TOPICAL FORMULATIONS OF DUAL PI3K/MTOR INHIBITORS

The present invention relates to topical compositions comprising compounds of Formula (I) as defined herein. The invention also relates to uses of said topical compositions for the treatment of diseases or disorders alleviated by inhibition of PI3K and/or mTOR in a subject, preferably in a human, and particularly, for the treatment of skin lesions and/or skin disorders.

RELATED ART

Mammalian target of rapamycin (mTOR) is a large serine/threonine specific protein kinase which can combine with protein binding partners to form one of two functionally distinct mTOR complexes, mTORC1 and mTORC2, which regulate different cellular processes. mTOR can be inhibited by either inhibition of upstream kinases such as PI3K and/or AKT or by directly inhibiting the mTOR kinase either allosterically (e.g., by rapamycin) or by ATP site directed inhibitors (Saxton RA, Sabatini DM *Cell*, (2017) 168:960-976).

There is evidence that PI3K/mTOR signaling plays a role in the development of skin disease. For example, PI3K/mTOR signaling has been implicated in non-melanoma skin cancer (NMSC), in particular in the development of actinic keratosis (AK) and cutaneous squamous cell carcinoma (cSCC) (Ayli EE *et al.*, *J. Cutaneous Pathology* (2008) 35:273-277). Recent advances in the understanding of the mTOR signaling pathway and its downstream effects in vascular proliferation have further broadened the clinical applications of mTOR inhibitors to many challenging genodermatoses such as tuberous sclerosis complex, pachyonychia congenita, complex vascular anomalies, and inflammatory dermatoses (A. L. Fogel *et al.*, *J. Am. Acad. Dermatol.*, (2015) 72:879-89 and references cited therein).

Bimiralisib is a dual PI3K/mTOR inhibitor that has shown activity in mouse models of skin disorders such as AK and cSCC (WO 2017/198347).

In humans and pigs, the stratum corneum (SC) is the outermost layer of the epidermis. It forms a protective barrier comprising dead tissue. When topical formulations of drugs are applied, the SC can act as a reservoir, sequestering the active agent of the topical formulations and thus limiting its ability to penetrate to deeper layers of the skin such as the epidermis and dermis. This can limit the effectiveness of such topical drug formulations.

WO 2019/087158 teaches a formulation comprising an oxazolidin-2-one-pyrimidine

compound. However, attempts to prepare topical galenic compositions comprising this compound faced difficulties because it showed limited solubility, and solubility is an important factor influencing drug loading. Moreover, the compound was found to be unstable in the presence of solvents such as PEG400 (WO 2019/087158). Accordingly, the topical pharmaceutical compositions taught in WO 2019/087158 only contained up to 0.3% of active compound, and only provided a skin concentration of 1.12 µg/g even after once daily application for two weeks in a minipig study. Notably, the value of 1.12 µg/g was obtained without prior removal of the stratum corneum, and thus represents the drug concentration in the skin including the concentration in the stratum corneum, which as noted above can act as a reservoir to sequester active agents away from, e.g., the epidermis and dermis. Accordingly, there is a need for clinically acceptable topical formulations of PI3K and/or dual PI3K/mTOR inhibitors that can penetrate through the stratum corneum to the epidermis and dermis of human skin.

SUMMARY OF THE INVENTION

The present invention relates to topical pharmaceutical compositions comprising a compound of Formula (I). As set forth below, it was discovered that the inventive topical pharmaceutical compositions comprise mixtures of solvents and excipients (e.g., polyethylene glycol and diethylene glycol monoethyl ether) that are surprisingly able to dissolve increased amounts of compounds of Formula (I) in a synergistic manner. Accordingly, greater amounts of compounds of Formula (I) were able to be dissolved in the inventive topical pharmaceutical compositions than would have been predicted based on the solubility of the compounds of Formula (I) in the individual solvents and excipients alone. The resulting increased solubility of the compounds of Formula (I) in the inventive topical pharmaceutical concentrations helped contribute to greater skin penetration of the compounds of Formula (I) in human skin and pig skin models. Without wishing to be bound by theory, the increased penetration of compounds of Formula (I) through the stratum corneum and into the epidermis and dermis is expected to enable more favorable clinical outcomes in patients with skin lesions including AK and cSCC. Moreover, the compounds of Formula (I) were found to be stable under most accelerated degradation conditions. The compounds of Formula (I) were also found to be stable under accelerated degradation conditions when formulated in the inventive topical pharmaceutical compositions disclosed herein.

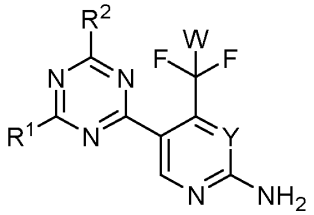
Also surprisingly, other formulations tested were not able to dissolve increased

amounts of compounds of Formula (I) in a synergistic manner. For example, a composition comprising less than 50% of a polyethylene glycol (e.g., less than 45%, less than 30% polyethylene glycol) was able to dissolve less of a compound of Formula (I) than would have been expected based on the solubility of the compound of Formula (I) in the individual solvents and excipients alone.

Additional features and advantages of the technology are described in the Detailed Description, below.

In one aspect, the present invention provides a topical pharmaceutical composition comprising:

at least 0.1 weight percent of a compound of Formula (I):



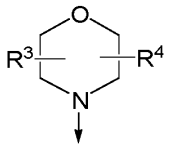
Formula (I)

wherein:

W is H or F;

Y is N or CH;

R^1 and R^2 are independently of each other a morpholinyl of Formula (II)



Formula (II)

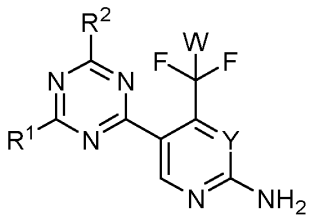
wherein R^3 and R^4 are independently of each other H or C_1-C_3alkyl, or R^3 and R^4 combine to form a bivalent C_1-C_3alkylene residue;

at least 30 weight percent polyalkylene glycol, preferably at least 45 weight percent polyalkylene glycol; and

at least 10 weight percent diethylene glycol monoethyl ether, preferably at least 15 weight percent diethylene glycol monoethyl ether.

In one aspect, the present invention provides a topical pharmaceutical composition comprising:

at least 0.3 weight percent of a compound of Formula (I):



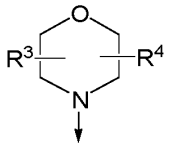
Formula (I)

wherein:

W is H or F;

Y is N or CH;

R^1 and R^2 are independently of each other a morpholinyl of Formula (II)



Formula (II)

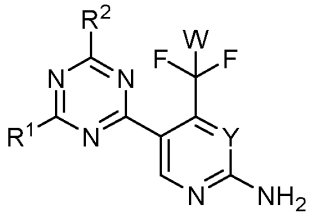
wherein R^3 and R^4 are independently of each other H or C_1-C_3alkyl, or R^3 and R^4 combine to form a bivalent C_1-C_3alkylene residue;

at least 30 weight percent polyalkylene glycol, preferably at least 45 weight percent polyalkylene glycol; and

at least 10 weight percent diethylene glycol monoethyl ether, preferably at least 15 weight percent diethylene glycol monoethyl ether.

In one aspect, the present invention provides a topical pharmaceutical composition comprising:

at least 0.5 weight percent of a compound of Formula (I):



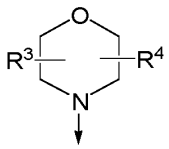
Formula (I)

wherein:

W is H or F;

Y is N or CH;

R^1 and R^2 are independently of each other a morpholinyl of Formula (II)



Formula (II)

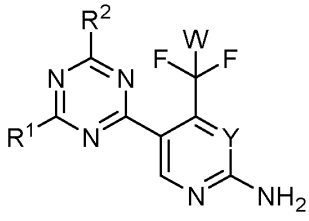
wherein R^3 and R^4 are independently of each other H or C_1-C_3alkyl, or R^3 and R^4 combine to form a bivalent C_1-C_3alkylene residue;

at least 30 weight percent polyalkylene glycol, preferably at least 45 weight percent polyalkylene glycol; and

at least 10 weight percent diethylene glycol monoethyl ether, preferably at least 15 weight percent diethylene glycol monoethyl ether.

In one aspect, the present invention provides a topical pharmaceutical composition comprising:

at least 0.9 weight percent of a compound of Formula (I):



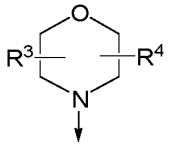
Formula (I)

wherein:

W is H or F;

Y is N or CH;

R^1 and R^2 are independently of each other a morpholinyl of Formula (II)



Formula (II)

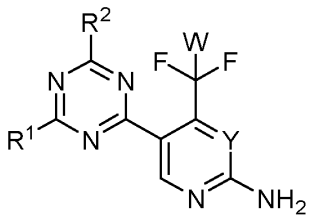
wherein R^3 and R^4 are independently of each other H or C_1-C_3alkyl, or R^3 and R^4 combine to form a bivalent C_1-C_3alkylene residue;

at least 45 weight percent polyalkylene glycol; and

at least 15 weight percent diethylene glycol monoethyl ether.

In one aspect, the present invention provides a topical pharmaceutical composition comprising:

at least 1.5 weight percent of a compound of Formula (I):



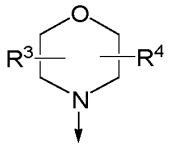
Formula (I)

wherein:

W is H or F;

Y is N or CH;

R^1 and R^2 are independently of each other a morpholinyl of Formula (II)



Formula (II)

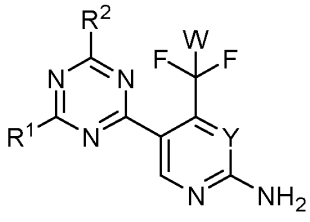
wherein R^3 and R^4 are independently of each other H or C_1-C_3alkyl, or R^3 and R^4 combine to form a bivalent C_1-C_3alkylene residue;

at least 45 weight percent polyalkylene glycol; and

at least 15 weight percent diethylene glycol monoethyl ether.

In one aspect, the present invention provides a topical pharmaceutical composition comprising:

at least 1.9 weight percent of a compound of Formula (I):



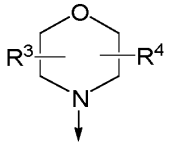
Formula (I)

wherein:

W is H or F;

Y is N or CH;

R^1 and R^2 are independently of each other a morpholinyl of Formula (II)



Formula (II)

wherein R^3 and R^4 are independently of each other H or C_1-C_3alkyl, or R^3 and R^4

combine to form a bivalent C_1-C_3alkylene residue;

at least 45 weight percent polyalkylene glycol; and

at least 15 weight percent diethylene glycol monoethyl ether.

In one aspect, the present invention provides a topical pharmaceutical composition as described herein for use in a method of treating a skin lesion or skin disorder in a subject, preferably wherein said skin lesion or skin disorder is actinic keratosis (AK).

DESCRIPTION OF THE FIGURES

FIG 1 is a schematic of the static Franz cell used to assess the release profile of Compound 1 across a synthetic cellulose membrane for the ten experimental formulations tested in Example 3.

FIG 2 is a plot of the mean cumulative amount of Compound 1 released per unit area ($\mu g/cm^2$) between one and seven hours from ten formulations tested in Example 3 across a synthetic cellulose membrane into a receiver fluid (2% Brij® in 50/50 ethanol/water). Data is presented as mean ± standard deviation (n=6). The top-to-bottom order of the formulation labels on the right-hand legend is the same as the top-to-bottom order of the cumulative amount of Compound 1 released after $(2.65)^2$ hours, i.e., the highest amount of Compound 1 was released by NA03, and the lowest amount was released by AG18.

FIG 3 is a schematic of the diffusion cell used to test the *ex vivo* skin penetration of selected formulations as described in Example 4.

FIG 4 is a plot of the amount of Compound 1 recovered from human skin (epidermis and dermis) as set forth in Example 4.

FIG 5 is a schematic showing where the tested formulations were applied on the back of a domestic pig as described in Example 5.

FIG 6 is a plot of the mean tissue concentration (± SD; n = 6) after *in vivo* administration to a domestic pig of 11 tested formulations as a function of time as described in Example 5.

FIG 7 is a bar graph showing the total amount of Compound 1 isolated from domestic pig skin biopsies after *in vivo* administration of 11 tested formulations, integrated over the timepoints 6, 9, and 12 hours.

FIG 8 is a schematic showing where the tested formulations were applied on the back of a domestic pig as described in Example 6.

FIG 9 shows the averaged (mean ± SEM) concentrations of Compound 1 in the skin of

a domestic pig after application of all formulations, and integrated over all time points (6h, 9h, 12 h).

FIG 10 is a schematic of the design of the clinical trial protocol described in Example 7.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to topical pharmaceutical compositions comprising a compound of Formula (I). The inventive topical pharmaceutical compositions comprise mixtures of solvents and excipients (e.g., at least 45 weight percent polyalkylene glycol and at least 15 weight percent diethylene glycol monoethyl ether) that are able to dissolve increased amounts of compounds of Formula (I) in a synergistic manner. In other words, compositions comprising at least 45 weight percent polyalkylene glycol (e.g., polyethylene glycol) and at least 15 weight percent diethylene glycol monoethyl ether were able to dissolve greater amounts of compounds of Formula (I) than would have been expected based on the solubility of the compounds of Formula (I) in the individual solvents and excipients alone. Surprisingly, other formulations tested were not able to dissolve increased amounts of compounds of Formula (I) in a synergistic manner, and in some cases even dissolved less of a compound of Formula (I) than would have been predicted based on the solubility of the compound of Formula (I) in the individual solvents and excipients alone.

As set forth in the examples, the formulation NA03 was expected to dissolve 1.85 g Compound 1 per 100 g of total formulation based on the solubility of Compound 1 in the individual solvents and excipients comprising NA03. Surprisingly, NA03 was capable of dissolving up to 7.88 g Compound 1. This represents a synergistic solubility factor of 4.26. Similarly, the formulation AG20 was expected to dissolve 1.89 g Compound 1 per 100 g of total formulation based on the solubility of Compound 1 in the individual solvents and excipients comprising AG20. Surprisingly, AG20 was capable of dissolving up to 4 g compound 1. This represents a synergistic solubility factor of 2.11.

In contrast, the formulation CR01, which comprises less than 45% (wt/wt) PEG 400, was expected to dissolve 1.7 g Compound 1 per 100 g of total formulation based on the solubility of Compound 1 in the individual solvents and excipients comprising CR01. However, CR01 was only capable of dissolving up to 1.375 g Compound 1 per 100 g of total formulation. This represents a solubility factor of 0.8.

The resulting increased solubility of the compounds of Formula (I) in the inventive

topical pharmaceutical concentrations helped contribute to greater skin penetration of the compounds of Formula (I) through the stratum corneum and into the epidermis and dermis in human skin and pig skin models. For instance, as further shown in the examples and figures, the non-aqueous gel (NA03) showed the fastest release rate of Compound 1 through a synthetic membrane, which represented an approximately 2- to 5-fold increase over all other tested formulations. The formulations AG20, EG01, and AG21 all had statistically the same release rates and were the next-highest ranked formulations for release rate after NA03.

Similarly, as further shown in the examples and figures, in an *ex vivo* experiment using a pig skin model, the formulation NA03 delivered 1.7 to 17-fold more Compound 1 to the epidermis compared with all other tested formulations. Formulation NA03 was also the third-highest ranked formulation for dermal delivery. Formulations AG20 and AG21 delivered the highest amount of Compound 1 to both the dermis and epidermis of the tested aqueous gels.

As further shown in the examples and figures, in an *in vivo* experiment using a live pig, formulations NA03 and AG20 gave the highest concentrations of Compound 1 in the skin of the experimental compounds tested. As shown in FIG 7, when integrated over the three timepoints tested (i.e., 6 h, 9 h and 12 h), the formulations NA03 and AG20 delivered an amount of Compound 1 above the IC_{90} for phosphoS6 inhibition after a single application.

As further shown in the examples and figures, the formulation NA03 (containing 6.3% wt/wt Compound 1) delivered a clinically effective dose (i.e., above the IC_{90} for phosphoS6 inhibition) after a single application to the skin even when applied in small amounts (e.g., at applications as low as 1.0 mg/cm^2). Even when the formulation NA03 contained lower concentrations of Compound 1 (e.g., as low as 2%), it was still able to deliver clinically relevant amounts of Compound 1 after a single application.

Moreover, the compounds of Formula (I) were found to be stable under forced degradation conditions designed to accelerate degradation. As shown in Table 4, compound 1 was stable under all conditions tested except for 0.1N HCl at 90 °C.

Without wising to be bound by theory, and as described in the Examples below, the increased penetration of compounds of Formula (I) through the stratum corneum and into the epidermis and dermis enabled more favorable clinical outcomes in patients with skin lesions and/or skin disorders including AK and cSCC and genodermatoses.

Definitions

The term “about” as used herein shall have the meaning of +/- 10%. For example, about

50% shall mean 45% to 55%. Preferably, the term “about” as used herein shall have the meaning of +/- 5%. For example, about 50% shall mean 47.5% to 52.5%. In a preferred embodiment, said term “about” refers to any value of a range of and between - 10% and +10% of the value it refers to. In a preferred embodiment, said term “about” refers to any value of a range of and between - 8% and +8% of the value it refers to. In a preferred embodiment, said term “about” refers to any value of and between a range of - 7% and +7% of the value it refers to. In a preferred embodiment, said term “about” refers to any value of and between a range of - 5% to +5% of the value it refers to. In a preferred embodiment, said term “about” refers to any value of and between a range of - 4% and +4% of the value it refers to. In a preferred embodiment, said term “about” refers to any value of and between a range of - 3% and +3% of the value it refers to. In a preferred embodiment, said term “about” refers to any value of and between a range of - 2% and +2% of the value it refers to. In a preferred embodiment, said term “about” refers to any value of and between a range of - 1% and +1% of the value it refers to. In some embodiments, the term “about” refers to the exact value stated.

The phrase "between value X and value Y", as used herein, shall refer to include the value X and the value Y and any value in between. For example, the phrase "between 0.01 mg and 50 mg” refers to 0.01 mg and 50 mg and any value in between. The same applies to the phrase "between about value X and about value Y” taking further the variations of the term “about” into account. Analogously, the phrase "from value X to value Y", as used herein, shall refer to include the value X and the value Y and any value in between. For example, the phrase "between 65% and 75%” refers to 65% and 75% and any value in between. The same applies to the phrase "from about value X to about value Y” taking further the variations of the term “about” into account.

The term “% (w/w)”, “% (wt/wt)” or “weight percent,” as used herein refers to (mass of the component / total mass of the composition) x 100. By way of example, 70 wt% PEG400 is 70 g PEG400 per 100 g of the composition.

When the terms "a," or "an" are used herein, they mean "at least one" unless indicated otherwise.

As used herein, the term "topically" and "topical" refers to application of the composition of the present invention to the surface of the skin of a subject, preferably of a human, and thus, the term "topical administration", as used herein, refers to administration to the skin of a subject, preferably of a human, preferably for the treatment of a skin lesion.

As used herein the term "topical composition" refers to a composition that is suitable

for topical administration and may be applied to skin of a subject, preferably of a human.

As used herein, the terms “treatment”, “treat”, “treated” or “treating” refer to prophylaxis and/or therapy. In one embodiment, the terms “treatment”, “treat”, “treated” or “treating” refer to a therapeutic treatment. In another embodiment, the terms “treatment”, “treat”, “treated” or “treating” refer to a prophylactic treatment. Preferably, beneficial or desired clinical results of said treatment include, but are not limited to, alleviation of symptoms, diminishment of extent of disease or disorder, stabilized (*i.e.*, not worsening) state of disease or disorder, delay or slowing of disease or disorder progression, amelioration or palliation of the disease or disorder state.

As used herein, the term “effective amount” refers to an amount necessary or sufficient to realize a desired biologic effect. Preferably, the term “effective amount” refers to an amount of a compound of Formula (I) of the present invention that (i) treats or prevents the particular disease or disorder, (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular disease or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease or disorder, described herein. An effective amount of the inventive compound of Formula (I), or said topical composition or said pharmaceutical composition, would be the amount that achieves this selected result, and such an amount could be determined as a matter of routine by a person skilled in the art. Further preferably, the term “effective amount”, as used herein, refers to an amount necessary or sufficient to inhibit PI3K and/or mTOR (e.g., to inhibit 50%, 90%, or more of the activity of PI3K and/or mTOR). The effective amount can vary depending on the particular composition being applied and the size of the subject. One of ordinary skill in the art can empirically determine the effective amount of a particular the inventive compound of Formula (I), or said topical composition or said pharmaceutical composition of the present invention without necessitating undue experimentation.

The term "mammal", as used herein, includes, but is not limited to, humans, mice, rats, guinea pigs, monkeys, dogs, cats, horses, cows, pigs, and sheep. The term "mammal", as used herein, preferably refers to humans. The term “subject”, as used herein, includes, but is not limited to, humans and mammals. The term "subject", as used herein, preferably refers to humans.

The term “AG” stands for aqueous gel. Formulations described herein starting with the letters AG are understood as aqueous gels. An aqueous gel as used herein is understood as a topical pharmaceutical composition in the form of a gel and that comprises at least 5%

water (wt/wt), preferably at least 9% water (wt/wt).

The term "EG" stands for emulsified gel. Formulations described herein starting with the letters EG are understood as emulsified gels.

The term "NA" stands for non-aqueous gel. Formulations described herein starting with the letters NA are understood as non-aqueous gels. A non-aqueous gel as used herein is understood as a topical pharmaceutical composition in the form of a gel that is substantially anhydrous.

As used herein, the term "substantially anhydrous" is understood to mean that the topical pharmaceutical composition has no added water, and that solvents and excipients used to prepare the topical pharmaceutical composition do not comprise water. In some embodiments, a "substantially anhydrous" topical pharmaceutical composition can comprise trace amounts of water (e.g., below about 1% wt/wt, preferably below about 0.1% wt/wt). Said trace amounts of water can be absorbed from the environment, e.g., by diffusion of moisture from the air into the topical pharmaceutical composition (e.g., the non-aqueous gel), for example during preparation and/or storage of the topical pharmaceutical composition (e.g., the non-aqueous gel). Nevertheless, one of skill in the art will understand that a "substantially anhydrous" topical pharmaceutical composition is one in which no water is added and in which no water is desired.

In some embodiments, the non-aqueous gel is anhydrous. In some embodiments, the non-aqueous gel comprises 0.0% water.

The term "CR" stands for "cream." Formulations described herein starting with the letters CR are understood as creams.

As used herein, when a formulation is referred to by a descriptor followed by a dash and a percentage, the percentage refers to the amount of a compound of Formula I (preferably Compound 1) in said formulation. For example, the formulation "NA03-2.0%" comprises 2.0% Formula I, whereas the formulation "NA03-3%" comprises 3% Compound 1. The formulation "AG20-3.2%" comprises 3.2% Compound 1. Unless otherwise indicated, the formulation "NA03" comprises 6.3% Compound 1.

Compounds of Formula (I) comprised in the topical compositions of the present invention include pharmaceutically acceptable salts of said compounds. In particular, the term "pharmaceutically acceptable salt" as used herein, refers to pharmaceutically acceptable organic or inorganic salts of a compound of the present invention, in particular acid addition salts. Exemplary salts include, but are not limited to, salts of physiologically acceptable

mineral acids, such as hydrochloric acid, sulfuric acid, nitric acid and phosphoric acid, or salts of organic acids, such as methane-sulfonic acid, *p*-toluenesulfonic acid, lactic acid, malic acid, tartaric acid, acetic acid, trifluoroacetic acid, citric acid, succinic acid, fumaric acid, maleic acid and salicylic acid. Further examples of pharmacologically acceptable salts of the compounds of Formula (I) are alkali metal and alkaline earth metal salts such as, for example, sodium, potassium, lithium, calcium or magnesium salts, ammonium salts or salts of organic bases such as, for example, methylamine, dimethylamine, triethylamine, piperidine, ethylenediamine, lysine, choline hydroxide, meglumine, morpholine or arginine salts. Further examples of pharmaceutically acceptable salts of the compounds of Formula (I) include the hydrochloride, hydrobromide, sulfate, bisulfate, phosphate, hydrogen phosphate, nitrate, acetate, benzoate, succinate, fumarate, maleate, lactate, citrate, benzenesulfonate, *p*-toluenesulphonate or the like.

As used herein, the term "lower mono aliphatic alcohol" refers to a saturated organic compound comprising a single hydroxyl group, and further comprising from one to six carbon atoms, wherein said lower mono aliphatic alcohol does not comprise an ether linkage. Examples are methanol, ethanol, propanol (e.g., isopropanol), butanol (e.g., isobutanol or tert-butanol), pentanol (e.g., isopentanol), and hexanol (e.g., isohexanol). For the avoidance of doubt, diethylene glycol monoethyl ether is not considered a lower mono aliphatic alcohol.

As used herein, the term "fatty mono aliphatic alcohol" refers to a saturated or mono- or di-unsaturated organic compound comprising a single hydroxyl group, and further comprising at least seven carbon atoms. Preferred fatty mono aliphatic alcohols comprise between 15 and 25 carbon atoms.

As used herein, the term "polyalkylene glycol" refers to a polymer having the chemical formula $H–[O\text{-}CHR\text{-}CH_2]_m–H$, wherein "m" represents the average number of repeating oxyethylene groups, and wherein R represents -H or a C_1-C_6 alkyl group. Preferred polyalkylene glycols are polyethylene glycol, polypropylene glycol, and polybutylene glycol.

The term "PEG" refers to a polyethylene glycol, i.e., a polymer having the chemical formula $H–[O\text{-}CH_2\text{-}CH_2]_m–H$, wherein "m" represents the average number of repeating oxyethylene groups.

One of skill in the art will understand that PEG can be prepared in a wide variety of molecular weights, all of which are contemplated by the present disclosure. Moreover, one of skill in the art will understand that, as a polymer, even purified compositions of PEG do not necessarily all comprise the exact same molecular weight or number of repeating oxyethylene

groups. Instead, compositions of PEG can typically comprise a range of average molecular weights and can be characterized by an average number of repeating oxyethylene groups "m."

For example, the *Handbook of Pharmaceutical Excipients*, Sixth Edition, R. C. Rowe, P. J. Sheskey, M. E. Quinn, Pharmaceutical Press (2009), teaches the following common PEG polymers, which is not to be understood as an exhaustive list.

Grade	m	Average Molecular Weight
PEG 200	4.2	190-210
PEG 300	6.4	285–315
PEG 400	8.7	380–420
PEG 540 (blend)	-	500–600
PEG 600	13.2	570–613
PEG 900	15.3	855–900
PEG 1000	22.3	950–1050
PEG 1450	32.5	1,300–1,600
PEG 1540	28.0-36.0	1,300–1,600
PEG 2000	40.0-50.0	1,800–2,200
PEG 3000	60.0-75.0	2,700–3,300
PEG 3350	75.7	3,000–3,700
PEG 4000	69.0-84.0	3,000–4,800
PEG 4600	104.1	4,400–4,800
PEG 8000	181.4	7,000–9,000

The term "Transcutol® P" is a registered trademark. Transcutol® P is a trade name referring to diethylene glycol monoethyl ether, also abbreviated herein as "DEGEE."

The term "DIPA" as used herein refers to diisopropyl adipate.

In some embodiments, the inventive pharmaceutical compositions comprise polyacrylic acid. In preferred embodiments, said polyacrylic acid is crosslinked with allyl sucrose or allyl pentaerythritol. In preferred embodiments, said polyacrylic acid is sold under the trade name "Carbopol®," preferably Carbopol® 974 or Carbopol® 980.

In some embodiments, the inventive pharmaceutical compositions comprise a polyethylene glycol alkyl ether. In preferred embodiments, said polyethylene glycol alkyl ether is a dialkylene glycol alkyl ether, e.g., a compound of the formula $C_nH_{2n+1}(OCH_2CH_2)_mOH$), wherein "n" is an integer between 1 and 24 and "m" is the average

number of repeating oxyethylene units, preferably wherein m is between about 2 and about 20. In preferred embodiments, said polyethylene glycol alkyl ether is sold under the trade name "Brij®." In preferred embodiments, said polyethylene glycol alkyl ether is Brij® S2, i.e., diethylene glycol-octadecyl ether ($C_{18}H_{37}(OCH_2CH_2)_2OH$). In preferred embodiments, said polyethylene glycol alkyl ether is Brij® S20, i.e., polyethylene glycol-octadecyl ether ($C_{18}H_{37}(OCH_2CH_2)_mOH$), wherein m is about 20.

As used herein, "GTCC" refers to caprylic/capric triglyceride.

The term "pharmaceutically acceptable excipient" as used herein includes any physiologically inert additive that is routinely used in pharmaceutical dosage forms. Pharmaceutically acceptable excipients are selected from the group comprising binders, diluents, carriers, lubricants, glidants, coating additives or combinations thereof.

As used herein, the term "solubility synergy factor" refers to a measure of the fold-increase in solubility of a compound of Formula (I), e.g., Compound 1, in the inventive topical pharmaceutical compositions over the solubility that would have been expected based on the solubility of the compound of Formula (I) in the individual solvents and excipients alone.

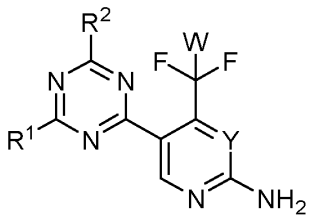
As used herein, the term "hyperkeratosis" is understood as the thickening of the stratum corneum. In some embodiments, hyperkeratosis is associated with the presence of an abnormal quantity of keratin. Skin that exhibits hyperkeratosis is described herein as "hyperkeratotic". Skin that does not exhibit hyperkeratosis is described as "non-hyperkeratotic".

As used herein, the term "hypertrophy" is understood to mean the increase in the volume of an organ or tissue due to the enlargement of its component cells. When used in the context of a skin lesion, e.g., an actinic keratosis lesion, lesions that exhibit hypertrophy are described as being "hypertrophic". Cells that do not exhibit hypertrophy are described as being "non-hypertrophic".

Formulations of the Invention

In one aspect, the present invention provides a topical pharmaceutical composition comprising:

at least 0.5 weight percent of a compound of Formula (I):



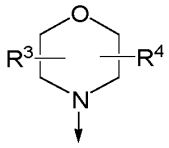
Formula (I)

wherein:

W is H or F;

Y is N or CH;

R^1 and R^2 are independently of each other a morpholinyl of Formula (II)



Formula (II)

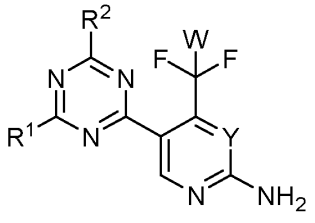
wherein R^3 and R^4 are independently of each other H or C_1-C_3alkyl, or R^3 and R^4 combine to form a bivalent C_1-C_3alkylene residue;

at least 30 weight percent, preferably at least 45 weight percent polyalkylene glycol; and

at least 10 weight percent, preferably at least 15 weight percent diethylene glycol monoethyl ether.

In one aspect, the present invention provides a topical pharmaceutical composition comprising:

at least 0.9 weight percent of a compound of Formula (I):



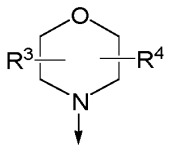
Formula (I)

wherein:

W is H or F;

Y is N or CH;

R^1 and R^2 are independently of each other a morpholinyl of Formula (II)



Formula (II)

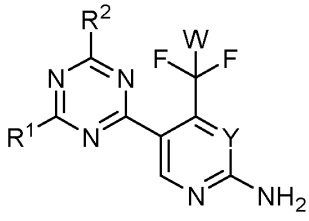
wherein R^3 and R^4 are independently of each other H or C_1-C_3alkyl, or R^3 and R^4 combine to form a bivalent C_1-C_3alkylene residue;

at least 30 weight percent, preferably at least 45 weight percent polyalkylene glycol; and

at least 10 weight percent, preferably at least 15 weight percent diethylene glycol monoethyl ether.

In one aspect, the present invention provides a topical pharmaceutical composition comprising:

at least 1.5 weight percent of a compound of Formula (I):



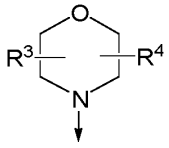
Formula (I)

wherein:

W is H or F;

Y is N or CH;

R^1 and R^2 are independently of each other a morpholinyl of Formula (II)



Formula (II)

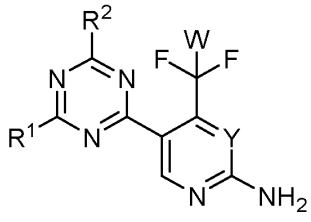
wherein R^3 and R^4 are independently of each other H or C_1-C_3alkyl, or R^3 and R^4 combine to form a bivalent C_1-C_3alkylene residue;

at least 30 weight percent, preferably at least 45 weight percent polyalkylene glycol; and

at least 10 weight percent, preferably at least 15 weight percent diethylene glycol monoethyl ether.

In one aspect, the present invention provides a topical pharmaceutical composition comprising:

at least 1.9 weight percent of a compound of Formula (I):



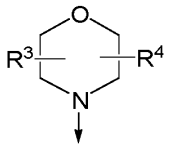
Formula (I)

wherein:

W is H or F;

Y is N or CH;

R^1 and R^2 are independently of each other a morpholinyl of Formula (II)



Formula (II)

wherein R^3 and R^4 are independently of each other H or C_1-C_3alkyl, or R^3 and R^4 combine to form a bivalent C_1-C_3alkylene residue;

at least 30 weight percent, preferably at least 45 weight percent polyalkylene glycol; and

at least 10 weight percent, preferably at least 15 weight percent diethylene glycol monoethyl ether.

In some embodiments, said topical pharmaceutical composition comprises less than about 5 weight percent water. In some embodiments, said topical pharmaceutical composition comprises less than about 4 weight percent water. In some embodiments, said topical pharmaceutical composition comprises less than about 3 weight percent water. In some embodiments, said topical pharmaceutical composition comprises less than about 2 weight percent water. In some embodiments, said topical pharmaceutical composition comprises less than about 1 weight percent water. In some embodiments, said topical pharmaceutical composition comprises less than about 0.5 weight percent water. In some embodiments, said topical pharmaceutical composition comprises less than about 0.4 weight percent water. In some embodiments, said topical pharmaceutical composition comprises less than about 0.3 weight percent water. In some embodiments, said topical pharmaceutical composition comprises less than about 0.2 weight percent water. In some embodiments, said topical pharmaceutical composition comprises less than about 0.1 weight percent water. In some embodiments, said topical pharmaceutical composition is substantially anhydrous, as defined

above.

In some embodiments, said topical pharmaceutical composition is anhydrous. In some preferred embodiments, said topical pharmaceutical composition comprises 0.0 weight percent water.

Without wishing to be bound by theory, inclusion of DMSO in a topical formulation can contribute to permeation of compounds dissolved therein through the skin of a subject and into systemic circulation. Accordingly, in preferred embodiments, said topical pharmaceutical composition does not comprise DMSO. In some embodiments, said topical pharmaceutical composition comprises less than about 1 weight percent DMSO. In some embodiments, said topical pharmaceutical composition comprises less than about 0.9 weight percent DMSO. In some embodiments, said topical pharmaceutical composition comprises less than about 0.8 weight percent DMSO. In some embodiments, said topical pharmaceutical composition comprises less than about 0.7 weight percent DMSO. In some embodiments, said topical pharmaceutical composition comprises less than about 0.6 weight percent DMSO. In some embodiments, said topical pharmaceutical composition comprises less than about 0.5 weight percent DMSO. In some embodiments, said topical pharmaceutical composition comprises less than about 0.4 weight percent DMSO. In some embodiments, said topical pharmaceutical composition comprises less than about 0.3 weight percent DMSO. In some embodiments, said topical pharmaceutical composition comprises less than about 0.2 weight percent DMSO. In some embodiments, said topical pharmaceutical composition comprises less than about 0.1 weight percent DMSO. In some preferred embodiments, said topical pharmaceutical composition does not comprise DMSO, i.e., said topical pharmaceutical composition comprises 0.0 weight percent DMSO.

In some embodiments, said topical pharmaceutical composition comprises less than about 1 weight percent lower mono aliphatic alcohol. In some embodiments, said topical pharmaceutical composition comprises less than about 0.9 weight percent lower mono aliphatic alcohol. In some embodiments, said topical pharmaceutical composition comprises less than about 0.8 weight percent lower mono aliphatic alcohol. In some embodiments, said topical pharmaceutical composition comprises less than about 0.7 weight percent lower mono aliphatic alcohol. In some embodiments, said topical pharmaceutical composition comprises less than about 0.6 weight percent lower mono aliphatic alcohol. In some embodiments, said topical pharmaceutical composition comprises less than about 0.5 weight percent lower mono aliphatic alcohol. In some embodiments, said topical pharmaceutical composition comprises

less than about 0.4 weight percent lower mono aliphatic alcohol. In some embodiments, said topical pharmaceutical composition comprises less than about 0.3 weight percent lower mono aliphatic alcohol. In some embodiments, said topical pharmaceutical composition comprises less than about 0.2 weight percent lower mono aliphatic alcohol. In some embodiments, said topical pharmaceutical composition comprises less than about 0.1 weight percent lower mono aliphatic alcohol. In some preferred embodiments, said topical pharmaceutical composition does not comprise mono aliphatic alcohol, i.e., said topical pharmaceutical composition comprises 0.0 weight percent lower mono aliphatic alcohol.

In some embodiments, said topical pharmaceutical composition comprises less than about 1 weight percent ethanol. In some embodiments, said topical pharmaceutical composition comprises less than about 0.9 weight percent ethanol. In some embodiments, said topical pharmaceutical composition comprises less than about 0.8 weight percent ethanol. In some embodiments, said topical pharmaceutical composition comprises less than about 0.7 weight percent ethanol. In some embodiments, said topical pharmaceutical composition comprises less than about 0.6 weight percent ethanol. In some embodiments, said topical pharmaceutical composition comprises less than about 0.5 weight percent ethanol. In some embodiments, said topical pharmaceutical composition comprises less than about 0.4 weight percent ethanol. In some embodiments, said topical pharmaceutical composition comprises less than about 0.3 weight percent ethanol. In some embodiments, said topical pharmaceutical composition comprises less than about 0.2 weight percent ethanol. In some embodiments, said topical pharmaceutical composition comprises less than about 0.1 weight percent ethanol. In some embodiments, said topical pharmaceutical composition does not comprise ethanol, i.e., said topical pharmaceutical composition comprises 0.0 weight percent ethanol.

In some embodiments, said topical pharmaceutical composition comprises polyacrylic acid. In some embodiments, said composition comprises from about 0.1 weight percent to about 10 weight percent polyacrylic acid. In some embodiments, said composition comprises from about 0.5 weight percent to about 5 weight percent polyacrylic acid. In some embodiments, said composition comprises from about 0.5 weight percent to about 2.5 weight percent polyacrylic acid. In some embodiments, said composition comprises from about 0.5 weight percent to about 1.5 weight percent polyacrylic acid.

In some embodiments, said composition comprises at least 1 weight percent polyacrylic acid. In some embodiments, said composition comprises at most 1 weight percent polyacrylic acid. In some embodiments, said composition comprises about 1 weight percent

polyacrylic acid.

In some embodiments, said polyacrylic acid is Carbopol® 974. In some embodiments, said polyacrylic acid is Carbopol® 980.

In some embodiments, said topical pharmaceutical composition comprises less than about 1 weight percent polyacrylic acid, preferably less than about 0.1 weight percent polyacrylic acid. In some embodiments, said topical pharmaceutical composition does not comprise polyacrylic acid, i.e., said topical pharmaceutical composition comprises 0.0 weight percent polyacrylic acid.

In some embodiments, said topical pharmaceutical composition comprises a preservative. Preservatives are known to the skilled person in the art and includes, for example, benzyl alcohol, benzoic acid, phenol, m-cresol, methyl paraben, propyl paraben, or a combination thereof. In preferred embodiments, said preservative is benzyl alcohol.

In some embodiments, the preservative is present from about 0.01% (w/w) to about 5% (w/w), preferably about 0.1% (w/w) to about 5% (w/w), more preferably about 1% (w/w) to about 3% (w/w), based on the total weight of said topical composition.

In a preferred embodiment, said topical composition comprises one or more other preservative, wherein said preservative is benzyl alcohol, and wherein said benzyl alcohol is present from about 0.01% (w/w) to about 5% (w/w), preferably about 0.1% (w/w) to about 5% (w/w), more preferably about 1% (w/w) to about 3% (w/w) and even more preferably of about 2% (w/w) based on the total weight of said topical composition. In a preferred embodiment, said topical composition comprises a preservative, wherein said preservative is benzyl alcohol, and wherein said benzyl alcohol is present from about 0.01% (w/w) to about 5% (w/w), preferably about 0.1% (w/w) to about 5% (w/w), more preferably about 1% (w/w) to about 3% (w/w) and even more preferably of about 2% (w/w) based on the total weight of said topical composition.

In some embodiments, said topical pharmaceutical composition does not comprise any preservative, i.e., said topical pharmaceutical composition comprises 0.0 weight percent preservative.

In a preferred embodiment, said topical composition comprises benzyl alcohol, and wherein said benzyl alcohol is present from about 0.01% (w/w) to about 5% (w/w), preferably about 0.1% (w/w) to about 5% (w/w), more preferably about 1% (w/w) to about 3% (w/w) and even more preferably of about 2% (w/w) based on the total weight of said topical composition.

In some embodiments, said topical pharmaceutical composition does not comprise

benzyl alcohol.

In preferred embodiments, said topical pharmaceutical composition comprises a fatty aliphatic alcohol, more preferably wherein said fatty alcohol comprises between 15 and 25 carbon atoms. In preferred embodiments, said fatty alcohol is fully saturated or comprises one or two olefins, more preferably one olefin. In some embodiments, said topical composition does not comprise a fatty aliphatic alcohol.

In preferred embodiments, said fatty aliphatic alcohol is oleyl alcohol. In preferred embodiments, said oleyl alcohol is present from about 1 weight percent to about 5 weight percent, more preferably from about 1 weight percent to about 4 weight percent, more preferably from about 1 weight percent to about 3 weight percent, more preferably from about 1 weight percent to about 2 weight percent, yet more preferably about 1.5 weight percent. In some embodiments, said topical composition does not comprise oleyl alcohol.

In some embodiments, said topical pharmaceutical composition comprises a thickening agent. Thickening agents are known to the skilled person in the art and includes a cellulose derivative, polyvinylpyrrolidone, a carbomer polymer, a carbomer derivative, maltodextrin, polydextrose, dextrates, carboxypolymethylene, polyvinyl alcohol, poloxamers and mixtures thereof. In preferred embodiments, thickening agents serve to increase the final viscosity of the topical composition, preferably to ensure and increase the time of stay of the topical composition on the skin of a subject, for example, on the site of a skin lesion and/or skin disorder.

In preferred embodiments, said thickening agent is selected from the group consisting of carboxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose ("HPC"), sodium hyaluronate and polyvinylpyrrolidone. In preferred embodiments, said thickening agent is carboxymethyl cellulose. In preferred embodiments, said thickening agent is hydroxyethyl cellulose. In preferred embodiments, said thickening agent is hydroxypropyl cellulose. In preferred embodiments, said thickening agent is sodium hyaluronate. In preferred embodiments, said thickening agent is polyvinylpyrrolidone. As used herein, the term "HPC HF" is understood to mean pharmaceutical grade hydroxypropyl cellulose. As used herein, the abbreviation "HPC" is understood to refer to "hydroxypropyl cellulose" and the abbreviation "HF", is understood to indicate that said HPC is pharmaceutical grade HPC. In preferred embodiments, said HPC HF is Klucel^{TM} HCF HF.

In some embodiments, said composition comprises from about 0.1 weight percent to about 10 weight percent thickening agent. In some embodiments, said composition comprises

from about 0.5 weight percent to about 5 weight percent thickening agent. In some embodiments, said composition comprises from about 0.5 weight percent to about 2.5 weight percent thickening agent. In some embodiments, said composition comprises from about 0.5 weight percent to about 1.5 weight percent thickening agent.

In some embodiments, said composition comprises at least 1 weight percent thickening agent. In some embodiments, said composition comprises at most 1 weight percent thickening agent. In some embodiments, said composition comprises about 1 weight percent thickening agent.

In some embodiments, said composition comprises from about 0.1 weight percent to about 10 weight percent hydroxypropyl cellulose. In some embodiments, said composition comprises from about 0.5 weight percent to about 5 weight percent hydroxypropyl cellulose. In some embodiments, said composition comprises from about 0.5 weight percent to about 2.5 weight percent hydroxypropyl cellulose. In some embodiments, said composition comprises from about 0.5 weight percent to about 1.5 weight percent hydroxypropyl cellulose.

In some embodiments, said composition comprises at least 1 weight percent hydroxypropyl cellulose. In some embodiments, said composition comprises at most 1 weight percent hydroxypropyl cellulose. In some embodiments, said composition comprises about 1 weight percent hydroxypropyl cellulose.

In some embodiments, said topical pharmaceutical composition comprises from about 0.1 weight percent to about 8 weight percent of a compound Formula (I). In some embodiments, said topical pharmaceutical composition comprises from about 0.2 weight percent to about 8 weight percent of a compound Formula (I). In some embodiments, said topical pharmaceutical composition comprises from about 0.3 weight percent to about 8 weight percent of a compound Formula (I). In some embodiments, said topical pharmaceutical composition comprises from about 0.4 weight percent to about 8 weight percent of a compound Formula (I). In some embodiments, said topical pharmaceutical composition comprises from about 0.5 weight percent to about 8 weight percent of a compound Formula (I). In some embodiments, said topical pharmaceutical composition comprises from about 0.9 weight percent to about 8 weight percent of a compound Formula (I). In some embodiments, said topical pharmaceutical composition comprises from about 1.0 weight percent to about 8 weight percent of a compound Formula (I). In some embodiments, said topical pharmaceutical composition comprises from about 1.5 weight percent to about 8 weight percent of a compound Formula (I). In some embodiments, said topical pharmaceutical composition comprises from

about 1.5 weight percent to about 7.9 weight percent of a compound Formula (I). In some embodiments, said topical pharmaceutical composition comprises from about 1.9 weight percent to about 7.5 weight percent of a compound Formula (I). In some embodiments, said topical pharmaceutical composition comprises from about 1.9 weight percent to about 7 weight percent of a compound Formula (I). In some embodiments, said topical pharmaceutical composition comprises from about 1.9 weight percent to about 6.5 weight percent of a compound Formula (I). In some embodiments, said topical pharmaceutical composition comprises from about 1.9 weight percent to about 6 weight percent of a compound Formula (I). In some embodiments, said topical pharmaceutical composition comprises from about 1.9 weight percent to about 5 weight percent of a compound Formula (I). In some embodiments, said topical pharmaceutical composition comprises from about 1.9 weight percent to about 4 weight percent of a compound Formula (I). In some embodiments, said topical pharmaceutical composition comprises from about 1.9 weight percent to about 3 weight percent of a compound Formula (I). In preferred embodiments, said topical pharmaceutical composition comprises from about 1.5 weight percent to about 2.5 weight percent of a compound Formula (I). In preferred embodiments, said topical pharmaceutical composition comprises from about 1.9 weight percent to about 2.5 weight percent of a compound Formula (I). In very preferred embodiments, said topical pharmaceutical composition comprises from about 1.9 weight percent to about 2.1 weight percent of a compound Formula (I). In some embodiments, said topical pharmaceutical composition comprises about 2.0 weight percent of a compound Formula (I).

In some embodiments, said topical pharmaceutical composition comprises at least about 0.1 weight percent of a compound of Formula (I). In some embodiments, said topical pharmaceutical composition comprises at least about 0.2 weight percent of a compound of Formula (I). In some embodiments, said topical pharmaceutical composition comprises at least about 0.3 weight percent of a compound of Formula (I). In some embodiments, said topical pharmaceutical composition comprises at least about 0.4 weight percent of a compound of Formula (I). In some embodiments, said topical pharmaceutical composition comprises at least about 0.5 weight percent of a compound of Formula (I). In some embodiments, said topical pharmaceutical composition comprises at least about 0.9 weight percent of a compound of Formula (I). In some embodiments, said topical pharmaceutical composition comprises at least about 1 weight percent of a compound of Formula (I). In some embodiments, said topical pharmaceutical composition comprises at least about 1.5 weight percent of a compound of

Formula (I). In some embodiments, said topical pharmaceutical composition comprises at least about 1.6 weight percent of a compound of Formula (I). In some embodiments, said topical pharmaceutical composition comprises at least about 1.7 weight percent of a compound of Formula (I). In some embodiments, said topical pharmaceutical composition comprises at least about 1.8 weight percent of a compound of Formula (I). In preferred embodiments, said topical pharmaceutical composition comprises at least about 1.9 weight percent of a compound of Formula (I). In some embodiments, said topical pharmaceutical composition comprises at least about 2.0 weight percent of a compound of Formula (I). In some embodiments, said composition comprises at least about 2.5 weight percent, of a compound of Formula (I). In some embodiments, said composition comprises at least about 3.0 weight percent of a compound of Formula (I). In some embodiments, said composition comprises at least about 3.5 weight percent of a compound of Formula (I). In some embodiments, said composition comprises at least about 4.0 weight percent, of a compound of Formula (I). In some embodiments, said composition comprises at least about 4.5 weight percent of a compound of Formula (I). In some embodiments, said composition comprises at least about 5.0 weight percent of a compound of Formula (I). In some embodiments, said composition comprises at least about 5.5 weight percent of a compound of Formula (I). In some embodiments, said composition comprises at least about 6.0 weight percent of a compound of Formula (I). In some embodiments, said composition comprises at least about 6.3 weight percent of a compound of Formula (I). In some embodiments, said topical pharmaceutical composition comprises at least about 6.5 weight percent of a compound of Formula (I). In some embodiments, said topical pharmaceutical composition comprises at least about 7.0 weight percent of a compound of Formula (I). In some embodiments, said topical pharmaceutical composition comprises at least about 7.5 weight percent of a compound of Formula (I). In some embodiments, said topical pharmaceutical composition comprises at least about 7.7 weight percent of a compound of Formula (I). In some embodiments, said topical pharmaceutical composition comprises at least about 7.8 weight percent of a compound of Formula (I). In some embodiments, said topical pharmaceutical composition comprises at least about 7.9 weight percent of a compound of Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 0.1 weight percent to about 8 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises from about 0.2 weight percent to about 8 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition

comprises from about 0.3 weight percent to about 8 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises from about 0.4 weight percent to about 8 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises from about 0.5 weight percent to about 8 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises from about 0.9 weight percent to about 8 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises from about 1.0 weight percent to about 8 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises from about 1.5 weight percent to about 8 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises from about 1.5 weight percent to about 7.9 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises from about 1.9 weight percent to about 7.5 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises from about 1.9 weight percent to about 7 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises from about 1.9 weight percent to about 6.5 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises from about 1.9 weight percent to about 6 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises from about 1.9 weight percent to about 5 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises from about 1.9 weight percent to about 4 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises from about 1.9 weight percent to about 3 weight percent of Compound 1. In preferred embodiments, said topical pharmaceutical composition comprises from about 1.5 weight percent to about 2.5 weight percent of Compound 1. In preferred embodiments, said topical pharmaceutical composition comprises from about 1.9 weight percent to about 2.5 weight percent of Compound 1. In very preferred embodiments, said topical pharmaceutical composition comprises from about 1.9 weight percent to about 2.1 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises at least about 0.1 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises at least about 0.2 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises at least about 0.3 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition

comprises at least about 0.4 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises at least about 0.5 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises at least about 0.9 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises at least about 1 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises at least about 1.5 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises at least about 1.6 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises at least about 1.7 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises at least about 1.8 weight percent of Compound 1. In preferred embodiments, said topical pharmaceutical composition comprises at least about 1.9 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises at least about 2.0 weight percent of Compound 1. In some embodiments, said composition comprises at least about 2.5 weight percent, of Compound 1. In some embodiments, said composition comprises at least about 3.0 weight percent of Compound 1. In some embodiments, said composition comprises at least about 3.5 weight percent of Compound 1. In some embodiments, said composition comprises at least about 4.0 weight percent, of Compound 1. In some embodiments, said composition comprises at least about 4.5 weight percent of Compound 1. In some embodiments, said composition comprises at least about 5.0 weight percent of Compound 1. In some embodiments, said composition comprises at least about 5.5 weight percent of Compound 1. In some embodiments, said composition comprises at least about 6.0 weight percent of Compound 1. In some embodiments, said composition comprises at least about 6.3 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises at least about 6.5 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises at least about 7.0 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises at least about 7.5 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises at least about 7.7 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises at least about 7.8 weight percent of Compound 1. In some embodiments, said topical pharmaceutical composition comprises at least about 7.9 weight percent of Compound 1.

In some embodiments, said polyalkylene glycol is selected from polyethylene glycol

(PEG), polypropylene glycol, and polybutylene glycol and combinations thereof. In preferred embodiments, said polyalkylene glycol is polyethylene glycol. In some embodiments, said polyethylene glycol is selected from PEG 200, PEG 300, PEG 400, PEG 540, PEG 600, PEG 900, PEG 1000, PEG 1450, PEG 1540, PEG 2000, PEG 3000, PEG 3350, PEG 4000, PEG 4600, PEG 8000, or a combination thereof. In some embodiments, said polyethylene glycol is selected from PEG 200, PEG 300, PEG 400, PEG 540, PEG 600, PEG 900, PEG 1000, or a combination thereof. In some embodiments, said polyethylene glycol is selected from PEG 200, PEG 300, PEG 400, PEG 540, PEG 600, or a combination thereof. In some embodiments, said polyethylene glycol is selected from PEG 300, PEG 400, PEG 540, or a combination thereof. In preferred embodiments, said polyethylene glycol is selected from PEG 400.

In some embodiments, said topical pharmaceutical composition comprises at least 30 weight percent polyalkylene glycol, preferably polyethylene glycol. In some embodiments, said topical pharmaceutical composition comprises at least 35 weight percent polyalkylene glycol, preferably polyethylene glycol. In some embodiments, said topical pharmaceutical composition comprises at least 40 weight percent polyalkylene glycol, preferably polyethylene glycol. In some embodiments, said topical pharmaceutical composition comprises at least 45 weight percent polyalkylene glycol, preferably polyethylene glycol. In some embodiments, said topical pharmaceutical composition comprises at least 50 weight percent polyalkylene glycol, preferably polyethylene glycol. In some embodiments, said topical pharmaceutical composition comprises at least 55 weight percent polyalkylene glycol, preferably polyethylene glycol. In some embodiments, said topical pharmaceutical composition comprises about 57.81 weight percent polyalkylene glycol, preferably polyethylene glycol.

In some embodiments, said topical pharmaceutical composition comprises from about 30 weight percent to about 80 weight percent polyalkylene glycol. In some embodiments, said topical pharmaceutical composition comprises from about 35 weight percent to about 80 weight percent polyalkylene glycol. In some embodiments, said topical pharmaceutical composition comprises from about 40 weight percent to about 80 weight percent polyalkylene glycol. In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent polyalkylene glycol. In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent polyalkylene glycol. In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 70 weight percent polyalkylene glycol. In some embodiments, said topical pharmaceutical composition comprises from about

45 weight percent to about 65 weight percent polyalkylene glycol. In some preferred embodiments, said topical pharmaceutical composition comprises from about 50 weight percent to about 60 weight percent polyalkylene glycol. In some preferred embodiments, said topical pharmaceutical composition comprises from about 53 weight percent to about 60 weight percent polyalkylene glycol. In some preferred embodiments, said topical pharmaceutical composition comprises from about 55 weight percent to about 60 weight percent polyalkylene glycol.

In some embodiments, said topical pharmaceutical composition comprises at least 45 weight percent PEG 400. In some embodiments, said topical pharmaceutical composition comprises at least 50 weight percent PEG 400. In some embodiments, said topical pharmaceutical composition comprises at least 55 weight percent PEG 400. In some embodiments, said topical pharmaceutical composition comprises about 57.8 weight percent PEG 400.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent PEG 400. In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent PEG 400. In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 70 weight percent PEG 400. In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 65 weight percent PEG 400. In some preferred embodiments, said topical pharmaceutical composition comprises from about 50 weight percent to about 60 weight percent PEG 400. In some preferred embodiments, said topical pharmaceutical composition comprises from about 53 weight percent to about 60 weight percent PEG 400. In some preferred embodiments, said topical pharmaceutical composition comprises from about 55 weight percent to about 60 weight percent PEG 400.

In some embodiments, said topical pharmaceutical composition comprises from about 10 weight percent to about 35 weight percent diethylene glycol monoethyl ether. In some embodiments, said topical pharmaceutical composition comprises from about 15 weight percent to about 35 weight percent diethylene glycol monoethyl ether. In some embodiments, said topical pharmaceutical composition comprises from about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether. In some embodiments, said topical pharmaceutical composition comprises from about 19 weight percent to about 30 weight percent diethylene glycol monoethyl ether. In some embodiments, said topical pharmaceutical

composition comprises from about 20 weight percent to about 30 weight percent diethylene glycol monoethyl ether. In some embodiments, said topical pharmaceutical composition comprises from about 20 weight percent to about 25 weight percent diethylene glycol monoethyl ether. In some embodiments, said topical pharmaceutical composition comprises from about 22 weight percent to about 25 weight percent diethylene glycol monoethyl ether.

In some embodiments, said topical pharmaceutical composition comprises at least 10 weight percent diethylene glycol monoethyl ether. In some embodiments, said topical pharmaceutical composition comprises at least 15 weight percent diethylene glycol monoethyl ether. In some embodiments, said topical pharmaceutical composition comprises at least 19 weight percent diethylene glycol monoethyl ether. In preferred embodiments, said composition comprises at least 20 weight percent diethylene glycol monoethyl ether. In preferred embodiments, said composition comprises at least 21 weight percent diethylene glycol monoethyl ether. In preferred embodiments, said composition comprises at least 22 weight percent diethylene glycol monoethyl ether. In preferred embodiments, said composition comprises at least 23 weight percent diethylene glycol monoethyl ether. In preferred embodiments, said composition comprises about 24.5 weight percent diethylene glycol monoethyl ether.

In some embodiments, said topical pharmaceutical composition comprises diisopropyl adipate. In some embodiments, said composition comprises from about 1 weight percent to about 20 weight percent diisopropyl adipate. In some embodiments, said composition comprises from about 1 weight percent to about 15 weight percent diisopropyl adipate. In some embodiments, said composition comprises from about 5 weight percent to about 15 weight percent diisopropyl adipate. In some embodiments, said composition comprises from about 7 weight percent to about 13 weight percent diisopropyl adipate. In some embodiments, said composition comprises from about 9 weight percent to about 11 weight percent diisopropyl adipate.

In some embodiments, said composition comprises at least about 5 weight percent diisopropyl adipate. In some embodiments, said composition comprises at least about 6 weight percent diisopropyl adipate. In some embodiments, said composition comprises at least about 7 weight percent diisopropyl adipate. In some embodiments, said composition comprises at least about 8 weight percent diisopropyl adipate. In some embodiments, said composition comprises at least about 9 weight percent diisopropyl adipate. In some embodiments, said composition comprises at least about 9.3 weight percent diisopropyl adipate. In some

embodiments, said composition comprises about 9.36 weight percent diisopropyl adipate. In some embodiments, said composition comprises about 9.8 weight percent diisopropyl adipate.

In some embodiments, said topical pharmaceutical composition comprises glycerol. In some embodiments, said composition comprises from about 1 weight percent to about 10 weight percent glycerol. In some embodiments, said composition comprises from about 3 weight percent to about 8 weight percent glycerol. In some embodiments, said composition comprises from about 4 weight percent to about 6 weight percent glycerol.

In some embodiments, said composition comprises at least 3 weight percent glycerol. In some embodiments, said composition comprises at least 4 weight percent glycerol. In some embodiments, said composition comprises at least 4.5 weight percent glycerol. In some embodiments, said composition comprises at least 5 weight percent glycerol. In some embodiments, said composition comprises 3 weight percent glycerol. In preferred embodiments, said composition comprises 4 weight percent glycerol. In some embodiments, said composition comprises 5 weight percent glycerol. In some embodiments, said composition comprises about 4.89 weight percent glycerol.

In some embodiments, said composition comprises from about 0.1 weight percent to about 10 weight percent hydroxypropyl cellulose. In some embodiments, said composition comprises from about 0.5 weight percent to about 5 weight percent hydroxypropyl cellulose. In some embodiments, said composition comprises from about 0.5 weight percent to about 2.5 weight percent hydroxypropyl cellulose. In some embodiments, said composition comprises from about 0.5 weight percent to about 1.5 weight percent hydroxypropyl cellulose.

In some embodiments, said composition comprises at least 1 weight percent hydroxypropyl cellulose. In some embodiments, said composition comprises at most 1 weight percent hydroxypropyl cellulose. In some embodiments, said composition comprises about 1 weight percent hydroxypropyl cellulose.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent polyalkylene glycol and from about 15 weight percent to about 35 weight percent diethylene glycol monoethyl ether. In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent polyalkylene glycol and from about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether. In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent polyalkylene glycol and about 15 weight percent to about 30 weight percent diethylene glycol monoethyl

ether. In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 65 weight percent polyalkylene glycol and about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether. In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 65 weight percent polyalkylene glycol and about 19 weight percent to about 30 weight percent diethylene glycol monoethyl ether. In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 65 weight percent polyalkylene glycol and about 20 weight percent to about 30 weight percent diethylene glycol monoethyl ether. In some embodiments, said topical pharmaceutical composition comprises from about 50 weight percent to about 60 weight percent polyalkylene glycol and about 20 weight percent to about 25 weight percent diethylene glycol monoethyl ether.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent PEG, preferably PEG400 and from about 15 weight percent to about 35 weight percent diethylene glycol monoethyl ether. In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent PEG, preferably PEG400 and from about 15 weight percent to about 35 weight percent diethylene glycol monoethyl ether. In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent PEG, preferably PEG400 and about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether. In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 65 weight percent PEG, preferably PEG400 and about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether. In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 65 weight percent PEG, preferably PEG400 and about 19 weight percent to about 30 weight percent diethylene glycol monoethyl ether. In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 65 weight percent PEG, preferably PEG400 and about 20 weight percent to about 30 weight percent diethylene glycol monoethyl ether. In some embodiments, said topical pharmaceutical composition comprises from about 50 weight percent to about 60 weight percent PEG, preferably PEG400 and about 20 weight percent to about 25 weight percent diethylene glycol monoethyl ether.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent polyalkylene glycol; from about 15 weight

percent to about 35 weight percent diethylene glycol monoethyl ether; and from about 0.1 weight percent to about 8 weight percent of a compound Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent polyalkylene glycol; from about 15 weight percent to about 35 weight percent diethylene glycol monoethyl ether; and from about 0.5 weight percent to about 8 weight percent of a compound Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent polyalkylene glycol; from about 15 weight percent to about 35 weight percent diethylene glycol monoethyl ether; and from about 0.9 weight percent to about 8 weight percent of a compound Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent polyalkylene glycol; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; and from about 1 weight percent to about 7.9 weight percent of a compound Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent polyalkylene glycol; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; and from about 1.9 weight percent to about 7 weight percent of a compound Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent polyalkylene glycol; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; and from about 1.9 weight percent to about 5 weight percent of a compound Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent polyalkylene glycol; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; and from about 1.9 weight percent to about 2.5 weight percent of a compound Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 65 weight percent polyalkylene glycol; about 19 weight percent to about 30 weight percent diethylene glycol monoethyl ether; and from about 1.9 weight percent to about 2.5 weight percent of a compound Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 65 weight percent polyalkylene glycol; about 20 weight percent to about 30 weight percent diethylene glycol monoethyl ether; and from about 1.9 weight percent

to about 2.5 weight percent of a compound Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 50 weight percent to about 60 weight percent polyalkylene glycol; about 20 weight percent to about 25 weight percent diethylene glycol monoethyl ether; and from about 1.9 weight percent to about 2.5 weight percent of a compound Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent PEG, preferably PEG400; from about 15 weight percent to about 35 weight percent diethylene glycol monoethyl ether; and from about 0.1 weight percent to about 8 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent PEG, preferably PEG400; from about 15 weight percent to about 35 weight percent diethylene glycol monoethyl ether; and from about 0.5 weight percent to about 8 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent PEG, preferably PEG400; from about 15 weight percent to about 35 weight percent diethylene glycol monoethyl ether; and from about 0.9 weight percent to about 8 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent PEG, preferably PEG400; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; and from about 1 weight percent to about 7.9 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent PEG, preferably PEG400; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; and from about 1.9 weight percent to about 7 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent PEG, preferably PEG400; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; and from about 1.9 weight percent to about 5 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent PEG, preferably PEG400; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; and from about 1.9 weight percent to about 2.5 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 65 weight percent PEG, preferably PEG400; about 19 weight percent to about 30 weight percent diethylene glycol monoethyl ether; and from about 1.9 weight percent to about 2.5 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 65 weight percent PEG, preferably PEG400; about 20 weight percent to about 30 weight percent diethylene glycol monoethyl ether; and from about 1.9 weight percent to about 2.5 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 50 weight percent to about 60 weight percent PEG, preferably PEG400; about 20 weight percent to about 25 weight percent diethylene glycol monoethyl ether; and from about 1.9 weight percent to about 2.5 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent polyalkylene glycol; from about 15 weight percent to about 35 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 20 weight percent diisopropyl adipate; and from about 0.1 weight percent to about 8 weight percent of a compound Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent polyalkylene glycol; from about 15 weight percent to about 35 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 20 weight percent diisopropyl adipate; and from about 0.5 weight percent to about 8 weight percent of a compound Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent polyalkylene glycol; from about 15 weight percent to about 35 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 20 weight percent diisopropyl adipate; and from about 0.9 weight percent to about 8 weight percent of a compound Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent polyalkylene glycol; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 15 weight percent diisopropyl adipate; and from about 1 weight percent to about 7.9 weight percent of a compound Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about

45 weight percent to about 75 weight percent polyalkylene glycol; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 15 weight percent diisopropyl adipate; and from about 1.9 weight percent to about 7 weight percent of a compound Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent polyalkylene glycol; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 5 weight percent to about 15 weight percent diisopropyl adipate; and from about 1.9 weight percent to about 5 weight percent of a compound Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent polyalkylene glycol; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 5 weight percent to about 15 weight percent diisopropyl adipate; and from about 1.9 weight percent to about 2.5 weight percent of a compound Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 65 weight percent polyalkylene glycol; about 19 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 7 weight percent to about 13 weight percent diisopropyl adipate; and from about 1.9 weight percent to about 2.5 weight percent of a compound Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 65 weight percent polyalkylene glycol; about 20 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 7 weight percent to about 13 weight percent diisopropyl adipate; and from about 1.9 weight percent to about 2.5 weight percent of a compound Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 50 weight percent to about 60 weight percent polyalkylene glycol; about 20 weight percent to about 25 weight percent diethylene glycol monoethyl ether; from about 9 weight percent to about 11 weight percent diisopropyl adipate; and from about 1.9 weight percent to about 2.5 weight percent of a compound Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent PEG, preferably PEG400; from about 15 weight percent to about 35 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 20 weight percent diisopropyl adipate; and from about 0.1 weight percent to

about 8 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent PEG, preferably PEG400; from about 15 weight percent to about 35 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 20 weight percent diisopropyl adipate; and from about 0.5 weight percent to about 8 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent PEG, preferably PEG400; from about 15 weight percent to about 35 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 20 weight percent diisopropyl adipate; and from about 0.9 weight percent to about 8 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent PEG, preferably PEG400; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 15 weight percent diisopropyl adipate; and from about 1 weight percent to about 7.9 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent PEG, preferably PEG400; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 15 weight percent diisopropyl adipate; and from about 1.9 weight percent to about 7 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent PEG, preferably PEG400; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 5 weight percent to about 15 weight percent diisopropyl adipate; and from about 1.9 weight percent to about 5 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent PEG, preferably PEG400; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 5 weight percent to about 15 weight percent diisopropyl adipate; and from about 1.9 weight percent to about 2.5 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 65 weight percent PEG, preferably PEG400; about 19 weight

percent to about 30 weight percent diethylene glycol monoethyl ether; from about 7 weight percent to about 13 weight percent diisopropyl adipate; and from about 1.9 weight percent to about 2.5 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 65 weight percent PEG, preferably PEG400; about 20 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 7 weight percent to about 13 weight percent diisopropyl adipate; and from about 1.9 weight percent to about 2.5 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 50 weight percent to about 60 weight percent PEG, preferably PEG400; about 20 weight percent to about 25 weight percent diethylene glycol monoethyl ether; from about 9 weight percent to about 11 weight percent diisopropyl adipate; and from about 1.9 weight percent to about 2.5 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent polyalkylene glycol; from about 15 weight percent to about 35 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 20 weight percent diisopropyl adipate; from about 1 weight percent to about 10 weight percent glycerol; and from about 0.1 weight percent to about 8 weight percent of a compound of Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent polyalkylene glycol; from about 15 weight percent to about 35 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 20 weight percent diisopropyl adipate; from about 1 weight percent to about 10 weight percent glycerol; and from about 0.5 weight percent to about 8 weight percent of a compound of Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent polyalkylene glycol; from about 15 weight percent to about 35 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 20 weight percent diisopropyl adipate; from about 1 weight percent to about 10 weight percent glycerol; and from about 0.9 weight percent to about 8 weight percent of a compound of Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent polyalkylene glycol; about 15 weight percent to

about 30 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 15 weight percent diisopropyl adipate; from about 1 weight percent to about 10 weight percent glycerol; and from about 1 weight percent to about 7.9 weight percent of a compound of Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent polyalkylene glycol; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 15 weight percent diisopropyl adipate; from about 1 weight percent to about 10 weight percent glycerol; and from about 1.9 weight percent to about 7 weight percent of a compound of Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent polyalkylene glycol; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 5 weight percent to about 15 weight percent diisopropyl adipate; from about 3 weight percent to about 8 weight percent glycerol; and from about 1.9 weight percent to about 5 weight percent of a compound of Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent polyalkylene glycol; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 5 weight percent to about 15 weight percent diisopropyl adipate; from about 3 weight percent to about 8 weight percent glycerol; and from about 1.9 weight percent to about 2.5 weight percent of a compound of Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 65 weight percent polyalkylene glycol; about 19 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 7 weight percent to about 13 weight percent diisopropyl adipate; from about 3 weight percent to about 8 weight percent glycerol; and from about 1.9 weight percent to about 2.5 weight percent of a compound of Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 65 weight percent polyalkylene glycol; about 20 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 7 weight percent to about 13 weight percent diisopropyl adipate; from about 4 weight percent to about 6 weight percent glycerol; and from about 1.9 weight percent to about 2.5 weight percent of a compound

of Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 50 weight percent to about 60 weight percent polyalkylene glycol; about 20 weight percent to about 25 weight percent diethylene glycol monoethyl ether; from about 9 weight percent to about 11 weight percent diisopropyl adipate; from about 4 weight percent to about 6 weight percent glycerol; and from about 1.9 weight percent to about 2.5 weight percent of a compound of Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent PEG, preferably PEG400; from about 15 weight percent to about 35 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 20 weight percent diisopropyl adipate; from about 1 weight percent to about 10 weight percent glycerol; and from about 0.1 weight percent to about 8 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent PEG, preferably PEG400; from about 15 weight percent to about 35 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 20 weight percent diisopropyl adipate; from about 1 weight percent to about 10 weight percent glycerol; and from about 0.5 weight percent to about 8 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent PEG, preferably PEG400; from about 15 weight percent to about 35 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 20 weight percent diisopropyl adipate; from about 1 weight percent to about 10 weight percent glycerol; and from about 0.9 weight percent to about 8 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent PEG, preferably PEG400; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 15 weight percent diisopropyl adipate; from about 1 weight percent to about 10 weight percent glycerol; and from about 1 weight percent to about 7.9 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent PEG, preferably PEG400; about 15 weight

percent to about 30 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 15 weight percent diisopropyl adipate; from about 1 weight percent to about 10 weight percent glycerol; and from about 1.9 weight percent to about 7 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent PEG, preferably PEG400; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 5 weight percent to about 15 weight percent diisopropyl adipate; from about 3 weight percent to about 8 weight percent glycerol; and from about 1.9 weight percent to about 5 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent PEG, preferably PEG400; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 5 weight percent to about 15 weight percent diisopropyl adipate; from about 3 weight percent to about 8 weight percent glycerol; and from about 1.9 weight percent to about 2.5 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 65 weight percent PEG, preferably PEG400; about 19 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 7 weight percent to about 13 weight percent diisopropyl adipate; from about 3 weight percent to about 8 weight percent glycerol; and from about 1.9 weight percent to about 2.5 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 65 weight percent PEG, preferably PEG400; about 20 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 7 weight percent to about 13 weight percent diisopropyl adipate; from about 4 weight percent to about 6 weight percent glycerol; and from about 1.9 weight percent to about 2.5 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 50 weight percent to about 60 weight percent PEG, preferably PEG400; about 20 weight percent to about 25 weight percent diethylene glycol monoethyl ether; from about 9 weight percent to about 11 weight percent diisopropyl adipate; from about 4 weight percent to about 6 weight percent glycerol; and from about 1.9 weight percent to about 2.5 weight percent of

Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent polyalkylene glycol; from about 15 weight percent to about 35 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 20 weight percent diisopropyl adipate; from about 1 weight percent to about 10 weight percent glycerol; from about 0.1 weight percent to about 10 weight percent hydroxypropyl cellulose; and from about 0.1 weight percent to about 8 weight percent of a compound of Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent polyalkylene glycol; from about 15 weight percent to about 35 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 20 weight percent diisopropyl adipate; from about 1 weight percent to about 10 weight percent glycerol; from about 0.1 weight percent to about 10 weight percent hydroxypropyl cellulose; and from about 0.5 weight percent to about 8 weight percent of a compound of Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent polyalkylene glycol; from about 15 weight percent to about 35 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 20 weight percent diisopropyl adipate; from about 1 weight percent to about 10 weight percent glycerol; from about 0.1 weight percent to about 10 weight percent hydroxypropyl cellulose; and from about 0.9 weight percent to about 8 weight percent of a compound of Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent polyalkylene glycol; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 15 weight percent diisopropyl adipate; from about 1 weight percent to about 10 weight percent glycerol; from about 0.1 weight percent to about 10 weight percent hydroxypropyl cellulose; and from about 1 weight percent to about 7.9 weight percent of a compound of Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent polyalkylene glycol; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 15 weight percent diisopropyl adipate; from about 1 weight percent to about 10 weight

percent glycerol; from about 0.5 weight percent to about 5 weight percent hydroxypropyl cellulose; and from about 1.9 weight percent to about 7 weight percent of a compound of Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent polyalkylene glycol; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 5 weight percent to about 15 weight percent diisopropyl adipate; from about 3 weight percent to about 8 weight percent glycerol; from about 0.5 weight percent to about 5 weight percent hydroxypropyl cellulose; and from about 1.9 weight percent to about 5 weight percent of a compound of Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent polyalkylene glycol; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 5 weight percent to about 15 weight percent diisopropyl adipate; from about 3 weight percent to about 8 weight percent glycerol; from about 0.5 weight percent to about 2.5 weight percent hydroxypropyl cellulose; and from about 1.9 weight percent to about 2.5 weight percent of a compound of Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 65 weight percent polyalkylene glycol; about 19 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 7 weight percent to about 13 weight percent diisopropyl adipate; from about 3 weight percent to about 8 weight percent glycerol; from about 0.5 weight percent to about 2.5 weight percent hydroxypropyl cellulose; and from about 1.9 weight percent to about 2.5 weight percent of a compound of Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 65 weight percent polyalkylene glycol; about 20 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 7 weight percent to about 13 weight percent diisopropyl adipate; from about 4 weight percent to about 6 weight percent glycerol; from about 0.5 weight percent to about 1.5 weight percent hydroxypropyl cellulose; and from about 1.9 weight percent to about 2.5 weight percent of a compound of Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 50 weight percent to about 60 weight percent polyalkylene glycol; about 20 weight percent to

about 25 weight percent diethylene glycol monoethyl ether; from about 9 weight percent to about 11 weight percent diisopropyl adipate; from about 4 weight percent to about 6 weight percent glycerol; from about 0.5 weight percent to about 1.5 weight percent hydroxypropyl cellulose; and from about 1.9 weight percent to about 2.5 weight percent of a compound of Formula (I).

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent PEG, preferably PEG400; from about 15 weight percent to about 35 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 20 weight percent diisopropyl adipate; from about 1 weight percent to about 10 weight percent glycerol; from about 0.1 weight percent to about 10 weight percent hydroxypropyl cellulose; and from about 0.1 weight percent to about 8 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent PEG, preferably PEG400; from about 15 weight percent to about 35 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 20 weight percent diisopropyl adipate; from about 1 weight percent to about 10 weight percent glycerol; from about 0.1 weight percent to about 10 weight percent hydroxypropyl cellulose; and from about 0.5 weight percent to about 8 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent PEG, preferably PEG400; from about 15 weight percent to about 35 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 20 weight percent diisopropyl adipate; from about 1 weight percent to about 10 weight percent glycerol; from about 0.1 weight percent to about 10 weight percent hydroxypropyl cellulose; and from about 0.9 weight percent to about 8 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent PEG, preferably PEG400; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 15 weight percent diisopropyl adipate; from about 1 weight percent to about 10 weight percent glycerol; from about 0.1 weight percent to about 10 weight percent hydroxypropyl cellulose; and from about 1 weight percent to about 7.9 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent PEG, preferably PEG400; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 15 weight percent diisopropyl adipate; from about 1 weight percent to about 10 weight percent glycerol; from about 0.5 weight percent to about 5 weight percent hydroxypropyl cellulose; and from about 1.9 weight percent to about 7 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent PEG, preferably PEG400; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 5 weight percent to about 15 weight percent diisopropyl adipate; from about 3 weight percent to about 8 weight percent glycerol; from about 0.5 weight percent to about 5 weight percent hydroxypropyl cellulose; and from about 1.9 weight percent to about 5 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent PEG, preferably PEG400; about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 5 weight percent to about 15 weight percent diisopropyl adipate; from about 3 weight percent to about 8 weight percent glycerol; from about 0.5 weight percent to about 2.5 weight percent hydroxypropyl cellulose; and from about 1.9 weight percent to about 2.5 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 65 weight percent PEG, preferably PEG400; about 19 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 7 weight percent to about 13 weight percent diisopropyl adipate; from about 3 weight percent to about 8 weight percent glycerol; from about 0.5 weight percent to about 2.5 weight percent hydroxypropyl cellulose; and from about 1.9 weight percent to about 2.5 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 45 weight percent to about 65 weight percent PEG, preferably PEG400; about 20 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 7 weight percent to about 13 weight percent diisopropyl adipate; from about 4 weight percent to about 6 weight percent glycerol; from about 0.5 weight percent to about 1.5 weight percent

hydroxypropyl cellulose; and from about 1.9 weight percent to about 2.5 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises from about 50 weight percent to about 60 weight percent PEG, preferably PEG400; about 20 weight percent to about 25 weight percent diethylene glycol monoethyl ether; from about 9 weight percent to about 11 weight percent diisopropyl adipate; from about 4 weight percent to about 6 weight percent glycerol; from about 0.5 weight percent to about 1.5 weight percent hydroxypropyl cellulose; and from about 1.9 weight percent to about 2.5 weight percent of Compound 1.

In some embodiments, said topical pharmaceutical composition comprises a weight ratio of polyalkylene glycol:diethylene glycol monoethyl ether of about 5:1. In some embodiments, said topical pharmaceutical composition comprises a weight ratio of polyalkylene glycol:diethylene glycol monoethyl ether of about 4.5:1. In some embodiments, said topical pharmaceutical composition comprises a weight ratio of polyalkylene glycol:diethylene glycol monoethyl ether of about 4:1. In some embodiments, said topical pharmaceutical composition comprises a weight ratio of polyalkylene glycol:diethylene glycol monoethyl ether of about 3.5:1. In some embodiments, said topical pharmaceutical composition comprises a weight ratio of polyalkylene glycol:diethylene glycol monoethyl ether of about 3:1. In some embodiments, said topical pharmaceutical composition comprises a weight ratio of polyalkylene glycol:diethylene glycol monoethyl ether of about 2.5:1. In some embodiments, said topical pharmaceutical composition comprises a weight ratio of polyalkylene glycol:diethylene glycol monoethyl ether of about 2.4:1. In some embodiments, said topical pharmaceutical composition comprises a weight ratio of polyalkylene glycol:diethylene glycol monoethyl ether of about 2:1.

In some embodiments, said topical pharmaceutical composition comprises a weight ratio of polyalkylene glycol:diethylene glycol monoethyl ether from about 1:1 to about 5:1. In some embodiments, said topical pharmaceutical composition comprises a weight ratio of polyalkylene glycol:diethylene glycol monoethyl ether from about 1.5:1 to about 4.5:1. In some embodiments, said topical pharmaceutical composition comprises a weight ratio of polyalkylene glycol:diethylene glycol monoethyl ether from about 2:1 to about 4:1. In some embodiments, said topical pharmaceutical composition comprises a weight ratio of polyalkylene glycol:diethylene glycol monoethyl ethe from about 2:1 to about 3.5:1. In some embodiments, said topical pharmaceutical composition comprises a weight ratio of

polyalkylene glycol:diethylene glycol monoethyl ether from about 2:1 to about 3:1.

In some embodiments, said topical pharmaceutical composition comprises a weight ratio of PEG 400:diethylene glycol monoethyl ether of about 5:1. In some embodiments, said topical pharmaceutical composition comprises a weight ratio of PEG 400:diethylene glycol monoethyl ether of about 4.5:1. In some embodiments, said topical pharmaceutical composition comprises a weight ratio of PEG 400:diethylene glycol monoethyl ether of about 4:1. In some embodiments, said topical pharmaceutical composition comprises a weight ratio of PEG 400:diethylene glycol monoethyl ether of about 3.5:1. In some embodiments, said topical pharmaceutical composition comprises a weight ratio of PEG 400:diethylene glycol monoethyl ether of about 3:1. In some embodiments, said topical pharmaceutical composition comprises a weight ratio of PEG 400:diethylene glycol monoethyl ether of about 2.5:1. In some embodiments, said topical pharmaceutical composition comprises a weight ratio of PEG 400:diethylene glycol monoethyl ether of about 2:1.

In some embodiments, said topical pharmaceutical composition comprises a weight ratio of PEG 400:diethylene glycol monoethyl ether from about 1:1 to about 5:1. In some embodiments, said topical pharmaceutical composition comprises a weight ratio of PEG 400:diethylene glycol monoethyl ether from about 1.5:1 to about 4.5:1. In some embodiments, said topical pharmaceutical composition comprises a weight ratio of PEG 400:diethylene glycol monoethyl ether from about 2:1 to about 4:1. In some embodiments, said topical pharmaceutical composition comprises a weight ratio of PEG 400:diethylene glycol monoethyl ether from about 2:1 to about 3.5:1. In some embodiments, said topical pharmaceutical composition comprises a weight ratio of PEG 400:diethylene glycol monoethyl ether from about 2:1 to about 3:1.

In some preferred embodiments, said composition comprises:

at least about 6.0 weight percent of Compound 1;

at least about 55 weight percent polyethylene glycol, preferably PEG400;

at least about 23 weight percent diethylene glycol monoethyl ether;

at least about 4.5 weight percent glycerol;

at least about 9 weight percent diisopropyl adipate; and

about 1 weight percent hydroxypropyl cellulose. In preferred embodiments, said composition comprises less than 1% water, preferably less than 0.1% water. In preferred embodiments, said composition comprises less than 1% ethanol, preferably less than 0.1% ethanol.

In some preferred embodiments, said composition comprises:

6.3 weight percent of Compound 1;

55.25 weight percent polyethylene glycol, preferably PEG400;

23.41 weight percent diethylene glycol monoethyl ether;

4.68 weight percent glycerol;

9.36 weight percent diisopropyl adipate; and

1 weight percent hydroxypropyl cellulose. In preferred embodiments, said composition comprises less than 1% water, preferably less than 0.1% water. In preferred embodiments, said composition comprises less than 1% ethanol, preferably less than 0.1% ethanol.

In some preferred embodiments, said composition comprises:

at least about 2.0 weight percent of Compound 1;

at least about 55 weight percent polyethylene glycol, preferably PEG400;

at least about 23 weight percent diethylene glycol monoethyl ether;

at least about 4.5 weight percent glycerol;

at least about 9 weight percent diisopropyl adipate; and

about 1 weight percent hydroxypropyl cellulose. In preferred embodiments, said composition comprises less than 1% water, preferably less than 0.1% water. In preferred embodiments, said composition comprises less than 1% ethanol, preferably less than 0.1% ethanol.

In some preferred embodiments, said composition comprises:

2.0 weight percent of Compound 1;

57.81 weight percent polyethylene glycol, preferably PEG400;

24.50 weight percent diethylene glycol monoethyl ether;

4.89 weight percent glycerol (anhydrous);

9.80 weight percent diisopropyl adipate; and

1 weight percent hydroxypropyl cellulose. In preferred embodiments, said composition comprises less than 1% water, preferably less than 0.1% water. In preferred embodiments, said composition comprises less than 1% ethanol, preferably less than 0.1% ethanol. In preferred embodiments, said composition does not comprise DMSO.

In some preferred embodiments, said composition comprises:

from about 1.5 weight percent to about 2.5 weight percent, preferably from about 1.9 weight percent to about 2.5 weight percent Compound 1;

from about 45 weight percent to about 75 weight percent polyethylene glycol, preferably PEG400;

from about 15 weight percent to about 30 weight percent diethylene glycol monoethyl ether;

from about 1 weight percent to about 10 weight percent glycerol;

from about 5 weight percent to about 15 weight percent diisopropyl adipate; and

from about 0.1 weight percent to about 10 weight percent hydroxypropyl cellulose.

In one aspect, the present disclosure provides a topical aqueous pharmaceutical composition.

In some embodiments, said topical aqueous pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent polyalkylene glycol; from about 10 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 10 weight percent diisopropyl adipate; from about 1 weight percent to about 10 weight percent glycerol; from about 1 weight percent to about 20 weight percent water; and from about 0.1 weight percent, preferably about 0.5 weight percent to about 8 weight percent of a compound of Formula (I).

In some embodiments, said topical aqueous pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent polyalkylene glycol; from about 10 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 10 weight percent diisopropyl adipate; from about 1 weight percent to about 10 weight percent glycerol; from about 1 weight percent to about 20 weight percent water; and from about 0.9 weight percent to about 8 weight percent of a compound of Formula (I).

In some embodiments, said topical aqueous pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent polyalkylene glycol; about 10 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 10 weight percent diisopropyl adipate; from about 1 weight percent to about 10 weight percent glycerol; from about 1 weight percent to about 20 weight percent water; and from about 1 weight percent to about 7.9 weight percent of a compound of Formula (I).

In some embodiments, said topical aqueous pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent polyalkylene glycol; about 10 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 10 weight percent diisopropyl adipate; from about 1 weight percent to about

10 weight percent glycerol; from about 1 weight percent to about 15 weight percent water; and from about 1.9 weight percent to about 7 weight percent of a compound of Formula (I).

In some embodiments, said topical aqueous pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent polyalkylene glycol; about 10 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 2 weight percent to about 8 weight percent diisopropyl adipate; from about 3 weight percent to about 8 weight percent glycerol; from about 1 weight percent to about 15 weight percent water; and from about 1.9 weight percent to about 5 weight percent of a compound of Formula (I).

In some embodiments, said topical aqueous pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent polyalkylene glycol; about 15 weight percent to about 25 weight percent diethylene glycol monoethyl ether; from about 2 weight percent to about 8 weight percent diisopropyl adipate; from about 3 weight percent to about 8 weight percent glycerol; from about 5 weight percent to about 15 weight percent water; and from about 1.9 weight percent to about 4 weight percent of a compound of Formula (I).

In some embodiments, said topical aqueous pharmaceutical composition comprises from about 45 weight percent to about 65 weight percent polyalkylene glycol; about 15 weight percent to about 25 weight percent diethylene glycol monoethyl ether; from about 2 weight percent to about 9 weight percent diisopropyl adipate; from about 3 weight percent to about 8 weight percent glycerol; from about 5 weight percent to about 15 weight percent water; and from about 1.9 weight percent to about 4 weight percent of a compound of Formula (I).

In some embodiments, said topical aqueous pharmaceutical composition comprises from about 45 weight percent to about 65 weight percent polyalkylene glycol; about 15 weight percent to about 25 weight percent diethylene glycol monoethyl ether; from about 3 weight percent to about 6 weight percent diisopropyl adipate; from about 4 weight percent to about 6 weight percent glycerol; from about 9 weight percent to about 11 weight percent water; and from about 1.9 weight percent to about 4 weight percent of a compound of Formula (I).

In some embodiments, said topical aqueous pharmaceutical composition comprises from about 50 weight percent to about 60 weight percent polyalkylene glycol; about 18 weight percent to about 22 weight percent diethylene glycol monoethyl ether; from about 3 weight percent to about 6 weight percent diisopropyl adipate; from about 4 weight percent to about 6 weight percent glycerol; from about 9 weight percent to about 11 weight percent water; and from about 1.9 weight percent to about 4 weight percent of a compound of Formula (I).

In some embodiments, said topical aqueous pharmaceutical composition comprises

from about 45 weight percent to about 80 weight percent PEG, preferably PEG400; from about 10 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 10 weight percent diisopropyl adipate; from about 1 weight percent to about 10 weight percent glycerol; from about 1 weight percent to about 20 weight percent water; and from about 0.1 weight percent, preferably about 0.5 weight percent, to about 8 weight percent of Compound 1.

In some embodiments, said topical aqueous pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent PEG, preferably PEG400; from about 10 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 10 weight percent diisopropyl adipate; from about 1 weight percent to about 10 weight percent glycerol; from about 1 weight percent to about 20 weight percent water; and from about 0.9 weight percent to about 8 weight percent of Compound 1.

In some embodiments, said topical aqueous pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent PEG, preferably PEG400; about 10 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 10 weight percent diisopropyl adipate; from about 1 weight percent to about 10 weight percent glycerol; from about 1 weight percent to about 20 weight percent water; and from about 1 weight percent to about 7.9 weight percent of Compound 1.

In some embodiments, said topical aqueous pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent PEG, preferably PEG400; about 10 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 10 weight percent diisopropyl adipate; from about 1 weight percent to about 10 weight percent glycerol; from about 1 weight percent to about 15 weight percent water; and from about 1.9 weight percent to about 7 weight percent of Compound 1.

In some embodiments, said topical aqueous pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent PEG, preferably PEG400; about 10 weight percent to about 30 weight percent diethylene glycol monoethyl ether; from about 2 weight percent to about 8 weight percent diisopropyl adipate; from about 3 weight percent to about 8 weight percent glycerol; from about 1 weight percent to about 15 weight percent water; and from about 1.9 weight percent to about 5 weight percent of Compound 1.

In some embodiments, said topical aqueous pharmaceutical composition comprises from about 45 weight percent to about 75 weight percent PEG, preferably PEG400; about 15 weight percent to about 25 weight percent diethylene glycol monoethyl ether; from about 2

weight percent to about 8 weight percent diisopropyl adipate; from about 3 weight percent to about 8 weight percent glycerol; from about 5 weight percent to about 15 weight percent water; and from about 1.9 weight percent to about 4 weight percent of Compound 1.

In some embodiments, said topical aqueous pharmaceutical composition comprises from about 45 weight percent to about 65 weight percent PEG, preferably PEG400; about 15 weight percent to about 25 weight percent diethylene glycol monoethyl ether; from about 2 weight percent to about 9 weight percent diisopropyl adipate; from about 3 weight percent to about 8 weight percent glycerol; from about 5 weight percent to about 15 weight percent water; and from about 1.9 weight percent to about 4 weight percent of Compound 1.

In some embodiments, said topical aqueous pharmaceutical composition comprises from about 45 weight percent to about 65 weight percent PEG, preferably PEG400; about 15 weight percent to about 25 weight percent diethylene glycol monoethyl ether; from about 3 weight percent to about 6 weight percent diisopropyl adipate; from about 4 weight percent to about 6 weight percent glycerol; from about 9 weight percent to about 11 weight percent water; and from about 1.9 weight percent to about 4 weight percent of Compound 1.

In some embodiments, said topical aqueous pharmaceutical composition comprises from about 50 weight percent to about 60 weight percent PEG, preferably PEG400; about 18 weight percent to about 22 weight percent diethylene glycol monoethyl ether; from about 3 weight percent to about 6 weight percent diisopropyl adipate; from about 4 weight percent to about 6 weight percent glycerol; from about 9 weight percent to about 11 weight percent water; and from about 1.9 weight percent to about 4 weight percent of Compound 1.

In some embodiments, said topical aqueous pharmaceutical composition comprises

at least about 3 weight percent of Compound 1;

at least about 9 weight percent water;

at least about 54 weight percent polyethylene glycol, preferably PEG400;

at least about 19 weight percent diethylene glycol monoethyl ether;

at least about 4 weight percent glycerol;

at least about 4 weight percent diisopropyl adipate;

at least about 2 weight percent benzyl alcohol; and

about 1 weight percent polyacrylic acid. In preferred embodiments, said composition comprises less than about 1% ethanol, preferably less than about 0.1% ethanol.

In some embodiments, said topical aqueous pharmaceutical composition comprises

3.2 weight percent of Compound 1;

9.64 weight percent water;

54.9 weight percent polyethylene glycol, preferably PEG400;

19.26 weight percent diethylene glycol monoethyl ether;

5 weight percent glycerol;

5 weight percent diisopropyl adipate;

2 weight percent benzyl alcohol; and

1 weight percent polyacrylic acid. In preferred embodiments, said composition comprises less than 1% ethanol, preferably less than 0.1% ethanol.

In some embodiments, said topical aqueous pharmaceutical composition comprises

at least about 3 weight percent of Compound 1;

at least about 9 weight percent water;

at least about 57 weight percent polyethylene glycol, preferably PEG400;

at least about 21 weight percent diethylene glycol monoethyl ether;

about 3 weight percent glycerol;

about 1.5 weight percent oleyl alcohol;

about 2 weight percent benzyl alcohol; and

about 1 weight percent polyacrylic acid. In preferred embodiments, said composition comprises less than 1% ethanol, preferably less than 0.1% ethanol.

In some embodiments, said topical aqueous pharmaceutical composition comprises

3.4 weight percent of Compound 1;

9.52 weight percent water;

57.67 weight percent polyethylene glycol, preferably PEG400;

21.91 weight percent diethylene glycol monoethyl ether;

3 weight percent glycerol;

1.5 weight percent oleyl alcohol;

2 weight percent benzyl alcohol; and

1 weight percent polyacrylic acid. In preferred embodiments, said composition comprises less than 1% ethanol, preferably less than 0.1% ethanol.

In some preferred embodiments, said composition comprises:

(i) at least about 1.9 weight percent of Compound 1;

at least about 55 weight percent polyethylene glycol, preferably PEG400;

at least about 23 weight percent diethylene glycol monoethyl ether;

at least about 4.5 weight percent glycerol;

at least about 9 weight percent diisopropyl adipate; and

about 1 weight percent hydroxypropyl cellulose;

(ii) at least about 3 weight percent of Compound 1;

at least about 9 weight percent water;

at least about 54 weight percent polyethylene glycol, preferably PEG400;

at least about 19 weight percent diethylene glycol monoethyl ether;

at least about 4 weight percent glycerol;

at least about 4 weight percent diisopropyl adipate;

at least about 2 weight percent benzyl alcohol; and

about 1 weight percent polyacrylic acid; or

(iii) at least about 3 weight percent of Compound 1;

at least about 9 weight percent water;

at least about 57 weight percent polyethylene glycol, preferably PEG400;

at least about 21 weight percent diethylene glycol monoethyl ether;

about 3 weight percent glycerol;

about 1.5 weight percent oleyl alcohol;

about 2 weight percent benzyl alcohol; and

about 1 weight percent polyacrylic acid. In preferred embodiments, said composition comprises less than 1% ethanol, preferably less than 0.1% ethanol.

In some preferred embodiments, said composition comprises:

(i) at least about 1.9 weight percent of Compound 1;

at least about 55 weight percent polyethylene glycol, preferably PEG400;

at least about 23 weight percent diethylene glycol monoethyl ether;

at least about 4.5 weight percent glycerol;

at least about 9 weight percent diisopropyl adipate; and

about 1 weight percent hydroxypropyl cellulose; or

(ii) at least about 3 weight percent of Compound 1;

at least about 9 weight percent water;

at least about 54 weight percent polyethylene glycol, preferably PEG400;

at least about 19 weight percent diethylene glycol monoethyl ether;

at least about 4 weight percent glycerol;

at least about 4 weight percent diisopropyl adipate;

at least about 2 weight percent benzyl alcohol; and

about 1 weight percent polyacrylic acid. In preferred embodiments, said composition comprises less than 1% ethanol, preferably less than 0.1% ethanol.

In some preferred embodiments, said composition comprises:

(i) at least about 1.9 weight percent of Compound 1;

at least about 55 weight percent polyethylene glycol, preferably PEG400;

at least about 23 weight percent diethylene glycol monoethyl ether;

at least about 4.5 weight percent glycerol;

at least about 9 weight percent diisopropyl adipate; and

about 1 weight percent hydroxypropyl cellulose; or

(ii) at least about 3 weight percent of Compound 1;

at least about 9 weight percent water;

at least about 57 weight percent polyethylene glycol, preferably PEG400;

at least about 21 weight percent diethylene glycol monoethyl ether;

about 3 weight percent glycerol;

about 1.5 weight percent oleyl alcohol;

about 2 weight percent benzyl alcohol; and

about 1 weight percent polyacrylic acid. In preferred embodiments, said composition comprises less than 1% ethanol, preferably less than 0.1% ethanol.

In some preferred embodiments, said composition comprises:

(i) at least about 3 weight percent of Compound 1;

at least about 9 weight percent water;

at least about 54 weight percent polyethylene glycol, preferably PEG400;

at least about 19 weight percent diethylene glycol monoethyl ether;

at least about 4 weight percent glycerol;

at least about 4 weight percent diisopropyl adipate;

at least about 2 weight percent benzyl alcohol; and

about 1 weight percent polyacrylic acid; or

(ii) at least about 3 weight percent of Compound 1;

at least about 9 weight percent water;

at least about 57 weight percent polyethylene glycol, preferably PEG400;

at least about 21 weight percent diethylene glycol monoethyl ether;

about 3 weight percent glycerol;

about 1.5 weight percent oleyl alcohol;

about 2 weight percent benzyl alcohol; and

about 1 weight percent polyacrylic acid. In preferred embodiments, said composition comprises less than 1% ethanol, preferably less than 0.1% ethanol.

In some preferred embodiments, said composition comprises:

(i) 2.0 weight percent of Compound 1;

57.81 weight percent polyethylene glycol, preferably PEG400;

23.41 weight percent diethylene glycol monoethyl ether;

4.68 weight percent glycerol;

9.36 weight percent diisopropyl adipate; and

1 weight percent hydroxypropyl cellulose;

(ii) 3.2 weight percent of Compound 1;

9.64 weight percent water;

54.9 weight percent polyethylene glycol, preferably PEG400;

19.26 weight percent diethylene glycol monoethyl ether;

5 weight percent glycerol;

5 weight percent diisopropyl adipate;

2 weight percent benzyl alcohol; and

1 weight percent polyacrylic acid; or

(iii) 3.4 weight percent of Compound 1;

9.52 weight percent water;

57.67 weight percent polyethylene glycol, preferably PEG400;

21.91 weight percent diethylene glycol monoethyl ether;

3 weight percent glycerol;

1.5 weight percent oleyl alcohol;

2 weight percent benzyl alcohol; and

1 weight percent polyacrylic acid. In preferred embodiments, said composition comprises less than 1% ethanol, preferably less than 0.1% ethanol.

In some preferred embodiments, said composition comprises:

(i) 2.0 weight percent of Compound 1;

57.81 weight percent polyethylene glycol, preferably PEG400;

23.41 weight percent diethylene glycol monoethyl ether;

4.68 weight percent glycerol;

9.36 weight percent diisopropyl adipate; and

1 weight percent hydroxypropyl cellulose; or

(ii) 3.2 weight percent of Compound 1;

9.64 weight percent water;

54.9 weight percent polyethylene glycol, preferably PEG400;

19.26 weight percent diethylene glycol monoethyl ether;

5 weight percent glycerol;

5 weight percent diisopropyl adipate;

2 weight percent benzyl alcohol; and

1 weight percent polyacrylic acid.

In preferred embodiments, said composition comprises less than 1% ethanol, preferably less than 0.1% ethanol.

In some preferred embodiments, said composition comprises:

(i) 3.2 weight percent of Compound 1;

9.64 weight percent water;

54.9 weight percent polyethylene glycol, preferably PEG400;

19.26 weight percent diethylene glycol monoethyl ether;

5 weight percent glycerol;

5 weight percent diisopropyl adipate;

2 weight percent benzyl alcohol; and

1 weight percent polyacrylic acid; or

(ii) 3.4 weight percent of Compound 1;

9.52 weight percent water;

57.67 weight percent polyethylene glycol, preferably PEG400;

21.91 weight percent diethylene glycol monoethyl ether;

3 weight percent glycerol;

1.5 weight percent oleyl alcohol;

2 weight percent benzyl alcohol; and

1 weight percent polyacrylic acid. In preferred embodiments, said composition comprises less than 1% ethanol, preferably less than 0.1% ethanol.

In some preferred embodiments, said composition comprises:

(i) 2.0 weight percent of Compound 1;

57.81 weight percent polyethylene glycol, preferably PEG400;

23.41 weight percent diethylene glycol monoethyl ether;

4.68 weight percent glycerol;

9.36 weight percent diisopropyl adipate; and

1 weight percent hydroxypropyl cellulose;

or

(ii) 3.4 weight percent of Compound 1;

9.52 weight percent water;

57.67 weight percent polyethylene glycol, preferably PEG400;

21.91 weight percent diethylene glycol monoethyl ether;

3 weight percent glycerol;

1.5 weight percent oleyl alcohol;

2 weight percent benzyl alcohol; and

1 weight percent polyacrylic acid. In preferred embodiments, said composition comprises less than 1% ethanol, preferably less than 0.1% ethanol.

In some embodiments, said composition comprises:

58.94 weight percent polyethylene glycol 400 (PEG400);

24.98 weight percent diethylene glycol monoethyl ether (Transcutol P®);

9.99 weight percent diisopropyl adipate;

4.99 weight percent glycerol, preferably anhydrous glycerol;

0.10 weight percent Compound 1; and

1.00 weight percent hydroxypropyl cellulose. In preferred embodiments, said composition comprises less than 1% water, preferably less than 0.1% water. In preferred embodiments, said composition comprises less than 1% ethanol, preferably less than 0.1% ethanol. In preferred embodiments, said composition does not comprise DMSO.

In some embodiments, said composition comprises:

58.70 weight percent polyethylene glycol 400 (PEG400);

24.88 weight percent diethylene glycol monoethyl ether (Transcutol P®);

9.95 weight percent diisopropyl adipate;

4.97 weight percent glycerol, preferably anhydrous glycerol;

0.50 weight percent Compound 1; and

1.00 weight percent hydroxypropyl cellulose. In preferred embodiments, said composition comprises less than 1% water, preferably less than 0.1% water. In preferred embodiments, said composition comprises less than 1% ethanol, preferably less than 0.1% ethanol. In preferred embodiments, said composition does not comprise DMSO.

In some embodiments, said composition comprises:

57.22 weight percent polyethylene glycol 400 (PEG400);

24.24 weight percent diethylene glycol monoethyl ether (Transcutol P®);

9.70 weight percent diisopropyl adipate;

4.84 weight percent glycerol, preferably anhydrous glycerol;

3.00 weight percent Compound 1; and

1.00 weight percent hydroxypropyl cellulose. In preferred embodiments, said composition comprises less than 1% water, preferably less than 0.1% water. In preferred embodiments, said composition comprises less than 1% ethanol, preferably less than 0.1% ethanol. In preferred embodiments, said composition does not comprise DMSO.

In some embodiments, said topical pharmaceutical composition further comprises one or more additional excipients and wherein said pharmaceutically acceptable excipient is selected from the group consisting of a thickening agent, a stabilizer, an antioxidant, a chelating agent, an oily material, an emulsifier, a penetration enhancer, a pH adjusting agent, a preservative, an antimicrobial agent, an opacifier, a fragrance, a colorant, a gelling agent, a moisturizer, a surfactant, and a combination thereof.

In one embodiment, said topical composition comprises one or more other pharmaceutically acceptable excipients, and said pharmaceutically acceptable excipient is selected from the group consisting of a thickening agent, a stabilizer, an antioxidant, a pH adjusting agent, a preservative, an antimicrobial agent, and a combination thereof.

The pharmaceutically acceptable excipients used in the topical composition of the present invention can act in more than one way. For example, a thickening agent can also function as a gelling agent.

In a preferred embodiment, said topical composition comprises one or more other pharmaceutically acceptable excipients, and one of said pharmaceutically acceptable excipients is a thickening agent. In a preferred embodiment, said topical composition comprises a thickening agent.

In a preferred embodiment, said topical composition comprises one or more other pharmaceutically acceptable excipients, and one of said pharmaceutically acceptable excipients is an antioxidant. In a preferred embodiment, said topical composition comprises an antioxidant.

Antioxidants are known to the skilled person in the art and includes, for example, butylated hydroxyanisole, butylated hydroxytoluene, vitamin C, vitamin E, vitamin A, lutein,

lycopene, retinyl palmitate, potassium metabisulfite, sodium metabisulfite, sodium thiosulfate pentahydrate, 3,4-dihydroxybenzoic acid, propyl gallate, alpha-lipoic acid, ascorbyl palmitate, sodium pyrosulfite, ubiquinone, selenium, or a combination thereof.

In a preferred embodiment, said topical composition comprises one or more excipient, wherein said excipient is an antioxidant selected from butylated hydroxyanisole, butylated hydroxytoluene, vitamin C, vitamin E, vitamin A, lutein, lycopene, retinyl palmitate, potassium metabisulfite, sodium metabisulfite, sodium thiosulfate pentahydrate, 3,4-dihydroxybenzoic acid, propyl gallate, alpha-lipoic acid, ascorbyl palmitate, sodium pyrosulfite, ubiquinone, selenium, or a combination thereof.

In some embodiments, the antioxidant is present from about 0.001% (w/w) to about 0.1% (w/w), preferably about 0.001% (w/w) to about 0.01% (w/w), more preferably about 0.002% (w/w) to about 0.008% (w/w), based on the total weight of said topical composition.

In some embodiments, said topical pharmaceutical composition further comprises a buffer, preferably a phosphate buffer.

In a preferred embodiment, said topical composition comprises a buffer, preferably a phosphate buffer, of a pH of about 6.5 to about 7.5, further preferably a buffer, preferably a phosphate buffer, of a pH of about 6.5 to about 7.0, even more preferably a buffer, preferably a buffer, of a pH of about 6.7.

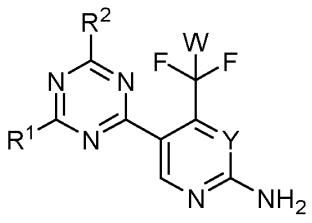
In a preferred embodiment, said topical composition is in the form of a non-aqueous gel, and wherein said topical composition comprises a phosphate buffer, wherein preferably said topical composition comprises a phosphate buffer of a pH of about 6.5 to about 7.5, further preferably a phosphate buffer of a pH of about 6.5 to about 7.0, even more preferably a phosphate buffer of a pH of about 6.7.

In a preferred embodiment, said topical composition is in the form of an aqueous gel, and wherein said topical composition comprises an aqueous phosphate buffer, wherein preferably said topical composition comprises an aqueous phosphate buffer of a pH of about 6.5 to about 7.5, further preferably an aqueous phosphate buffer of a pH of about 6.5 to about 7.0, even more preferably an aqueous phosphate buffer of a pH of about 6.7.

In a preferred embodiment, said buffer, preferably said phosphate buffer, has a molarity of about 10 to about 15 mM, preferably of about 12mM. In a preferred embodiment, said buffer is a phosphate buffer, wherein said phosphate buffer has a molarity of about 10 to about 15 mM, preferably of about 12mM.

Compounds of Formula (I)

In one aspect, the inventive pharmaceutical compositions comprise a compound of Formula (I):

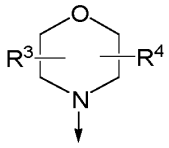

Formula (I)

wherein:

W is H or F;

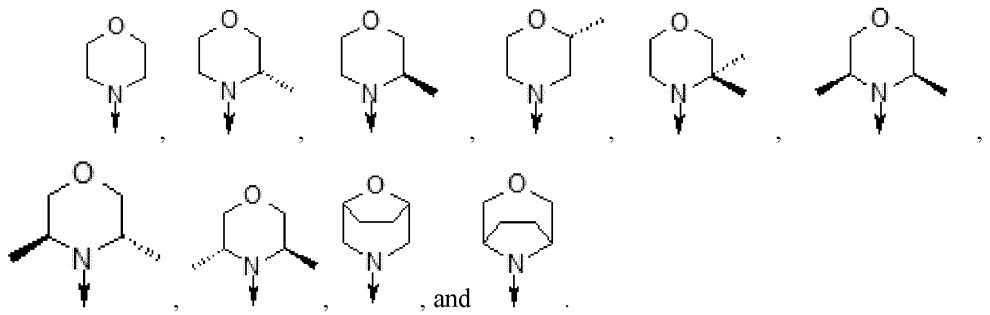
Y is N or CH;

R^1 and R^2 are independently of each other a morpholinyl of Formula (II)

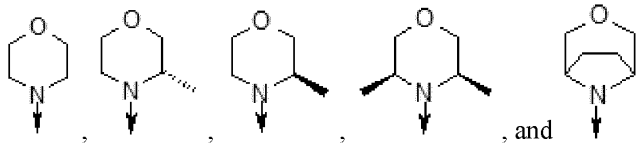

Formula (II)

wherein R^3 and R^4 are independently of each other H or -C_1-C_3alkyl; or R^3 and R^4 combine to form a bivalent C_1-C_3alkylene residue.

In some embodiments, R^1 and R^2 are each independently of each other selected from:


, and .

In some embodiments, R^1 and R^2 are each independently of each other selected from:


, and .

In some embodiments, the compound of Formula (I) is selected from:

5-(4,6-dimorpholino-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine (Compound 1);

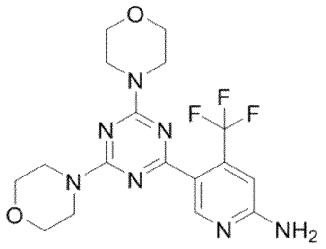
4-(difluoromethyl)-5-(4,6-dimorpholino-1,3,5-triazin-2-yl)pyrimidin-2-amine (Compound 2);

5-(4-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-6-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-1,3,5-triazin-2-yl)-4-(difluoromethyl)pyridin-2-amine (Compound 3);

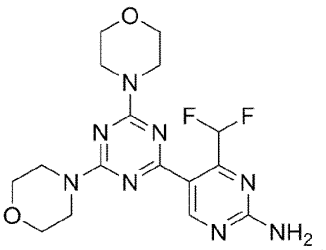
(S)-4-(difluoromethyl)-5-(4-(3-methylmorpholino)-6-morpholino-1,3,5-triazin-2-yl)pyridin-2-amine (Compound 4); and

4-(difluoromethyl)-5-[4-[(3R,5S)-3,5-dimethylmorpholin-4-yl]-6-[(3R)-3-methylmorpholin-4-yl]-1,3,5-triazin-2-yl]pyridin-2-amine (Compound 5).

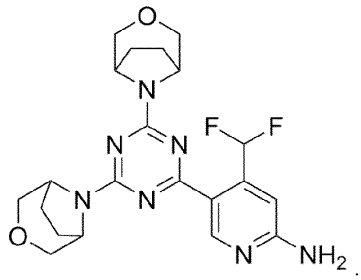
In some embodiments, the compound of Formula (I) is 5-(4,6-dimorpholino-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine (Compound 1), also known as "PQR309" and "bimiralisib":



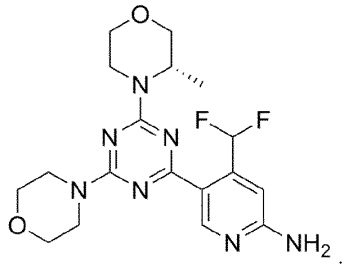
In some embodiments, the compound of Formula (I) is 4-(difluoromethyl)-5-(4,6-dimorpholino-1,3,5-triazin-2-yl)pyrimidin-2-amine (Compound 2):



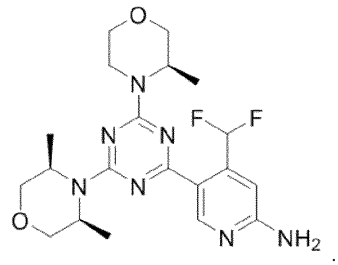
In some embodiments, the compound of Formula (I) is 5-(4-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-6-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-1,3,5-triazin-2-yl)-4-(difluoromethyl)pyridin-2-amine (Compound 3):



In some embodiments, the compound of Formula (I) is (S)-4-(difluoromethyl)-5-(4-(3-methylmorpholino)-6-morpholino-1,3,5-triazin-2-yl)pyridin-2-amine (Compound 4):



In some embodiments, the compound of Formula (I) is 4-(difluoromethyl)-5-[4-[(3R,5S)-3,5-dimethylmorpholin-4-yl]-6-[(3R)-3-methylmorpholin-4-yl]-1,3,5-triazin-2-yl]pyridin-2-amine (Compound 5):



Methods of Treatment

As used herein, the term "for use" as used in "topical pharmaceutical composition for use in treatment of a disease" shall disclose also the corresponding method of treatment and the corresponding use of a preparation for the manufacture of a medicament for the treatment of a disease.

Thus, in one aspect, the present invention provides the inventive topical pharmaceutical compositions for use as a medicament.

As shown in the Examples below, the inventive topical pharmaceutical compositions

were safe and effective for the treatment of skin lesions such as actinic keratosis as demonstrated by a randomized phase 2 clinical trial. The safety profile of the inventive topical pharmaceutical compositions suggested that they were well-tolerated, with related adverse events being mostly grade 1 in nature. Related adverse events such as lesion erosion, crusting and erythema resolved rapidly after the end of treatment. The four-week treatment period was not observed to add significant additional toxicity over the 2-week treatment. Only one patient out of a group of 42 patients treated stopped treatment before the full course was completed.

The inventive topical pharmaceutical compositions showed high levels of efficacy with 60% of patients exhibiting lesions that were either completely or partially cleared at the 4-week follow-up visit (70% in Arm B and 50% in Arm A of the phase 2 trial).

In one aspect, the present invention provides the inventive topical pharmaceutical compositions for use in the prevention or treatment of a skin lesion or skin disorder in a subject, wherein said inventive topical pharmaceutical compositions are administered topically to said subject.

In preferred embodiments, said inventive topical pharmaceutical composition is administered to said subject once daily. In some embodiments, said inventive topical composition is administered once daily for two weeks or four weeks. In some embodiments, said inventive topical composition is administered once daily for two weeks. In some embodiments, said inventive topical composition is administered once daily for four weeks.

In one aspect, the present invention provides the inventive topical pharmaceutical compositions for use in the prevention or treatment of a skin lesion or skin disorder in a subject, wherein said inventive topical pharmaceutical composition is administered once daily.

In one aspect, the present invention provides the inventive topical pharmaceutical compositions for use in the prevention or treatment of actinic keratosis in a subject, wherein said inventive topical pharmaceutical composition is administered once daily.

In one aspect, the present invention provides the inventive topical pharmaceutical compositions for use in the prevention or treatment of cutaneous squamous cell carcinoma in a subject, wherein said inventive topical pharmaceutical composition is administered once daily.

In one aspect, the present invention provides a method of treating a skin lesion or skin disorder in a subject in need thereof, the method comprising topically administering to said subject an inventive topical pharmaceutical composition of the disclosure, preferably wherein said topical pharmaceutical composition is administered once daily.

In one aspect, the present invention provides the use of an inventive topical pharmaceutical composition of the disclosure in the manufacture of a medicament for topical treatment of a skin lesion or skin disorder in a subject, preferably wherein said topical pharmaceutical composition is for once daily administration.

In one embodiment, there is provided a topical pharmaceutical composition comprising a compound of Formula (I) according to the invention (preferably Compound 1) for use in the prevention or treatment of a skin lesion in a subject, wherein said topical pharmaceutical composition comprising a compound of Formula (I) is administered topically, preferably once daily, to the subject.

In one embodiment, there is provided a topical pharmaceutical composition comprising a compound of Formula (I) according to the invention (preferably Compound 1) for use in the prevention or treatment of a skin lesion in a subject, preferably wherein said skin lesion is non-melanoma skin cancer (NMSC), a cutaneous lymphoma or a pre-invasive form thereof.

In a preferred embodiment of the present invention, said skin lesion is a pre-invasive form of non-melanoma skin cancer (NMSC).

In another preferred embodiment of the present invention, said skin lesion is a non-melanoma skin cancer (NMSC).

In another preferred embodiment of the present invention, said skin lesion is a cutaneous lymphoma.

In a further embodiment, there is provided a topical pharmaceutical composition comprising a compound of Formula (I) according to the invention (preferably Compound 1) for use in the prevention or treatment of a non-melanoma skin cancer (NMSC) in a subject, wherein said non-melanoma skin cancer is a cutaneous squamous cell carcinoma (cSCC) or a basal cell carcinoma.

In a preferred embodiment, there is provided a topical pharmaceutical composition comprising a compound of Formula (I) according to the invention (preferably Compound 1) for use in the prevention or treatment of a cutaneous squamous cell carcinoma (cSCC) in a subject.

In a further embodiment, there is provided a topical pharmaceutical composition comprising a compound of Formula (I) according to the invention (preferably Compound 1) for use in the prevention or treatment of a cutaneous squamous cell carcinoma (cSCC) in a subject, wherein said cutaneous squamous cell carcinoma (cSCC) is an invasive cSCC.

In a further embodiment, there is provided a topical pharmaceutical composition

comprising a compound of Formula (I) according to the invention (preferably Compound 1) for use in the prevention or treatment of a cutaneous squamous cell carcinoma (cSCC) in a subject, wherein said cutaneous squamous cell carcinoma (cSCC) is a metastatic cSCC.

In one embodiment, there is provided a topical pharmaceutical composition comprising a compound of Formula (I) according to the invention (preferably Compound 1) for use in the prevention or treatment of a basal cell carcinoma in a subject.

In a further embodiment, there is provided a topical pharmaceutical composition comprising a compound of Formula (I) according to the invention (preferably Compound 1) for use in the prevention or treatment of a basal cell carcinoma in a subject, wherein said basal cell carcinoma is selected from the group consisting of superficial basal cell carcinoma (also known as "in situ basal cell carcinoma" or "superficial multicentric basal-cell carcinoma"), infiltrative basal cell carcinoma and nodular basal cell carcinoma.

In a preferred embodiment, there is provided a topical pharmaceutical composition comprising a compound of Formula (I) according to the invention (preferably Compound 1) for use in the prevention or treatment of a basal cell carcinoma in a subject, wherein said basal cell carcinoma is a superficial basal cell carcinoma (also known as "in situ basal cell carcinoma" or "superficial multicentric basal-cell carcinoma").

In a further preferred embodiment, there is provided a topical pharmaceutical composition comprising a compound of Formula (I) according to the invention (preferably Compound 1) for use in the prevention or treatment of a basal cell carcinoma in a subject, wherein said basal cell carcinoma is an infiltrative basal cell carcinoma.

In a further preferred embodiment, there is provided a topical pharmaceutical composition comprising a compound of Formula (I) according to the invention (preferably Compound 1) for use in the prevention or treatment of a basal cell carcinoma in a subject, wherein said basal cell carcinoma is a nodular basal cell carcinoma.

In one embodiment, there is provided a topical pharmaceutical composition comprising a compound of Formula (I) according to the invention (preferably Compound 1) for use in the prevention or treatment of a basal cell carcinoma in a subject, wherein said basal cell carcinoma is selected from the group consisting of cystic basal cell carcinoma, cicatricial basal cell carcinoma (also known as "morpheaform basal cell carcinoma" or "morphoeic basal cell carcinoma"), micronodular basal cell carcinoma, pigmented basal cell carcinoma, rodent ulcer (also known as "Jacob's ulcer"), fibroepithelioma of Pinkus, polypoid basal cell carcinoma, pore-like basal cell carcinoma and aberrant basal cell carcinoma.

In a further embodiment, there is provided a topical pharmaceutical composition comprising a compound of Formula (I) according to the invention (preferably Compound 1) for use in the prevention or treatment of a pre-invasive form of non-melanoma skin cancer (NMSC) in a subject, wherein said pre-invasive form is selected from the group consisting of cutaneous squamous cell carcinoma *in situ* (cSCCis, also known as "Bowen's disease"), precancerous actinic keratosis (AK) and chronic UV damage.

In a preferred embodiment, there is provided a topical pharmaceutical composition comprising a compound of Formula (I) according to the invention (preferably Compound 1) for use in the prevention or treatment of a pre-invasive form of non-melanoma skin cancer (NMSC), wherein said pre-invasive form is cutaneous squamous cell carcinoma in situ (cSCCis, also known as "Bowen's disease").

In a further preferred embodiment, there is provided a topical pharmaceutical composition comprising a compound of Formula (I) according to the invention (preferably Compound 1) for use in the prevention or treatment of a pre-invasive form of non-melanoma skin cancer (NMSC) in a subject, wherein said pre-invasive form is precancerous actinic keratosis (AK).

In a further preferred embodiment, there is provided a topical pharmaceutical composition comprising a compound of Formula (I) according to the invention (preferably Compound 1) for use in the prevention or treatment of a pre-invasive form of non-melanoma skin cancer (NMSC) in a subject, wherein said pre-invasive form is chronic UV damage.

In one embodiment, there is provided a topical pharmaceutical composition comprising a compound of Formula (I) according to the invention (preferably Compound 1) for use in the prevention or treatment of actinic keratosis (AK), e.g., precancerous actinic keratosis (AK) in a subject, wherein said AK is a field cancerization.

In some embodiments, there is provided a topical pharmaceutical composition comprising a compound of Formula (I) according to the invention (preferably Compound 1) for use in the prevention or treatment of actinic keratosis (AK), preferably wherein said actinic keratosis comprises at least 3 actinic keratosis lesions, preferably wherein said at least 3 actinic keratosis lesions are of Olsen grade 1 or 2. In preferred embodiments, said at least 3 actinic keratosis lesions are non-hypertrophic. In preferred embodiments, said at least 3 actinic keratosis lesions are non-hyperkeratotic. In preferred embodiments, said at least 3 actinic keratosis lesions are contained within contiguous treatment regions, preferably up to a total area of about 100 cm^2, more preferably wherein said at least 3 actinic keratosis lesions are on

the face, scalp, and/or the back of the hands of a subject.

In some embodiments, there is provided a topical pharmaceutical composition comprising a compound of Formula (I) according to the invention (preferably Compound 1) for use in the prevention or treatment of actinic keratosis (AK), wherein said actinic keratosis comprises at least 3 actinic keratosis lesions of Olsen grade 1 or 2, wherein said actinic keratosis lesions are non-hypertrophic and non-hyperkeratotic and contained within contiguous treatment regions up to a total area of about 100 cm^2 on the face, scalp, and/or the back of the hands of a subject.

In a preferred embodiment, there is provided a topical pharmaceutical composition comprising a compound of Formula (I) according to the invention (preferably Compound 1) for use in the prevention or treatment of a cutaneous lymphoma in a subject, wherein said cutaneous lymphoma is a cutaneous T-cell lymphoma (CTCL) or a cutaneous B-cell lymphoma (CBCL).

In another preferred embodiment, there is provided a topical pharmaceutical composition comprising a compound of Formula (I) according to the invention (preferably Compound 1) for use in the prevention or treatment of a cutaneous T-cell lymphoma (CTCL) in a subject.

In another preferred embodiment, there is provided a topical pharmaceutical composition comprising a compound of Formula (I) according to the invention (preferably Compound 1) for use in the prevention or treatment of a cutaneous lymphoma in a subject, wherein said cutaneous lymphoma is a cutaneous B-cell lymphoma (CBCL).

In a preferred embodiment, there is provided a topical pharmaceutical composition comprising a compound Formula (I) according to the invention (preferably Compound 1) for use in the prevention or treatment of a skin disorder in a subject. In a preferred embodiment, said skin disorder is a genodermatosis. In a further preferred embodiment, said genodermatosis is selected from tuberous sclerosis complex (TSC), Birt-Hogg-Dubé (BHD, phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome, and hereditary keratinopathy, wherein preferably said genodermatosis is selected from a skin disorder associated with tuberous sclerosis complex (TSC), a skin disorder associated with Birt-Hogg-Dubé (BHD, phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome, and hereditary keratinopathy.

In a further preferred embodiment, said genodermatosis is tuberous sclerosis complex (TSC). In a further preferred embodiment, said genodermatosis is tuberous sclerosis complex minus (TSC-). In a further preferred embodiment, said genodermatosis is Birt-Hogg-Dubé

(BHD or also named hereditary fibroma). In a further preferred embodiment, said genodermatosis is phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome (PHTS). In a further preferred embodiment, said genodermatosis is hereditary keratinopathy. In a further preferred embodiment, said genodermatosis is hereditary keratinopathy, wherein said hereditary keratinopathy is pachyonychia congenita. In a further preferred embodiment, said genodermatosis is a skin disorder associated with tuberous sclerosis complex (TSC). In a further preferred embodiment, said genodermatosis is a skin disorder associated with Birt-Hogg-Dubé (BHD).

In a further preferred embodiment, said skin disorder associated with tuberous sclerosis complex (TSC) is an angiofibroma (AF). In a very preferred embodiment, said skin disorder associated with tuberous sclerosis complex (TSC) is a facial angiofibroma. In a further preferred embodiment, said skin disorder associated with tuberous sclerosis complex (TSC) is a hamartoma. In a further preferred embodiment, said skin disorder associated with tuberous sclerosis complex (TSC) is a periungual fibroma. In another preferred embodiment, said skin disorder associated with Birt-Hogg-Dubé (BHD) are fibrofolliculomas of BHD. In a further preferred embodiment, said skin disorder is hereditary keratinopathy. In a further preferred embodiment, said skin disorder is pachyonychia congenita.

In a further preferred embodiment, said PTEN hamartoma tumor syndrome (PHTS) is selected from Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), Lhermitte-Duclos syndrome and Proteus-like syndrome. In a further preferred embodiment, said PTEN hamartoma tumor syndrome (PHTS) is Cowden syndrome (CS). In a further preferred embodiment, said PTEN hamartoma tumor syndrome (PHTS) is Bannayan-Riley-Ruvalcaba syndrome (BRRS). In a further preferred embodiment, said PTEN hamartoma tumor syndrome (PHTS) is PTEN-related Proteus syndrome (PS). In a further preferred embodiment, said PTEN hamartoma tumor syndrome (PHTS) is Lhermitte-Duclos syndrome. In a further preferred embodiment, said PTEN hamartoma tumor syndrome (PHTS) is Proteus-like syndrome. In a further preferred embodiment, said hereditary keratinopathy, wherein preferably said hereditary keratinopathy is pachyonychia congenita.

In a further preferred embodiment, said skin disorder is PTEN hamartoma tumor syndrome (PHTS), wherein preferably said PTEN hamartoma tumor syndrome (PHTS) is selected from Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), Lhermitte-Duclos syndrome and Proteus-like syndrome. In a further preferred embodiment, said skin disorder is Cowden syndrome (CS). In a further

preferred embodiment, said skin disorder is Bannayan-Riley-Ruvalcaba syndrome (BRRS). In a further preferred embodiment, said skin disorder is PTEN-related Proteus syndrome (PS). In a further preferred embodiment, said skin disorder is Lhermitte-Duclos syndrome. In a further preferred embodiment, said skin disorder is Proteus-like syndrome. In a further preferred embodiment, said skin disorder is skin fibrosis. In a further preferred embodiment, said skin disorder is hamartoma. In a further preferred embodiment, said skin disorder is periungual fibroma.

In a further preferred embodiment, said skin disorder is a genodermatosis, wherein said genodermatosis is selected from tuberous sclerosis complex (TSC), Birt-Hogg-Dubé (BHD, phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome (PHTS), and hereditary keratinopathy.

In a further preferred embodiment, said skin disorder is a vascular anomaly, wherein said vascular anomaly is selected from port-wine stain (PWS), infantile hemangioma, blue rubber bleb nevus syndrome and a complex vascular anomaly.

In a preferred embodiment, said skin disorder is a vascular anomaly. In a further preferred embodiment, said vascular anomaly is selected from port-wine stain (PWS), infantile hemangioma, blue rubber bleb nevus syndrome and a complex vascular anomaly. In a further preferred embodiment, said vascular anomaly is port-wine stain (PWS or also named as Sturge Weber syndrome). In a further preferred embodiment, said vascular anomaly is infantile hemangioma. In a further preferred embodiment, said vascular anomaly is blue rubber bleb nevus syndrome. In a further preferred embodiment, said vascular anomaly is a complex vascular anomaly. In a further preferred embodiment, said vascular anomaly is a complex vascular anomaly, wherein said complex vascular anomaly is kaposiform hemangioendothelioma.

In a further preferred embodiment, said skin disorder is selected from port-wine stain (PWS), infantile hemangioma, blue rubber bleb nevus syndrome and a complex vascular anomaly. In a further preferred embodiment, said skin disorder is port-wine stain (PWS or also named as Sturge Weber syndrome). In a further preferred embodiment, said skin disorder is infantile hemangioma. In a further preferred embodiment, said skin disorder is blue rubber bleb nevus syndrome. In a further preferred embodiment, said skin disorder is a complex vascular anomaly. In a further preferred embodiment, said skin disorder is a complex vascular anomaly, wherein said complex vascular anomaly is kaposiform hemangioendothelioma. In a further preferred embodiment, said skin disorder is kaposiform hemangioendothelioma.

In a further preferred embodiment, said skin disorder is selected from scleroderma, sclerodermatous chronic graft-versus-host disease, lichen sclerosus, lichen planus, lichen ruber planus and scars, preferably hypertrophic scars.

In a preferred embodiment, said skin disorder is scleroderma. In a further preferred embodiment, said skin disorder is sclerodermatous chronic graft-versus-host disease. In a further preferred embodiment, said skin disorder is lichen sclerosus. In a further preferred embodiment, said skin disorder is lichen planus. In a further preferred embodiment, said skin disorder is lichen ruber planus. In a further preferred embodiment, said skin disorder is a scar. In a further preferred embodiment, said skin disorder is a hypertrophic scar.

In a further very preferred embodiment, said skin disorder is selected from a skin disorder associated with tuberous sclerosis complex (TSC) or Birt-Hogg-Dubé (BHD, an angiofibroma (AF), preferably a facial angiofibroma, fibrofolliculoma of BHD, phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome (PHTS), Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), Lhermitte-Duclos syndrome, Proteus-like syndrome, hereditary keratinopathy, pachyonychia congenita, vascular anomaly, skin fibrosis, hamartoma, periungual fibroma, a vascular anomaly, port-wine stain (PWS), infantile hemangioma, blue rubber bleb nevus syndrome, a complex vascular anomaly, kaposiform hemangioendothelioma, scleroderma, sclerodermatous chronic graft-versus-host disease, lichen sclerosus, lichen planus, lichen ruber planus and scars, preferably hypertrophic scars.

In a very preferred embodiment, said skin disorder is an angiofibroma (AF). In a further very preferred embodiment, said skin disorder is a facial angiofibroma.

In a very preferred embodiment, there is provided a topical pharmaceutical composition comprising a compound Formula (I) according to the invention (preferably Compound 1) for use in the prevention or treatment of a skin disorder in a subject wherein said skin disorder is a genodermatosis, wherein said genodermatosis is selected from tuberous sclerosis complex (TSC), Birt-Hogg-Dubé (BHD, phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome (PHTS), and hereditary keratinopathy, wherein said compound of Formula (I) is administered topically to the subject.

In a further preferred embodiment, there is provided a topical pharmaceutical composition comprising a compound Formula (I) according to the invention (preferably Compound 1) for use in the prevention or treatment of a skin disorder in a subject, wherein said skin disorder is a vascular anomaly, wherein said vascular anomaly is selected from port-

wine stain (PWS), infantile hemangioma, blue rubber bleb nevus syndrome and a complex vascular anomaly, and wherein said topical pharmaceutical composition is administered topically to the subject.

In a further preferred embodiment, there is provided a topical pharmaceutical composition comprising a compound Formula (I) according to the invention (preferably Compound 1) for use in the prevention or treatment of a skin disorder in a subject, wherein said skin disorder is selected from a skin disorder associated with tuberous sclerosis complex (TSC) or Birt-Hogg-Dubé (BHD, an angiofibroma (AF), preferably a facial angiofibroma, fibrofolliculoma of BHD, phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome (PHTS), Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), Lhermitte-Duclos syndrome, Proteus-like syndrome, hereditary keratinopathy, pachyonychia congenita, vascular anomaly, skin fibrosis, hamartoma, periungual fibroma, a vascular anomaly, port-wine stain (PWS), infantile hemangioma, blue rubber bleb nevus syndrome, a complex vascular anomaly, kaposiform hemangioendothelioma, scleroderma, sclerodermatous chronic graft-versus-host disease, lichen sclerosus, lichen planus, lichen ruber planus and scars, preferably hypertrophic scars, wherein said topical pharmaceutical composition is administered topically to the subject.

In a further preferred embodiment, there is provided a topical pharmaceutical composition comprising a compound Formula (I) according to the invention (preferably Compound 1) for use in the prevention or treatment of a skin disorder in a subject, wherein said skin disorder is an angiofibroma (AF), preferably a facial angiofibroma, wherein said topical pharmaceutical composition is administered topically to the subject.

In some embodiments, the inventive topical pharmaceutical compositions have a solubility synergy factor of at least 1.1. In some embodiments, the inventive topical pharmaceutical compositions have a solubility synergy factor of at least 1.5. In some embodiments, the inventive topical pharmaceutical compositions have a solubility synergy factor of at least 2.0. In some embodiments, the inventive topical pharmaceutical compositions have a solubility synergy factor of at least 2.5. In some embodiments, the inventive topical pharmaceutical compositions have a solubility synergy factor of at least 3.0. In some embodiments, the inventive topical pharmaceutical compositions have a solubility synergy factor of at least 3.5. In some embodiments, the inventive topical pharmaceutical compositions have a solubility synergy factor of at least 4.0. In some embodiments, the inventive topical pharmaceutical compositions have a solubility synergy factor of at least 4.5.

In some embodiments, the inventive topical pharmaceutical compositions provide a clinically relevant concentration of a compound of Formula (I) to the skin of a patient, preferably after a single application to said patient.

In some embodiments, said clinically relevant concentration of a compound of Formula (I) is above the clinical IC_{90} for inhibition of pAKT, e.g., said clinically relevant concentration of a compound of Formula (I) is above 1,000 ng/g, preferably wherein said concentration is reached after a single application of the inventive topical pharmaceutical composition.

In some embodiments, said clinically relevant concentration of a compound of Formula (I) is above the clinical IC_{90} for inhibition of pS6, e.g., said clinically relevant concentration of a compound of Formula (I) is above 3,000 ng/g, preferably wherein said concentration is reached after a single application of the inventive topical pharmaceutical composition.

In some embodiments, the inventive topical pharmaceutical compositions provide a clinically relevant concentration of a compound of Formula (I) to the dermis and/or epidermis of a patient, preferably after a single application to said patient.

In some embodiments, said clinically relevant concentration of a compound of Formula (I) in the dermis and/or epidermis of said patient is above the clinical IC_{90} for inhibition of pAKT, e.g., said clinically relevant concentration of a compound of Formula (I) is above 1,000 ng/g, preferably wherein said concentration is reached after a single application of the inventive topical pharmaceutical composition.

In some embodiments, said clinically relevant concentration of a compound of Formula (I) in the dermis and/or epidermis of said patient is above the clinical IC_{90} for inhibition of pS6, e.g., said clinically relevant concentration of a compound of Formula (I) is above 3,000 ng/g, preferably wherein said concentration is reached after a single application of the inventive topical pharmaceutical composition.

In some embodiments, the inventive topical pharmaceutical compositions provide a clinically relevant concentration of a compound of Formula (I) to the dermis of a patient, preferably after a single application to said patient.

In some embodiments, said clinically relevant concentration of a compound of Formula (I) in the dermis of said patient is above the clinical IC_{90} for inhibition of pAKT, e.g., said clinically relevant concentration of a compound of Formula (I) is above 1,000 ng/g, preferably wherein said concentration is reached after a single application of the inventive topical pharmaceutical composition.

In some embodiments, said clinically relevant concentration of a compound of Formula

(I) in the dermis of said patient is above the clinical IC_{90} for inhibition of pS6, e.g., said clinically relevant concentration of a compound of Formula (I) is above 3,000 ng/g, preferably wherein said concentration is reached after a single application of the inventive topical pharmaceutical composition.

In some embodiments, the inventive topical pharmaceutical compositions provide a clinically relevant concentration of a compound of Formula (I) to the epidermis of a patient, preferably after a single application to said patient.

In some embodiments, said clinically relevant concentration of a compound of Formula (I) in the epidermis of said patient is above the clinical IC_{90} for inhibition of pAKT, e.g., said clinically relevant concentration of a compound of Formula (I) is above 1,000 ng/g, preferably wherein said concentration is reached after a single application of the inventive topical pharmaceutical composition.

In some embodiments, said clinically relevant concentration of a compound of Formula (I) in the epidermis of said patient is above the clinical IC_{90} for inhibition of pS6, e.g., said clinically relevant concentration of a compound of Formula (I) is above 3,000 ng/g, preferably wherein said concentration is reached after a single application of the inventive topical pharmaceutical composition.

In some embodiments, the inventive topical pharmaceutical compositions provide a clinically relevant concentration of Compound 1 to the skin of a patient, preferably after a single application to said patient.

In some embodiments, said clinically relevant concentration of Compound 1 is above the clinical IC_{90} for inhibition of pAKT, e.g., said clinically relevant concentration of Compound 1 is above 1,000 ng/g, preferably wherein said concentration is reached after a single application of the inventive topical pharmaceutical composition.

In some embodiments, said clinically relevant concentration of Compound 1 is above the clinical IC_{90} for inhibition of pS6, e.g., said clinically relevant concentration of Compound 1 is above 3,000 ng/g, preferably wherein said concentration is reached after a single application of the inventive topical pharmaceutical composition.

In some embodiments, the inventive topical pharmaceutical compositions provide a clinically relevant concentration of Compound 1 to the dermis and/or epidermis of a patient, preferably after a single application to said patient.

In some embodiments, said clinically relevant concentration of Compound 1 in the dermis and/or epidermis of said patient is above the clinical IC_{90} for inhibition of pAKT, e.g.,

said clinically relevant concentration of Compound 1 is above 1,000 ng/g, preferably wherein said concentration is reached after a single application of the inventive topical pharmaceutical composition.

In some embodiments, said clinically relevant concentration of Compound 1 in the dermis and/or epidermis of said patient is above the clinical IC_{90} for inhibition of pS6, e.g., said clinically relevant concentration of Compound 1 is above 3,000 ng/g, preferably wherein said concentration is reached after a single application of the inventive topical pharmaceutical composition.

In some embodiments, the inventive topical pharmaceutical compositions provide a clinically relevant concentration of Compound 1 to the dermis of a patient, preferably after a single application to said patient.

In some embodiments, said clinically relevant concentration of Compound 1 in the dermis of said patient is above the clinical IC_{90} for inhibition of pAKT, e.g., said clinically relevant concentration of Compound 1 is above 1,000 ng/g, preferably wherein said concentration is reached after a single application of the inventive topical pharmaceutical composition.

In some embodiments, said clinically relevant concentration of Compound 1 in the dermis of said patient is above the clinical IC_{90} for inhibition of pS6, e.g., said clinically relevant concentration of Compound 1 is above 3,000 ng/g, preferably wherein said concentration is reached after a single application of the inventive topical pharmaceutical composition.

In some embodiments, the inventive topical pharmaceutical compositions provide a clinically relevant concentration of Compound 1 to the epidermis of a patient, preferably after a single application to said patient.

In some embodiments, said clinically relevant concentration of Compound 1 in the epidermis of said patient is above the clinical IC_{90} for inhibition of pAKT, e.g., said clinically relevant concentration of Compound 1 is above 1,000 ng/g, preferably wherein said concentration is reached after a single application of the inventive topical pharmaceutical composition.

In some embodiments, said clinically relevant concentration of Compound 1 in the epidermis of said patient is above the clinical IC_{90} for inhibition of pS6, e.g., said clinically relevant concentration of Compound 1 is above 3,000 ng/g, preferably wherein said concentration is reached after a single application of the inventive topical pharmaceutical

composition.

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EXAMPLES

The disclosure is further illustrated by the following examples, which are not to be construed as limiting this disclosure in scope or spirit to the specific procedures herein described. It is to be understood that the examples are provided to illustrate certain embodiments and that no limitation to the scope of the disclosure is intended thereby. It is to be further understood that resort may be had to various other embodiments, modifications, and equivalents thereof which may suggest themselves to those skilled in the art without departing from the spirit of the present disclosure and/or scope of the appended claims.

The composition of the formulations tested in the Examples below is given in Table 1:

Table 1. Formulations Comprising Compound 1

	Formulation Name					
Excipient	AG02	AG08	AG11	AG12	AG13	AG15
Compound 1	1.7	2.2	1.7	1.7	2.5	2.2
Water	19.68	9.72	19.68	19.68	14.61	9.72
PEG 400	51.07	50.51	51.07	51.07	55.53	50.51
Transcutol® P	24.55	14.57	24.55	24.55	24.36	14.57
Ethanol						
Glycerol						
Propylene glycol		20				20
DIPA						
Oleyl alcohol						
Benzyl alcohol	2	2	2	2	2	2
Carbopol® 974	1	1				
Carbopol® 980			1		1	1
HPC HF				1		
Isopropyl myristate						
Brij® S2						
Brij® S20						
Cetyl alcohol						
GTCC						
Liquid Paraffin						
Total	100	100	100	100	100	100

Table 1 Continued

	Formulation Name					
Excipient	AG17	AG18	AG20	AG21	NA03	EG01
Compound 1	1.1	1.1	3.2	3.4	6.3	2.8
Water	9.89	9.89	9.64	9.52		9.54
PEG 400	66.24	66.24	54.9	57.67	55.25	45.8
Transcutol P			19.26	21.91	23.41	23.86
Ethanol	4.94	4.94				
Glycerol	14.83	14.83	5	3	4.68	
Propylene glycol						
DIPA			5		9.36	
Oleyl alcohol				1.5		
Benzyl alcohol	2	2	2	2		2
Carbopol® 974	1					
Carbopol® 980		1	1	1		1
HPC HF					1	
Isopropyl myristate						11
Brij® S2						1.46
Brij® S20						2.54
Cetyl alcohol						
GTCC						
Liquid Paraffin						
Total	100	100	100	100	100	100

Table 1 Continued

	Formulation Name					
Excipient	EG03	CR01				
Compound 1	2.1	1.1				
Water	12.22	23.66				
PEG 400	47.26	14.28				
Transcutol P	20.42	39.36				
Ethanol						
Glycerol						
Propylene glycol						
DIPA						
Oleyl alcohol						
Benzyl alcohol	2	1.6				
Carbopol® 974						
Carbopol® 980	1					
HPC HF						
Isopropyl myristate	11					
Brij® S2	1.46	1.6				
Brij® S20	2.54	2.4				
Cetyl alcohol		3				
GTCC		8				
Liquid Paraffin		5				
Total	100	100				

The concentration of Compound 1 in the formulations described in Table 1 represents the upper limit (i.e., 80-90%) of the total solubility of Compound 1 in those formulations.

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Animal Welfare

All animal studies were carried out under conditions approved by the Austrian Federal Ministry of Science, Research, and Economy.

EXAMPLE 1 – SOLUBILITY OF COMPOUND 1 IN INDIVIDUAL SOLVENTS AND CALCULATION OF SOLUBILITY FACTOR

Compound 1 was first tested for solubility in various individual solvents and excipients. Table 2 below gives the solubility of Compound 1 in individual solvents and excipients at 25 °C, measured in weight/weight ratios. For example, for PEG400, 1.66% wt/wt solubility means that 1.66 g Compound 1 were soluble in 100 g PEG400.

Table 2. Solubility of Compound 1 in Individual Solvents and Excipients (wt/wt)

Solvent/Excipient	Compound 1 solubility (wt/wt)
Water	0.1%
PEG400	1.66%
Diethylene glycol monoethyl ether	3.53%
Glycerol	0.03
Diisopropyl Adipate	1.1%
Benzyl Alcohol	
Cetyl Alcohol	
Caprylic triglyceride	
Liquid paraffin	

The inventive formulations were able to dissolve greater amounts of Compound 1 than would have been predicted based on the solubility of Compound 1 in individual solvents and excipients as measured above in Table 2 (i.e., exhibited synergistic solubility of Compound 1).

Table 3 below shows the solubility synergy factors observed for the formulations NA03, AG20, and CR01. For each tested formulation, the amount of Compound 1 added represented 80% of the total amount of Compound 1 possible to dissolve in the formulation.

Table 3. Solubility Synergy Factors of Tested Formulations

	Solvent and amt	% solubility in solvent	Expected amt dissolved Cpd. 1
NA03	55.25 g PEG400	1.66%	0.917 mg
	23.41 g DEGEE	3.53%	0.83 mg
	4.68 g Glycerol	0.03%	~0 mg

	9.36 g DIPA	1.1%	0.1 mg
	1 g HPC HF	0%	0 mg
	Total Solubility Expected		1.85 mg
	Total Solubility Observed		7.875 mg
	Solubility Synergy Factor		4.26
AG20	9.64 g water	0.1%	0.1 mg
	54.9 g PEG400	1.66%	0.91 mg
	19.26 g DEGEE	3.53%	0.68 mg
	5.00 g Glycerol	0.03%	~0 mg
	5.00 g DIPA	1.1%	0.1 mg
	2.00 g benzyl alcohol		0.1 mg
	1 g Carbopol® 980		
	Total Solubility Expected		1.89 mg
	Total Solubility Observed		4 mg
	Solubility Synergy Factor		2.11
CR01	23.66 g water	0.1%	0.002 mg
	14.28 g PEG400	1.66%	0.24 mg
	39.36 g DEGEE	3.53%	1.4 mg
	1.6 g benzyl alcohol		0.6 mg
	3.00 g cetyl alcohol		~0 mg
	8.00 g GTCC		~0 mg
	5.00 g liquid paraffin		~0 mg
	BRIJ® S2		
	BRIJ® S20		
	Total Solubility Expected		1.7 mg
	Total Solubility Observed		1.375 mg
	Solubility Synergy Factor		0.8

EXAMPLE 2: STABILITY OF COMPOUND 1 IN VARIOUS SOLVENTS

Forced degradation studies were performed to determine the stability of Compound 1 under various conditions designed to accelerate degradation. The results are given below in Table 4.

Table 4. Stability of Compound 1 in Various Excipients

	Photostability 1200 kLux/h	Dry 1 week, 90 °C	H_2O 1 week, 60 °C	1% H_2O 1 week, 25 °C
HPLC Purity				
Total impurities detected	0.0%	0.1%	0.2%	0.1%
	0.1 N HCl 1 week, 60 °C	0.1 N HCl 1 week, 90 °C	0.1 N NaOH 1 week, 60 °C	0.1 N NaOH 1 week, 90 °C
HPLC Purity				
Total impurities detected	0.1%	0.8%	0.1%	0.1%

EXAMPLE 3: *IN VITRO* DRUG RELEASE TESTING

An *in vitro* drug release test was performed using a static Franz cell as shown in FIG 1 to assess the release profile of Compound 1 across a synthetic cellulose membrane from the ten experimental formulations AG02, AG11, AG12, AG15, AG18, AG20, AG21, NA03, EG01, and CR01. Briefly, a formulation comprising Compound 1 was placed above a synthetic cellulose membrane and allowed to diffuse over time through the membrane and into a receiver fluid which did not initially contain Compound 1 as shown in FIG 1.

Three receiver fluids were initially tested to confirm the stability of Compound 1 in the receiver fluid. The receiver fluid selected for use was of 2% Brij® in 50/50 ethanol/water. Compound 1 was found to be stable over five days in the selected receiver fluid at 5, 25, and 32 °C.

Six membranes were initially tested to assess the potential for back diffusion from the receiver fluid to the formulation solution and/or binding of Compound 1 to the membrane. A cellulose membrane was selected for use because it did not allow any back diffusion when used with the receiver fluid and did not bind to Compound 1. The Franz cell had a dosing area of 1.9 to 2.4 cm^2 and a volume of 7.5-11 mL.

In a preliminary experiment, an infinite dose (300 mg) of a single batch of formulation AG18 was dosed onto cellulose membranes mounted in static Franz cells (n=3). A single static cell was mounted with a cellulose membrane and not dosed to act as a blank control. The receptor solution was collected at seven time points (1, 2, 4, 6, 24, 30, and 48 hours), and

analyzed using HPLC-UV. The data indicated that the range of 1-7 hours was the optimum time frame for a full-scale experiment because the slope was linear when plotted as a square root over time. Back diffusion was only observed after 24 hours.

In a subsequent full-scale experiment, the *in vitro* release investigation was performed based on conditions determined during the small-scale experiment with the ten experimental formulations above (AG02, AG11, AG12, AG15, AG18, AG20, AG21, NA03, EG01, and CR01).

FIG 2 and Table 5 show the amount of Compound 1 released across the synthetic cellulose membrane and into the receptor solution over seven hours. The non-aqueous gel (NA03) showed the fastest release rate of Compound 1 ($P<0.0001$ for all formulations), which ranged from approximately 2-5-fold increase compared to all other formulations. The release rate of the ten tested formulations ranged from 216-1084 $\mu g/cm^2/hr$, with the slowest release rate of Compound 1 observed in CR01 and AG18. The cumulative amount of Compound 1 in the receiver fluid seven hours after dosing escalated with the percent of Compound 1 present in the applied formulation. The formulations AG20, EG01, and AG21 all had statistically the same release rates and were the next-highest ranked formulations for release rate after NA03.

Table 5. Cumulative Amount of Compound 1 Released into Receptor Fluid through Cellulose Membrane ($\mu g/cm^2$)

		Formulation				
Time (hr)	√ Time (hr)	AG02	AG11	AG12	AG15	AG18
1	1	90	91	119	117	59
2	1.41	187	182	251	242	122
3	1.73	321	284	416	354	181
4	2	431	370	538	465	241
5	2.24	550	484	661	583	309
6	2.45	645	572	761	688	364
7	2.65	718	635	829	773	407
		Formulation				
Time (hr)	√ Time (hr)	AG20	AG21	NA03	EG01	CR01
1	1	130	170	214	129	128
2	1.41	292	341	518	297	256
3	1.73	464	488	837	465	352

4	2	640	633	1160	624	432
5	2.24	813	758	1433	779	496
6	2.45	931	904	1727	912	528
7	2.65	1064	1021	1957	1034	543

EXAMPLE 4: *EX VIVO* HUMAN SKIN PERMEATION AND PENETRATION

The *ex vivo* skin permeation experiments involve the use of a diffusion cell designed to mimic the physiological and anatomical conditions of skin *in situ*. A schematic of the model used to test skin permeation in this Example is shown in FIG 3. Human skin was placed between the donor and receptor compartments. A flow path with small void volumes provided local clearance beneath the dermatomed skin to generate accurate and detailed flux profiles through automated collection and optimized fluidics.

Human skin from cosmetic reduction surgery from a single donor was used. The subcutaneous fat was removed mechanically and the skin was dermatomed to a thickness of 500 ± 50 µm using an Integra Life Sciences Model SB Slimline Dermatome. The skin was stored at -80 °C when not used immediately, and was allowed to thaw to room temperature prior to placement into the diffusion cells.

A receiver solution of PBS with 0.01% Brij® was used based on non-specific binding experiments and the high stability of Compound 1 in the receiver solution. The extraction solution used as 90/10 (ethanol/water).

In a preliminary experiment, Formulation AG11 was used to test the experimental conditions. Cumulative levels of approximately 100 ng/cm^2 Compound 1 were detected in the receptor solution after 24 hours, and Compound 1 was recovered from the epidermis and dermis. Based on these results, the conditions were deemed suitable for a full-scale *ex vivo* skin permeation and penetration study.

The full-scale *ex vivo* skin permeation and penetration study was performed using the setup above with the formulations AG02, AG11, AG12, AG15, AG18, AG20, AG21, CR01, EG01, and NA03. For each active formulation, n=5 repetitions were performed. A single repetition was performed for the respective placebo formulations and the blank.

The recovery of the residual formulation on the skin for the full-scale experiment was performed as follows: A total of three cotton swabs were used to recover the drug (Compound 1) from the surface of the skin. After removing the skin from the diffusion cell, one dry cotton wool swab was used to remove all of the formulation from the surface of the skin and the swab

was discarded. A second swab was then immersed into the extraction solution and used to swab the surface of the skin. The swab was then discarded. The final swab was used to dry swab the surface of the skin and then discarded.

Compound 1 was removed from the stratum corneum using the following procedure: Tape strips (5 strips) were removed from the surface of the skin to separate the stratum corneum from the epidermis and were discarded. The remaining epidermis and partial dermis were heat-separated from each other by placing the skin into an incubator at 60 °C for 2 min. The epidermal and dermal layers were placed into individual tissue homogenizer vials and 1 mL of extraction solution was added. The tissue homogenizer vials were placed in a bead mill homogenizer and the contents were homogenized at 5 m/s for 3 x 30 seconds at ambient laboratory temperature. The vials were then shaken on an orbital shaker at ambient temperature for 0.5-1 h. The homogenate was then transferred to a 96-well plate, which was then centrifuged. The dermis and epidermis samples were analyzed using LC-MS/MS.

No significant differences in the concentrations of Compound 1 were found in the receptor solution between any of the tested formulations.

The mean amount (ng) of Compound 1 recovered from epidermis and dermis is presented in FIG 4 and below in Table 6. Formulation NA03 delivered 1.7 to 17-fold more Compound 1 to the epidermis compared with all other tested formulations. Formulation NA03 was also the third-highest ranked formulation for dermal delivery. Formulations AG20 and AG21 delivered the highest amount of Compound 1 to both the dermis and epidermis of the tested aqueous gels.

Table 6. Amount (ng) and Percent Applied Dose of Compound 1 recovered from Epidermis and Dermis 24 Hours Post Formulation Application.

	Epidermis Amount (ng)			Dermis Amount (ng)		
Formulation	n	Mean	Std Dev	n	Mean	Std Dev
AG02	5	886	287	5	1180	256
AG11	5	1093	871	5	590	142
AG12	5	2948	2339	5	2623	965
AG15	5	1485	381	5	1807	1070
AG18	5	910	197	5	507	293
AG20	5	4864	3106	5	3545	744
AG21	5	9422	4951	5	6058	6580
CR01	5	3006	1609	5	7102	6539

EG01	5	4461	1016	5	3595	2919
NA03	5	15028	8596	5	4577	2450

EXAMPLE 5: *IN VIVO* PIG SKIN PENETRATION STUDY

The PK profiles of ten experimental formulations and one control formulation were determined in an *in vivo* pig skin study using biopsy extraction. Prior to biopsy extraction, the stratum corneum was removed with tape stripping. Three replicate biopsies were taken from each application site (20 x 40 mm). Additionally, three biopsies were taken from a non-treated tape-stripped site (blank samples) for analytical validation. All biopsies were stored at -80 °C until they were analyzed. The formulations tested were AG08, AG11, AG13, AG15, AG17, AG20, AG21, NA03, EG01, and CR01. The control formulation comprised 1% Compound 1, PG and thickener.

A four-month old domestic pig with a weight of 40 kg was used. Three days before the study, the back and both flanks of the pig were shaved. On the day of the study, the pig was anesthetized. The skin was cleaned with water and inspected for wounds, abrasions, or other alterations. The application sites were marked on the skin with a stencil and a surgical marker. A schematic of the application sites is shown in FIG 5.

The applied dose for each formulation was 56 mg (7mg/cm^2 of formulation on application area of 4 x 2 cm). The dose was weighed using an analytical balance and applied with a plastic spatula. Dosing was done sequentially. Exposure times were 6, 9 and 12 hours.

Upon completion of the exposure times, the pig was euthanized by dosing a pre-medication of 10 mg/kg ketamine, 0.2 mg/kg midazolam, and 2 mg/kg azaperone and an overdose of propofol and potassium chloride.

Prior to tape stripping, the remaining formulations were removed from the application sites by cleaning the application sites twice with gauze. To remove the stratum corneum, a piece of tape was attached to the skin at all relevant application sites. The tape was uniformly pressed to the skin surface using gloved fingers to ensure homogenous contact of the tape to the skin surface and was abruptly removed with one smooth motion. To completely remove the SC, tape stripping was repeated 80 times using a fresh piece of tape each time and alternating the peeling direction (from left to right and from right to left).

Three replicate biopsies were taken with a biopsy punch (4.0 mm) from each application site. Subcutaneous tissue was removed from the biopsies. The biopsies were placed in 1.8 mL cryotubes and weighed. Additionally, three blank biopsies were taken from

untreated and tape-stripped sites to determine the background in the analytical runs. The samples were stored in a temperature-monitored freezer at -80 °C until sample shipment.

The concentrations of Compound 1 in all ten formulations and the control formulation were quantifiable in all tissue samples using LC-MS/MS. Mean concentrations, standard deviations (SD) and coefficient of variance (CV) were calculated for each formulation and point in time. The resulting CVs were between 6% and 89%.

The results are presented in Table 7, below and FIGs 6 and 7. FIG 6 shows the concentration of Compound 1 in pig skin biopsies at each time point tested. FIG 7 shows the amount of Compound 1 in biopsies integrated over the three time points tested (6, 9 and 12 hours). The dotted line represents the IC_{90} of Compound 1 on phosphoS6, and the dashed line represents the IC_{90} of Compound 1 on phosphoAKT.

Formulations NA03 and AG20 gave the highest concentrations of Compound 1 in the skin of the experimental compounds tested. As shown in FIG 7, when integrated over the three timepoints tested, formulations NA03 and AG20 delivered an amount of Compound 1 above the IC_{90} for phosphoS6 inhibition.

Table 7. Concentration of Compound 1 in Skin Tissue after *in vivo* Skin Penetration Study

Sample ID	Time (h)	Skin conc. [ng/g] per biopsy	Mean [ng/g]	SD [ng/g]	CV%
Formulation AG08	6	1063.4	1045	139	13
		896.9			
		1173.3			
	9	833.8	972	122	13
		1020.1			
		1063.3			
	12	1765.9	2177	649	30
		1841.1			
		2925.0			
Formulation AG11	6	722.2	869	127	15
		948.9			
		935.5			
	9	633.0	724	79	11

		760.7			
		778.7			
		913.5			
	12	1192.8	890	316	36
		562.4			
		597.8			
	6	610.9	1245	1110	89
		2526.4			
		824.8			
Formulation AG13	9	1533.0	1440	574	40
		1961.8			
		1629.5			
	12	859.6	1291	393	30
		1382.5			
		1850.4			
	6	1612.9	1552	332	21
		1194.0			
		835.3			
Formulation AG15	9	1244.6	1080	216	20
		1159.4			
		1470.8			
	12	1076.9	1416	315	22
		1699.5			
		489.3			
	6	375.9	493	119	24
		612.9			
		315.1			
Formulation AG17	9	208.9	351	163	46
		528.6			
		478.5			
	12	508.7	432	107	25

		310.2			
Formulation AG20	6	2900.7 1589.0 1032.4	1841	959	52
	9	1086.0 1141.8 1325.3	1184	125	11
	12	1607.8 3179.9 3086.5	2625	882	34
Formulation AG21	6	1840.4 1395.6 1856.5	1697	262	15
	9	1678.1 1892.2 1230.3	1600	338	21
	12	2664.7 1532.1 715.3	1637	979	60
Formulation NA03	6	1633.9 2135.2 2368.1	2046	375	18
	9	1118.9 3010.5 3370.1	2500	1209	48
	12	2890.7 4921.7 7223.9	5012	2168	43
Formulation EG01	6	494.4 2907.2 3355.4	2252	1539	68

	9	706.1 735.0 591.0	677	76	11
	12	1131.5 1107.1 1228.7	1156	64	6
Formulation CR01	6	812.0 1087.2 771.9	890	172	19
	9	893.4 748.5 958.5	867	107	12
	12	1137.0 1147.2 2378.2	1554	714	46
Formulation II (Control)	6	1707.7 1559.3 6543.9	3270	2836	87
	9	829.4 1512.7 1820.5	1388	507	37
	12	2041.5 5840.2 1682.4	3188	2304	72

EXAMPLE 6: *IN VIVO* PIG SKIN PENETRATION STUDY USING FORMULATIONS NA03 AND AG20 AT VARIOUS CONCENTRATIONS

Based on the results of the Examples above, two formulations NA03 and AG20 were selected for further study. Five different formulations based on the original NA03 and AG20 formulations, but with different concentrations of Compound 1, were prepared and applied to pig skin *in vivo* as shown below in Table 8.

Table 8. Formulations Used

Formulation	Nominal concentration of Compound 1 [mg/g]	Dose (Applied amount of formulation per cm^2)	Applied amount of formulation
NA03 – 6.3%	63	7.0 mg/cm^2	84 mg
NA03 – 4.5%	45	7.0 mg/cm^2	84 mg
NA03 – 3.0%	30	7.0 mg/cm^2	84 mg
NA03 – 2.0%	20	7.0 mg/cm^2	84 mg
AG20 – 3.2%	32	7.0 mg/cm^2	84 mg
NA03 – 6.3%	63	3.5 mg/cm^2	42 mg
NA03 – 6.3%	63	2.0 mg/cm^2	24 mg
NA03 – 6.3%	63	1.0 mg/cm^2	12 mg
NA03 – 4.5%	45	2.0 mg/cm^2	24 mg
AG20 – 3.2%	32	2.0 mg/cm^2	24 mg
NA03	NA	7.0 mg/cm^2	84 mg
AG20	NA	7.0 mg/cm^2	84 mg

The formulations were applied at different doses of 1.0 mg/cm^2, 2.0 mg/cm^2, 3.5 mg/cm^2, and 7.0 mg/cm^2. The application area was 12 cm^2 (4 cm x 3 cm).

A 2.5-month old domestic pig (weight: 33 kg) was delivered to the study site. Four days before the study start, the application areas on the back and both flanks of the pig were shaved with a hair clipper. On the day of the study, the pig was anesthetized and the skin was cleaned with water and inspected for wounds, abrasions, and other alterations. The application sites were marked on the skin with a surgical stencil and surgical marker.

The test formulations containing Compound 1 were applied on ten application sites for an exposure time of 6 hours; on ten application sites for an exposure time of 9 hours; and on a further ten application sites for an exposure time of 12 hours. On two additional application sites, the placebo formulations (i.e., formulations NA03 and AG20 not containing Compound 1) were applied for an exposure time of 12 hours. The location of application of the formulations to the pig is shown in FIG 8. The formulations were applied with a plastic spatula.

At the end of the study, the pig was euthanized. The remaining experimental formulations were removed from the application sites by cleaning the application sites twice with gauze. Afterwards, the stratum corneum was removed by tape stripping. Tape was

applied to the skin on the application sites. The tape was uniformly pressed to the skin surface with gloved fingers to provide homogenous contact of the tape to the skin surface and was then immediately removed in one smooth motion. To completely remove the stratum corneum, tape stripping was repeated 80 times by using a fresh piece of tape each time and by alternating peeling direction (from left to right and right to left). The tape stripping procedure took approximately 70 minutes for all sites.

Biopsies consisted of the remaining epidermis and the entire dermis. From the application sites treated with formulations containing Compound 1, six replicate biopsies were taken with a biopsy punch (4.0 mm), three of which were tested for pharmacokinetic profiling. From the two application sites treated with placebo cream, three biopsies were taken. Additionally, three blank biopsies from a non-treated tape-stripped site were taken to determine the background in the analytical runs. The biopsies were placed in 1.8 mL cryotubes and weighed. All biopsy samples were stored at -80 °C until analysis.

Table 9, below, shows the Compound 1 concentrations in the skin for each formulation tested. FIG 9 shows the averaged (mean ± SEM) Compound 1 concentrations of all formulations over all time points (6h, 9h, 12 h). The dotted line represents the IC_{90} of Compound 1 on phosphoS6, and the dashed line represents the IC_{90} of Compound 1 on phosphoAKT.

Table 9. Concentration of Compound 1 in Skin Tissue after *in vivo* Pharmacokinetic Study

Formulation – Dose	Time (h)	Skin conc. [ng/g]	Mean [ng/g]	SD [ng/g]	CV%
NA03-6.3% 7 mg/cm^2	6	3522.40	4918	1209	25
		5660.82			
		5569.63			
	9	2663.82	2646	522	20
		2115.72			
		3158.39			
	12	9366.76	8109	3986	49
		3645.02			
		11314.03			
NA03-4.5% 7 mg/cm^2	6	1565.55	1788	440	25
		2294.50			
		1503.26			
	9	2469.05	1459	875	60
		980.21			

		926.54			
	12	4273.23	4249	35	1
		4224.01			
		[33122.10]*			
NA03-3% 7 mg/cm^2	6	2955.99	2463	708	29
		1651.76			
		2779.96			
	9	3172.47	2382	685	29
		1963.66			
		2010.05			
	12	1492.99	1848	423	23
		2316.70			
		1735.20			
NA03-2% 7 mg/cm^2	6	1722.74	1481	222	15
		1432.98			
		1286.74			
	9	1265.89	1310	685	52
		648.05			
		2015.90			
	12	4696.92	6044	2480	41
		4529.52			
		8906.36			
AG20-3.2% 7 mg/cm^2	6	7609.88	5867	2390	41
		6847.67			
		3142.75			
	9	846.90	1012	405	40
		715.08			
		1473.51			
	12	1293.78	1202	776	65
		1927.32			
		384.39			
NA03-6.3% 3.5 mg/cm^2	6	5944.86	7193	2207	31
		9740.75			
		5893.07			
	9	5288.00	3599	1716	48
		3652.55			
		1857.59			
	12	5480.49	5511	451	8
		5076.21			
		5976.58			
NA03-6.3% 2 mg/cm^2	6	1978.32	2752	1269	46
		4216.34			
		2061.96			

	9	7801.55	5829	2167	37
		3509.30			
		6176.66			
	12	7797.05	6300	1845	29
		4238.74			
		6863.52			
NA03-6.3% 1 mg/cm^2	6	10496.58	6956	3090	44
		5567.72			
		4803.90			
	9	1266.17	2381	1475	62
		1824.34			
		4053.38			
	12	6370.87	7675	3514	46
		11654.34			
		4999.40			
NA03-4.5% 2 mg/cm^2	6	2972.18	3060	775	25
		2332.17			
		3874.22			
	9	4595.70	3228	1195	37
		2701.11			
		2387.18			
	12	2202.79	2270	478	21
		1829.05			
		2778.66			
AG20-3.2% 2 mg/cm^2	6	1701.39	1778	1313	74
		504.38			
		3127.22			
	9	3626.85	3668	506	14
		4194.06			
		3183.68			
	12	4254.85	3003	1193	40
		2873.65			
		1879.17			

(*) Value excluded from further calculations.

Compound 1 from all applied formulations penetrated to a significant amount into the lower epidermis and dermis 6-12 hours after treatment. The formulation NA03-6.3% showed the highest skin concentrations for all applied doses (7.0 mg/cm^2; 3.5 mg/cm^2; 2.0 mg/cm^2; and 1.0 mg/cm^2). The formulation NA03-2% showed clinically relevant skin concentration.

EXAMPLE 7: A RANDOMIZED PHASE 2 PROOF-OF-CONCEPT STUDY TO

EVALUATE THE EFFICACY AND SAFETY OF TOPICAL BIMIRALISIB APPLICATION IN PATIENTS SUFFERING FROM ACTINIC KERATOSIS ON THE FACE AND/OR SCALP AND/OR BACK OF HANDS OVER A 2 AND 4-WEEK TREATMENT PERIOD

A study was conducted to evaluate efficacy and safety of bimiralisib gel treatment for treatment of actinic keratosis on the face and/or scalp and/or back of hands. The study was a multi-center, randomized, open label, parallel group study. The study products were applied to the target lesions for a duration of 2 or 4 weeks of treatment. The study consisted of the following periods: Screening (up to 30 days); Treatment (2 or 4 weeks); Follow-Up (4 weeks).

Patients were randomized to one of two groups (1:1): (1) Arm A: Topical bimiralisib) gel treatment for 2 weeks; (2) Arm B: Topical bimiralisib gel treatment for 4 weeks.

A schematic of the design of the clinical trial is shown in FIG 10.

Ages Eligible for Study: At least 50 years of age at time of signing the informed consent (Adult, Older Adult). Sexes eligible for study: All. No healthy volunteers are accepted.

Eligibility Criteria

1. Must be of at least 50 years of age, at the time of signing the informed consent.

2. Has a clinical diagnosis of stable, clinically typical actinic keratosis.

3. Have at least 3 actinic keratosis lesions (Olsen grade 1 or 2) contained within contiguous treatment regions of face and/or scalp and/or back of hands.

4. Must agree not to use any product on the treatment area during the entire course of study except for Investigator-approved cleanser, sunscreen, wash, and non-medicated makeup.

5. Must be willing to comply with sun avoidance measures for all exposed areas including use of Investigator-approved sunscreen and/or hats, have limited sun exposure time, and have no tanning bed use.

6. Must be in good general health (ECOG 0-1).

7. Patients of reproductive potential must agree to use double effective contraception from screening until 90 days after discontinuing study treatment.

8. Female patients who had a menstrual cycle within 2 years prior to screening must have a negative serum pregnancy test at screening and a negative urine pregnancy test on their first treatment day.

9. Must be capable of giving signed informed consent.

Exclusion Criteria

1. Known or suspected hypersensitivity to any of the excipients of bimiralisib gel.

2. Clinically atypical and/or rapidly changing actinic keratosis lesions in the treatment area.

3. Clinical evidence of severe, uncontrolled autoimmune, cardiovascular, gastrointestinal, hematological, hepatic, neurologic, pulmonary or renal disease.

4. Participation in any clinical research study within 30 days of the Baseline Visit.

5. Cosmetic or therapeutic procedures (e.g. laser, peeling, photodynamic therapy, cryotherapy) within 4 weeks of the Baseline visit and within 2 cm of the selected treatment area.

6. Other skin diseases (e.g. vitiligo, rosacea, psoriasis, atopic dermatitis, eczema, basal or squamous cell carcinoma or albinism) or conditions (e.g. scarring, open wounds, tattoos, piercing, sunburn) within the selected treatment area that, in the opinion of the Investigator, might interfere with the study conduct or evaluations, or which exposes the subject to an unacceptable risk by study participation.

7. Use of sun lamps, tanning beds, and tanning booths during the 4 weeks prior to the Baseline Visit or planned use during the study.

8. Use of any retinoids within 90 days of the Baseline Visit, or systemic glucocorticosteroids, methotrexate or other anti-metabolites or nicotinamide within 28 days of the Baseline Visit. Topical steroidal use outside of the selected treatment area for non-AK indications is allowed.

9. Any systemic cancer therapy or diagnosis within 6 months of the Baseline Visit.

10. Any other malignancy within 5 years prior to Screening except basal or squamous cell carcinoma not in the treatment area that were treated with curative intent and are without recurrence.

11. Other significant uncontrolled or unstable medical diseases or conditions that, in the opinion of the Investigator, would expose the subject to unacceptable risk by study participation.

12. A known history of human immunodeficiency virus (HIV), chronic hepatitis C, or chronic hepatitis B infection (testing not mandatory).

13. Patients receiving immuno-suppressive treatment which in the opinion of the investigator would impact on the development of non-melanoma skin cancer.

14. Females who are pregnant or lactating or planning to become pregnant during the study period.

15. Patients who are unable to comply with the study requirements for any reason.

Study Plan

Primary purpose: Treatment. Allocation: Randomized. Interventional Model: Parallel assignment. Masking: None (open label).

Arms and Interventions

Participant Group/Arm	Intervention/Treatment
Treatment arm A	topical bimiralisib for 2 weeks
Treatment arm B	topical bimiralisib for 4 weeks

Patients were treated with a topical formulation comprising Compound 1 as described herein, comprising:

2.0 weight percent of Compound 1;

57.81 weight percent polyethylene glycol, preferably PEG400;

24.50 weight percent diethylene glycol monoethyl ether;

4.89 weight percent glycerol (anhydrous);

9.80 weight percent diisopropyl adipate; and

1 weight percent hydroxypropyl cellulose.

The topical formulation was administered once daily.

Primary Outcome Measures

Outcome Measure	Measure Description	Time Frame
To evaluate the preliminary efficacy of topical bimiralisib gel when used once daily for 2 or 4 weeks in the treatment of AK of the face and/or scalp and/or back of hands	Improvement from baseline in AK lesions as measured by achieving an IGA score of 0 or 1.	Baseline, Day 43 (Treatment Arm A), Day 57 (Treatment Arm B)
To evaluate the activity of bimiralisib gel administered topically to the face and/or scalp and/or back of hands in patients with AK by	The proportion of subjects with complete clearance of AK lesions at the End of Treatment Visit (Week 2 or 4 depending on treatment arm)	Day 15 (Treatment Arm A), Day 29 (Treatment Arm B),

determining complete and partial clearance rates after 2 or 4 weeks of treatment		
To determine the safety and tolerability of topical bimiralisib gel when applied to AK lesions	Safety and tolerability endpoints assessed by: • Adverse events (including laboratory adverse events and vital signs) • Specific local skin reactions	From first application of bimiralisib until 28 days after the last application

Response Assessments

The target lesion on-treatment response were measured as the change from baseline for (i) Investigator Global Assessment (IGA), (ii) absolute lesion count, and (iii) lesion size.

Investigator Global Assessment (IGA) Score was measured using a five-point response scale compared to baseline with the following scores attributed:

0 (completely cleared)

1 (partially cleared)

2 (moderately cleared)

3 (minimally cleared)

4 (no improvement).

IGA success were defined as achieving an IGA score of 0 or 1 at the follow-up visit.

Absolute lesion count was characterized by “Complete clearance”: absence of clinically visible or palpable AK lesions in the treatment area; “Partial clearance”: at least 75% reduction in the number of AK lesions in the treatment area.

Lesion size was calculated by measuring perpendicular dimensions and calculated area for each of the selected target lesions, and as the sum total value of area of all selected target lesions.

Secondary outcomes include safety, tolerability, and the percentage of partial clearance of AK lesions.

Twenty-nine (29) patients were initially enrolled. No treatment interruptions occurred. Administration of the topical formulation led to significant reductions in AK lesions: 50% (Arm A) and 58% (Arm B) achieved an IGA score of 0-1, respectively. Related adverse events (AEs) included pruritus (n=5), irritation (n=1), erythema (n=1) and burning sensation (n=1),

all of which were mild and resolved. Seven (7) patients also had mild lesion erosion as part of the treatment effect. Topical bimiralisib gel (2%) thus demonstrated efficacy in the treatment of AK, with a favorable safety profile.

At a later timepoint, 46 adult patients with actinic keratosis Olsen Grade 1 or 2 of the face and/or scalp and/or back of hands had been randomly assigned for treatment with bimiralisib gel for 2 or 4 weeks in a 1:1 ratio. Forty-two (42) patients were actually treated (4 patients withdrew following randomization and prior to treatment). At the time of patient evaluation, 35 patients had completed the initial treatment period and follow-up visit (18 patients in Arm A and 17 patients in Arm B). Two (2) patients were in the initial treatment period. Five (5) patients were in the safety/efficacy follow-up period (4 weeks). Sixteen (16) patients had entered the optional 8-week treatment extension period (offered to patients showing at least a 50% improvement in lesion size from baseline at the end of the 4-week follow-up period).

Safety

Adverse events were based on the initial treatment period (2- or 4- weeks) and safety follow-up of 28 days. Table 10 summarizes all adverse events for the 42 patients treated at the time of patient evaluation. Table 11 summarizes the treatment-related adverse events. Table 12 gives the details of treatment-related adverse events.

Table 10. All Adverse Events

	Arm A		Arm B	
CTCAE Grading	Events	Patients with AEs	Events	Patients with AEs
Grade 1	26	13	29	14
Grade 2	7	4	3	3
Grade 3	2	2	0	0
Grade 4	0	0	0	0
Total	36	19	35	17

Table 11. Treatment-Related Adverse Events

	Arm A		Arm B	
CTCAE Grading	Events	Patients with AEs	Events	Patients with AEs
Grade 1	19	11	19	10
Grade 2	3	2	0	0

Grade 3	0	0	0	0
Grade 4	0	0	0	0
Total	23	13	22	10

Table 12. Details of Treatment-Related Adverse Events

Adverse Event Term	Number of Related Adverse Events			
	Arm A		Arm B	
	Grade 1	Grade 2	Grade 1	Grade 2
Erosion	6	3	2	
Erythema	5		3	
Crusting	3		4	
Skin irritation	1		4	
Application site pruritis	2		3	
Burning sensation			2	
Itching			1	
Flaking skin	1			
Scaling	1			

At the time of patient evaluation, most treatment-related adverse events had resolved (2 events were ongoing awaiting follow-up visits).

All patients completed the initial treatment period without interruption except one patient in Arm B who discontinued the study after 2 weeks due to a grade 1 burning sensation in the treatment area. No significant laboratory abnormalities were noted.

Efficacy

Table 13 is a summary of the efficacy results that were observed in the 35 patients that had reached the primary endpoint at the time of patient evaluation based on the Investigator Global Assessment compared to the baseline.

Table 13. Summary of Efficacy Results

		IGA Score				
	No. of Patients	0	1	2	3	4
ARM A (2 week)	18	1	8	8	1	0

ARM B (4 week)	17	5	7	5	0	0

Sixty (60)% of patients reached an IGA score of 0 or 1 at the primary endpoint (70% in Arm B and 50% in Arm A). All 35 patients that reached the primary endpoint at the time of patient evaluation showed some clearance (6 patients with completely cleared, 15 patients partially cleared, 13 patients moderately cleared and 1patient minimally cleared).

EXAMPLE 8: INVENTIVE FORMULATIONS

The following formulations were prepared:

Table 14. NA03-0.1%

Component	Unit Quantity (% w/w)	Grade
Polyethylene Glycol 400 (PEG400)	58.94	Ph. Eur., JP
Diethylene glycol monoethyl ether (Transcutol P®)	24.98	Ph. Eur., NF
Diisopropyl adipate	9.99	JPE
Glycerol, anhydrous	4.99	Ph. Eur., BP, JP, USP
Compound 1	0.10	N/A
Hydroxypropyl cellulose	1.00	NF, Ph. Eur., JP,
Total	100.00	

Table 15. NA03-0.5%

Component	Unit Quantity (% w/w)	Grade
Polyethylene Glycol 400 (PEG400)	58.70	Ph. Eur., JP
Diethylene glycol monoethyl ether (Transcutol P®)	24.88	Ph. Eur., NF
Diisopropyl adipate	9.95	JPE
Glycerol, anhydrous	4.97	Ph. Eur., BP, JP, USP
Compound 1	0.50	N/A
Hydroxypropyl cellulose	1.00	NF, Ph. Eur., JP,

Total	100.00	

Table 16. NA03-2%

Component	Unit Quantity (% w/w)	Grade
Polyethylene Glycol 400 (PEG400)	57.81	Ph. Eur., JP
Diethylene glycol monoethyl ether (Transcutol P®)	24.50	Ph. Eur., NF
Diisopropyl adipate	9.80	JPE
Glycerol, anhydrous	4.89	Ph. Eur., BP, JP, USP, FCC
Compound 1	2.00	N/A
Hydroxypropyl cellulose	1.00	NF, Ph. Eur., JP, FCC
Total	100.00	

Table 17. NA03-3%

Component	Unit Quantity (% w/w)	Grade
Polyethylene Glycol 400 (PEG400)	57.22	Ph. Eur., JP
Diethylene glycol monoethyl ether (Transcutol P®)	24.24	Ph. Eur., NF
Diisopropyl adipate	9.70	JPE
Glycerol, anhydrous	4.84	Ph. Eur., BP, JP, USP, FCC
Compound 1	3.00	N/A
Hydroxypropyl cellulose	1.00	NF, Ph. Eur., JP, FCC
Total	100.00	

The formulations above were prepared by transferring pre-weighed PEG400, Transcutol P®, diisopropyl adipate, and glycerol into a glass laboratory vessel. The mixture was stirred at a suitable speed to create a flow throughout the vessel until the solution was visually homogenous. Pre-weighed Compound 1 was transferred into the vessel while stirring at a speed to create a flow throughout the vessel. The mixture was stirred until the Compound

1 was dissolved. Pre-weighed hydroxypropyl cellulose was transferred into the vessel while stirring at a speed suitable to create a sufficient vortex. The stirring was continued at a suitable speed to create a flow throughout the vessel until the hydroxypropyl cellulose had completely dissolved.

EXAMPLE 9: STABILITY TESTING OF NON-AQUEOUS GEL FORMULATIONS NA03-2% AND NA03-6.3%

Non-aqueous gel formulations NA03-2% and NA03-6.3% were tested for stability based on International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) stability testing standards for up to 24 months. All procedures were performed according to current EU GMP guidelines for Investigational Medicinal Products (IMPs) as defined in the "EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines". QC testing was conducted based on the principles of European Directives 2001/20/EC, 2003/94/EC, and EudraLex cGMP guidelines.

Program of Work

Stability samples were stored in stability testing chambers for the duration of the study and were removed from the stability testing chambers at designated time points for analysis as specified below. A single vessel containing NA03-2% was used to fill each test sample tube related to NA03-2%, and a single vessel containing NA03-6.3% was used to fill each test sample tube related to NA03-6.3%. To ensure that the content of the single vessel(s) were well mixed, three sample tubes were tested at the initial timepoint (T=0) that were filled at the start, middle, and end of the filling process. Samples were stored at ambient conditions after removal from the stability testing chambers prior to and during stability testing.

The number of samples required for stability testing of each batch of formulation is given in Table 18.

Table 18. Number of test sample tubes to be placed into stability testing chambers at the stated temperature for each formulation, based on a 15 g fill tube (excluding QC release/t=0 tubes).

Storage condition	Minimum number of tubes required for stability testing	Number of contingency tubes	Total
25 °C 60 % RH	33	18	51
30 °C / 65 % RH	21	4	25
40 °C / 75 % RH	11	5	16

Total	65	27	92

The formulations were stored and tested in accordance with the ICH stability program, as detailed in Table 19, where the stated number of tubes were removed from stability testing chambers and tested using the specified methods summarised below.

Table 19. Summary of stability storage conditions, time points and testing based on a 15 g fill weight.

Storage Conditions	ICH stability testing time points (months)							
	Initial t=0 [R]	1	3	6	9	12	18	24
25°C/60% RH	XMP	X	X	X	X	XM	X	XMP
30°C/65% RH		(X)	(X)	(X)	(X)	(X)	(X)	(X)
40°C/75% RH		X	X	XM				

X = Full testing performed (macroscopic appearance, microscopic appearance, API assay and related substances, apparent viscosity) — from 3 tubes

M = Modified quantitative testing (MQT) testing — from 2 tubes.

P = Preservative efficacy testing — from 8 tubes.

( ) = Back-up condition. Products were tested for a specific test if an unexpected or out of trend ('out of specification') result was obtained for that test at 40 °C / 75 % RH storage condition.

[R] = Batch release data were used for t=0 if possible.

A total of 3 tubes for full testing were removed from stability testing chambers as per Table 19 at each time point. An additional 2 tubes for microbial quality testing and 8 tubes for preservative efficacy testing were only removed at the specified time points, as detailed in Table 19.

The following analysis was performed on each batch:

- Compound 1 assay and related substances.
- Macroscopic appearance (n=1 replicate in total for each batch per condition).
- Microscopic appearance (n=1 replicate in total for each batch per condition).
- Apparent viscosity (n=1 replicate in total for each batch per condition).
- Microbial quality testing (n=1 replicate in total for each batch, from the additional 2 tubes).

- Preservative efficacy testing (n=1 replicate in total for each batch, from the additional 8 tubes).

The formulations were analysed by HPLC. HPLC chromatograms were manually integrated using Empower software.

Table 20. Stability Testing Results for NA03-2.0%.

Time Point (months)	Macroscopic Appearance	Microscopic Appearance	Compound 1 Content	Apparent Viscosity
Initial / T=0	Slightly yellow, very slightly turbid gel	No crystalline material present	Start 1) 98.9 2) 97.6 3) 99.2 Mean = 98.6	99,800 mPa•s
			Middle 1) 99.5 2) 98.7 3) 98.8 Mean = 99.0	
			End 1) 99.2 2) 98.0 3) 98.3 Mean = 98.5	
T=1M 25°C/60%RH	Very slightly turbid, slightly yellow gel	No crystalline material present	1) 101.4 2) 101.2 3) 100.2 Mean = 100.9	112,600 mPa•s
T=1M 40°C/75%RH	Very slightly turbid, slightly yellow gel	No crystalline material present	1) 101.1 2) 100.7 3) 99.6 Mean = 100.5	121,400 mPa•s
T=3M 25°C/60%RH	Very slightly turbid, slightly yellow gel	No crystalline material present	1) 97.7 2) 98.3	118,800 mPa•s

			3) 98.0 Mean = 98.0	
T=3M 40°C/75%RH	Very slightly turbid, slightly yellow gel	No API crystals present	1) 98.5 2) 98.6 3) 98.1 Mean = 98.4	131,600 mPa•s

Table 21. HPLC Testing Results for NA03-2.0%.

		Related Substances/ Impurities	
RRT		1.18	Total
Initial / T=0	Start	0.09%	0.09%
	Middle	0.09%	0.09%
	End	0.09%	0.09%
T=1M 25°C/60%RH	n=2	0.07%	0.07%
T=1M 40°C/75%RH	n=2	< 0.05%	0.00%
T=3M 25°C/60%RH	n=2	Not Detected	0.00%
T=3M 40°C/75%RH	n=2	Not Detected	0.00%

Table 22. Microbial Testing Results for NA03-2.0%.

Time Point (months)	Microbial Quality			
	TAMC	TYMC	*Pseudomonas aeruginosa*	*Staphylococcus aureus*
Initial / T=0	< 1.0^2 CFU/g	< 1.0^1 CFU/g	Not isolated in 1 g	Not isolated in 1 g

TAMC = Total Aerobic Microbial Count

TYMC = Total Combined Yeast/Moulds Count

Table 23. Stability Testing Results for NA03-6.3%.

Time Point (months)	Macroscopic Appearance	Microscopic Appearance	Compound 1 Content	Apparent Viscosity
Initial / T=0	Very slightly turbid, yellow gel	No crystalline material present	Start 1) 99.5 2) 99.5 3) 99.3 Mean = 99.5	112,000 mPa•s
			Middle 1) 99.2 2) 99.4 3) 99.9 Mean = 99.5	
			End 1) 99.5 2) 99.2 3) 99.1 Mean = 99.2	
T=1M 25°C/60% RH	Very slightly turbid, yellow gel	No crystalline material present	1) 100.0 2) 99.7 3) 100.9 Mean = 100.2	117,400 mPa•s
T=1M 40°C/75% RH	Very slightly turbid, yellow gel	No crystalline material present	1) 98.8 2) 95.8 3) 98.0 Mean = 97.5	132,200 mPa•s
T=3M 25°C/60%RH	Very slightly turbid, yellow gel	No crystalline material present	1) 99.1 2) 98.7 3) 98.9 Mean = 98.9	131,800 mPa•s

T=3M 40°C/75%RH	Very slightly turbid, yellow gel	No crystalline material present	1) 99.9 2) 98.4 3) 98.9 Mean = 99.1	130,000 mPa•s

Table 24. HPLC Testing Results for NA03-6.3%.

		Related Substances / Impurities	
RRT		1.18	Total
Initial / T=0	Start	0.06%	0.06%
	Middle	0.06%	0.06%
	End	0.06%	0.06%
T=1M 25°C/60%RH	n=2	0.08%	0.08%
T=1M 40°C/75%RH	n=2	0.07%	0.07%
T=3M 25°C/60%RH	n=2	Not Detected	0.00%
T=3M 40°C/75%RH	n =2	Not Detected	0.00%

Table 25. Microbial Testing Results for NA03-6.3%.

Time Point (months)	Microbial Quality			
	TAMC	TYMC	*Pseudomonas aeruginosa*	*Staphylococcus aureus*
Initial / T=0	$< 1.0^2$ CFU/g	$< 1.0^1$ CFU/g	Not isolated in 1 g	Not isolated in 1 g

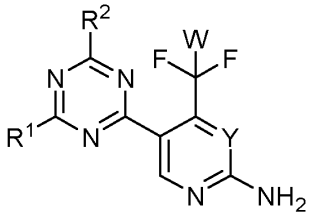
TAMC = Total Aerobic Microbial Count

TYMC = Total Combined Yeast/Moulds Count

Claims

1. A topical pharmaceutical composition comprising:

at least 0.1 weight percent of a compound of Formula (I):



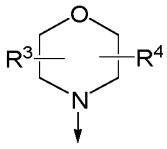
Formula (I)

wherein:

W is H or F;

Y is N or CH;

R^1 and R^2 are independently of each other a morpholinyl of Formula (II)



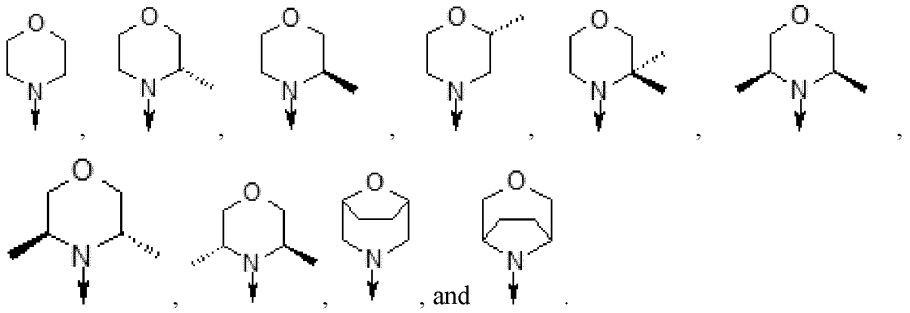
Formula (II)

wherein R^3 and R^4 are independently of each other H or C_1-C_3alkyl, or R^3 and R^4 combine to form a bivalent C_1-C_3alkylene residue;

at least 30 weight percent polyalkylene glycol, preferably at least 45 weight percent polyalkylene glycol; and

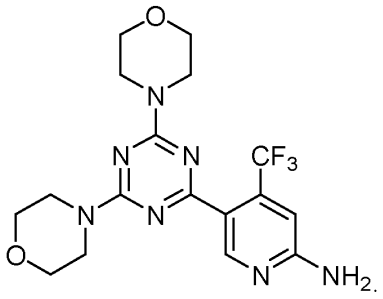
at least 10 weight percent diethylene glycol monoethyl ether, preferably at least 15 weight percent diethylene glycol monoethyl ether.

2. The topical pharmaceutical composition of claim 1, wherein R^1 and R^2 are each independently of each other selected from:



, and .

3. The topical pharmaceutical composition of claim 1, wherein the compound of Formula (I) is 5-(4,6-dimorpholino-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine:



4. The topical pharmaceutical composition of any of the preceding claims, wherein said composition comprises less than 1% water.

5. The topical pharmaceutical composition of any of the preceding claims, wherein said composition comprises less than 1% DMSO.

6. The topical pharmaceutical composition of any of the preceding claims, wherein said composition comprises diisopropyl adipate, preferably from about 1 weight percent to about 20 weight percent diisopropyl adipate.

7. The topical pharmaceutical composition of any of the preceding claims, wherein said composition comprises glycerol, preferably from about 1 weight percent to about 10 weight percent glycerol.

8. The topical pharmaceutical composition of any of the preceding claims, wherein said composition comprises hydroxypropyl cellulose, preferably from about 0.1 weight percent to about 10 weight percent.

9. The topical pharmaceutical composition of any of the preceding claims, wherein said composition comprises from about 45 weight percent to about 80 weight percent polyethylene glycol.

10. The topical pharmaceutical composition of any of the preceding claims, wherein said composition comprises from 15 weight percent to about 35 weight percent diethylene

glycol monoethyl ether.

11. The topical pharmaceutical composition of any of the preceding claims, wherein said composition comprises at least 1.9 weight percent of a compound of Formula (I).

12. The topical pharmaceutical composition any of the preceding claims, wherein said topical pharmaceutical composition comprises from about 45 weight percent to about 80 weight percent PEG, preferably PEG400; from about 15 weight percent to about 35 weight percent diethylene glycol monoethyl ether; from about 1 weight percent to about 20 weight percent diisopropyl adipate; from about 1 weight percent to about 10 weight percent glycerol; from about 0.1 weight percent to about 10 weight percent hydroxypropyl cellulose; and from about 0.5 weight percent to about 8 weight percent of Compound 1.

13. A topical aqueous pharmaceutical composition, wherein said topical aqueous pharmaceutical composition comprises:

from about 45 weight percent to about 80 weight percent polyalkylene glycol;

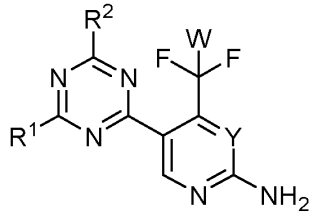
from about 10 weight percent to about 30 weight percent diethylene glycol monoethyl ether;

from about 1 weight percent to about 10 weight percent diisopropyl adipate;

from about 1 weight percent to about 10 weight percent glycerol;

from about 1 weight percent to about 20 weight percent water; and

from about 0.9 weight percent to about 8 weight percent of a compound of Formula (I):



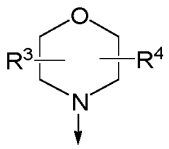
Formula (I)

wherein:

W is H or F;

Y is N or CH;

R^1 and R^2 are independently of each other a morpholinyl of Formula (II)



Formula (II)

wherein R^3 and R^4 are independently of each other H or C_1-C_3alkyl, or R^3 and R^4 combine to form a bivalent C_1-C_3alkylene residue.

14. A topical pharmaceutical composition of any of claims 1-12, for use as a medicament.

15. A topical pharmaceutical composition of claim 13, for use as a medicament.