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Bausch Health Americas Inc.*

**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

BAUSCH HEALTH IRELAND LIMITED;
BAUSCH HEALTH US, LLC; and
BAUSCH HEALTH AMERICAS INC.,

Plaintiffs,

v.

PADAGIS ISRAEL PHARMACEUTICALS
LTD.; PADAGIS US LLC; and
PADAGIS LLC,

Defendants.

Civil Action No. 22-4248

Document Electronically Filed

COMPLAINT

This is a patent infringement action brought by Plaintiffs Bausch Health Ireland Limited (“Bausch Ireland”), Bausch Health US, LLC (“Bausch US”), and Bausch Health Americas Inc. (“Bausch Americas”) (collectively, “Bausch” or “Plaintiffs”) for infringement of U.S. Patent No. 11,311,482 (the “’482 Patent” or the “Patent-In-Suit”) by Defendants Padagis Israel Pharmaceuticals Ltd., Padagis US LLC, and Padagis LLC (collectively, “Padagis” or “Defendants”), through the filing of Abbreviated New Drug Application (“ANDA”) No. 215393

IPR2023-01114
Padagis v. Bausch
Bausch Ex. 2007

for the approval of Defendant's generic version of Plaintiffs' Arazlo® product described therein. Plaintiffs hereby alleged as follows:

THE PARTIES

1. Plaintiff Bausch Ireland is a private company incorporated in Ireland with its office located at 3013 Lake Drive, Citywest Business Campus, Dublin 24, Ireland.

2. Plaintiff Bausch US is a corporation organized and existing under the law of Delaware. Its headquarters is located at 400 Somerset Corporate Blvd., Bridgewater, New Jersey 08807.

3. Plaintiff Bausch Americas is a corporation organized and existing under the laws of Delaware. Its headquarters is located at 400 Somerset Corporate Blvd., Bridgewater, New Jersey 08807.

4. Upon information and belief, Defendant Padagis Israel Pharmaceuticals Ltd. ("Padagis Israel") is a corporation operating and existing under the laws of Israel, having a principal place of business at 1 Rakefet St., Shoham 608500, Israel. Upon information and belief, Padagis Israel is a wholly owned subsidiary of Padagis LLC.

5. Upon information and belief, Defendant Padagis US LLC ("Padagis US") is a corporation operating and existing under the laws of Delaware, having a principal place of business at 1251 Lincoln Road, Allegan, Michigan, 49010. Upon information and belief, Padagis US is a wholly owned subsidiary of Padagis LLC.

6. Upon information and belief, Defendant Padagis LLC ("Padagis LLC") is a corporation operating and existing under the laws of Delaware, having a principal place of business at 1251 Lincoln Road, Allegan, Michigan, 49010.

7. Upon information and belief, Padagis seeks to, sell, market, and distribute generic pharmaceutical products throughout the United States, including in this district.

NATURE OF THE ACTION

8. This is a civil action for infringement of the Patent-In-Suit. This action arises under the Patent Laws of the United States, 35 U.S.C. § 100 et seq.

9. This action arises out of Padagis’s filing of ANDA No. 215393 (“Padagis ANDA”) including its Paragraph IV Certification (defined below) under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) alleging, *inter alia*, that the Patent-In-Suit is invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, or sale of the Padagis ANDA Product (defined below).

JURISDICTION AND VENUE

10. This Court has subject matter jurisdiction under 28 U.S.C. §§ 1331, 1338(a), and 2201–02.

11. Upon information and belief, this Court has jurisdiction over Padagis Israel. Upon information and belief, Padagis Israel is in the business of, *inter alia*, developing, manufacturing, marketing, importing, and/or selling pharmaceutical products, including generic drug products. Upon information and belief, Padagis Israel directly, or indirectly, develops, manufactures, markets, and sells generic drug products throughout the United States and in this judicial district, and this judicial district is a likely destination for the Padagis ANDA Product. Upon information and belief, Padagis Israel purposefully has conducted and continues to conduct business in this judicial district. Upon information and belief, Padagis Israel has previously submitted to the jurisdiction of this Court and has further previously availed itself of this Court by asserting counterclaims in other civil actions initiated in this jurisdiction.

12. Padagis Israel has taken the costly, significant step of applying to the FDA for approval to engage in future activities—including the marketing of its generic drug—that will be purposefully directed at, upon information and belief, New Jersey and elsewhere. Padagis Israel’s ANDA filing constitutes a formal act that reliably indicates plans to engage in marketing of the proposed generic drug. Upon information and belief, Padagis Israel intends to direct sales of its drugs into New Jersey, among other places, once it has the requested FDA approval to market them. Upon information and belief, Padagis Israel will engage in marketing of its proposed ANDA product in New Jersey upon approval of its ANDA.

13. Plaintiffs are further informed and believe, and on that basis allege, that this Court has personal jurisdiction over Padagis Israel pursuant to Federal Rule of Civil Procedure 4(k)(2)

because Padagis Israel has extensive contacts with the United States, including but not limited to the above-described commercial contact, is not subject to jurisdiction in any particular state, and exercising jurisdiction over Padagis Israel is consistent with the laws of the United States and the United States Constitution.

14. Upon information and belief, this Court has jurisdiction over Padagis US. Upon information and belief, Padagis US is in the business of, *inter alia*, developing, manufacturing, marketing, importing, and/or selling pharmaceutical products, including generic drug products. Upon information and belief, Padagis US directly, or indirectly, develops, manufactures, markets, and sells generic drug products throughout the United States and in this judicial district, and this judicial district is a likely destination for the Padagis ANDA Product. Upon information and belief, Padagis US purposefully has conducted and continues to conduct business in this judicial district. Upon information and belief, Padagis US has previously submitted to the jurisdiction of this Court and has further previously availed itself of this Court by asserting counterclaims in other civil actions initiated in this jurisdiction.

15. Upon information and belief, this Court has jurisdiction over Padagis LLC. Upon information and belief, Padagis LLC is in the business of, *inter alia*, developing, manufacturing, marketing, importing, and selling pharmaceutical products, including generic drug products. Upon information and belief, Padagis LLC directly, or indirectly, develops, manufactures, markets, and/or sells generic drug products throughout the United States and in this judicial district through its subsidiaries, and this judicial district is a likely destination for the Padagis ANDA Product. Upon information and belief, Padagis LLC purposefully has conducted and continues to conduct business in this judicial district, at least through its wholly owned subsidiaries Padagis Israel and Padagis US.

16. Upon information and belief, Padagis Israel, Padagis US, and Padagis LLC hold themselves out as a unitary entity for purposes of manufacturing, marketing, selling and distributing generic products. Upon information and belief, Padagis LLC exercises control over Padagis Israel and Padagis US.

17. In addition, jurisdiction is proper in this district with respect to Padagis Israel, Padagis US and Padagis LLC because, by stipulation dated June 24, 2022, to be filed concurrently herewith, these entities confirmed that they do not contest jurisdiction in the District of New Jersey for the purposes of this action, and thus have consented to jurisdiction in this District for the purposes of this action.

18. Upon information and belief, venue is proper in this district under 28 U.S.C. §§ 1391(c) and (d), and 1400(b).

19. Venue is further proper as to Padagis Israel, a foreign corporation, in any judicial district that has personal jurisdiction, including this judicial district, and has previously consented to venue in this jurisdiction.

20. Venue is further proper as to Padagis US and Padagis LLC because both entities have previously consented to venue in this jurisdiction.

21. In addition, venue is proper in this district with respect to Padagis Israel, Padagis US, and Padagis LLC because, by stipulation dated June 24, 2022, to be filed concurrently herewith, these entities confirmed that they do not oppose venue in the District of New Jersey for the purposes of this action, and thus have consented to venue in this District for the purposes of this action.

THE PATENT-IN-SUIT

22. On April 26, 2022, the '482 Patent entitled "Topical Compositions and Methods for Treating Skin Diseases" was duly and legally issued. A copy of the '482 Patent is attached as Exhibit A.

23. The named inventors of the '482 Patent are Arturo Angel and Radhakrishnan Pillai.

24. The FDA's Electronic Orange Book, Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book") lists the expiration of the '482 Patent as May 11, 2038.

25. Bausch Ireland is the assignee of the '482 Patent.

ACTS GIVING RISE TO THIS ACTION

26. Bausch US holds the approved New Drug Application (“NDA”) No. 211882 for Arazlo® (tazarotene 0.045%) (the “Arazlo® NDA”).

27. Arazlo® is indicated for the topical treatment of acne vulgaris in patients 9 years of age or older.

28. Pursuant to 21 U.S.C. § 355(b)(1), the ’482 Patent is listed in Orange Book for Arazlo® (tazarotene 0.045%).

29. Upon information and belief, Padagis Israel submitted the Padagis ANDA to the FDA seeking approval to engage in the commercial manufacture, use or sale of a generic tazarotene (0.045%) lotion, referred to herein as the “Padagis ANDA Product.”

30. Plaintiffs received from Padagis Israel a letter, dated May 12, 2022, (the “Padagis Notice Letter”), stating that Padagis Israel had included a certification in the Padagis ANDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), that the ’482 Patent is invalid, or will not be infringed by the commercial manufacture, use, or sale of the Padagis ANDA Product (the “Paragraph IV Certification.”)

31. The Padagis ANDA refers to and relies upon the Arazlo® NDA and contains data that, according to Padagis Israel, demonstrate the bioequivalence of the Padagis ANDA Product and Arazlo®.

32. This action was commenced by Plaintiffs within 45 days of the date of receipt of the Padagis Notice Letter.

CLAIMS FOR RELIEF

COUNT I (Infringement of the ’482 Patent)

33. Plaintiffs reallege and incorporate by reference the allegations contained in the preceding paragraphs.

34. Upon information and belief, Padagis has infringed at least one claim of the ’482 Patent, pursuant to 35 U.S.C. § 271(e)(2), by submitting the Padagis ANDA, by which Padagis seeks approval from the FDA to engage in the commercial manufacture, use, offer to sell, sale

within the United States, or importation into the United States of the Padagis ANDA Product prior to the expiration of the '482 Patent.

35. Upon information and belief, the Padagis ANDA Product will, if approved and marketed, infringe, either literally or under the doctrine of equivalents, at least one claim of the '482 Patent.

36. Upon information and belief, Padagis will, through the manufacture, use, import, offer for sale, and/or sale of the Padagis ANDA Product, directly infringe, contributorily infringe, and/or induce infringement of at least one claim of the '482 Patent.

37. If Padagis's marketing and sale of the Padagis ANDA Product prior to the expiration of the '482 Patent is not enjoined, Plaintiffs will suffer substantial and irreparable harm for which there is no adequate remedy at law.

COUNT II (Declaratory Judgment of Infringement of the '482 Patent)

38. Plaintiffs reallege and incorporate by reference the allegations contained in the preceding paragraphs.

39. These claims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

40. There is an actual case or controversy such that the Court may entertain Plaintiffs' request for declaratory relief consistent with Article III of the United States Constitution, and this actual case or controversy requires a declaration of rights by this Court.

41. Padagis has made, and will continue to make, substantial preparation in the United States to manufacture, use, offer to sell, sell, and/or import the Padagis ANDA Product before the expiration date of the '482 Patent, including Padagis's filing of ANDA No. 215393.

42. Upon information and belief, any commercial manufacture, use, offer for sale, sale, and/or importation of the Padagis ANDA Product will directly infringe, contributorily infringe, and/or induce infringement of at least one claim of the '482 Patent.

43. Plaintiffs are entitled to a declaratory judgment that future commercial manufacture, use, offer for sale, sale, and/or importation of the Padagis ANDA Product will constitute infringement of at least one claim of the '482 Patent.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request that the Court enter judgment in their favor against Padagis on the patent infringement claims set forth above and respectfully request that this Court:

1. enter judgment that, under 35 U.S.C. § 271(e)(2), Padagis has infringed at least one claim of the '482 Patent by submitting or causing to be submitted ANDA No. 215393 to the FDA to obtain approval for the commercial manufacture, use, import, offer for sale, and/or sale in the United States of the Padagis ANDA Product before the expiration of the '482 Patent;

2. order that that the effective date of any approval by the FDA of the Padagis ANDA Product be a date that is not earlier than the expiration of the Patent-In-Suit, or such later date as the Court may determine;

3. enjoin Padagis from the commercial manufacture, use, import, offer for sale, and/or sale of the Padagis ANDA Product until expiration of the Patent-In-Suit, or such later date as the Court may determine;

4. enjoin Padagis and all persons acting in concert with Padagis from seeking, obtaining, or maintaining approval of Padagis's ANDA No. 215393 until expiration of the Patent-In-Suit;

5. declare this to be an exceptional case under 35 U.S.C. §§ 285 and 271(e)(4) and award Plaintiffs costs, expenses, and disbursements in this action, including reasonable attorney's fees; and

9. award Plaintiffs such further and additional relief as this Court deems just and proper.

Dated: June 24, 2022
Newark, New Jersey

s/ William P. Deni, Jr.
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CERTIFICATION OF NON-ARBITRABILITY
PURSUANT TO LOCAL CIVIL RULE 201.1(d)

Pursuant to Local Civil Rule 201.1(d), the undersigned counsel hereby certifies that this action seeks declaratory and injunctive relief and, therefore, is not subject to mandatory arbitration.

I certify under penalty of perjury that the foregoing is true and correct.

Dated: June 24, 2022
Newark, New Jersey

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EXHIBIT A



US011311482B2

(12) **United States Patent**
Angel et al.

(10) **Patent No.:** **US 11,311,482 B2**
(45) **Date of Patent:** **Apr. 26, 2022**

(54) **TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES**

(71) Applicant: **BAUSCH HEALTH US, LLC**,
Bridgewater, NJ (US)

(72) Inventors: **Arturo Angel**, Santa Rosa, CA (US);
Radhakrishnan Pillai, Santa Rosa, CA (US)

(73) Assignee: **BAUSCH HEALTH US, LLC**,
Bridgewater, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **16/179,561**

(22) Filed: **Nov. 2, 2018**

(65) **Prior Publication Data**

US 2019/0133942 A1 May 9, 2019

Related U.S. Application Data

(63) Continuation-in-part of application No. 15/977,088, filed on May 11, 2018, now abandoned.

(60) Provisional application No. 62/505,421, filed on May 12, 2017.

(51) **Int. Cl.**

A61K 9/107 (2006.01)
A61K 9/00 (2006.01)
A61P 17/00 (2006.01)
A61K 31/4436 (2006.01)
A61K 47/34 (2017.01)
A61K 47/14 (2017.01)
A61K 47/44 (2017.01)
A61P 17/10 (2006.01)
A61K 9/06 (2006.01)
A61K 47/06 (2006.01)
A61K 47/32 (2006.01)

(52) **U.S. Cl.**

CPC **A61K 9/107** (2013.01); **A61K 9/0014** (2013.01); **A61K 9/06** (2013.01); **A61K 31/4436** (2013.01); **A61K 47/06** (2013.01); **A61K 47/14** (2013.01); **A61K 47/32** (2013.01); **A61K 47/34** (2013.01); **A61K 47/44** (2013.01); **A61P 17/00** (2018.01); **A61P 17/10** (2018.01)

(58) **Field of Classification Search**

USPC 514/337
See application file for complete search history.

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(Continued)

Primary Examiner — Kathrien A Cruz

(74) Attorney, Agent, or Firm — Kilpatrick Townsend & Stockton LLP

(57) **ABSTRACT**

Topical pharmaceutical compositions include tazarotene or a pharmaceutically acceptable salt of tazarotenic acid and an oil-in-water emulsion vehicle that forms a lotion. The compositions are used to treat skin diseases, such as acne vulgaris.

11 Claims, 10 Drawing Sheets

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(56)

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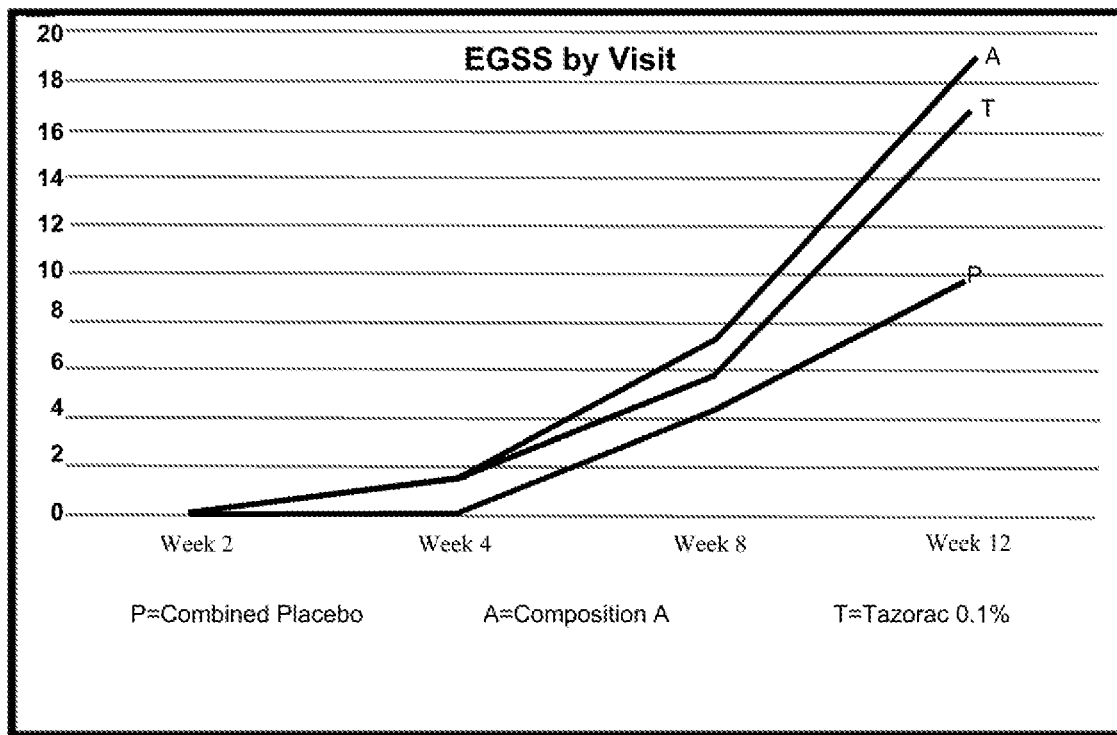


FIG. 1

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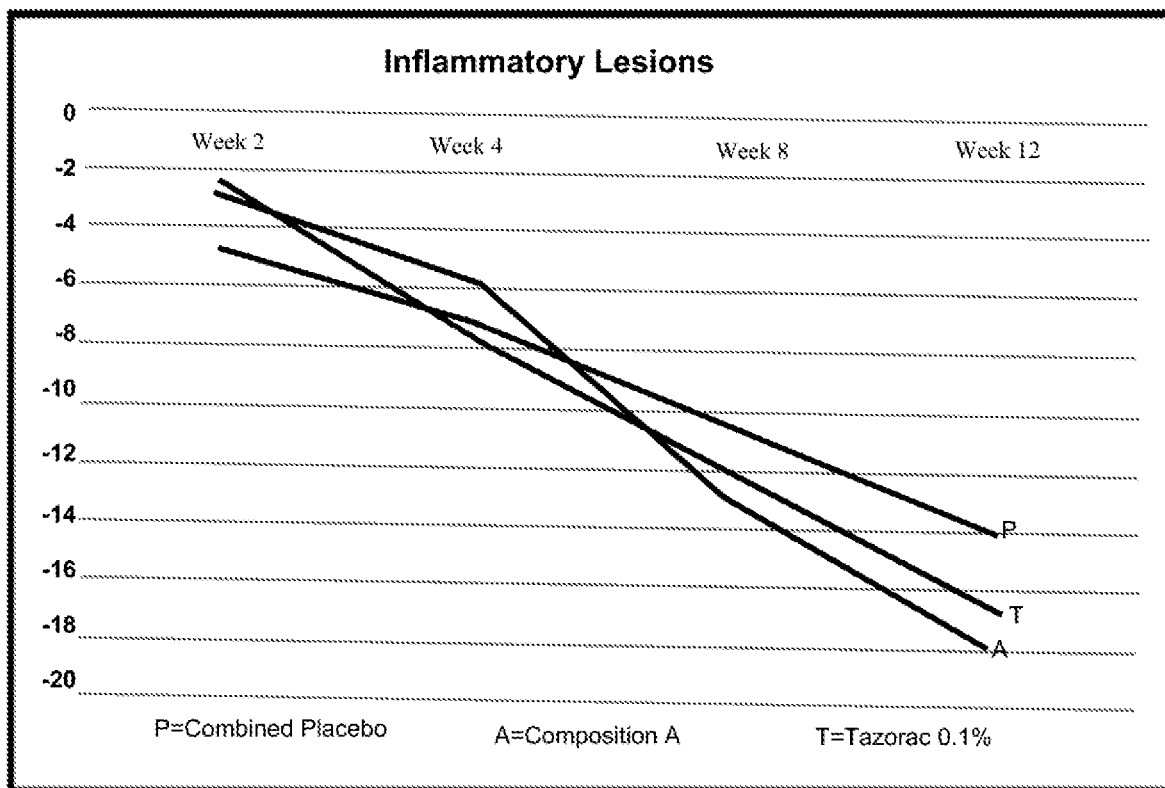


FIG. 2

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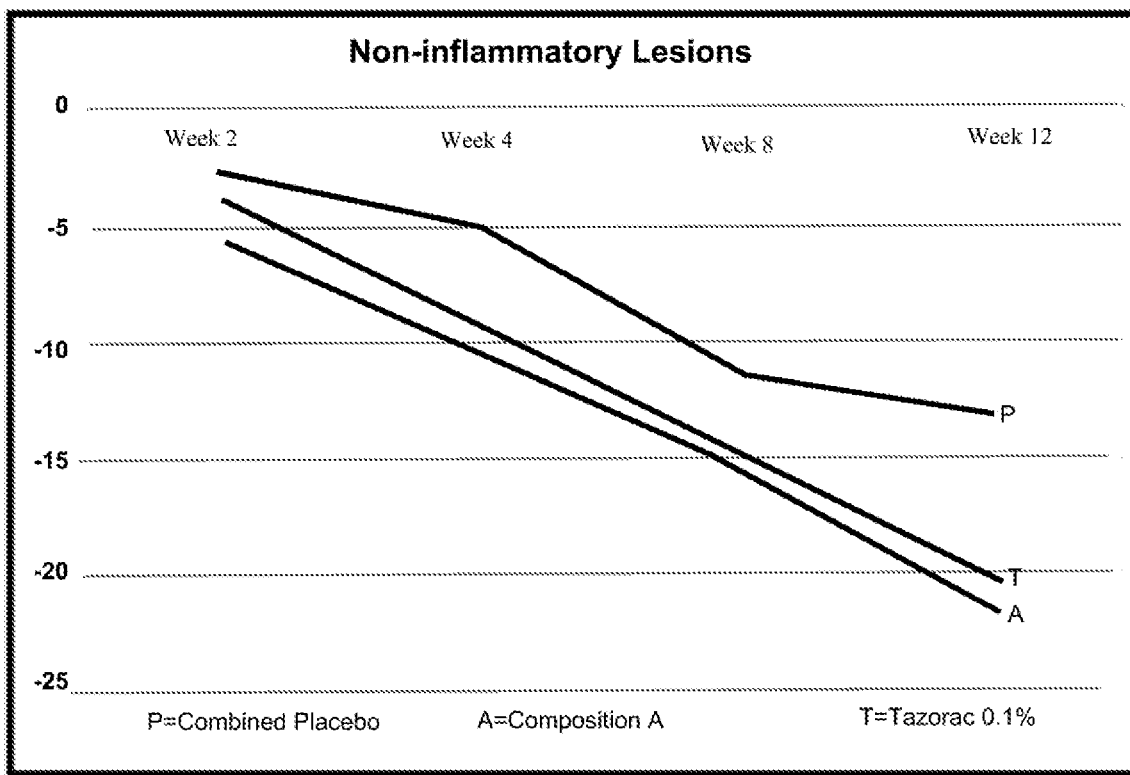


FIG. 3

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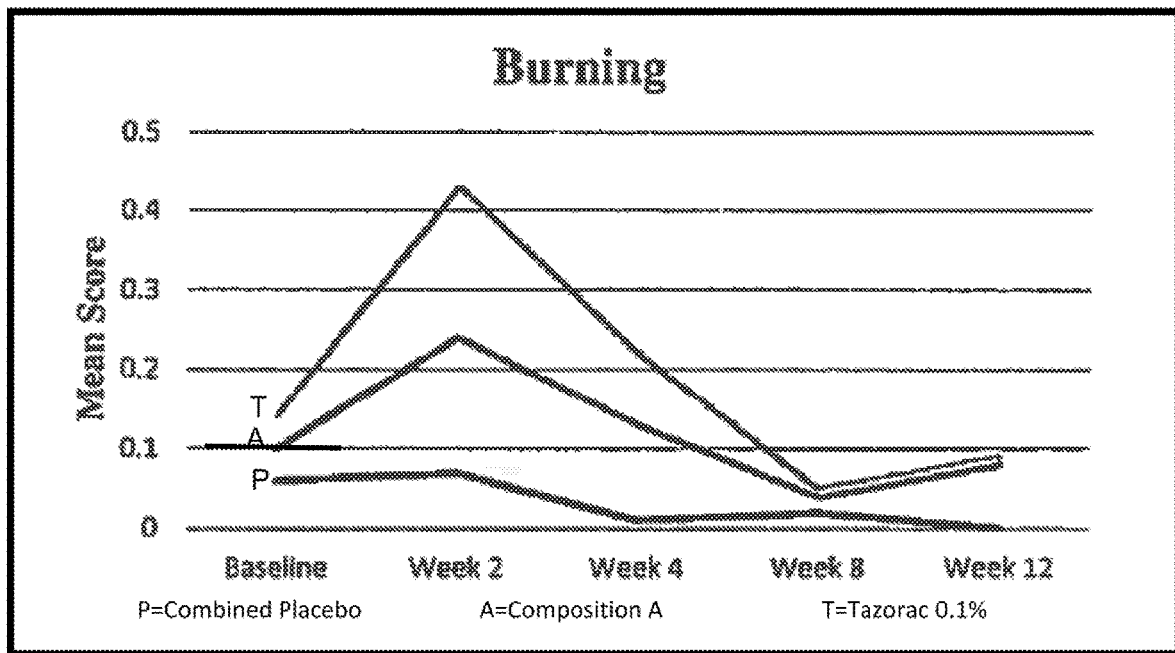


FIG. 4A

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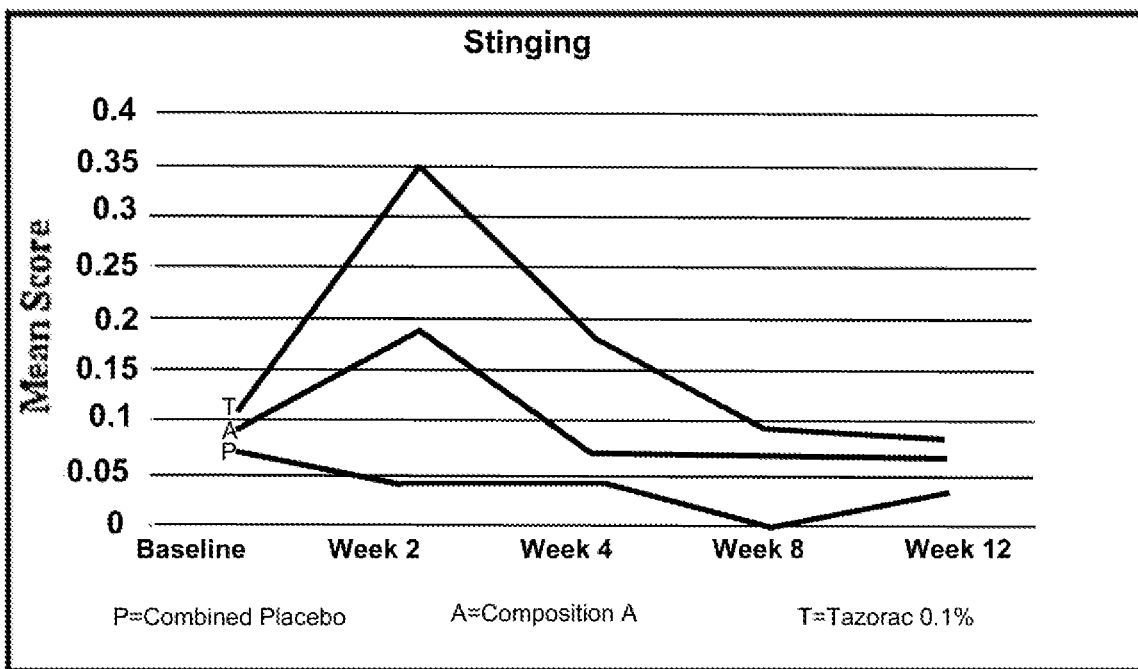


FIG. 4B

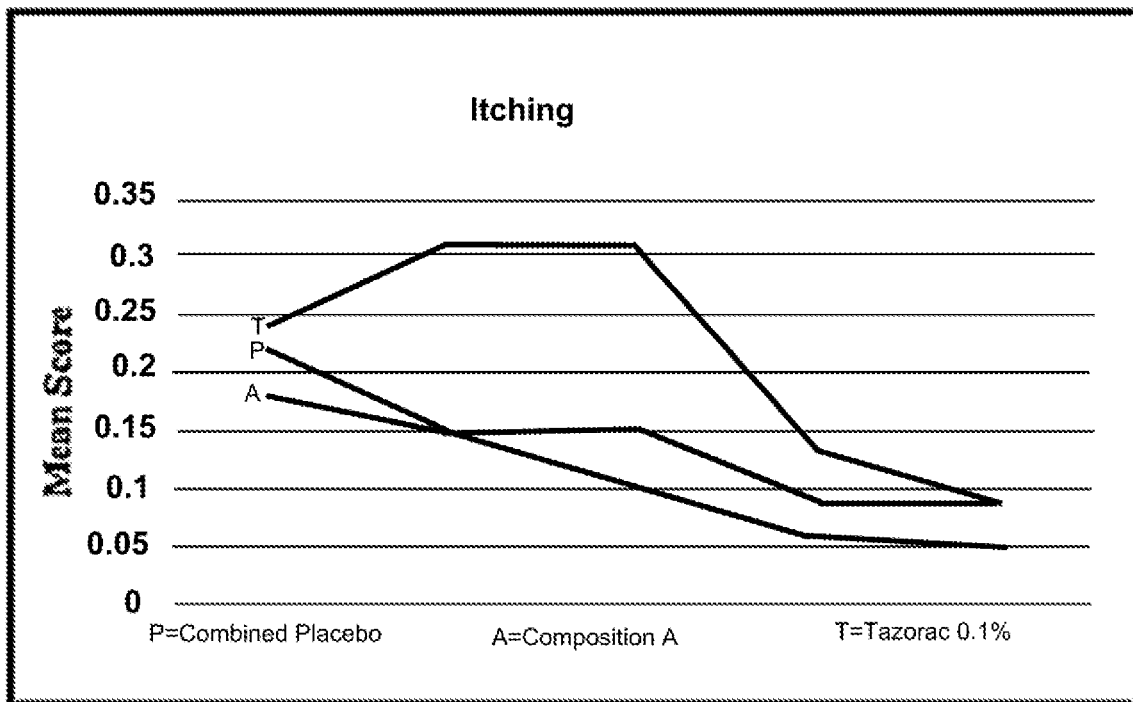


FIG. 4C

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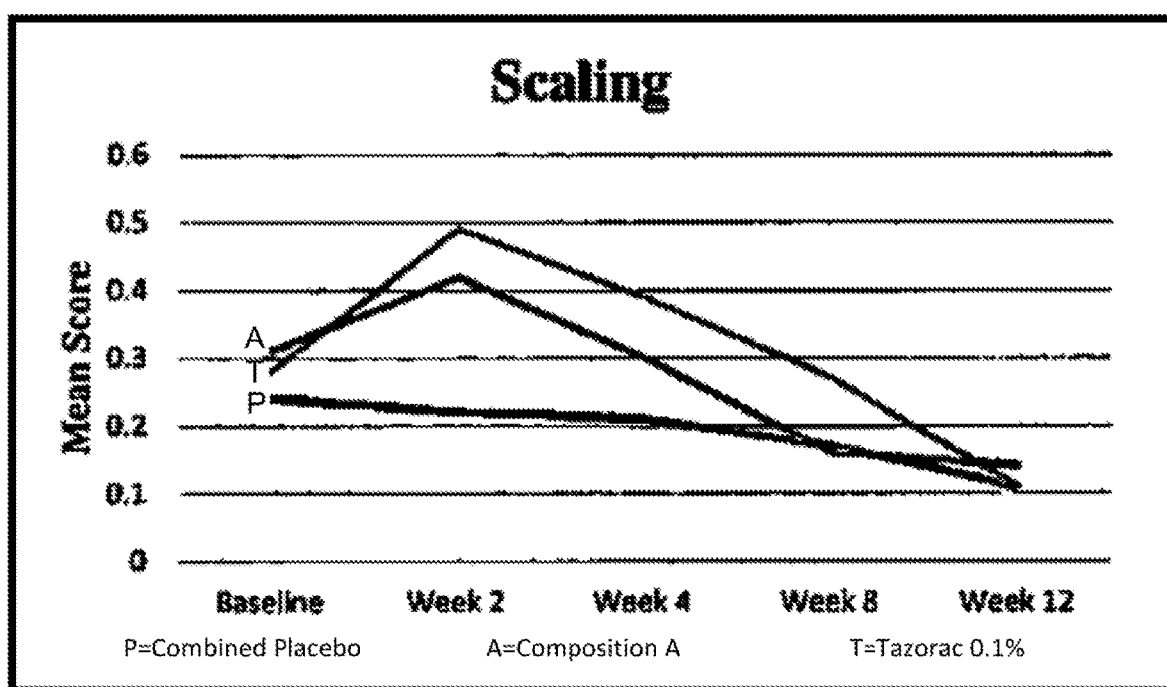


FIG. 5A

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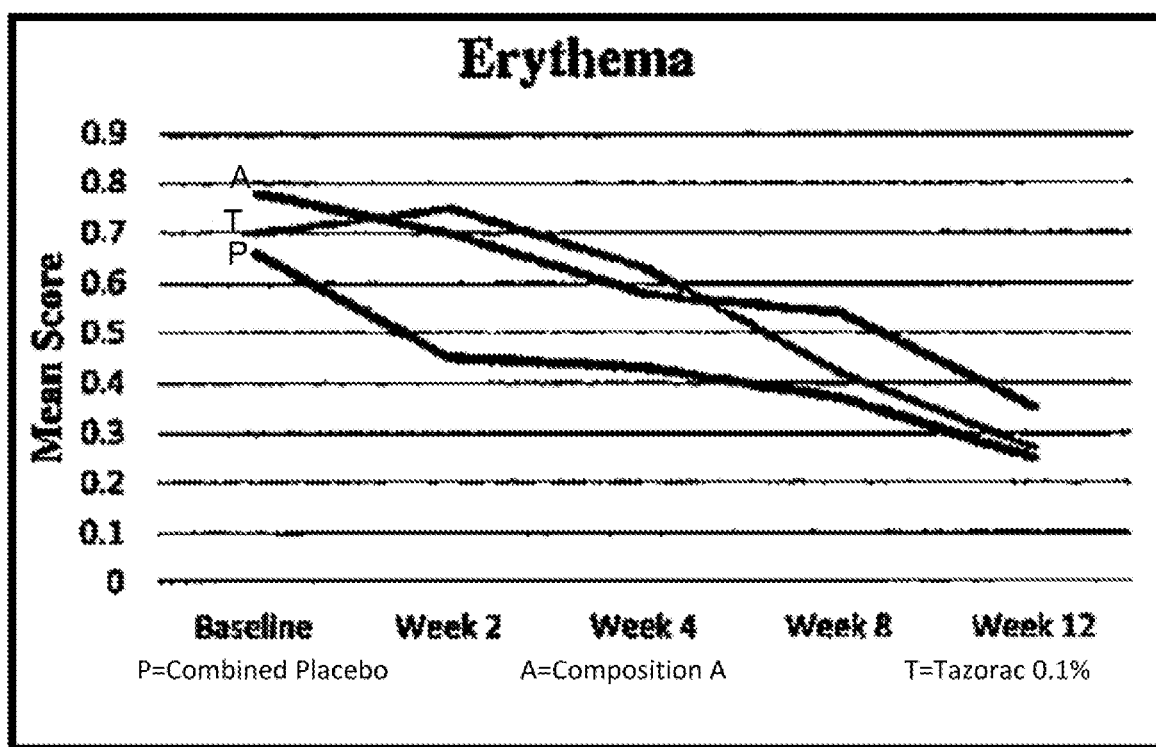


FIG. 5B

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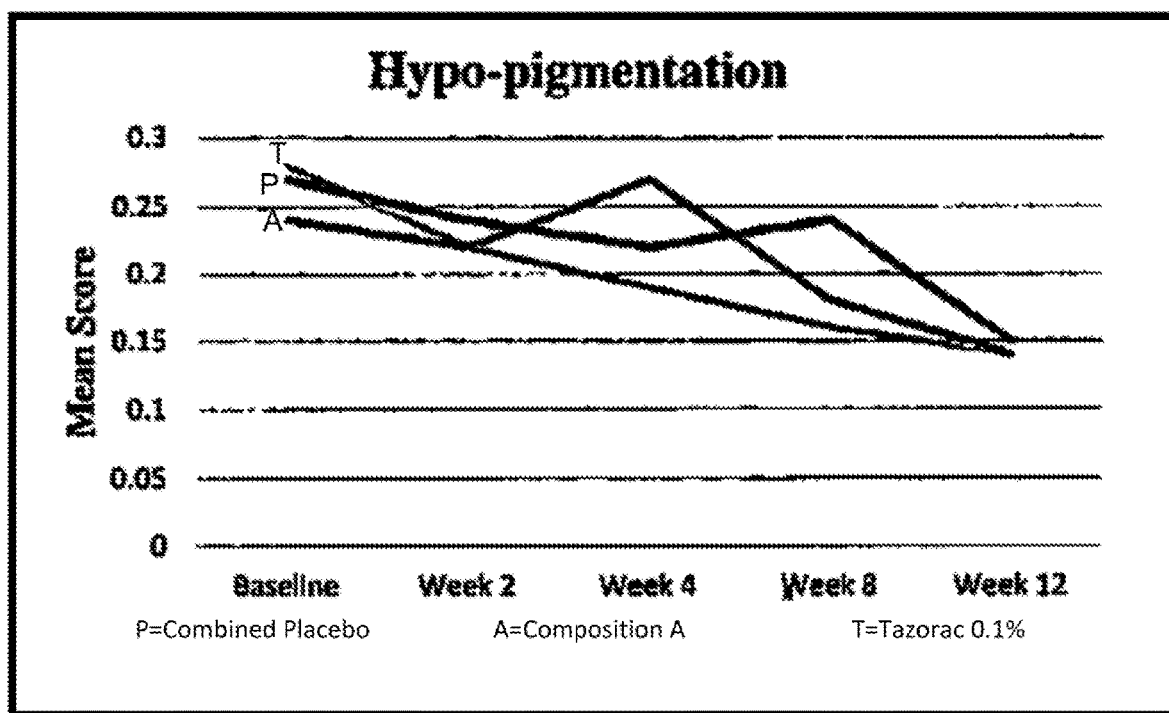


FIG. 5C

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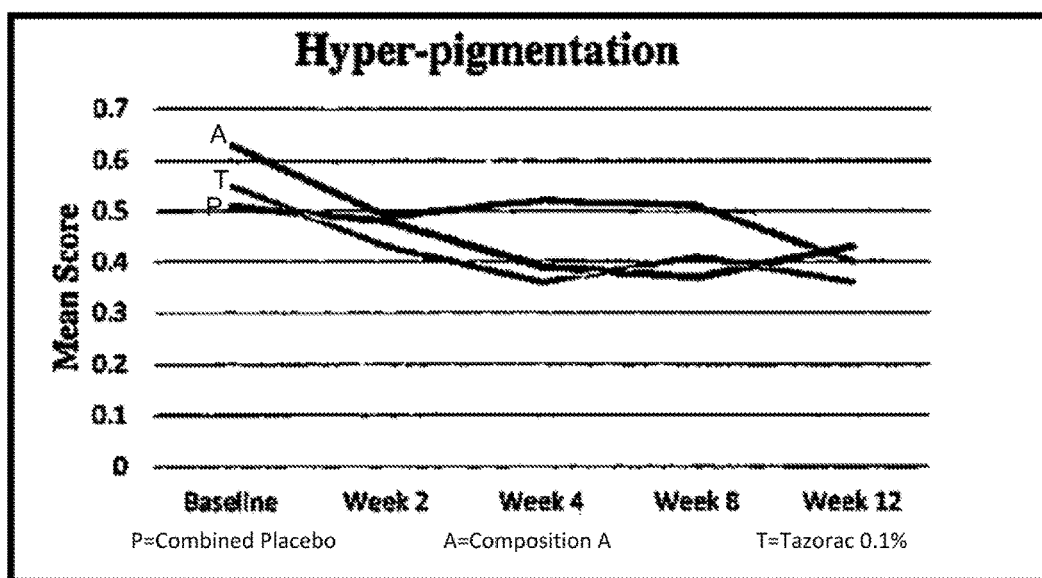


FIG. 5D

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1

**TOPICAL COMPOSITIONS AND METHODS
FOR TREATING SKIN DISEASES****CROSS REFERENCE TO RELATED
APPLICATIONS**

This application is a continuation-in-part application of U.S. patent application Ser. No. 15/977,088, filed May 11, 2018, which claims priority to U.S. Provisional Patent 62/505,421, filed May 12, 2017.

BACKGROUND

The present invention relates to topical compositions and methods for treating skin diseases such as acne and psoriasis. In particular, this invention relates to topical pharmaceutical compositions comprising tazarotene or a pharmaceutically acceptable tazarotenic acid salt, in an oil-in-water emulsion vehicle, for treating skin diseases.

The retinoid tazarotene has been commercially available and has been used to treat acne and psoriasis topically. However, tazarotene may cause significant local skin irritation, especially early in the first through fourth weeks of therapy, thus limiting its use for a prolonged period because many patients stop treatment due to skin irritation. The need exists for more effective and safer topical medicaments with reduced adverse effects for the management of acne, psoriasis and other skin diseases.

SUMMARY OF THE INVENTION

In general, the present invention provides topical compositions and methods for treating skin diseases such as acne and psoriasis.

In one aspect, this invention provides a topical pharmaceutical composition for treating skin diseases, including acne and psoriasis, comprising: tazarotene or a pharmaceutically acceptable tazarotenic acid salt present in the composition at a positive concentration of less than 0.050 percent by weight of the composition; and a dermatologically acceptable oil-in-water emulsion vehicle.

In another aspect, this invention provides a method of treating skin diseases, including acne and psoriasis, comprising topically applying a pharmaceutical composition to an affected area of a body of a subject suffering from the skin disease, wherein the composition comprises: tazarotene or a pharmaceutically acceptable tazarotenic acid salt present in the composition at a positive concentration of less than 0.050 percent by weight of the composition; and a dermatologically acceptable oil-in-water emulsion vehicle.

According to other aspects, the topical pharmaceutical composition may comprise tazarotene or the salt thereof at 0.01 to 0.049 percent by weight of the composition, or at about 0.045 percent by weight of the composition.

According to another aspect, the tazarotene or tazarotenic acid salt may be dissolved in a liquid oil component of the emulsion.

According to another aspect, the topical pharmaceutical composition may contain the tazarotene or the tazarotenic acid salt as a sole active pharmaceutical ingredient.

According to various aspects, the oil phase of the emulsion may comprise a liquid oil component comprising a DCAE, a MCAE, or combinations thereof. In other aspects, the oil phase includes diethyl sebacate as the DCAE.

According to other aspects, the aqueous phase of the emulsion may comprise water and a carbomer homopolymer.

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According to another aspect, the topical pharmaceutical composition may comprise: an aqueous phase comprising water, a carbomer homopolymer, and a polymeric emulsifier; an oil phase comprising at least one member selected from the group consisting of a dicarboxylic acid ester and a mineral oil, and the tazarotene or the tazarotenic acid salt. According to other aspects, the aqueous phase may further comprise a humectant or a preservative, such as at least one member selected from the group consisting of methylparaben, propylparaben and sorbitol.

According to other aspects, the topical pharmaceutical composition may have the form of a lotion, or of a cream.

According to another aspect, the topical pharmaceutical composition may have a pH of about 4 to about 6.

For the methods of this invention, the step of applying may be carried out once per day for at least eight weeks. According to one aspect, the applying is carried out once per day for at least twelve weeks.

According to other aspects, the composition may be applied is to an affected area of a body of a subject suffering from acne vulgaris in order to treat that condition.

Other features and advantages of the present invention will become apparent from the accompanying drawings and the following detailed description and claims.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a graph of EGSS by visit.

FIG. 2 is a graph of change in inflammatory lesions from baseline.

FIG. 3 is a graph of change in non-inflammatory lesions from baseline.

FIGS. 4A, 4B, and 4C are graphs of cutaneous tolerability to burning, stinging, and itching, respectively.

FIGS. 5A, 5B, 5C, and 5D are graphs of cutaneous safety assessed by scaling, erythema, hypo-pigmentation, and hyper-pigmentation, respectively.

**DETAILED DESCRIPTION OF THE
INVENTION**

In general, the present invention provides topical compositions and methods for treating skin diseases, including acne and psoriasis.

Throughout this disclosure, unless otherwise indicated, the concentration of an ingredient of the composition is in percent by weight of the total composition.

In one aspect, the topical pharmaceutical composition comprises tazarotene, or a pharmaceutically acceptable salt of tazarotenic acid, at a concentration below that which is presently utilized in topical formulations. For example, tazarotene or the tazarotenic acid salt is included in a composition at a positive concentration less than 0.05 wt %.

In certain embodiments of the present invention, tazarotene or the tazarotenic acid salt is present in the composition at a positive concentration of less than 0.05% based on the weight of the composition ("wt %"). For example, this component is present in the range from about 0.01 to about 0.049 wt %, or from about 0.01 to about 0.045 wt %, or from about 0.02 to about 0.045 wt %, or from about 0.03 to about 0.045 wt %, or at about 0.045 wt %. Specific concentrations of this component may be 0.01 wt %, 0.015 wt %, 0.02 wt %, 0.025 wt %, 0.03 wt %, 0.035 wt %, 0.04 wt %, and 0.045 wt %.

In one aspect, the topical pharmaceutical composition comprises an oil-in-water emulsion as a carrier vehicle, in which an internal oil phase is dispersed in a continuous

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aqueous phase. The emulsion may be a macroemulsion, a microemulsion, or a nanoemulsion. The composition may have the dosage form of gel, lotion, or cream, or ointment, or liquid, or oil, or spray or foam.

In addition to the tazarotene active ingredient, the composition of the present invention may comprise one or more dermatologically acceptable excipients, such as liquid oils, waxes viscosity-modifying agents, thickening agents, gelling agents, alcohols, surfactants, chelating agents, buffers, preservatives, humectants, emollients, stabilizers, diluents, dispersing agents, emulsifiers, wetting agents, stabilizers, pH adjusters, solvents or cosolvents.

The composition of the invention may desirably contain a thickening agent to provide viscosity so that the formulation may be provided in the form of a gel, lotion, cream, or ointment. The thickening agent may be miscible or soluble in an aqueous fluid. Non-limiting examples of suitable thickening agents include acacia, alginic acid and its salts, hyaluronic acid and its salts, carbomers (also known as carboxy vinyl polymers, which are cross-linked polyacrylic acid), carboxymethylcellulose, ethylcellulose, gelatin, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methylcellulose, poloxamers, polyvinylpyrrolidone, polyvinyl alcohol, tragacanth, xanthan gum, magnesium aluminum silicate, and bentonite. The thickening agent may also reside in the oil or lipophilic portion of the formulation. Examples of suitable lipophilic thickening agents include cetyl alcohol, stearyl alcohol, glyceryl stearate, white beeswax, microcrystalline wax, hydrogenated polyisobutane polymers, and emulsifying wax.

A suitable group of thickening agents is carbomers, such as Carbopol® and polycarbophil (The Lubrizol Corporation, Wickliffe, Ohio). Carbopol® homopolymers are polymers of acrylic acid crosslinked with allyl sucrose or allylpentaerythritol. Carbopol® copolymers are polymers of acrylic acid and C₁₀-C₃₀ alkyl acrylate crosslinked with allylpentaerythritol. Carbopol® interpolymers are carbomer homopolymers or copolymers that contain a block copolymer of polyethylene glycol and a long chain alkyl acid ester. Noveon® polycarbophil is a polymer of acrylic acid crosslinked with divinyl glycol.

A surfactant or emulsifier is optionally included, if desired or required. Pharmaceutically acceptable anionic, cationic, or non-ionic surfactants may be included in a composition of the present invention. Non-ionic surfactants are preferred. Non-limiting examples of non-ionic surfactants are Octoxynol (also known as Macrogol tetramethylbutylphenyl ether, octylphenoxy polyethoxyethanol, or polyoxyethylene octylphenyl ether), such as Octoxynol 1, 3, 5, 8, 9, 10, 12, 13, 16, 30, 40, 70 (wherein the number indicates the number of repeating oxyethylene units), or other Octoxynols that comprise different numbers of repeating units of oxyethylene in the side chain, sorbitan esters (such as sorbitan monooleate and sorbitan monostearate, commonly known by their trade names Span 80 and Span 60), polysorbates (such as polysorbate 80 (polyoxyethylene sorbitan monooleate), polysorbate 60 (polyoxyethylene sorbitan monostearate), polysorbate 20 (polyoxyethylene sorbitan monolaurate), commonly known by their trade names of Tween® 80, Tween® 60, Tween® 20), poloxamers (synthetic block polymers of ethylene oxide and propylene oxide, such as those commonly known by their trade names of Pluronic®; e.g., Pluronic® F127 or Pluronic® F108), or poloxamines (synthetic block polymers of ethylene oxide and propylene oxide attached to ethylene diamine, such as those commonly known by their trade names of Tetronic®;

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e.g., Tetronic® 1508 or Tetronic® 908, etc.), other nonionic surfactants such as Brij® (polyoxyethylene alkyl ether having a formula of CH₃—(CH₂)₁₀₋₁₆—(O—C₂H₄)₁₋₂₅—OH), Myrj® (stearic acid esterified with polyoxyethylene having 40-100 repeating oxyethylene units), and long chain fatty alcohols (e.g., oleyl alcohol, stearyl alcohol, myristyl alcohol, docosahexaenoyl alcohol, etc.) with carbon chains having about 12 or more carbon atoms (e.g., such as from about 12 to about 24 carbon atoms).

In addition, polymeric emulsifiers such as those known under the trade name Pemulen™ (The Lubrizol Corporation, Wickliffe, Ohio) may be used. These are polymers of acrylic acid, modified by long chain (C₁₀-C₃₀) alkyl acrylates, and crosslinked with allylpentaerythritol.

An anionic emulsifier may be used, such as sodium or potassium oleate, triethanolamine stearate, sodium lauryl sulfate, sodium dioctyl sulfosuccinate, and sodium docusate. Less preferred are cationic emulsifiers such as quaternary ammonium salts. Still other emulsifiers include glyceryl monostearate, polyoxyethylene monooleate, polyoxyethylene monostearate, polyoxyethylene monolaurate, potassium oleate, sodium lauryl sulfate, sodium oleate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, sorbitan trioleate, triethanolamine oleate, polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan tristearate, polyoxyethylene sorbitan monooleate, and polyoxyethylene sorbitan trioleate.

The formulation desirably contains a dermatologically acceptable humectant such as glycerin, sorbitol, hexylene glycol, propylene glycol, or urea. In addition, the formulation may contain an emollient such as petrolatum, lanolin, mineral oil, light mineral oil, stearic acid, cyclomethicone, or dimethicone. Chelating agents such as EDTA and citric acid and their salts may be included in a formulation of the present invention.

The liquid oil component of the composition includes one or more materials that are practically insoluble or insoluble in water and which are liquid at room temperature. For example, in one embodiment, the liquid oil component of the composition includes one or more materials that are practically insoluble or insoluble in water and which are liquid at room temperature of 22° C. The liquid oil component may be selected from one or more ingredients from the group consisting of dicarboxylic acid esters ("DCAE"), monocarboxylic acid esters ("MCAE"), fish-liver oil, long-chain triglycerides (wherein each side chain has 14-18 carbons, such as peanut oil, sesame oil, coconut oil, sunflower oil, corn oil, olive oil, cotton seed oil, or derivatives thereof), propylene glycol diesters, medium-chain triglycerides (such as those wherein each side chains has 8-10 carbons; e.g., capric/caprylic acid triglycerides), hydrocarbons like mineral oil, light mineral oil, squalene, and squalane, fatty alcohols (such as octyldodecanol and isostearyl alcohol), and fatty acids (such as isostearic acid and oleic acid).

In some embodiments, the liquid oil component comprises a dicarboxylic acid ester and light mineral oil. In some other embodiments, the liquid oil component comprises one or more long-chain triglycerides.

The formulation may include other lipophilic liquids in an amount that is sufficient to be miscible with the dicarboxylic acid ester and/or monocarboxylic acid ester. The lipophilic liquid may be an emollient such as lanolin oil, mineral oil, light mineral oil, isostearic acid, squalene, octyldodecanol, fractionated coconut oil, cyclomethicone, or dimethicone.

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In addition to the liquid oil component, the formulation may contain water insoluble or practically insoluble ingredients that are not liquid at room temperature, but are soluble in the liquid oil component.

A DCAE that is suitable for the present invention has the formula $R_1OOC-(CH_2)_n-COOR_2$, wherein R_1 and R_2 are alkyl groups containing between 1 and 4 carbons or aryl groups and may be the same or may be different and wherein $(CH_2)_n$ is a straight or branched chain and n is between 1 and 12. Examples of DCAEs containing one or more aryl groups are dibenzyl esters of dicarboxylic acids. A preferred dicarboxylic acid ester is diethyl sebacate, which has the formula $CH_3CH_2OOC-(CH_2)_8-COOCH_2CH_3$. Examples of other suitable dicarboxylic acid esters (where R_1 and R_2 are the same) are dimethyl, diethyl, dipropyl, diisopropyl, dibutyl and diisobutyl esters such as oxalate, malate, succinate, glutarate, adipate, pimelate, suberate, and azalate. Examples of suitable dicarboxylic acid esters (where R_1 is different from R_2) are methyl ethyl, methyl propyl, methyl butyl, methyl isopropyl, ethyl propyl, ethyl butyl, ethyl isopropyl, and propyl butyl esters such as oxalate, malate, succinate, glutarate, adipate, pimelate, suberate, azalate, and sebacate.

In some aspects, diethyl sebacate is included at 0.1 to 20 wt %, or at 0.5 to 10 wt %, or at 2 to 4 wt % of the weight of the composition.

Alternatively, or in combination with the DCAE, the formulation may contain a MCAE. The MCAE that is suitable for the present invention has the formula $CH_3-(CH_2)_n-COOR_1$, wherein R_1 is an alkyl group containing between 1 and 4 carbons or an aryl group, and wherein $(CH_2)_n$ is straight or branched chain and n is between 1 and 12. Examples of such monocarboxylic acid esters include methyl, ethyl, propyl, isopropyl, butyl, or an aryl such as benzyl formate, acetate, propionate, butyrate, valerate, lau-

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the case wherein the tazarotene component is suspended in the formulation, this suspended active ingredient may be micronized, namely that the mean particle size is preferably about 25 microns in diameter or less.

In one aspect, a composition of the present invention comprises the ingredients at the concentrations shown in Table 1.

TABLE 1

Compositions of the Present Invention for Treating Skin Diseases			
Ingredient	Concentration (wt %)		
	Range 1	Range 2	Range 3
Tazarotene or Tazarotenic Acid Compound	0.01-0.049	0.02-0.045	0.03-0.045
Emollient, Solvent, and/or Thickener	0.5-40	1-25	2-20
Emulsifier	0.25-10	0.5-7	1-5
Humectant	0-15	2-12	3-10
Polymeric Thickener	0.05-2	0.1-1.5	0.3-1
Pharmaceutical Aids	q.s.	q.s.	q.s.
Purified water	q.s. to 100	q.s. to 100	q.s. to 100

Non-limiting examples of compositions of the present invention are shown in Table 2.

TABLE 2

Some Emulsion Compositions of the Present Invention for Treating Acne					
Ingredient	Function	Concentration (wt %)			
		Range 1	Range 2	Range 3	Composition A
Tazarotene	Retinoid	0.02-0.049	0.03-0.049	0.04-0.049	0.045
Diethyl sebacate	Liquid Oil & Solvent	1-5	2-4	2.5-3.5	2.97
Light mineral oil	Liquid Oil & Co-Solvent	5-15	5-10	7.5-8.5	8.03
Sorbitan monooleate	Surfactant/Emulsifying Agent	0.01-1	0.02-0.5	0.05-0.2	0.1
Sorbitol solution, 70%	Humectant	5-15	7-12	10-11	10.7
Methyl paraben	Antimicrobial Preservative ⁽¹⁾	0.05-0.3	0.1-0.3	0.1-0.2	0.17
Propyl paraben	Antimicrobial Preservative ⁽¹⁾	0.01-0.1	0.01-0.05	0.02-0.04	0.03
Edetate disodium dihydrate	Chelating Agent ⁽¹⁾	0.02-0.1	0.02-0.7	0.03-0.06	0.05
Carbomer copolymer type B (e.g., Pemulen™ TR-1)	Emulsifying Agent	0.1-1	0.2-0.7	0.3-0.5	0.4
Carbomer homopolymer type A (e.g., Carbomer 981)	Thickener	0.2-1.5	0.3-1	0.5-0.7	0.6
Sodium hydroxide, 10% Solution	pH-adjusting Agent ⁽¹⁾	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5
Purified water	Carrier	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100

Note:

⁽¹⁾These ingredients are broadly classified as Pharmaceutical Aids.

rate, myristate, palmitate, and stearate. Examples of preferred monocarboxylic acid esters are isopropyl palmitate and isopropyl myristate.

The liquid oil phase may beneficially be used to dissolve one or more of the active ingredients within the emulsion. In one embodiment the tazarotene component is dissolved in the liquid oil phase within the formulation at room temperature. In another embodiment the tazarotene component is suspended within the formulation at room temperature. In

A lotion having a composition as shown Composition A of Table 2 may be prepared as follows.

A separate aqueous phase is made. In a manufacturing vessel equipped with a mixing implement (such as a propeller) and temperature control, purified water and disodium edetate dihydrate are combined and the mixture is agitated until a clear solution is achieved. Sorbitol, methylparaben, and propylparaben are then added to the mixture. The mixture is continuously mixed and heated to approximately

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75° C. The mixture is agitated until a solution is obtained. The mixture is then removed from the heat source and allowed to cool to below 40° C. with continued mixing. With continuous mixing, Carbopol® 981 and Pemulen™ TR-1 carbomers are added to the mixture and dispersed. Mixing continues until the two carbomers are fully dispersed and hydrated.

A separate oil phase is made. In a vessel equipped with a mixing implement such as a propeller, diethyl sebacate, and tazarotene are combined. The mixture is agitated until a solution is achieved. With continuous mixing, light mineral oil and sorbitan monooleate are added. Mixing is continued until a solution is obtained.

In a separate vessel, an approximate 2.5 N solution of sodium hydroxide is prepared.

With high speed mixing, the oil phase containing the active ingredient (tazarotene) is added to the aqueous phase. Mixing is continued until a homogeneous emulsion is obtained. Mixing speed is decreased and mixing continued for an additional time of 10 minutes to 1 hour. With continuous mixing, an appropriate amount of the sodium hydroxide solution is added incrementally to obtain a pH of 5.5±0.5. Mixing continues further until a homogeneous lotion is obtained, such as for 30 minutes to 3 hours.

A first clinical study in acne patients was conducted to compare the efficacy of a composition of the present invention containing tazarotene (the "Composition A" lotion of Table 2).

A first placebo ("Lotion Placebo") corresponded to and had a similar viscosity as Composition A but lacked tazarotene. A second placebo ("Cream Placebo") corresponded to the Lotion Placebo but employed carbomer homopolymer type C in place of carbomer homopolymer type A to yield a higher viscosity emulsion with a viscosity similar to 0.1% tazarotene cream employed in the study. This allows for better blinding of the test formulations and control of the clinical study. In the following results, data for Lotion Placebo and Cream Placebo may be combined and reported as "Combined Placebo".

Additionally, commercially available 0.1% tazarotene cream (Tazorac® 0.1% cream) was employed in this clinical study for comparison purposes.

A double blind, multi-site, randomized clinical study was conducted on patients suffering from acne vulgaris, whereby neither the acne patient nor the investigator knew the identity of the test composition assigned. 210 patients were randomized to receive either Composition A lotion, Tazorac® 0.1% cream, Placebo Lotion and Placebo Cream at a 2:2:1:1 randomization:

69 subjects "Composition A lotion"

72 subjects "Tazorac® 0.1% cream"

34 subjects "Lotion Placebo"

35 subjects "Cream Placebo".

Primary inclusion criteria were moderate to severe acne, inflammatory lesion count of at least 20 but no more than 40, and non-inflammatory lesion count of at least 20 but no more than 100. The blindly labeled lotions were applied to the affected area once daily for twelve weeks, with assessments at 2 weeks, 4 weeks, 8 weeks and 12 weeks.

The investigator monitored the efficacy at each study visit by assessing the treatable area, determining the Evaluator's Global Severity Score (EGSS), and determining the grade of improvement. EGSS included the following grades:

Clear=0; Almost Clear=1; Mild=2; Moderate=3; Severe=4.

Clinical Efficacy was determined primarily based on the percentage of subjects who were treatment successes at 12

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weeks. To be judged as a treatment success, as reported in Tables 4, 6, and 7, subjects had to show at least two-grade improvement from the baseline and EGSS score equating to "clear" or "almost clear". Also, the numbers of inflammatory and non-inflammatory lesions were assessed.

Table 3 reports Baseline Characteristics.

TABLE 3

Baseline Characteristics - Inflammatory Lesions and Non-inflammatory lesions			
	Combined Placebo N = 69	Composition A N = 69	Tazorac ® 0.1% Cream N = 72
Inflammatory Lesions			
Mean (SD)	27.2 (5.49)	28.3 (6.0)	27.3 (5.95)
Median	26.0	27.0	26.0
Non-inflammatory Lesions			
Mean (SD)	36.6 (13.17)	37.6 (14.70)	36.6 (13.31)
Median	34.0	34.0	34.0

Table 4 reports treatment % success on an intention-to-treat (ITT) basis.

TABLE 4

EGSS (Clear or Almost Clear) by Visit (ITT)			
	Combined Placebo N = 69	Composition A N = 69	Tazorac ® 0.1% Cream N = 72
Week 2	0%	0%	0%
Week 4	0%	1.4%	1.4%
Week 8	4.3%	7.2%	5.6%
Week 12	10.1%	18.8%	16.7%

Table 5 reports absolute change in inflammatory lesions from baseline. Change in inflammatory and non-inflammatory lesions from baseline is reported in FIGS. 2 and 3.

TABLE 5

Inflammatory Lesions by Visit Absolute Change from Baseline			
	Combined Placebo N = 69	Composition A N = 69	Tazorac ® 0.1% Cream N = 72
Week 2	-4.7	-2.9	-2.4
Week 4	-7.2	-5.8	-7.8
Week 8	-10.9	-13.2	-12.0
Week 12	-14.0	-18.1	-16.8

Table 6 reports treatment % success for primary efficacy on an intention-to-treat basis for EGSS at week 12. For EGSS, to be judged as a treatment success, subjects had to show at least two-grade improvement from the baseline and EGSS score equating to "clear" or "almost clear". For inflammatory and non-inflammatory lesions, absolute change from baseline to week 12 in mean inflammatory and non-inflammatory counts is reported.

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TABLE 6

Treatment % Success (ITT) at 12 Weeks			
	Combined Placebo N = 69	Composition A N = 69	Tazorac® 0.1% Cream N = 72
EGSS - Clear or Almost Clear Inflammatory Lesions	10.1%	18.8%	16.7%
Absolute Change	-14.0	-18.1	-16.8
% Change	-51.41%	-63.75%	-59.99%
Non-inflammatory Lesions			
Absolute Change	-13.1	-21.6	-20.3
% Change	-35.18%	-56.86%	-54.09%

Table 7 reports treatment % success on a per-protocol basis for EGSS. For lesions, absolute change from baseline to Week 12 in mean inflammatory and non-inflammatory counts is reported.

TABLE 7

Treatment % Success (PP)			
	Combined Placebo N = 57	Composition A N = 54	Tazorac® 0.1% Cream N = 56
EGSS - Clear or Almost Clear Inflammatory Lesions	12.3%	20.4%	16.1%
Absolute Change	-14.2	-18.3	-18.2
% Change	-11.8	-20.8	-21.9

The compositions were tested for cutaneous safety and tolerability. Cutaneous tolerability was assessed by burning, stinging or itching reported by the subjects. This data is summarized in FIGS. 4A, 4B, and 4C. Cutaneous safety was assessed by scaling, erythema, hypo-pigmentation and hyper-pigmentations as evaluated by the investigator. This data is summarized in FIGS. 5A, 5B, 5C, and 5D.

Table 8 reports treatment emergent adverse event characteristics.

TABLE 8

Treatment Emergent Adverse Event Characteristics			
	Combined Placebo	Composition A	Tazorac® 0.1% Cream
% Subjects Reporting Any Adverse Event	13.4%	14.7%	26.8%
% Subjects Reporting Any Serious Adverse Event	0%	0%	0%
% Subjects Discontinued Study Due to Adverse Event	0%	0%	1.4%

Notably, this clinical study showed that Composition A, containing less than half of the tazarotene active ingredient, had a numerically better efficacy than the Tazorac® 0.1% Cream. Also, the adverse event profile was lower for Composition A than for Tazorac® 0.1% Cream.

In another aspect, the present invention provides a method for treating acne. The method comprises topically applying to an affected area of the body of a subject suffering from acne any one of the compositions of the present invention, as disclosed herein, one or more times per day for a period of time sufficient to treat such acne. For example, such a period of time may be 1 to 30 days or longer as needed For

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example, such a period of time may be one week, two weeks, four weeks, eight weeks, twelve weeks, or longer as needed. For example, a composition of the present invention is applied topically to affected areas of the body once per day for 7-14 days. Alternatively, it may be applied two or three times per day for 7-14 days. Alternatively, it may be applied once per day for one week to six months. For example, it may be applied once per day for two weeks, four weeks, eight weeks, or twelve weeks. In one embodiment, the treatment may be stopped for 1-7 days (e.g., 2, 3, 4, 5, 6, or 7 days) after an extended treatment period before it is resumed for another extended treatment period. Such an extended period may be 7 days, 7-14 days, 7-21 days, 7-30 days, or longer before more treatment is needed or desired.

In yet another aspect, the present invention provides a method of treating acne topically with any of the pharmaceutical compositions of this invention, wherein the composition is applied once daily for more than 2 weeks, such as 4 weeks, for 6 weeks, for 8 weeks or for 12 weeks, without any serious adverse events, and/or with an improved adverse event profile compared to 0.1% tazarotene cream.

In yet another aspect, the present invention provides a method of treating acne topically with any of the pharmaceutical compositions of this invention, wherein the composition is applied once daily for 12 weeks, and has better clinical efficacy and a lower adverse event profile as compared to commercial compositions containing 0.1% tazarotene.

Two larger clinical studies (Studies 301 and 302) in acne patients were conducted to compare the efficacy of a composition of the present invention containing tazarotene (the "Composition A" Lotion of Table 2) to that of a placebo that was the vehicle of Composition A (i.e., without the active ingredient tazarotene).

These studies were phase-3, multi-center, randomized, double-blind, vehicle-controlled, two-arm, parallel group studies comparing the safety and efficacy of Composition A ("IDP-123 Lotion" or "Composition A Lotion") and IDP-123 vehicle lotion ("Placebo Lotion") in the treatment of acne vulgaris. Neither the acne patient nor the investigator knew the identity of the test composition assigned.

In the first study (Study 301), 813 patients were randomized to receive either Composition A Lotion or Placebo Lotion, as follows.

402 subjects receiving "Composition A Lotion,"
411 subjects receiving "Placebo Lotion."

In the second study (Study 302), 801 patients were randomized to receive either Composition A Lotion or Placebo Lotion, as follows.

397 subjects receiving "Composition A Lotion,"
404 subjects receiving "Placebo Lotion."

Primary inclusion criteria were moderate to severe acne, inflammatory lesion count of at least 20 but no more than 50, and non-inflammatory lesion count of at least 25 but no more than 100. The blindly labeled lotions were applied to the affected facial area once daily for twelve weeks, with assessments at 2 weeks, 4 weeks, 8 weeks and 12 weeks.

The investigator monitored the efficacy at each study visit by assessing the treatable area, determining the Evaluator's Global Severity Score ("EGSS"), and determining the grade of improvement. EGSS included the following grades:

Clear=0; Almost Clear=1; Mild=2; Moderate=3; Severe=4.

Clinical Efficacy was determined primarily based on: (1) superiority in absolute change from baseline to week 12 in mean inflammatory counts; (2) superiority in absolute change from baseline to week 12 in mean non-inflammatory

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counts; and (3) percentage of subjects who achieve at least a two-grade reduction from baseline and are “Clear” or “Almost Clear” at week 12 in the EGSS.

Table 9 reports Baseline Characteristics.

TABLE 9

Subject Baseline Characteristics - Inflammatory Lesions and Non-inflammatory Lesion Counts				
	Study 301		Study 302	
	Composition A Lotion N = 402 ⁽¹⁾	Placebo Lotion N = 411 ⁽¹⁾	Composition A Lotion N = 397 ⁽¹⁾	Placebo Lotion N = 404 ⁽¹⁾
Inflammatory Lesions				
Mean (SD)	28.5(7.04)	28.1 (7.04)	28.0 (7.32)	27.9 (7.10)
Median	26.0	26.0	26.0	26.0
Non-inflammatory Lesions				
Mean (SD)	41.1 (15.67)	40.7 (16.29)	41.8 (17.87)	40.6 (16.31)
Median	36.0	34.0	36.0	35.0

Table 10 reports treatment % success at week 12 on an intention-to-treat (ITT) basis.

TABLE 10

EGSS (Clear or Almost Clear) at Week 12 (ITT)				
	Study 301		Study 302	
	Composition A Lotion N = 402	Placebo Lotion N = 411	Composition A Lotion N = 397	Placebo Lotion N = 404
Week 12	25.5% (p < 0.001)	13.0%	29.6% (p < 0.001)	17.3

Table 11 reports absolute changes in inflammatory and non-inflammatory lesions from baseline at week 12.

TABLE 11

Inflammatory and Non-Inflammatory Lesions Absolute Changes from Baseline at Week 12				
	Study 301		Study 302	
	Composition A Lotion N = 402	Placebo Lotion N = 411	Composition A Lotion N = 397	Placebo Lotion N = 404
Inflammatory Lesions	-15.6 (p < 0.001)	-12.4	-16.7 (p < 0.001)	-13.4
Non-inflammatory Lesions	-21.0 (p < 0.001)	-16.4	-24.6 (p < 0.001)	-16.6

Table 12 reports assessment of treatment success on a per-protocol basis for EGSS. For lesions, absolute changes from baseline to week 12 in mean inflammatory and non-inflammatory counts are reported.

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TABLE 12

Treatment Success (Per-Protocol Basis)				
	Study 301		Study 302	
	Composition A Lotion N = 402	Placebo Lotion N = 411	Composition A Lotion N = 397	Placebo Lotion N = 404
EGSS - Clear or Almost Clear	26.8%	14.4%	30.6%	18.3%
Inflammatory Lesions	-15.8	-12.4	-16.4	-13.4
Non-inflammatory Lesions	-21.3	-16.3	-24.1	-15.4

The compositions were tested for cutaneous safety and tolerability. Cutaneous tolerability was assessed by itching, burning, or stinging reported by the subjects. Cutaneous safety was assessed by scaling, erythema, hypo-pigmentation, and hyper-pigmentations, as evaluated by the investigator.

Table 13 shows the number of subjects reporting moderate or severe itching, burning, or stinging; or being observed to have moderate or severe scaling, erythema, hypopigmentation, or hyperpigmentation. In general, the reported numbers of these conditions are similar between those subjects using Composition A Lotion and Placebo Lotion.

TABLE 13

Cutaneous Safety and Tolerability				
	Study 301		Study 302	
	Composition A Lotion N = 387	Placebo Lotion N = 392	Composition A Lotion N = 392	Placebo Lotion N = 399
Scaling				
Moderate	4	2	6	1
Severe	0	0	1	0
Erythema				
Moderate	7	8	13	6
Severe	0	0	1	0
Hypopigmentation				
Moderate	1	1	0	0
Severe	0	0	0	0
Hyperpigmentation				
Moderate	7	9	8	17
Severe	1	2	0	1
Itching				
Moderate	4	2	4	4
Severe	0	0	0	0
Burning				
Moderate	2	0	5	0
Severe	0	0	2	0
Stinging				
Moderate	1	1	3	0
Severe	0	0	1	0

Table 13 reports treatment emergent adverse event characteristics.

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TABLE 13

Treatment Emergent Adverse Event Characteristics				
	Study 301		Study 302	
	Composition A Lotion N = 392 ⁽¹⁾	Placebo Lotion N = 399 ⁽¹⁾	Composition A Lotion N = 387 ⁽¹⁾	Placebo Lotion N = 392 ⁽¹⁾
% Subjects Reporting Any Adverse Event	25.5%	19.5%	28.2%	18.6%
% Subjects Reporting Any Serious Adverse Event	0.8%	0.8%	0.3%	0.3%
% Subjects Discontinued Study Due to Adverse Event	3.1%	0.5%	2.6%	0.5%

Note:

⁽¹⁾safety population, which comprises all randomized subjects who were presumed to have used the study drug at least once and who provided at least one post-baseline safety evaluation.

Notably, these clinical studies showed that the percentages of subjects reporting any serious adverse event for Composition A are no higher than those for the Placebo Lotion, indicating the excellent safety of Composition A.

The treatment success, as measured by investigator's global assessment of Composition A Lotion (denoted as "EGSS" above) and some commercial products containing a retinoid (as gleaned from their package inserts) is shown in Table 14.

TABLE 14

Comparison of Treatment Success of Various Products Containing a Retinoid			
		Number of Subjects	Treatment Success (%)
Tazarotene Products	Composition A Lotion, 0.045% tazarotene	402	25.5
	Tazorac Cream, 0.1% tazarotene	397	29.6
		218	18
		206	20
	Fabior Foam, 0.1% tazarotene	371	29
Tretinoin Products		373	28
	Altreno Lotion, 0.05% tretinoin	406	16.5
		413	19.8
	Atralin Gel, 0.05% tretinoin	375	21
Adapalene Products		299	23
	Adapalene Gel, 0.3%	258	21
	Adapalene Gel, 0.1%	261	16
	Adapalene Lotion, 0.1%	533	26.3
		535	24.1
	Epiduo Gel, 0.1% adapalene/2.5% benzoyl peroxide	149	21.5
		415	30.1
	0.1% Adapalene in Epiduo vehicle	148	12.2
		420	19.8

Surprisingly, Composition A Lotion achieved at least similar or higher success rate than other products that contain at least twice the concentration of the active ingredient.

In another aspect, the present invention provides a method for treating acne vulgaris (acne). The method comprises topically applying to an affected area of the body of a subject suffering from acne any one of the compositions of the present invention, as disclosed herein, one or more (such as 1, 2, 3, or more) times per day for a period of time sufficient to treat such acne vulgaris. For example, such a period of time may be 1 to 30 days or longer as needed. For example,

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such a period of time may be one week, two weeks, four weeks, eight weeks, twelve weeks, or longer as needed. For example, a composition of the present invention is applied topically to affected areas of the body once per day for 7-14 days. Alternatively, it may be applied two or three times per day for 7-14 days. Alternatively, it may be applied once per day for one week to six months. For example, it may be applied once per day for two weeks, four weeks, eight weeks, or twelve weeks. In one embodiment, the treatment may be stopped for 1-7 days (e.g., 2, 3, 4, 5, 6, or 7 days) after an extended treatment period before it is resumed for another extended treatment period. Such an extended period may be 7 days, 7-14 days, 7-21 days, 7-30 days, or longer before more treatment is needed or desired.

In yet another aspect, the present invention provides a method of treating acne vulgaris topically with any of the pharmaceutical compositions of this invention, wherein the composition is applied once daily for more than 2 weeks, such as 4 weeks, for 6 weeks, for 8 weeks or for 12 weeks, without any serious adverse events, and/or with an improved adverse event profile compared to 0.1% tazarotene cream.

In yet another aspect, the present invention provides a method of treating acne vulgaris topically with any of the pharmaceutical compositions of this invention, wherein the composition is applied once daily for 12 weeks, and has better clinical efficacy and a lower adverse event profile as compared to commercial compositions containing 0.1% tazarotene (Tazorac® Cream).

While the present disclosure shows and describes a number of exemplary embodiments, it will be manifest to those skilled in the art that various further modifications may be made without departing from the spirit and scope of the underlying inventive concept and that the same is not limited to particular compositions, processes, methods, or structures herein shown and described.

What is claimed is:

1. A method of treating acne vulgaris, the method comprising topically applying a pharmaceutical composition once per day to an affected area of a body of a subject suffering from acne vulgaris, wherein:

the composition comprises tazarotene at a concentration of about 0.045 percent by weight of the composition as a sole active pharmaceutical ingredient

the composition is an oil-in-water emulsion lotion comprising an oil phase and an aqueous phase;

the oil phase comprises a dicarboxylic acid ester and a mineral oil at a total concentration of 10-12 percent by weight of the composition;

the aqueous phase comprises water and a carbomer homopolymer, wherein the concentration of the carbomer homopolymer is 0.5-0.7 percent by weight of the composition; and

the composition further comprises a polymeric emulsifier at a concentration of 0.3-0.5 percent by weight of the composition.

2. The method of claim 1, wherein the dicarboxylic acid ester in the oil phase is diethyl sebacate.

3. The method of claim 1, wherein the oil phase comprises diethyl sebacate and light mineral oil.

4. The method of claim 1, wherein said applying is carried out for at least eight weeks.

5. The method of claim 1, wherein said applying is carried out for at least twelve weeks.

6. The method of claim 1, wherein said applying is carried out for twelve weeks.

7. The method of claim 1, wherein the tazarotene is in solution in the oil phase of the oil-in-water emulsion lotion.

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8. The method of claim 1, wherein the composition has a pH of about 4 to about 6.

9. The method of claim 1, wherein the composition consists essentially of:

0.045 weight % tazarotene;
diethyl sebacate;
light mineral oil;
sorbitan monooleate;
sorbitol solution, 70%;
methylparaben;
propylparaben;
edetate disodium dihydrate;
carbomer polymer type B;
carbomer homopolymer type A;
sodium hydroxide;
purified water.

10. The method of claim 1, wherein the composition consists essentially of:

0.045 weight % tazarotene;
2.5-3.5 weight % diethyl sebacate;
7.5-8.5 weight % light mineral oil;
0.05-0.2 weight % sorbitan monooleate;
10-11 weight % sorbitol solution, 70%;
0.1-0.2 weight % methylparaben;

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0.02-0.04 weight % propylparaben;
0.03-0.06 weight % edetate disodium dihydrate;
0.3-0.5 weight % carbomer polymer type B;
0.5-0.7 weight % carbomer homopolymer type A;
sodium hydroxide, q.s. to pH 5.5±0.5; and
purified water, q.s. to 100 weight %.

11. A method of treating acne vulgaris, the method comprising topically applying a pharmaceutical composition to an affected area of a body of a subject suffering from acne vulgaris; wherein the composition consists essentially of:

0.045 weight % tazarotene;
2.97 weight % diethyl sebacate;
8.03 weight % light mineral oil;
0.1 weight % sorbitan monooleate;
10.7 weight % sorbitol solution, 70%;
0.17 weight % methylparaben;
0.03 weight % propylparaben;
0.05 weight % edetate disodium dihydrate;
0.4 weight % carbomer polymer type B;
0.6 weight % carbomer homopolymer type A;
sodium hydroxide, q.s. to pH 5.5±0.5; and
purified water, q.s. to 100 weight %.

* * * * *

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. (SEE INSTRUCTIONS ON NEXT PAGE OF THIS FORM.)

I. (a) PLAINTIFFS

BAUSCH HEALTH IRELAND LIMITED; BAUSCH HEALTH US, LLC; and
BAUSCH HEALTH AMERICAS INC.

(b) County of Residence of First Listed Plaintiff Ireland
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorneys (Firm Name, Address, and Telephone Number)

William P. Deni, Jr.
Gibbons P.C., One Gateway Center, Newark, NJ 07102
973-596-4853; wdeni@gibbonslaw.com

DEFENDANTS

PADAGIS ISRAEL PHARMACEUTICALS LTD.; PADAGIS US LLC; and
PADAGIS LLC

County of Residence of First Listed Defendant Israel
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF
THE TRACT OF LAND INVOLVED.

Attorneys (If Known)

II. BASIS OF JURISDICTION (Place an "X" in One Box Only)

- ☐ 1 U.S. Government Plaintiff
☒ 3 Federal Question (U.S. Government Not a Party)
☐ 2 U.S. Government Defendant
☐ 4 Diversity (Indicate Citizenship of Parties in Item III)

III. CITIZENSHIP OF PRINCIPAL PARTIES (Place an "X" in One Box for Plaintiff and One Box for Defendant)

- | | PTF | DEF | | PTF | DEF |
|---|----------------------------|----------------------------|---|----------------------------|----------------------------|
| Citizen of This State | ☐ 1 | ☐ 1 | Incorporated or Principal Place of Business In This State | ☐ 4 | ☐ 4 |
| Citizen of Another State | ☐ 2 | ☐ 2 | Incorporated and Principal Place of Business In Another State | ☐ 5 | ☐ 5 |
| Citizen or Subject of a Foreign Country | ☐ 3 | ☐ 3 | Foreign Nation | ☐ 6 | ☐ 6 |

IV. NATURE OF SUIT (Place an "X" in One Box Only)

Click here for: [Nature of Suit Code Descriptions.](#)

CONTRACT	TORTS	FORFEITURE/PENALTY	BANKRUPTCY	OTHER STATUTES
☐ 110 Insurance ☐ 120 Marine ☐ 130 Miller Act ☐ 140 Negotiable Instrument ☐ 150 Recovery of Overpayment & Enforcement of Judgment ☐ 151 Medicare Act ☐ 152 Recovery of Defaulted Student Loans (Excludes Veterans) ☐ 153 Recovery of Overpayment of Veteran's Benefits ☐ 160 Stockholders' Suits ☐ 190 Other Contract ☐ 195 Contract Product Liability ☐ 196 Franchise	PERSONAL INJURY ☐ 310 Airplane ☐ 315 Airplane Product Liability ☐ 320 Assault, Libel & Slander ☐ 330 Federal Employers' Liability ☐ 340 Marine ☐ 345 Marine Product Liability ☐ 350 Motor Vehicle ☐ 355 Motor Vehicle Product Liability ☐ 360 Other Personal Injury ☐ 362 Personal Injury - Medical Malpractice PERSONAL INJURY ☐ 365 Personal Injury - Product Liability ☐ 367 Health Care/Pharmaceutical Personal Injury Product Liability ☐ 368 Asbestos Personal Injury Product Liability PERSONAL PROPERTY ☐ 370 Other Fraud ☐ 371 Truth in Lending ☐ 380 Other Personal Property Damage ☐ 385 Property Damage Product Liability	☐ 625 Drug Related Seizure of Property 21 USC 881 ☐ 690 Other LABOR ☐ 710 Fair Labor Standards Act ☐ 720 Labor/Management Relations ☐ 740 Railway Labor Act ☐ 751 Family and Medical Leave Act ☐ 790 Other Labor Litigation ☐ 791 Employee Retirement Income Security Act IMMIGRATION ☐ 462 Naturalization Application ☐ 465 Other Immigration Actions	☐ 422 Appeal 28 USC 158 ☐ 423 Withdrawal 28 USC 157 PROPERTY RIGHTS ☐ 820 Copyrights ☐ 830 Patent ☒ 835 Patent - Abbreviated New Drug Application ☐ 840 Trademark SOCIAL SECURITY ☐ 861 HIA (1395ff) ☐ 862 Black Lung (923) ☐ 863 DIWC/DIWW (405(g)) ☐ 864 SSID Title XVI ☐ 865 RSI (405(g)) FEDERAL TAX SUITS ☐ 870 Taxes (U.S. Plaintiff or Defendant) ☐ 871 IRS—Third Party 26 USC 7609	☐ 375 False Claims Act ☐ 376 Qui Tam (31 USC 3729(a)) ☐ 400 State Reapportionment ☐ 410 Antitrust ☐ 430 Banks and Banking ☐ 450 Commerce ☐ 460 Deportation ☐ 470 Racketeer Influenced and Corrupt Organizations ☐ 480 Consumer Credit ☐ 485 Telephone Consumer Protection Act ☐ 490 Cable/Sat TV ☐ 850 Securities/Commodities/Exchange ☐ 890 Other Statutory Actions ☐ 891 Agricultural Acts ☐ 893 Environmental Matters ☐ 895 Freedom of Information Act ☐ 896 Arbitration ☐ 899 Administrative Procedure Act/Review or Appeal of Agency Decision ☐ 950 Constitutionality of State Statutes
REAL PROPERTY ☐ 210 Land Condemnation ☐ 220 Foreclosure ☐ 230 Rent Lease & Ejectment ☐ 240 Torts to Land ☐ 245 Tort Product Liability ☐ 290 All Other Real Property	CIVIL RIGHTS ☐ 440 Other Civil Rights ☐ 441 Voting ☐ 442 Employment ☐ 443 Housing/Accommodations ☐ 445 Amer. w/Disabilities - Employment ☐ 446 Amer. w/Disabilities - Other ☐ 448 Education PRISONER PETITIONS Habeas Corpus: ☐ 463 Alien Detainee ☐ 510 Motions to Vacate Sentence ☐ 530 General ☐ 535 Death Penalty Other: ☐ 540 Mandamus & Other ☐ 550 Civil Rights ☐ 555 Prison Condition ☐ 560 Civil Detainee - Conditions of Confinement			

V. ORIGIN (Place an "X" in One Box Only)

- ☒ 1 Original Proceeding
☐ 2 Removed from State Court
☐ 3 Remanded from Appellate Court
☐ 4 Reinstated or Reopened
☐ 5 Transferred from Another District (specify)
☐ 6 Multidistrict Litigation - Transfer
☐ 8 Multidistrict Litigation - Direct File

VI. CAUSE OF ACTION

Cite the U.S. Civil Statute under which you are filing (Do not cite jurisdictional statutes unless diversity):
35 U.S.C. § 271

Brief description of cause:
Patent infringement (ANDA)

VII. REQUESTED IN COMPLAINT:

☐ CHECK IF THIS IS A CLASS ACTION UNDER RULE 23, F.R.Cv.P. DEMAND \$

CHECK YES only if demanded in complaint:

JURY DEMAND: ☐ Yes ☒ No

VIII. RELATED CASE(S) IF ANY

(See instructions):

JUDGE

DOCKET NUMBER

DATE

06/24/2022

SIGNATURE OF ATTORNEY OF RECORD

s/ William P. Deni, Jr.

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RECEIPT #

AMOUNT

APPLYING IFP

JUDGE

MAG. JUDGE

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Attorneys for Plaintiffs

**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

BAUSCH HEALTH IRELAND LIMITED;
BAUSCH HEALTH US, LLC; and
BAUSCH HEALTH AMERICAS INC.,

Plaintiffs,

v.

PADAGIS ISRAEL PHARMACEUTICALS
LTD.; PADAGIS US LLC; and
PADAGIS LLC,

Defendants.

Civil Action No. 22-4248

Document Electronically Filed

**CERTIFICATION PURSUANT TO
LOCAL CIVIL RULE 11.2**

Pursuant to Local Civil Rule 11.2, the undersigned, attorney of record for Plaintiffs, hereby certifies that to the best of my knowledge and based upon the information available to me, the matter in controversy is not the subject of any other action pending in any court or of any pending arbitration or administrative proceeding.

Dated: June 24, 2022
Newark, New Jersey

s/ William P. Deni, Jr.
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