2) 13
Any TEAE ^a	2 (16.7) 3	4 (33.3) 7	2 (16.7) 3	8 (22.2) 13

TEAE of Special Interest	0 (0.0) 0	3 (25.0) 3	1 (8.3) 2	4 (11.1) 5
Contact dermatitis	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Follicular event	0 (0.0) 0	1 (8.3) 1	0 (0.0) 0	1 (2.8) 1
Headache	0 (0.0) 0	2 (16.7) 2	1 (8.3) 2	3 (8.3) 4
Treatment-related TEAE ^b	0 (0.0) 0	2 (16.7) 2	1 (8.3) 2	3 (8.3) 4
TEAE leading to study drug discontinuation	0 (0.0) 0	1 (8.3) 2	0 (0.0) 0	1 (2.8) 2
TEAE leading to study discontinuation	0 (0.0) 0	1 (8.3) 2	0 (0.0) 0	1 (2.8) 2
SAE, non-fatal	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
SAE, all	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Death	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Treatment-related ^b serious TEAE	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Serious TEAE leading to study drug discontinuation	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
Serious TEAE leading to study discontinuation	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0
TEAE (COVID-19) ^c	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	a (0.0) 0

a. TEAEs were defined as those AEs that occurred after dosing and those pre-existing AEs (prior to first application of study treatment) that worsened during the study. If it could not have been determined whether the AE was treatment emergent due to a partial onset date, then it was counted as such.

b. If relationship to treatment was missing, the event was conservatively treated as related to study drug.

c. Positive COVID-19 diagnosis.

Note: Subjects reporting > 1 event were counted only once for the subject count. Percentages are based on total number of subjects in each age group and overall.

AE = adverse event; COVID-19 = Coronavirus Disease 2019; n = number of subjects; m = number of events; SAE = serious adverse event; TEAE = treatment-emergent adverse event

[0641] Eight subjects (22.2%) reported a total of 13 TEAEs during the study. Of the total number of subjects reporting any TEAE, half were reported by subjects in the 7-to-11-year age group. Additionally, approximately half (53.8%) of all TEAEs were reported by these subjects (7-to-11-year age group).

[0642] Four of the 13 total reported TEAEs (30.8%) were considered treatment related by the investigators, and none led to study drug or study discontinuation.

[0643] Four subjects experienced 5 AESIs; 3 events were considered related to study drug (1 event of folliculitis in 1 subject and 2 events of headache in the same subject). These events led to study drug interruption (headache), a decrease in study drug (folliculitis), or study

discontinuation (headache). No subjects reported contact dermatitis. Brief overviews of the AESIs are provided below:

- An AESI of headache, Grade 2 in severity, 2 days in duration (Days 1–2), considered not related to study drug was reported by a 9-year-old White male subject (Subject 4006-004). Coinciding with the headache, the subject experienced 2 days of Grade 2 vomiting (also not considered related to study drug) that was managed by administering a concomitant medication (ondansetron). These events led to the withdrawal of study drug and withdrawal from the study; both events resolved.
- An AESI of headache, Grade 1 in severity, 1 day in duration (Day 1), considered not related to study drug was reported by an 11-year-old Asian male subject (Subject 4008-002). The event resolved without intervention.
- Two episodes of the AESI of headache, both Grade 2 in severity and considered related to study drug, were reported by a 12-year-old White female subject (Subject 4901-002). The events were managed by administering a concomitant medication (paracetamol). The first event resolved after 5 days (Days 1–5), and the second event began on Day 14 and was ongoing at the end of the study.
- An AESI of folliculitis, Grade 1 in severity, 10 days in duration (Days 9–18), and considered related to study drug, was reported for a 7-year-old Asian male subject (Subject 4008-005). The event was managed by reducing the dose of study drug (interruption of application at the sites of folliculitis) and administering a concomitant medication (mupirocin).

Investigator-Assessed Local Tolerability Scale

[0644] The results from the LTS are provided in Table 30 below.

Table 30. Summary of Investigator Overall Assessment of Local Tolerability Scale (Safety Population)

Dryness/Erythema/Peeling	2-6 years (N = 12)	7-11 years (N = 12)	12-17 years (N = 12)	Total (N = 36)
Baseline, n (%)				
n	12	11	12	35
0 - No irritation	12 (100.0)	9 (81.8)	11 (91.7)	32 (91.4)
1 - Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2 - Moderate	0 (0.0)	2 (18.2)	0 (0.0)	2 (5.7)
3 - Severe	0 (0.0)	0 (0.0)	1 (8.3)	1 (2.9)

4 - Very Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
n	12	11	12	35
Mean (SD)	0.0 (0.00)	0.4 (0.81)	0.3 (0.87)	0.2 (0.68)
Median	0.0	0.0	0.0	0.0
Min, Max	0, 0	0, 2	0, 3	0, 3
Week 1, n (%)				
n	12	10	12	34
0 - No irritation	11 (91.7)	10 (100.0)	11 (91.7)	32 (94.1)
1 - Mild	1 (8.3)	0 (0.0)	0 (0.0)	1 (2.9)
2 - Moderate	0 (0.0)	0 (0.0)	1 (8.3)	1 (2.9)
3 - Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4 - Very Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
n	12	10	12	34
Mean (SD)	0.1 (0.29)	0.0 (0.00)	0.2 (0.58)	0.1 (0.38)
Median	0.0	0.0	0.0	0.0
Min, Max	0, 1	0, 0	0, 2	0, 2
Week 4, n (%)				
n	11	10	10	31
0 - No irritation	11 (100.0)	10 (100.0)	8 (80.0)	29 (93.5)
1 - Mild	0 (0.0)	0 (0.0)	1 (10.0)	1 (3.2)
2 - Moderate	0 (0.0)	0 (0.0)	1 (10.0)	1 (3.2)
3 - Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4 - Very Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
n	11	10	10	31
Mean (SD)	0.0 (0.00)	0.0 (0.00)	0.3 (0.67)	0.1 (0.40)
Median	0.0	0.0	0.0	0.0
Min, Max	0, 0	0, 0	0, 2	0, 2

Note: Percentages are based on total number of subjects in each column with an evaluation at a corresponding visit.

Max = maximum; Min = minimum; n = number of subjects; SD = standard deviation

[0645] Overall, > 90% of subjects entered the study with no baseline irritation (i.e., prior to starting tapinarof) and experienced no irritation on the LTS at Weeks 1 and 4. For the 3 subjects with baseline scores > 0, 1 subject had a score of 3 (severe) and 2 subjects had scores of 2 (moderate). There was no trend of increased irritation with increased weeks of treatment with study drug in any age group or overall.

[0646] LTS scores for all subjects applying tapinarof cream, 1% on sensitive areas showed no irritation for the last reported assessment (Week 4: face [n = 20], neck [n = 21], skin folds [n = 12], axilla [n = 2], and inframammary [n = 4]; Week 1: anal crux [n = 3] and genitalia [n = 3]).

[0647] *Discussion.* Maximal usage trials evaluate systemic exposure under conditions that would maximize the potential for drug absorption with the intended use of the product (Bashaw

2014). These trials enroll patients with the disease under study and at the upper range of severity who are most likely to have higher systemic exposures based on their higher doses and widespread application. These studies also provide an assessment of safety and tolerability in patients who may be most vulnerable to systemic AEs.

[0648] This study evaluated the safety, tolerability, and PK of tapinarof cream, 1% in pediatric subjects with extensive AD. Subjects had vIGA-AD scores of 3 (moderate) or 4 (severe) and Baseline mean values for EASI and %BSA affected of 23.81 and 42.78%, respectively, representing a population with high disease burden. Baseline %BSA affected values ranged from 26.0 to 90.0%, satisfying the criteria for evaluating tapinarof cream, 1% under conditions of maximal usage.

[0649] This study represents the first report on the use of tapinarof cream, 1% in subjects < 12 years of age. Of note, the same dosing regimen was used as that approved by the US FDA for treatment of plaque psoriasis in adults (tapinarof cream, 1% QD). Across the study population from ages 2 to 17, tapinarof cream, 1% was well tolerated with a low incidence of TEAEs (22.2% overall). Despite the widespread disease and high usage of the product, only 8 subjects reported a total of 13 TEAEs; the events were distributed across the age groups, and a relationship between TEAEs and systemic exposure was not observed. Most of the TEAEs were Grade 1 (mild), and there were no SAEs and no Grade 3 or 4 TEAEs. One subject was discontinued due to 2 TEAEs; on Day 1, 5 hours post application, the subject experienced Grade 2 events of headache (AESI) and vomiting. These TEAEs were reported as not related to study drug by the investigator. Two other subjects reported AESIs of headache during the study. Regarding other AESIs as predefined for this study (contact dermatitis, follicular events), there were no cases of contact dermatitis and 1 case of Grade 1 folliculitis. Tolerability was assessed by the investigator for dryness, erythema, and peeling using the LTS. Overall, > 90% of subjects entered the study with no baseline irritation (i.e., prior to starting tapinarof) and experienced no irritation on the LTS at Weeks 1 and 4. For the 3 subjects with baseline scores > 0, 1 subject had a score of 3 (severe) and 2 subjects had scores of 2 (moderate). There was no trend of increased irritation with increased weeks of treatment with study drug in any age group or overall. LTS scores for all subjects applying tapinarof cream, 1% on sensitive areas showed no irritation for the last reported assessment (Week 4: face [n = 20], neck [n = 21], skin folds [n = 12], axilla [n = 2], and inframammary [n = 4]; Week 1: anal crux [n = 3] and genitalia [n = 3]).

[0650] The PK profile of tapinarof in this population was consistent with previous studies. Plasma concentrations were low, and the mean Day 1 C_{max} was 2440 pg/mL. C_{max} was highest in the 2-to-6-year age group (3830 pg/mL) and lowest in the 12-to-17-year age group (1250 pg/mL); however, there was wide variability with overlap of individual values across age groups. Excluding samples collected at Screening, 24.6% of the PK samples were BQL (< 50 pg/mL) for tapinarof, even with a highly sensitive assay. Most samples were detectable on Day 1 at the early collection time points (1 and 3 hours postdose), but predose concentrations on Day 28 were BQL in most subjects (75.9%) and markedly lower than those on Day 1, indicating no accumulation. Tapinarof sulfate was not detected in any samples despite an assay having a LLOQ of 10 pg/mL. This confirms that tapinarof, when detectable, is the major circulating component in plasma.

[0651] Efficacy was a secondary endpoint in this open-label study. The ongoing Phase 3 pivotal studies (ADORING 1 and 2) in subjects aged ≥ 2 years with AD have an 8-week treatment duration while this study was only 4 weeks. Even with a shortened treatment period, improvement was noted in the majority of subjects, and no subjects had an increase (worsening) in their vIGA-AD score at Week 4. Overall, clinical improvement was observed in the majority of subjects in this population with extensive disease. The mean decrease in EASI score was 53.38%, and the mean decrease in %BSA affected was 49.40%. Ten subjects (31.3%) had a ≥ 2 -grade improvement in vIGA-AD score, and 8 subjects (25.0%) had a vIGA-AD score of clear (0) or almost clear (1) and a 2-grade improvement from Baseline. Given the limitations of an open-label study, these data demonstrate the activity of tapinarof cream, 1% with a rapid onset of effect. Furthermore, a high percentage of subjects completing the 4-week treatment period (87.5%) enrolled into the 48-week, open-label, LTE study (DMVT-505-3103), suggesting a favorable experience with tapinarof cream, 1%.

[0652] This maximal usage study evaluated tapinarof cream, 1% QD in a population of pediatric subjects aged 2 to 17 years with extensive skin involvement and high disease (AD) burden using the same dosing regimen approved for treatment of plaque psoriasis in adults. The following conclusions were observed:

- Tapinarof cream, 1% was generally well tolerated with a low incidence of AEs (22.2% overall), no SAEs, no Grade 3 or 4 AEs, and 1 study discontinuation due to 2 AEs deemed not related to study drug. Most subjects reported no irritation on the LTS including sensitive areas.

- Tapinarof plasma concentrations were low, with 24.6% of on-treatment samples being BQL (< 50 pg/mL).
- No relationships between tapinarof exposure and either Baseline %BSA affected or amount of tapinarof cream, 1% applied per day were observed.
- The majority of subjects experienced improvements in vIGA-AD score, EASI score, and %BSA affected, even with a treatment duration of only 4 weeks.

CLAIMS

What is claimed:

1. A method for treating atopic dermatitis in a subject in need thereof, comprising:
applying a thin layer of about 1.0% tapinarof topical cream composition to an affected area of the subject once daily for a period of time of at least 8 weeks;
wherein, after the period of time, the subject has:
at least a 2-grade improvement in vIGA-AD score from baseline, and
an vIGA-AD score of 0;
a reduction in a PP-NRS score ≥ 4 points from baseline during the period of time; and
wherein the plasma concentration of tapinarof in the subject is below 50 pg/mL while applying the 1.0% tapinarof topical cream.
2. The method of claim 1, wherein the subject has an improvement in an EASI score of about 75% from baseline during the period of time.
3. The method of claim 1, wherein the subject is at least 12 years old.
4. The method of claim 1, wherein the subject is at least 2 years old.
5. The method of claim 1, wherein the subject does not experience an adverse event during the period of time, wherein the adverse event is selected from the group consisting of contact dermatitis, folliculitis, headache, and a combination thereof.
6. The method of claim 1, wherein the subject has an affected BSA of about 43%.
7. The method of claim 1 wherein the subject as an affected BSA of up to about 90%.
8. The method of claim 1, wherein the subject has a patient-reported Local Tolerability Score (LTS) < 1 .
9. The method of claim 1, wherein the subject does not experience burning, stinging, or local irritation at the affected area.
10. The method of claim 1, wherein the affected area comprises a sensitive area, an intertriginous area, or a combination thereof.

11. A method for treating atopic dermatitis in a subject from 2-17 years old, the method comprising:

wherein the subject has a vIGA-AD™ score of 3 or greater and the subject has been diagnosed with atopic dermatitis having a percent body surface area (BSA) affected of $\geq 25\%$ of the BSA;

topically administering a topical composition containing about 1.0% tapinarof to affected areas of the subject once a day for about 4 weeks,

wherein after topically administering the topical composition an Investigator Global Assessment (IGA) score of the subject is improved by 2 grades or has improved to a score of 0 or 1, and the adolescent subject has a maximum observed plasma tapinarof concentration ($C_{\max}$) of < 50 pg/mL.

12. The method of claim 11, wherein the topical composition is an oil-in-water emulsion.

13. The method of claim 12, wherein the oil phase of the oil-in-water emulsion 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.

14. The method of claim 12, wherein the water phase of the oil-in-water emulsion is comprised of sodium citrate, edetate disodium, citric acid monohydrate, and water.

15. The method of claim 11, wherein the topically administering includes application to the affected area of the skin selected from the group consisting of body, arms, legs, back, chest, buttocks, neck, scalp, fingernails, toenails, and combinations thereof.

16. The method of claim 11, wherein the subject has been diagnosed with atopic dermatitis having a percent body surface area (BSA) affected of about 26% to about 90%.

17. The method of claim 11, wherein the subject is 12-17 years of age and has been diagnosed with atopic dermatitis having a percent body surface area (BSA) affected of $\geq 25\%$.

18. The method of claim 11, wherein the subject is 2-11 years of age and has been diagnosed with atopic dermatitis having a percent body surface area (BSA) affected of $\geq 35\%$.

19. The method of claim 11, wherein the subject has been diagnosed with atopic dermatitis having an Investigator Global Assessment (IGA) score of greater than or equal to 3.

20. The method of claim 11, further comprising an improvement of one or more symptoms of atopic dermatitis as measured according to an assessment selected from the group consisting

of Investigator Global Assessment (IGA) score, daily Itch/Pruritus numeric rating scale, Eczema Area and Severity Index (EASI), 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, and patient reported outcomes.

21. The method of claim 20, wherein the Itch/Pruritus numeric rating scale is improved by ≥ 4 points after topically administering the topical composition.

22. The method of claim 20, wherein the Eczema Area and Severity Index (EASI) is improved by greater than or equal to 50% or is improved by greater than or equal to 75% after topically administering the topical composition.

23. The method of claim 20, wherein the percent body surface area (BSA) affected is decreased to less than 20% after topically administering the topical composition.

24. The method of claim 20, wherein the patient reported outcomes demonstrate that subject's impression of symptom severity was improved after topically administering the topical composition, and wherein the symptoms are selected from the group consisting 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, and disturbed sleep.