

CRYSTALLINE FORMS OF NU-3 AND USES THEREOF**CROSS-REFERENCE TO RELATED APPLICATION**

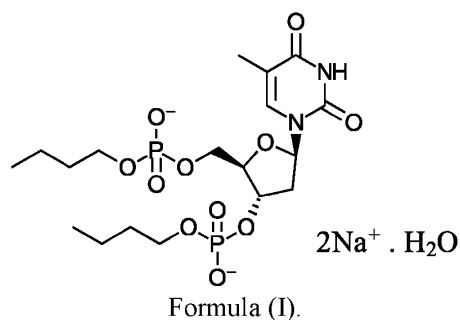
This application claims priority to U.S. Provisional Patent Application No. 63/556,774
5 filed on February 22, 2024, the entire content of which is incorporated herein by reference.

BACKGROUND

A continuing need exists for antimicrobial and antiviral compounds.

SUMMARY

The present disclosure provides crystalline forms of 1-[(2*R*,4*S*,5*R*)-4-
10 (hydroxybutoxyphosphoryloxy)-5-[(hydroxybutoxyphosphoryloxy)methyl]tetrahydro-2-furyl]-5-
methyl-2,4(1*H*,3*H*)-pyrimidinedione (referred to herein as “Nu-3”) having enhanced stability
during manufacture, handling, and storage compared to other crystalline forms or amorphous
forms. In one aspect, the crystalline form of Nu-3 is a disodium monohydrate crystalline form.
The crystalline form of Nu-3 may be referred to by its chemical name disodium (2*R*,3*S*,5*R*)-
15 butoxy({3-[butoxy(oxido)(oxo)- λ^5 -phosphanyloxy]-5-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1-
pyrimidinyl)tetrahydro-2-furyl}methoxy)(oxo)- λ^5 -phosphanolate. In some embodiments, a
crystalline form of Nu-3 is disclosed having the formula:



In some embodiments, the crystalline form of Nu-3 is characterized by an X-ray powder diffraction (XRPD) pattern having one or more 2θ peaks at about 5.47°, 7.71°, 12.19, 15.41, 17.25°, 18.12, 18.97, 19.67, 21.95, 22.6, 23.23, and 27.47° 2θ ±0.2° 2θ.

5 One advantage of a crystalline form of Nu-3 according to an embodiment of the present disclosure is that it is less sensitive to moisture compared to amorphous Nu-3 (herein referred to as Form 4). Form 4, or amorphous Nu-3 disodium salt, is described in U.S. Patent No. 7,868,162, the entire contents of which are incorporated herein by reference. Prior attempts to isolate a solid form of Nu-3 as a free acid have been challenging due to its extreme hygroscopicity
10 (deliquescence). The improved stability of the crystalline forms of Nu-3 disclosed herein, can make the disodium salt monohydrate a useful form of Nu-3 for drug substance manufacture and for drug product manufacture. For example, the crystalline form of Nu-3 described herein may be conveniently formulated in gels, creams, capsules, lozenges, powders, and the like for topical or inhaled administration. Another advantage is the crystalline forms of Nu-3 as disclosed herein
15 may be readily filterable and dried. Finally, the described crystalline forms of Nu-3 may be

prepared, purified, and stored for extended periods of time without the need for specialized protections from heat, light, oxygen, or moisture

In some embodiments, a pharmaceutical composition includes any crystalline form of Nu-3 disclosed herein and one or more pharmaceutically acceptable carriers, excipients, diluents, or a mixture of two or more thereof.

In some embodiments, a method of treating an infection in a patient in need thereof includes administering an effective amount of any crystalline form of Nu-3 disclosed herein or a pharmaceutically acceptable salt thereof, to the patient.

In some embodiments, a method of treating an infection of at least one of a wound or an ulcer in a patient in need thereof includes administering an effective amount of any crystalline form of Nu-3 disclosed herein or a pharmaceutically acceptable salt thereof, to the patient.

In some embodiments, a method of treating an infection of a diabetic foot ulcer in a patient in need thereof includes administering an effective amount of any crystalline form of Nu-3 disclosed herein or a pharmaceutically acceptable salt thereof, to the patient.

In some embodiments, a method of treating a bladder and/or a urinary tract infection in a patient in need thereof includes administering an effective amount of any crystalline form of Nu-3 disclosed herein or a pharmaceutically acceptable salt thereof, to the patient.

In some embodiments, a method of treating a lung infection in a patient in need thereof includes administering an effective amount of any crystalline form of Nu-3 disclosed herein or a pharmaceutically acceptable salt thereof, to the patient. In some embodiments, the lung infection arises from a pulmonary condition. In some embodiments, the pulmonary condition is selected

from the group consisting of genetic conditions, acquired conditions, primary conditions, secondary conditions, asthma, chronic obstructive pulmonary disease, cystic fibrosis, bronchiolitis, pneumonia, bronchitis, emphysema, adult respiratory distress syndrome, allergies, lung cancer, small cell lung cancer, primary lung cancer, metastatic lung cancer, bronchiectasis, 5 bronchopulmonary dysplasia, chronic bronchitis, chronic lower respiratory diseases, croup, high altitude pulmonary edema, pulmonary fibrosis, interstitial lung disease, reactive airway disease, lymphangioleiomyomatosis, neonatal respiratory distress syndrome, parainfluenza, pleural effusion, pleurisy, pneumothorax, primary pulmonary hypertension, psittacosis, pulmonary edema secondary to various causes, pulmonary embolism, pulmonary hypertension secondary to various 10 causes, respiratory failure secondary to various causes, sleep apnea, sarcoidosis, smoking, stridor, acute respiratory distress syndrome, infectious diseases, SARS, tuberculosis, psittacosis infection, Q fever, parainfluenza, respiratory syncytial virus, combinations thereof, and conditions caused by any one or combination of the above.

In some embodiments, the pulmonary condition arises from a coronavirus. In some 15 embodiments, the coronavirus is selected from the group consisting of an alphacoronavirus, a betacoronavirus, a gammacoronavirus, a deltacoronavirus, and an omicroncoronavirus, or combinations thereof.

In some embodiments, the coronavirus is selected from the group consisting of porcine epidemic diarrhea virus (PEDv), scotophilus bat coronavirus 512, bat coronavirus CDPHE15, 20 BtRF-Alpha-CoV HuB-2013, bat coronavirus HKU10, miniopterus bat coronavirus HKU8, miniopterus bat coronavirus 1, *Nyctalus velutinus* alphacoronavirus SC-2013, *Pipistrellus kuhlii*

coronavirus 3398, *Myotis ricketti* alphacoronavirus Sax-2011, HumCoV 229E, 229E-related bat coronavirus, camel alphacoronavirus, alpaca respiratory coronavirus, HumCoV NL63, NL63-related Bat-CoV BtKYNL63-9b, HKU2, SADSr-CoV, SADS-CoV, Lucheng Rn rat coronavirus2, FIPV, TGEV, PRCV, alphacoronavirus 1, mink coronavirus 1, FRCoV-NL-2010, *Sorex araneus* coronavirus T14, *Suncus murinus* coronavirus X74, HumCoV OC43, HumCoV OC43 isolate TNP F1778_2, HKU23, BovCoV, SACoV, GiCoV, bovine coronavirus isolate alpaca, canine respiratory coronavirus K37, PHEV, equine coronavirus, HKU14, HKU24, myodes coronavirus 2JL14, HKU1, MHV, rat coronavirus Parker, HKU4, HKU5, human MERS-CoV, camel MERS-CoV, hedgehog coronavirus 1, HKU9, rousettus bat coronavirus GCCDC1, eidolon bat coronavirus C704, human SARS-CoV, palm civet SARS-CoV, badger SARS-CoV, bat-SL-CoV RsSHC014, bat-SL-CoV Rs3367, bat-SL-CoV WIV1, HKU3, bat-SL-CoV ZC45, bat-SL-CoV ZXC21, bat-CoV RaTG13, bat-CoV RmYN02, human SARS-CoV-2, cat-CoV, tiger-CoV, dog-CoV, mink-CoV, GD pangolin-CoV, bat Hp-betacoronavirus Zhejiang2013, peafowl IBV, avian coronavirus 9203, fowl IBV, avian coronavirus, duck-CoV, partridge IBV, goose coronavirus CB17, beluga whale coronavirus SW1, HKU22, HKU19, HKU20, HKU21, HKU11, HKU12, HKU16, HKU27, HKU28, HKU29, HKU18, HKU13, HKU30-UAE, HKU30-Poland, HKU17-USA, HKU17-China, AICCoV, and HKU15, or combinations thereof.

In some embodiments, the coronavirus is a betacoronavirus selected from the group consisting of HumCoV OC43 isolate TNP F1778_2, HKU23, BovCoV, SACoV, GiCoV, bovine coronavirus isolate alpaca, canine respiratory coronavirus K37, PHEV, equine coronavirus, HKU14, HKU24, myodes coronavirus 2JL14, HKU1, MHV, rat coronavirus Parker, HKU4,

HKU5, human MERS-CoV, camel MERS-CoV, hedgehog coronavirus 1, HKU9, rousettus bat coronavirus GCCDC1, eidolon bat coronavirus C704, human SARS-CoV, palm civet SARS-CoV, badger SARS-CoV, bat-SL-CoV RsSHC014, bat-SL-CoV Rs3367, bat-SL-CoV WIV1, HKU3, bat-SL-CoV ZC45, bat-SL-CoV ZXC21, bat-CoV RaTG13, bat-CoV RmYN02, human SARS-CoV-2, cat-CoV, tiger-CoV, dog-CoV, mink-CoV, GD pangolin-CoV, and bat Hp-betacoronavirus Zhejiang2013, or combinations thereof.

In some embodiments, a method of treating cystic fibrosis in a patient in need thereof includes administering an effective amount of any crystalline form of Nu-3 disclosed herein or a pharmaceutically acceptable salt thereof, to the patient.

10 In some embodiments, a method of treating pneumonia in a patient in need thereof includes administering an effective amount of any crystalline form of Nu-3 disclosed herein or a pharmaceutically acceptable salt thereof, to the patient. In some embodiments, the pneumonia is ventilator acquired pneumonia.

In some embodiments, a method of treating an infection in a burn wound in a patient in need thereof includes administering an effective amount of any crystalline form of Nu-3 disclosed herein or a pharmaceutically acceptable salt thereof, to the patient.

15 In some embodiments, a method of treating otitis externa in a patient in need thereof includes administering an effective amount of any crystalline form of Nu-3 disclosed herein or a pharmaceutically acceptable salt thereof, to the patient.

In some embodiments, a method of treating bacterial vaginosis in a patient in need thereof includes administering an effective amount of any crystalline form of Nu-3 disclosed herein or a pharmaceutically acceptable salt thereof, to the patient.

In some embodiments, a method of treating impetigo in a patient in need thereof includes
5 administering an effective amount of any crystalline form of Nu-3 disclosed herein or a pharmaceutically acceptable salt thereof, to the patient.

In some embodiments, a method of treating oral mucositis in a patient in need thereof includes administering an effective amount of any crystalline form of Nu-3 disclosed herein or a pharmaceutically acceptable salt thereof, to the patient.

10 Another aspect of the present disclosure provides a crystalline form of a compound according to Formula (I), or a pharmaceutically acceptable salt thereof, for use in therapy.

Another aspect of the present disclosure provides the use of a crystalline form of a compound according to Formula (I), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament.

15 **BRIEF DESCRIPTION OF THE DRAWINGS**

The concepts described herein are illustrative by way of example and not by way of limitation in the accompanying figures. For simplicity and clarity of illustration, elements illustrated in the figures are not necessarily drawn to scale.

FIG. 1 shows a ¹H-NMR spectrum of Nu-3 di-Na salt (Form 1).

20 FIG. 2 shows a PXRD of di-Na salt of Nu-3 (Form 1).

FIG. 3 shows a DSC thermogram of Nu-3 di-Na salt (Form 1).

- FIG. 4 shows a mDSC thermogram of Nu-3 di-Na salt (Form 1).
- FIG. 5 shows a TGA of Nu-3 di-Na salt (Form 1).
- FIG. 6 shows a GC analysis of Nu-3 di-Na salt (Form 1).
- FIG. 7 shows a water content report of Form 1.
- 5 FIG. 8 shows a microscopic image of Form 1.
- FIG. 9 shows a heat-cool-heat DSC analysis of Nu-3 di-Na salt (Form 1).
- FIG. 10A shows a PXRD of Form 1 after heating to 180°C.
- FIG. 10B shows an NMR of Form 1 after heating to 180°C.
- FIG. 11A shows a PXRD of Form 1 after heating to 220°C.
- 10 FIG. 11B shows an NMR of Form 1 after heating at 220°C.
- FIG. 12A shows a PXRD of Form 1 after exposure to 22% RH.
- FIG. 12B shows a TGA of Form 1 after exposure to 22% RH.
- FIG. 13A shows a PXRD of Form 1 after heating to 100°C for 24 hrs.
- FIG. 13B shows an NMR of Form 1 after heating to 100°C for 24 hrs.
- 15 FIG. 13C shows a TGA of Form 1 after heating at 100°C for 24 hrs.
- FIG. 14 shows PXRD data for anti-solvent crystallization.
- FIG. 15 shows PXRD data for slurry crystallization.
- FIG. 16 shows PXRD data for cooling crystallization.
- FIG. 17 shows PXRD data for de-hydration of Form 1.
- 20 FIG. 18 shows a PXRD of amorphous Form 4.
- FIG. 19 shows a PXRD data for slurry crystallization of amorphous Form 4.

- FIG. 20 shows PXRD data of Form 2.
- FIG. 21 shows DSC thermogram of Form 2.
- FIG. 22 shows mDSC thermogram of Form 2.
- FIG. 23 shows a ¹H-NMR spectrum for Form 2.
- 5 FIG. 24 shows a heat-cool-heat DSC analysis of Form 2.
- FIG. 25 shows a TGA of Form 2.
- FIG. 26 shows a GC analysis of Form 2.
- FIG. 27 shows a water content report of Form 2.
- FIG. 28 shows a PXRD pattern of Form 3.
- 10 FIG. 29 shows a DSC thermogram of Form 3 obtained from IPA/water.
- FIG. 30 shows a PXRD pattern of Form 3 obtained from DMF.
- FIG. 31 shows a DSC thermogram of Form 3 obtained from DMF.
- FIG. 32 shows an mDSC thermogram of Form 3 obtained from DMF.
- FIG. 33 shows a TGA of Form 3 obtained from DMF.
- 15 FIG. 34 shows a GC analysis of Form 3 obtained from DMF.
- FIG. 35 shows a water content report of Form 3.
- FIG. 36 shows a ¹H-NMR spectrum of Form 3 obtained from DMF.
- FIG. 37 shows a PXRD data for Form 4.
- FIG. 38 shows an mDSC thermogram of Form 4.
- 20 FIG. 39 shows a ¹H-NMR spectrum of Form 4.
- FIG. 40 shows a PXRD of Form 5 obtained from MeOH/MTBE.

- FIG. 41 shows a DSC thermogram of Form 5 obtained from MeOH/MTBE.
- FIG. 42 shows an mDSC thermogram of Form 5 obtained from MeOH/MTBE.
- FIG. 43 shows a PXRD of Form 5 obtained from MeOH/1,4-dioxane.
- FIG. 44 shows a DSC thermogram of Form 5 obtained from MeOH/1,4-dioxane.
- 5 FIG. 45 shows an mDSC thermogram of Form 5 obtained from MeOH/1,4-dioxane.
- FIG. 46 shows a TGA of Form 5 obtained from MeOH/1,4-dioxane.
- FIG. 47 shows a GC analysis of Form 5 obtained from MeOH/1,4-dioxane.
- FIG. 48 shows a PXRD of de-solvated of Form 5 in TGA and an NMR.
- FIG. 49 shows a microscopic image of the crystals of Form 5.
- 10 FIG. 50 shows a PXRD pattern for Form 6.
- FIG. 51 shows a DSC thermogram of Form 6.
- FIG. 52 shows an mDSC thermogram of Form 6.
- FIG. 53 shows a TGA of Form 6.
- FIG. 54 shows a ¹H-NMR of Form 6.
- 15 FIG. 55 shows a water content report of Form 6.
- FIG. 56 shows a PXRD pattern comparing Form 1 with a recrystallized, purified Form 1.
- FIG. 57 shows a PXRD pattern of a recrystallized and purified Form 1.
- FIG. 58 shows a TGA of a recrystallized and purified Form 1.
- FIG. 59 shows a ¹H-NMR of the recrystallized and purified Form 1.
- 20 FIG. 60 shows a GC analysis of the recrystallized and purified Form 1.
- FIG. 61 shows a water content report of the recrystallized and purified Form 1.

FIG. 62 shows a PXRD data for stability studies at variable humidity conditions.

FIG. 63 shows a PXRD data for relative stability studies (Form 1, 4, and 6) under non-competitive conditions.

FIG. 64 shows a PXRD data for relative stability studies (Form 2, 3, and 5) under non-competitive conditions.

FIG. 65 shows a PXRD pattern showing physical stability studies of Form 1.

FIG. 66 shows a PXRD pattern showing stability studies of Form 1 at 2-8°C.

FIG. 67 shows a DSC thermogram of Form 7.

FIG. 68 shows a TGA of Form 7.

FIG. 69 shows an ¹H-NMR of Form 7.

DETAILED DESCRIPTION

As used herein, unless indicated otherwise, a percent of any substance refers to the weight percent of that substance as calculated by dividing the weight of the substance by the total weight of the mixture in which the substance is found, multiplied by 100%.

Definitions

“Purity,” when used in reference to a composition including a polymorph of a compound of Formula I, refers to the percentage of one specific polymorph form relative to another polymorph form or an amorphous form of a compound of Formula I in the referenced composition. For example, a composition comprising polymorph Form 1 having a purity of 90% would comprise 90 weight parts of Form 1 and 10 weight parts of another polymorph and/or amorphous forms of the compound of Formula I.

As used herein, a compound or composition is “substantially free of” one or more other components if the compound or composition contains no significant amount of such other components. For example, the composition can contain less than 5%, 4%, 3%, 2%, or 1% by weight of other components. Such components can include starting materials, residual solvents, or any other impurities that can result from the preparation of and/or isolation of the compounds and compositions provided herein. In some embodiments, a polymorph form provided herein is substantially free of other polymorph forms. In some embodiments, a particular polymorph of the compound of Formula I is “substantially free” of other polymorphs if the particular polymorph (i.e., Form 1) constitutes at least about 95% by weight of the compound of Formula I present. In some embodiments, a particular polymorph of the compound of Formula I is “substantially free” of other polymorphs if the particular polymorph constitutes at least about 97%, about 98%, about 99%, or about 99.5% by weight of the compound of Formula I present.

As used herein, “substantially pure,” when used in reference to a polymorph form of the compound of Formula I, means a sample of a polymorph form of the compound having a purity greater than 90%, including greater than 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, and 99%, and also including equal to about 100% of the compound, based on the weight of the compound. The remaining material comprises other form(s) of the compound, and/or reaction impurities and/or processing impurities arising from its preparation. For example, a polymorph form of the compound of Formula I may be deemed substantially pure in that it has a purity greater than 90% of a polymorph form of the compound of Formula I, as measured by means that are at this time known and generally accepted in the art, where the remaining less than

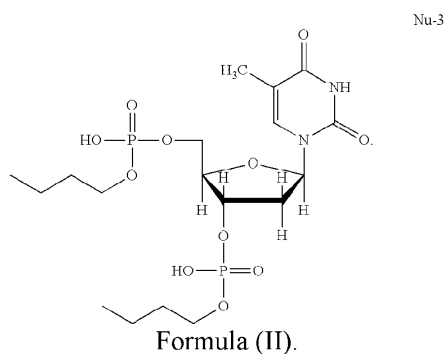
10% of material comprises other form(s) of the compound of Formula I and/or reaction impurities and/or processing impurities. The presence of reaction impurities and/or processing impurities may be determined by analytical techniques known in the art, such as, for example, chromatography, nuclear magnetic resonance spectroscopy, mass spectrometry, or infrared
5 spectroscopy.

To provide a more concise description, some of the quantitative expressions herein are recited as a range from about amount X to about amount Y. It is understood that when a range is recited, the range is not limited to the recited upper and lower bounds, but rather includes the full range from about amount X through about amount Y, or any range therein.

10 “Room temperature” or “RT” refers to the ambient temperature of a typical laboratory, which is typically around 25° C.

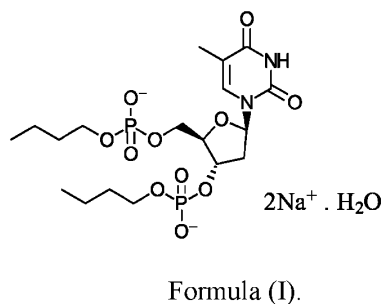
The embodiments described below are not intended to be exhaustive or to limit the invention to the precise forms disclosed in the following detailed description. Rather, the embodiments are chosen and described so that others skilled in the art may appreciate and
15 understand the principles and practices of this disclosure.

The present disclosure provides crystalline forms of the compound Nu-3. The compound Nu-3 has the formula:



Nu-3 belongs to the class of anti-microbial compounds referred to as Bisphosphocins. Methods of synthesizing and using Nu-3 are described in U.S. Pat. Nos. 6,211,349, 6,627,215, 6,211,162, 7,868,162, 7,176,191, 8,435,960, and 11,096,954, all of which are hereby incorporated by reference in their entireties.

5 In some embodiments, a disodium monohydrate crystalline form of Nu-3 is disclosed. In some embodiments, the crystalline form of Nu-3 is disclosed having the following formula:



Disclosed herein are several isomorphs of the disodium monohydrate crystalline form of Nu-3 identified as Form 1, Form 1', Form 2, Form 3, Form 5, Form 6, and Form 7. Additionally
10 disclosed herein is an amorphous form of the disodium monohydrate crystalline form of Nu-3

identified as Form 4. Amorphous Form 4 of Nu-3 is included to show the improved stability and other properties gained from the crystalline forms of Nu-3 disclosed herein.

In some embodiments, the crystalline forms disclosed herein of Nu-3 can be characterized by their X-ray powder diffraction (XRPD) patterns. The XRPD analyses were carried out on a
5 Malvern Panalytical EMPYREAN instrument and data analyzed using the software Highscore plus, version 4.8 (4.8.0.25518) having zero-background holder of Pan analytical (X-ray Cu/40 kV/30mA) and measured in the scan range of 3-40°2θ in continuous scan mode. In some embodiments, the crystalline forms disclosed herein of Nu-3 are characterized by one or more 2θ peaks at about 4.1° to about 4.3°, about 5.4° to about 5.7°, about 6.2° to about 6.4°, about 7.6° to
10 about 7.8°, about 7.8° to about 8.1°, about 10.4° to about 10.7°, about 11.2° to about 11.4°, about 12.1° to about 12.5°, about 15.0° to about 15.5°, about 15.6° to about 15.9°, about 16.6° to 16.8°, about 17.2° to about 17.3°, about 17.4° to about 17.6°, about 18.1° to about 18.7°, about 18.9° to about 19.5°, about 19.6° to about 19.7°, about 20° to about 20.2°, about 21.2° to about 21.4°, about 21.9° to about 22°, about 22.5° to about 23.0°, about 23.2° to about 23.8°, about 24.0° to about
15 24.3°, about 25.3° to about 25.6°, about 27.4° to about 27.5°, or about 28.2° to about 28.4°, each peak being ±0.2, ±0.1, ±0.05, ±0.02, or ±0.01 °2θ. In some embodiments, the crystalline forms disclosed herein of Nu-3 are characterized by one or more 2θ peaks at about 5.4°, about 5.6°, about 7.7°, about 12.4°, about 15.0°, about 15.7°, about 16.7°, about 17.2°, about 17.5°, about 18.5°, about 18.6°, about 18.9°, about 19.3°, about 21.3°, about 22.9°, about 24.0°, about 24.2°, or about
20 27.7°, each peak being ±0.2, ±0.1, ±0.05, ±0.02, or ±0.01 °2θ. In some embodiments, the deviation in °2θ is selected from ±0.2, ±0.1, ±0.05, ±0.02, or ±0.01.

In some embodiments, a Form 1 of the crystalline form of Nu-3 is characterized by an XRPD pattern having one or more 2θ peaks at about 5.4° , about 7.7° , about 12.1° , about 15.4° , about 17.2° , about 18.1° , about 18.9° , about 19.6° , about 21.9° , about 22.5° , about 23.2° , or about 27.4° , each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^\circ 2\theta$. In some embodiments, a Form 1 of the crystalline form of Nu-3 is characterized by an XRPD pattern having one or more 2θ peaks at about 5.4° , about 7.7° , or about 17.2° , each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^\circ 2\theta$. In some embodiments, a Form 1 of the crystalline form of Nu-3 is characterized by an XRPD pattern having one or more 2θ peaks at about 5.472° , about 7.714° , or about 17.252° , each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^\circ 2\theta$. In some embodiments, a Form 1 of the crystalline form of Nu-3 is characterized by an XRPD pattern having 2θ peaks at about 5.4° , about 7.7° , about 12.1° , about 15.4° , and about 17.2° , each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^\circ 2\theta$. In some embodiments, a Form 1 of the crystalline form of Nu-3 is characterized by an XRPD pattern having 2θ peaks at about 5.4° , about 7.7° , about 12.1° , about 15.4° , about 17.2° , about 18.1° , about 18.9° , about 19.6° , about 21.9° , about 22.5° , about 23.2° , and about 27.7° , each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^\circ 2\theta$. In some embodiments, a Form 1 of the crystalline form of Nu-3 is characterized by an XRPD pattern having 2θ peaks at about 5.472° , about 7.714° , about 12.190° , about 15.413° , about 17.252° , about 18.116° , about 18.972° , about 19.674° , about 21.947° , about 22.598° , about 23.235° , and about 27.41° , with each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^\circ 2\theta$.

In some embodiments, a Form 2 of the crystalline form of Nu-3 is characterized by an XRPD pattern having one or more unique 2θ peaks at about 7.9° , about 16.7° , about 18.5° , about

22.7°, about 23.6°, about 24.2°, and about 25.4°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ . In some embodiments, a Form 2 of the crystalline form of Nu-3 is characterized by an XRPD pattern having one or more 2 θ peaks at about 7.9°, about 16.7°, about 18.5°, about 22.7°, and about 24.2°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ . In some embodiments, a

5 Form 2 of the crystalline form of Nu-3 is characterized by an XRPD pattern having one or more 2 θ peaks at about 7.989°, about 16.717°, about 18.529°, about 22.770°, and about 24.228°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ . In some embodiments, a Form 2 of the crystalline form of Nu-3 is characterized by an XRPD pattern having 2 θ peaks at about 7.9°, about 16.7°, about 18.5°, about 22.7°, about 23.6°, about 24.2°, and about 25.5°, each peak being ± 0.2 ,

10 ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ . In some embodiments, a Form 2 of the crystalline form of Nu-3 is characterized by an XRPD pattern having 2 θ peaks at about 7.989°, about 16.717°, about 18.529°, about 22.770°, about 23.682°, about 24.228°, and about 25.494°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .

In some embodiments, a Form 3 of the crystalline form of Nu-3 is characterized by an

15 XRPD pattern having one ore more unique 2 θ peaks at about 4.2°, about 15.0°, or about 19.3°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ . In some embodiments, a Form 3 of the crystalline form of Nu-3 is characterized by an XRPD pattern having one or more unique 2 θ peaks at about 15.1° or about 19.4°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ . In some embodiments, a Form 3 of the crystalline form of Nu-3 is characterized by an XRPD pattern having

20 one or more unique 2 θ peaks at about 15.069° or about 19.356°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ . In some embodiments, a Form 3 of the crystalline form of Nu-3 is

characterized by an XRPD pattern having 2θ peaks at about 4.3° , about 15.1° , or about 19.4° , each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^\circ 2\theta$. In some embodiments, a Form 3 of the crystalline form of Nu-3 is characterized by an XRPD pattern having 2θ peaks at about 4.290° , about 15.069° , or about 19.356° , each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^\circ 2\theta$.

5 In some embodiments, a Form 5 of the crystalline form of Nu-3 is characterized by an XRPD pattern having one or more unique 2θ peaks at about 7.9° , 12.4° or about 20.1° , each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^\circ 2\theta$. In some embodiments, a Form 5 of the crystalline form of Nu-3 is characterized by an XRPD pattern having a 2θ peak at about 12.4° each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^\circ 2\theta$. In some embodiments, a Form 5 of the crystalline form of
10 Nu-3 is characterized by an XRPD pattern having a 2θ peak at about 12.424° each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^\circ 2\theta$. In some embodiments, a Form 5 of the crystalline form of Nu-3 is characterized by an XRPD pattern having one or more unique 2θ peaks at about 7.924° , 12.424° or about 20.081° , each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^\circ 2\theta$. In some
15 embodiments, a Form 5 of the crystalline form of Nu-3 is characterized by an XRPD pattern having 2θ peaks at about 7.924° , 12.424° or about 20.081° , each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^\circ 2\theta$.

In some embodiments, a Form 7 of the crystalline form of Nu-3 is characterized by an XRPD pattern having one or more unique 2θ peaks at about 5.7° , about 6.3° , about 10.6° , about 11.3° , about 15.8° , about 17.6° , about 18.6° , about 21.3° about 23° , about 24° , or about 28.3° , each
20 peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^\circ 2\theta$. In some embodiments, a Form 7 of the crystalline form of Nu-3 is characterized by an XRPD pattern having one or more unique 2θ peaks

at about 5.7°, about 10.6°, about 15.8°, about 17.6°, about 18.6°, about 21.3°, about 23°, or about 24°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ . In some embodiments, a Form 7 of the crystalline form of Nu-3 is characterized by an XRPD pattern having one or more unique 2 θ peaks at about 5.692°, about 10.590°, about 15.759°, about 17.554°, about 18.640°, about 21.302°, about 22.958°, or about 24.041°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ . Table 1 provides exemplary XRPD patterns. In some embodiments, a Form 7 of the crystalline form of Nu-3 is characterized by an XRPD pattern having 2 θ peaks at about 5.692°, about 6.331°, about 10.590°, about 11.314°, about 15.759°, about 17.554°, about 18.640°, about 21.302°, about 22.958°, about 24.041°, and 28.301°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .

Tables 1 and 2 provide exemplary XRPD patterns.

Table 1. Exemplary XRPD pattern and the relative intensity (%) of each peak for the crystalline Form 1 of Nu-3.

Form 1		
S.No.	Peak position (°2 θ)	Relative intensity (%)
1	5.472	100
2	7.714	15.37
3	12.19	6.94
4	15.413	3.15
5	17.252	10.96
6	18.116	7.43
7	18.972	4.02
8	19.674	4.79
9	21.947	2.60
10	22.598	4.55
11	23.235	6.89
12	27.471	3.52

Table 2. Exemplary XRPD pattern and the relative intensity (%) of each peak for the crystalline Forms 2, 3, 5, 6, and 7 of Nu-3.

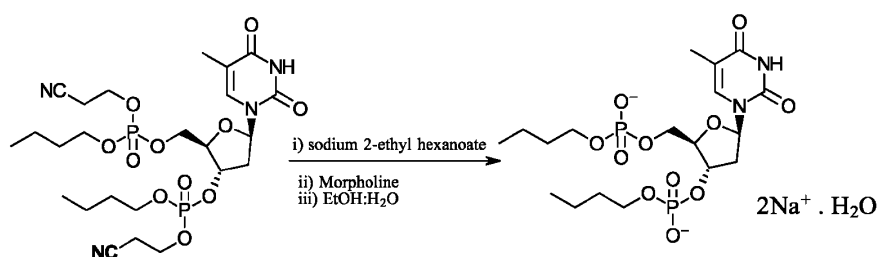
Form 2*		
S.No.	Peak position (°2θ)	Relative intensity (%)
1	7.989	6.29
2	16.717	21.30
3	18.529	27.75
4	22.770	9.21
5	23.682	6.61
6	24.228	10.07
7	25.494	5.96
Form 3*		
S.No.	Peak position (°2θ)	Relative intensity (%)
1	4.290	4.61
2	15.069	34.41
3	19.356	17.97
Form 5*		
S.No.	Peak position (°2θ)	Relative intensity (%)
1	7.924	6.88
2	12.424	9.60
3	20.081	4.34
Form 6*		
S.No.	Peak position (°2θ)	Relative intensity (%)
1	11.014	--
2	16.948	--
3	21.566	--
4	24.729	--
Form 7 ⁺		
S.No.	Peak position (°2θ)	Relative intensity (%)
1	5.692	65.05
2	6.331	6.33
3	10.590	27.58
4	11.314	2.44
5	15.759	12.16

6	17.554	10.65
7	18.640	14.31
8	21.302	12.40
9	22.958	25.55
10	24.041	17.95
11	28.301	6.62

* Unique peaks with respect to Form 1 and Form 7

+ Unique peaks with respect to Form 1

The crystalline structure of Nu-3 may be formed using various known crystallization methods. In some embodiments, the crystallization methods may be selected from an antisolvent crystallization, slurry crystallization, cooling crystallization, or evaporative crystallization. The examples section provides additional description of these methods. In some embodiments, the crystalline Form 1 may be synthesized by combining 3- $\{[(2R,3S,5R)$ -3-(2-cyanoethoxybutoxyphosphoryloxy)-5-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)tetrahydro-2-furyl]methoxybutoxyphosphoryloxy $\}$ propiononitrile in ethanol and water to form a solution. Then sodium 2 ethyl hexanoate and morpholine were added to the solution and heated to reflux for 20 hours. After cooling, the solution was filtered and washed. The filtered solution was then combined with acetone and seeded with crystalline Nu-3 disodium salt to form a slurry. Additional acetone was added and the slurry was then filtered, washed, and dried to yield disodium (2*R*,4*S*,5*R*) butoxy($\{3$ -[butoxy(oxido)(oxo)- λ^5 -phosphanyloxy]-5-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)tetrahydro-2-furyl $\}$ methoxy)(oxo)- λ^5 -phosphanolate monohydrate (also referred to as the Nu-3 disodium salt monohydrate).



Recrystallisation the Nu-3 disodium salt monohydrate was achieved by redissolving in an ethanol:water mixture and then filtering the solution followed by a seed of crystalline Nu-3 disodium salt added as a slurry in acetone to induce crystallization of the disodium salt monohydrate. The crystallized solid was filtered through filter paper, washed with a water:ethanol:acetone mixture and dried to yield disodium (2*R*,4*S*,5*R*) butoxy({3-[butoxy(oxido)(oxo)-λ⁵-phosphanyloxy]-5-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)tetrahydro-2-furyl}methoxy)(oxo)-λ⁵-phosphanolate monohydrate (i.e, Nu-3 disodium salt monohydrate). Additional details of an exemplary synthesis of a Form 1 of the crystalline form of Nu-3 is described in the Examples.

A crystalline form of Nu-3 may be isolated as a composition after the crystallization process. The isolated crystalline form of Nu-3 (e.g., Form 1) may be substantially pure of other polymorphs of Formula I (e.g., Form 2, Form 3, Form 4, Form 5, or Form 7). The composition may comprise at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 97%, at least about 98%, at least about 99%, or about 100% of Form 1. In some embodiments, the composition comprises Form 1. The composition of Form 1 may be substantially free of other impurities.

In some embodiments, the composition can be substantially pure. For example, the composition has a purity of at least about 90%. In some embodiments, the composition has a purity of at least about 95%. In some embodiments, the composition has a purity of at least about 98%. For example, the composition can have a purity of at least 98.5%, 98.6%, 98.7%, 98.8%, 98.9%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9%. In some
5 embodiments, the composition is substantially free of other forms of the compound of Formula I. In some embodiments, the composition contains less than about 15% by weight of other forms of the compound of Formula I. For example, the composition can contain less than 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1% by weight of one or more other forms of the
10 compound of Formula I. For example, the composition can contain less than about 15% of amorphous Form 4.

A composition comprising a crystalline form of Nu-3 may be prepared and isolated at varying levels of desired purity. The composition may be prepared comprising a mixture of polymorphs/isomorphs. In some embodiments, the composition comprises Form 1. In some
15 embodiments, the composition comprises at least about 50% Form 1, at least about 60% Form 1, at least about 70% Form 1, at least about 75% Form 1, at least about 80% Form 1, at least about 85% Form 1, at least about 90% Form 1, at least about 95% Form 1, at least about 97% Form 1, or at least about 99% Form 1. In some embodiments, the composition comprises at least about 99.5% Form 1.

20 The structured organization of crystalline forms of Nu-3, and in particular Form 1, result in an acquired increased stability during manufacture, handling, and storage compared to the

amorphous crystalline form of Nu-3 (i.e., Form 4) as described and exemplified herein. For example, Form 1 retains its dry-powder state at relative humidities of about 50% or less. In some embodiments, Form 1 remains a dry-powder up to about 50% relative humidity, while the amorphous form of crystalline Nu-3 begins to sorb water from the air. This stability imparts advantageous to the crystalline forms of Nu-3, and in particular Form 1, over the amorphous form including less strenuous manufacturing and storage requirements. In some embodiments, the crystal structure of Form 1 results in Form 1 remaining stable at about 55%, about 50%, about 45%, about 40%, about 35%, about 30%, about 25%, about 20%, about 15%, about 10%, or about 5% relative humidity. In some embodiments, the crystal structure of Form 1 results in Form 1 remaining stable at 55%, 54%, 53%, 52%, 51%, or 50% relative humidity.

As used herein “remaining stable” refers to the powder form of the crystalline forms of Nu-3 sorbing less than 1%, less than 1.5%, less than 2%, less than 2.5%, less than 3%, less than 3.5%, less than 4%, less than 4.5%, less than 5%, less than 5.5%, less than 6%, less than 6.5%, less than 7%, less than 7.5%, less than 8%, less than 8.5%, less than 9%, less than 9.5%, or less than 10% weight of water. In some embodiments, remaining stable refers to the powder form of the crystalline forms of Nu-3 sorbing less than about 5%, less than about 10%, less than 15%, less than about 20%, or less than about 25% weight water.

The stability imparted by the crystal structure of Form 1 remains at temperatures up to 60°C. In some embodiments, Form 1 remains stable at temperatures of less than 60°C, less than 55°C, less than 50°C, less than 45°C, less than 40°C, less than 35°C, less than 30°C, less than 25°C, less than 20°C, less than 15°C, less than 10°C, less than 5°C, or less than 0°C. In some

embodiments, Form 1 remains stable at temperatures between about -80°C to about 60°C. In some embodiments, Form 1 remains stable at temperatures between about -80°C to about 30°C, about -30°C to about 30°C, about 0°C to about 30°C, about 10°C to about 25°C, about 15°C to about 30°C, or about 25°C.

5 In some embodiments, a compound comprising the crystalline form of Nu-3 of the present disclosure is disclosed herein. In addition, a compound of the present disclosure may exist in any number of different forms or derivatives, all within the scope of the present disclosure. Alternative forms or derivatives, include, for example, prodrugs and active metabolites, tautomers, pharmaceutically acceptable salts, and solid forms, including without limitation different crystal
10 forms, polymorphic or amorphous solids, including hydrates and solvates thereof, and other forms.

 As used herein, the term “pharmaceutically acceptable,” with respect to salts and formulation components such as carriers, excipients, and diluents, refers to those salts and components which are not deleterious to a patient and which are compatible with other ingredients, active ingredients, salts or components. Pharmaceutically acceptable includes “veterinarily
15 acceptable,” and thus includes both human and non-human mammal applications independently.

 Prodrugs are compounds or pharmaceutically acceptable salts thereof which, when metabolized under physiological conditions or when converted by solvolysis, yield the desired active compound. Typically, the prodrug is inactive, or less active than the active compound, but may provide one or more advantageous handling, administration, and/or metabolic properties.
20 Some prodrugs are activated enzymatically to yield the active compound, or a compound may undergo further chemical reaction to yield the active compound. Prodrugs may proceed from

prodrug form to active form in a single step or may have one or more intermediate forms which such forms have activity or may be inactive.

As described in *The Practice of Medicinal Chemistry*, Ch. 31-32 (Ed. Wermuth, Academic Press, San Diego, Calif., 2001), prodrugs can be conceptually divided into two non-exclusive categories, including bioprecursor prodrugs and carrier prodrugs. Generally, bioprecursor prodrugs are compounds that are inactive or have low activity compared to the corresponding active drug compound that contain one or more protective groups and are converted to an active form by metabolism or solvolysis. Both the active drug form and any released metabolic products should have acceptably low toxicity.

Carrier prodrugs are drug compounds that contain a transport moiety, e.g., that improves uptake and/or localized delivery to a site(s) of action. Desirably for such a carrier prodrug, the linkage between the drug moiety and the transport moiety is a covalent bond, the prodrug is inactive or less active than the drug compound, and the prodrug and any release transport moiety are acceptably non-toxic. For prodrugs where the transport moiety is intended to enhance uptake, typically the release of the transport moiety should be rapid. In other cases, it is desirable to utilize a moiety that provides slow release, e.g., certain polymers or other moieties, such as cyclodextrins. Such carrier prodrugs are often advantageous for orally administered drugs. In some instances, the transport moiety provides targeted delivery of the drug. For example, the drug may be conjugated to an antibody or antibody fragment. Carrier prodrugs can, for example, be used to improve one or more of the following properties: increased lipophilicity, increased duration of pharmacological effects, increased site-specificity, decreased toxicity and adverse reactions,

and/or improvement in drug formulation (e.g., stability, water solubility, suppression of an undesirable organoleptic or physiochemical property). For example, lipophilicity can be increased by esterification of hydroxyl groups with lipophilic carboxylic acids, or of carboxylic acid groups with alcohols, e.g., aliphatic alcohols. Wermuth, *supra*.

5 Metabolites, e.g., active metabolites, overlap with prodrugs as described above, e.g., bioprecursor prodrugs. Thus, such metabolites are pharmacologically active compounds or compounds that further metabolize to pharmacologically active compounds that are derivatives resulting from metabolic processes in the body of a subject. Of these, active metabolites are such pharmacologically active derivative compounds. For prodrugs, the prodrug compound is generally
10 inactive or of lower activity than the metabolic product. For active metabolites, the parent compound may be either an active compound or may be an inactive prodrug. For example, in some compounds, one or more alkoxy groups can be metabolized to hydroxyl groups while retaining pharmacologic activity and/or carboxyl groups can be esterified, e.g., glucuronidation. In some cases, there can be more than one metabolite, where an intermediate metabolite(s) is
15 further metabolized to provide an active metabolite. For example, in some cases a derivative compound resulting from metabolic glucuronidation may be inactive or of low activity and can be further metabolized to provide an active metabolite.

Metabolites of a compound of the present disclosure may be identified using routine techniques known in the art, and their activities determined using tests such as those described in
20 Bertolini et al., 1997, *J. Med. Chem.*, 40:2011-2016; Shan et al., 1997, *J Pharm Sci* 86(7):756-757; Bagshawe, 1995, *Drug Dev. Res.*, 34:220-230; Wermuth, *supra*.

It is understood by those skilled in the art that some compounds may exhibit tautomerism. In such cases, the formulae provided herein expressly depict only one of the possible tautomeric forms. It is therefore to be understood that a compound of the present disclosure intends to represent any tautomeric form of the depicted compound and is not to be limited merely to the
5 specific tautomeric form depicted by the drawing of the compound.

One of ordinary skill in the art would understand that pharmaceutically acceptable salts may exist in different crystal or polymorphic forms, or may be formulated as co-crystals, or may be in an amorphous form, or may be any combination thereof (e.g. partially crystalline, partially amorphous, or mixtures of polymorphs) all of which are intended to be within the scope of the
10 present disclosure and specified formulae. Whereas salts are formed by acid/base addition (i.e., a free base or free acid of the compound of interest forms an acid/base reaction with a corresponding addition base or addition acid, respectively, resulting in an ionic charge interaction), co-crystals are a new chemical species that is formed between neutral compounds, resulting in the compound and an additional molecular species in the same crystal structure.

15 A compound of the present disclosure in accordance with some embodiments is useful as an antimicrobial having activity against any microbe. As used herein, the terms "microbe," "microbial," and like terms refers to bacteria, fungi, protozoa, viruses, yeast, and the like. As used herein, the term "antimicrobial" refers to a compound of the present disclosure having the ability to kill or inhibit the growth of a microbe, or to attenuate the severity of a microbial infection. A
20 non-limiting list of the bacteria that a compound of the present disclosure is effective against include without limitation gram positive bacteria, gram negative bacteria, slow growing bacteria

and acid fast bacteria, and any species included in the following genera: *Aerococcus*, *Listeria*,
Streptomyces, *Chlamydia*, *Lactobacillus*, *Eubacterium*, *Burkholderia*, *Stentrophomonas*,
Achromobacter, *Arachnid*, *Mycobacterium*, *Peptostreptococcus*, *Staphylococcus*,
Corynebacterium, *Erysipelothrix*, *Dermatophilus*, *Rhodococcus*, *Pseudomonas*, *Streptococcus*,
5 *Bacillus*, *Peptococcus*, *Pneumococcus*, *Micrococcus*, *Neisseria*, *Klebsiella*, *Kurthia*, *Nocardia*,
Serratia, *Rothia*, *Escherichia*, *Propionibacterium*, *Actinomyces*, *Helicobacter*, *Enterococcus*,
Shigella, *Vibrio*, *Clostridium*, *Salmonella*, *Yersinia*, and *Haemophilus*.

A non-limiting list of the fungi that a compound of the present disclosure is effective
against include without limitation *Trichophyton*, *Epidermophyton*, *Microsporum*, *Candida*
10 *albicans* and other *Candida* species, *Pityrosporum orbiculare*, *Trichophyton mentagrophytes*,
Trichophyton rubrum, *Epidermophyton floccosurn*, and *Trichophyton tonsurans*. A non-limiting
list of the viruses that a compound of the present disclosure is effective against include without
limitation envelope viruses, human immunodeficiency virus (HIV), herpes simplex virus (HSV),
cytomegalovirus (CMV), Hepatitis B virus (HBV), Hepatitis C virus (HCV), coronaviruses, and
15 influenza virus.

In some embodiments, a compound of the present disclosure is useful in both therapeutic
and non-therapeutic medical applications. In some embodiments including non-therapeutic
medical applications, the antimicrobial effect of a compound of the present disclosure allows use
of a compound of the present disclosure for sterilization (e.g., sterilization of a patient's skin or of
20 a surface or an object, such as, for example, a surgical instrument), or sanitization (e.g., the
cleansing of a surface, instrument, as to render the surface free of undesirable concentrations of

disease causing microorganisms). In some embodiments, the compounds of the present disclosure are effective in combating microbial contamination of laboratory cultures, consumables (e.g., food or beverage preparations), medical devices, hospital apparatus, or industrial processes. Therapeutic applications of a compound of the present disclosure are described herein.

5 The present disclosure also provides pharmaceutical compositions. As used herein, the term “pharmaceutical composition” refers to a pharmaceutical preparation that contains a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, and is suitable for administration to a patient for therapeutic purposes. As used herein, the term “patient” refers to a living organism that is treated with a compound of the present disclosure, including without
10 limitation any mammal such as, for example, humans, other primates (e.g., monkeys, chimpanzees, etc.), companion animals (e.g., dogs, cats, horses, etc.), farm animals (e.g., goats, sheep, pigs, cattle, etc.), laboratory animals (e.g., mice, rats, etc.), and wild and zoo animals (e.g., wolves, bears, deer, etc.).

 One of ordinary skill in the art would understand that the compounds described herein may
15 be used in compositions that may include at least one pharmaceutically acceptable component to provide an improved formulation of a compound of the present disclosure, including without limitation one or more pharmaceutically acceptable carriers, excipients or diluents. The carrier, excipient or diluent may take a wide variety of forms depending on the form of preparation desired for administration.

20 As used herein, the term “carrier” includes without limitation calcium carbonate, calcium phosphate, various sugars, such as lactose, glucose, or sucrose, types of starch, cellulose

derivatives, gelatin, lipids, liposomes, nanoparticles, physiologically acceptable liquids as solvents or for suspensions, including, for example, sterile solutions of water for injection (WFI), saline solution, dextrose solution, Hank's solution, Ringer's solution, vegetable oils, mineral oils, animal oils, polyethylene glycols, liquid paraffin, and the like.

5 As used herein, the term "excipient" generally includes without limitation fillers, binders, disintegrants, glidants, lubricants, complexing agents, solubilizers, stabilizer, preservatives, and surfactants, which may be chosen to facilitate administration of the compound by a particular route. Suitable excipients may also include, for example, colloidal silicon dioxide, silica gel, talc, magnesium silicate, calcium silicate, sodium aluminosilicate, magnesium trisilicate, powdered
10 cellulose, macrocrystalline cellulose, carboxymethyl cellulose, cross-linked sodium carboxymethylcellulose, sodium benzoate, calcium carbonate, magnesium carbonate, stearic acid, aluminum stearate, calcium stearate, magnesium stearate, zinc stearate, sodium stearyl fumarate, syloid, stearrowet C, magnesium oxide, starch, sodium starch glycolate, glyceryl monostearate, glyceryl dibehenate, glyceryl palmitostearate, hydrogenated vegetable oil, hydrogenated cotton
15 seed oil, castor seed oil, mineral oil, polyethylene glycol (e.g., PEG 4000-8000), polyoxyethylene glycol, poloxamers, povidone, crospovidone, croscarmellose sodium, alginic acid, casein, methacrylic acid divinylbenzene copolymer, sodium docusate, cyclodextrins (e.g., 2-hydroxypropyl-delta-cyclodextrin), polysorbates (e.g., polysorbate 80), cetrimide, TPGS (d-alpha-tocopheryl polyethylene glycol 1000 succinate), magnesium lauryl sulfate, sodium lauryl sulfate,
20 polyethylene glycol ethers, di-fatty acid ester of polyethylene glycols, or a polyoxyalkylene sorbitan fatty acid ester (e.g., polyoxyethylene sorbitan ester Tween®), polyoxyethylene sorbitan

fatty acid esters, sorbitan fatty acid ester, e.g., a sorbitan fatty acid ester from a fatty acid such as oleic, stearic or palmitic acid, mannitol, xylitol, sorbitol, maltose, lactose, lactose monohydrate or lactose spray dried, sucrose, fructose, calcium phosphate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, dextrans, dextran, dextrin, dextrose, cellulose acetate, 5 maltodextrin, simethicone, polydextrose, chitosan, gelatin, HPMC (hydroxypropyl methyl celluloses), HPC (hydroxypropyl cellulose), hydroxyethyl cellulose, and the like.

As the skilled artisan understands, any diluent known in the art may be utilized in accordance with the present disclosure. In some embodiments of the present disclosure, the diluent is water soluble. In some embodiments of the present disclosure, the diluent is water insoluble. 10 As used herein, the term “diluent” includes without limitation water, saline, phosphate buffered saline (PBS), dextrose, glycerol, ethanol, buffered sodium or ammonium acetate solution, or the like, and combinations thereof.

In some embodiments, the pharmaceutical compositions of the present disclosure include at least one additional active ingredient. As used herein, the term “active ingredient” refers to a 15 therapeutically active compound, as well as any prodrugs thereof and pharmaceutically acceptable salts, hydrates, and solvates of the compound and the prodrugs. Additional active ingredients may be combined with a compound of the present disclosure and may be either administered separately or in the same pharmaceutical composition. The amount of additional active ingredients to be given may be determined by one skilled in the art based upon therapy with a compound of the 20 present disclosure.

In some embodiments, the composition is a human pharmaceutical composition. As used herein, the term “human pharmaceutical composition” refers to a pharmaceutical composition intended for administration to a human.

The pharmaceutical compositions of the present disclosure are suitable for administration
5 to a patient by any suitable means, including without limitation those means used to administer
conventional antimicrobials. The pharmaceutical compositions of the present disclosure may be
administered using any applicable route that would be considered by one of ordinary skill,
including without limitation oral, intravenous (“IV”) injection or infusion, intravesical,
subcutaneous (“SC”), intramuscular (“IM”), intraperitoneal, intradermal, intraocular, inhalation
10 (and intrapulmonary), intranasal, transdermal, epicutaneously, subdermal, topical, mucosal, nasal,
ophthalmic, impression into skin, intravaginal, intrauterine, intracervical, and rectal. Such dosage
forms should allow a compound of the present disclosure to reach target cells. Other factors are
well known in the art and include considerations such as toxicity and dosage forms that retard a
compound or composition from exerting its effects. Techniques and formulations generally may
15 be found in Remington: The Science and Practice of Pharmacy, 21st edition, Lippincott, Williams
and Wilkins, Philadelphia, Pa., 2005.

In some embodiments, the pharmaceutical compositions of the present disclosure are
adapted for topical administration. As used herein, the term “topical administration” refers to
administration of a compound of the present disclosure to the skin surface of a patient so that a
20 compound of the present disclosure passes through the skin layer. Transdermal administration and
transmucosal administration are also encompassed within the term topical administration. As used

herein, the term “transdermal” refers to passage of a compound of the present disclosure across at least one skin layer of a patient. As used herein, “transmucosal” refers to passage of a compound of the present disclosure across a mucous membrane of a patient. Unless otherwise stated or implied, the terms “topical administration,” “transdermal administration,” and “transmucosal administration” are used interchangeably herein.

A variety of topical delivery systems for delivering bioactive compounds to microbes in a patient are well known in the art. Such systems include without limitation lotions, creams, gels, oils, ointments, solutions, suspensions, emulsions, and the like by choice of appropriate carriers in the art.

10 Suitable carriers include without limitation vegetable or mineral oils, white petrolatum (e.g., white soft paraffin), branched chain fats or oils, animal fats and high molecular weight alcohol (e.g., greater than C12). In some embodiments, carriers are selected such that a compound of the present disclosure is soluble. In some embodiments, emulsifiers, stabilizers, humectants, and antioxidants may also be included as well as agents imparting color or fragrance, if desired.

15 In some embodiments, an organic solvent or co-solvent such as ethanol or propanol may be employed in the pharmaceutical compositions of the present disclosure. In some embodiments, evaporation of the solvent leaves a residue on the treated surface to inhibit reinfection. In some embodiments, penetrants appropriate to the barrier to be permeated are used. Such penetrants are generally known in the art and include without limitation bile salts and fusidic acid derivatives. In

20 some embodiments, detergents may be used to facilitate permeation. In some embodiments, creams for topical administration are formulated from a mixture of mineral oil, self-emulsifying

beeswax, and water in which mixture a compound of the present disclosure, dissolved in a small amount of solvent (e.g., an oil), is admixed. The specific topical delivery system used depends on the location of the microbes.

In some embodiments, other materials may also be added to the topical pharmaceutical compositions of the present disclosure have additional moisturizing effects and to improve the consistency of the pharmaceutical composition. Examples of such compounds include without limitation cetyl esters wax, stearyl alcohol, cetyl alcohol, glycerin, methyl paraben, propyl paraben, quaternium-15, humectants, volatile methylsiloxane fluids, and polydiorganosiloxane-polyoxyalkylene. See, e.g., U.S. Pat. Nos. 5,153,230 and 4,421,769. If it is desirable for the pharmaceutical composition to have additional cleaning effects in some embodiments, chemicals such as sodium lauryl sulfate or a metal salt of a carboxylic acid may be added.

In some embodiments, a wide variety of nonvolatile emollients are useful in the pharmaceutical compositions of the present disclosure. Non-limiting examples of such nonvolatile emollients are listed in McCutcheon's, Vol. 2 Functional Materials, North American Edition, (1992), pp. 137-168, and CTFA Cosmetic Ingredient Handbook, Second Edition (1992) which lists Skin-Conditioning Agents at pp. 572-575 and Skin Protectants at p. 580. In some embodiments, the nonvolatile emollients include silicones, hydrocarbons, esters, and mixtures thereof. In some embodiments, the esters include esters of monofunctional and difunctional fatty acids that have been esterified with alcohols and polyols (i.e., alcohols having two or more hydroxyl groups). In some embodiments, long chain esters of long chain fatty acids are utilized in the pharmaceutical compositions of the present disclosure (i.e., C10-40 fatty acids esterified

with C10-40 fatty alcohols). Non-limiting examples of esters useful in the pharmaceutical compositions of the present disclosure include without limitation those selected from the group consisting of diisopropyl adipate, isopropyl myristate, isopropyl palmitate, myristyl propionate, ethylene glycol distearate, 2-ethylhexyl palmitate, isodecyl neopentanoate, C12-15 alcohol
5 benzoate, di-2-ethylhexyl maleate, ceryl palmitate, myristyl myristate, stearyl stearate, cetyl stearate, behenyl behenrate, and mixtures thereof.

Examples of silicone emollients useful in the pharmaceutical compositions of the present disclosure include without limitation polyalkylsiloxanes, cyclic polyalkylsiloxanes, and polyalkylarylsiloxanes. Suitable commercially available polyalkylsiloxanes include the
10 polydimethylsiloxanes, which are also known as dimethicones, non-limiting examples of which include the Vicasil™ series sold by General Electric Company and the Dow Corning™ 200 series sold by Dow Corning Corporation. Commercially available polyalkylsiloxanes include cyclomethicones (Dow Corning™ 244 fluid), Dow Corning™ 344 fluid, Dow Corning™ 245 fluid and Dow Corning™ 345), among others. A suitable commercially available
15 trimethylsiloxysilicate is sold as a mixture with dimethicone as Dow Corning™ 593 fluid. Also useful in the pharmaceutical compositions of the present disclosure are dimethiconols, which are hydroxyl terminated dimethyl silicones. Suitable commercially available dimethiconols are typically sold as mixtures with dimethicone or cyclomethicone (e.g., Dow Corning™ 1401, 1402, and 1403 fluids). Suitable commercially available polyalkylarylsiloxanes include
20 SF1075 methylphenyl fluid (sold by General Electric Company) and 556 Cosmetic Grade phenyl trimethicone fluid (sold by Dow Corning Corporation).

Hydrocarbons suitable for use in the pharmaceutical compositions of the present disclosure include without limitation straight and branched chain hydrocarbons having from about 10 to about 30 carbon atoms. In some embodiments, the straight and branched chain hydrocarbons have from about 12 to about 24 carbon atoms. In some embodiments, the straight and branched chain hydrocarbons have from about 16 to about 22 carbon atoms. Non-limiting examples of such hydrocarbon materials include dodecane, squalane, cholesterol, 5 hydrogenated polyisobutylene, docosane (i.e., a C22 hydrocarbon), hexadecane, and isohexadecane (a commercially available hydrocarbon sold as Permethyl™ 101A by Presperse, South Plainsfield, N.J.), among others.

In some embodiments, the topical pharmaceutical compositions of the present disclosure include propylene glycol. In some embodiments, propylene glycol acts as a surfactant and assists in penetration, contact, and absorption of a compound of the present disclosure. In some embodiments, propylene glycol serves as a preservative. In some embodiments, the pharmaceutical compositions of the present disclosure include a non-ionic surfactant, such as, for example, polysorbate. Such a surfactant provides better surface contact of the pharmaceutical compositions of the present disclosure with mucosa (such as vaginal mucosa) by further reducing surface tension.

The topical pharmaceutical compositions of the present disclosure optionally may also be formulated with a lipophilic phase, such as, for example, emulsions and liposome dispersions. In some embodiments, liposomal formulations may extend circulation time of a compound of the present disclosure, increase permeability of a compound of the present disclosure, and improve overall efficacy of a compound of the present disclosure as an antimicrobial. In some

embodiments, a compound of the present disclosure may be combined with a lipid, cationic lipid or anionic lipid. In some embodiments, the resulting emulsion or liposomal suspension in conjunction with the pH stabilizing qualities of a compound of the present disclosure can effectively increase the *in vivo* half-life of the activity of a pharmaceutical composition of the present disclosure. Examples of suitable anionic lipids for use with the pharmaceutical compositions of the present disclosure include, but are not limited to, cardiolipin, dimyristoyl, dipalmitoyl, dioleoyl phosphatidyl choline, phosphatidyl glycerol, palmitoyl-oleoyl phosphatidyl choline, phosphatidyl glycerol, phosphatidic acid, lysophosphatidic acid, phosphatidyl serine, phosphatidyl inositol, and anionic forms of cholesterol.

In some embodiments, a compound of the present disclosure is incorporated into liposomes. In some embodiments, neutral lipids, cholesterol, and/or polyethylene glycol (PEG) are utilized in such liposomes. In some embodiments, the liposomal composition is composed of partially hydrogenated soy phosphatidylcholine (PHSC), cholesterol, methoxy-terminated PEG (mPEG), and/or distearoyl phosphatidyl ethanolamine (DSPE). The liposomes can be prepared according to any suitable method known in the art.

In some embodiments, topical administration is through nasal sprays or suppositories (rectal or vaginal). Suppositories are prepared by mixing a compound of the present disclosure with a lipid vehicle such as Theobroma oil, cacao butter, glycerin, gelatin, polyoxyethylene glycols, and the like. In some embodiments, topical administration comprises a transdermal patch or dressing such as a bandage impregnated with a compound of the present disclosure and optionally one or more carriers, excipients or diluents known in the art. In some embodiments,

such dressings include without limitation semipermeable films, foams, hydrocolloids, and calcium alginate swabs. In some embodiments, the dosage administration will be continuous rather than intermittent throughout the dosage regimen.

In some embodiments, the pharmaceutical compositions of the present disclosure are adapted for oral administration. As used herein, the term “oral administration” refers to administration of a compound of the present disclosure to the mouth of a patient for ingestion into the gastrointestinal tract. In some embodiments, the pharmaceutical compositions of the present disclosure can be formulated into conventional oral dosage forms including without limitation capsules, tablets, powders, and liquid preparations such as suspensions, solutions, elixirs, syrups, concentrated drops, and the like. In some embodiments, a compound of the present disclosure may be combined with solid excipients, optionally grinding a resulting mixture, and optionally processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain, for example, tablets, coated tablets, hard capsules, soft capsules, solutions (e.g., aqueous, alcoholic or oily solutions), and the like. In some embodiments, excipients suitable for use in the oral pharmaceutical compositions of the present disclosure include without limitation fillers such as sugars, including lactose, glucose, sucrose, mannitol, or sorbitol; cellulose preparations, for example, corn starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose (CMC), and/or polyvinylpyrrolidone (PVP or povidone); and oily excipients, including vegetable and animal oils, such as sunflower oil, olive oil, or cod liver oil. In some embodiments, the oral pharmaceutical compositions of the present disclosure may also contain disintegrating agents, such as, for

example, cross-linked polyvinylpyrrolidone, agar, or alginic acid, or a salt thereof such as sodium alginate; a lubricant, such as talc or magnesium stearate; a plasticizer, such as glycerol or sorbitol; a sweetening agent such as sucrose, fructose, lactose, or aspartame; a natural or artificial flavoring agent, such as, for example, peppermint, oil of wintergreen, or cherry flavoring; or dye-stuffs or pigments, which may be used for identification or characterization of different doses or combinations. In some embodiments, the oral pharmaceutical compositions of the present disclosure may also contain dragée cores with suitable coatings. In some embodiments, concentrated sugar solutions may be used, which may optionally contain, for example, gum arabic, talc, poly-vinylpyrrolidone, carbopol gel, polyethylene glycol, titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures.

In some embodiments, the pharmaceutical compositions of the present disclosure that can be used orally include without limitation push-fit capsules made of gelatin (“gelcaps”), as well as soft, sealed capsules made of gelatin, and a plasticizer, such as glycerol or sorbitol. In some embodiments, the push-fit capsules can contain a compound of the present disclosure in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In some embodiments including soft capsules, the active compound may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, liquid polyethylene glycols, and the like.

In some embodiments, the pharmaceutical compositions of the present disclosure are adapted for inhalation administration. As used herein, the term “inhalation administration” refers to delivery of a compound of the present disclosure by passage through a patient’s nose or mouth

during inhalation and passage of the compound through the walls of the lungs of the patient. In some embodiments, the pharmaceutical compositions of the present disclosure suitable for inhalation administration may be formulated as dry powder or a suitable solution, suspension or aerosol. In some embodiments, powders and solutions may be formulated with suitable additives
5 known in the art. In some embodiments, powders may include a suitable powder base such as lactose or starch. In some embodiments, solutions may comprise propylene glycol, sterile water, ethanol, sodium chloride, and other additives, such as, for example, acid, alkali, and buffer salts. In some embodiments, such solutions or suspensions may be administered by inhaling via a spray, pump, atomizer, nebulizer, and the like. In some embodiments, the pharmaceutical compositions
10 of the present disclosure suitable for inhalation administration may also be used in combination with other inhaled therapies, including without limitation corticosteroids such as, for example, fluticasone propionate, beclomethasone dipropionate, triamcinolone acetonide, budesonide, and mometasone furoate; beta agonists such as, for example, albuterol, salmeterol, and formoterol; anticholinergic agents such as, for example, ipratropium bromide or tiotropium; vasodilators such
15 as, for example, treprostinal and iloprost; enzymes such as, for example, DNAase; therapeutic proteins; immunoglobulin antibodies; an oligonucleotide, such as, for example, single or double stranded DNA or RNA, siRNA; antibiotics such as, for example, tobramycin; muscarinic receptor antagonists; leukotriene antagonists; cytokine antagonists; protease inhibitors; cromolyn sodium; nedocril sodium; and sodium cromoglycate.

20 In some embodiments, the pharmaceutical compositions of the present disclosure are adapted for intravesical administration. As used herein, the term “intravesical administration”

refers to delivery of a compound of the present disclosure directly into the bladder of a patient. In some embodiments, the pharmaceutical composition is administered via a catheter. In some embodiments, the catheter is a urethral catheter.

In some embodiments, the pharmaceutical compositions of the present disclosure are adapted for parenteral administration. As used herein, the term “parenteral administration” refers to a compound of the present disclosure being injected or infused into a patient and includes without limitation intravenous, intramuscular, intraarterial, intrathecal, intraventricular, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, sub capsular, subarachnoid, intraspinal, intracerebro spinal, and intrasternal injection and infusion. In some embodiments, the pharmaceutical compositions of the present disclosure suitable for parenteral administration may be formulated in sterile liquid solutions, including without limitation physiologically compatible buffers or solutions, such as, for example, saline solution, Hank’s solution or Ringer’s solution. In some embodiments, the pharmaceutical compositions of the present disclosure suitable for parenteral administration may be prepared as dispersions in non-aqueous solutions, such as, for example, glycerol, propylene glycol, ethanol, liquid polyethylene glycols, triacetin, vegetable oils, and the like. In some embodiments, solutions may also contain a preservative, such as, for example, methylparaben, propylparaben, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In addition, pharmaceutical compositions of the present disclosure suitable for parenteral administration may be formulated in solid form, including, for example, lyophilized forms, and redissolved or

suspended prior to use. In some embodiments, the pharmaceutical composition is administered via a needle.

In some embodiments, the present disclosure provides methods and compositions of pretreating a catheter with a compound of the present disclosure, for example, to prevent an infection after the catheter is inserted into a patient. In some embodiments, a method of the present disclosure includes coating a catheter with a compound of the present disclosure prior to inserting the catheter into a patient. In some embodiments, the present disclosure provides a composition comprising a catheter coated with a compound of the present disclosure. In some embodiments, such methods and compositions may be used as a prophylactic treatment of an infection in a patient.

The present disclosure also provides methods of treatment. As used herein, the terms “treating,” “treatment,” “therapy,” and like terms refer to administration of a compound or pharmaceutical composition of the present disclosure in an amount effective to prevent, alleviate or ameliorate one or more symptoms of a disease or condition (i.e., indication) and/or to prolong the survival of the patient being treated. In some embodiments, “treating,” “treatment,” “therapy,” and like terms also include without limitation reducing or eliminating infection in a patient.

In carrying out the methods of the present disclosure, an effective amount of a compound of the present disclosure is administered to a patient in need thereof. As used herein, the term “effective amount,” in the context of administration, refers to the amount of a compound or pharmaceutical composition of the present disclosure that when administered to a patient is sufficient to prevent, alleviate or ameliorate one or more symptoms of a disease or condition (i.e.,

indication) and/or to prolong the survival of the patient being treated. Such an amount should result in no or few adverse events in the treated patient. Similarly, such an amount should result in no or few toxic effects in the treated patient. As those familiar with the art will understand, the amount of a compound or pharmaceutical composition of the present disclosure will vary
5 depending upon a number of factors, including without limitation the activity of a compound of the present disclosure (in vitro, e.g. a compound of the present disclosure vs. target, or in vivo activity in animal efficacy models), pharmacokinetic results in animal models (e.g., biological half-life or bioavailability), the type of patient being treated, the patient's age, size, weight, and general physical condition, the disorder associated with the patient, and the dosing regimen being
10 employed in the treatment.

In some embodiments of the present disclosure, an effective amount of a compound of the present disclosure to be delivered to a patient in need thereof can be quantified by determining micrograms of a compound of the present disclosure per kilogram of patient body weight. In some embodiments, the amount of a compound of the present disclosure administered to a patient is
15 from about 0.1 to about 1000 milligram (mg) of a compound of the present disclosure per kilogram (kg) of patient body weight. In some embodiments, the amount of a compound of the present disclosure administered to a patient is from about 0.1 to about 500 mg of a compound of the present disclosure per kg of patient body weight. In some embodiments, the amount of a compound of the present disclosure administered to a patient is from about 0.1 to about 300 mg of a compound of
20 the present disclosure per kg of patient body weight. In some embodiments, the amount of a compound of the present disclosure administered to a patient is from about 0.1 to about 200 mg of

a compound of the present disclosure per kg of patient body weight. In some embodiments, the amount of a compound of the present disclosure administered to a patient is from about 0.1 to about 100 mg of a compound of the present disclosure per kg of patient body weight. As those of ordinary skill in the art understand multiple doses may be used.

5 In some embodiments of the present disclosure, a compound of the present disclosure is administered as a multiple dose regimen. As used herein, the term “multiple dose regimen” refers to a treatment time period of more than one day. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 2 days. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 3 days. In some
10 embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 4 days. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 5 days. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 6 days. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 7 days. In some embodiments of the present
15 disclosure, the multiple dose regimen is a time period of up to about 14 days. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about one month. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about two months. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about three months. In some
20 disclosure, the multiple dose regimen is a time period of up to about four months. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about

five months. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about six months. Other time periods may be used herein.

In some embodiments of the present disclosure, a compound of the present disclosure is administered as part of a chronic treatment regimen. As used herein, the term “chronic treatment
5 regimen” refers to treatment with a compound of the present disclosure over an extended period of time during a patient’s lifetime. In some embodiments, chronic treatment is lifelong treatment.

In some embodiments of the present disclosure, a compound of the present disclosure is administered as a single dose. In some embodiments of the present disclosure, a compound of the present disclosure is administered as a single unit dose. As used herein, the term “unit dose” is a
10 predetermined amount of a compound of the present disclosure. The amount of a compound of the present disclosure is generally equal to the dosage of a compound of the present disclosure that would be administered to a patient or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage. According to the methods of the present disclosure, the terms “single dose” and “single unit dose” include embodiments wherein the composition can be
15 administered as a single application and administered as multiple applications.

In some embodiments, a compound of the present disclosure may also be used in combination with one or more additional active ingredients for treating the same disease or condition. In some embodiments, such combination use includes administration of a compound of the present disclosure and one or more additional active ingredient at different times, or co-
20 administration of a compound of the present disclosure and one or more additional active ingredients. In some embodiments, dosage may be modified for a compound of the present

disclosure or one or more additional active ingredients used in combination, e.g., reduction in the amount dosed relative to a compound of the present disclosure or one or more additional active ingredients used alone, by methods well known to those of ordinary skill in the art. In some embodiments, co-administration includes simultaneous administration of a compound of the present disclosure and an additional active ingredient in the same dosage form, simultaneous administration of a compound of the present disclosure and an additional active ingredient in separate dosage forms, and separate administration of a compound of the present disclosure and an additional active ingredient.

It is understood that use in combination includes use with one or more additional active ingredients or other medical procedure in which the one or more additional active ingredients or other medical procedure may be administered at different times (e.g., within a short time, such as within hours (e.g., 1, 2, 3, 4-24 hours, etc.), or within a longer time (e.g. 1-2 days, 2-4 days, 4-7 days, 1-4 weeks, etc.)) than a compound or pharmaceutical composition of the present disclosure, or at the same time as a compound or pharmaceutical composition of the present disclosure. Use in combination also includes use with one or more additional active ingredients or other medical procedure that is administered once or infrequently, such as surgery, along with a compound or pharmaceutical composition of the present disclosure administered within a short time or longer time before or after the administration of the one or more additional active ingredients or completion of the other medical procedure.

In some embodiments, the present disclosure provides for delivery of a compound or pharmaceutical composition of the present disclosure and one or more additional active ingredients

delivered by a different route of administration or by the same route of administration. In some embodiments, the use in combination for any route of administration includes delivery of a compound or pharmaceutical composition of the present disclosure and one or more additional active ingredients delivered by the same route of administration together in any pharmaceutical composition, including pharmaceutical compositions in which the two compounds are chemically linked in such a way that such compounds maintain their therapeutic activity when administered. In some embodiments, the one or more additional active ingredients may be co-administered with a compound or pharmaceutical composition of the present disclosure. In some embodiments, use in combination by co-administration includes administration of co-formulations or formulations of chemically joined compounds, or administration of two or more compounds in separate formulations within a short time of each other (e.g., within an hour, 2 hours, 3 hours, up to 24 hours, etc.), administered by the same or different routes. In some embodiments, co-administration of separate formulations includes co-administration by delivery via one device, for example, the same inhalant device, the same syringe, etc., or administration from separate devices within a short time of each other. In some embodiments, co-formulations of a compound or pharmaceutical composition of the present disclosure and one or more additional active ingredients delivered by the same route includes preparation of the materials together such that they can be administered by one device, including the separate compounds combined in one formulation, or compounds that are modified such that the compounds are chemically joined, yet still maintain their biological activity. In some embodiments, such chemically joined compounds may have a linkage that is

substantially maintained *in vivo*, or the linkage may break down *in vivo*, separating the two active components.

The present disclosure also provides a method of treating an infection in a patient in need thereof. In some embodiments, the method comprises administering an effective amount of a
5 compound of the present disclosure, or a pharmaceutically acceptable salt thereof, to the patient. As used herein, the term “infection” refers to any microbe infection of a patient’s body. Infection includes the invasion of a patient’s body by a microbe and subsequent multiplication in the patient’s body.

The present disclosure also provides a method of treating an infection of a lower extremity
10 ulcer in a patient in need thereof. In some embodiments, the method comprises administering an effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, to the patient. As used herein, the term “infection” refers to any microbe infection of a patient’s body. Infection includes the invasion of a patient’s body by a microbe and subsequent multiplication in the patient’s body. As used herein, the term “lower extremity” refers to a lower
15 limb of a patient’s body, including without limitation the hip, thigh, leg, ankle, and foot. As used herein, the term “ulcer” refers to an open wound found anywhere on the lower extremity of a patient.

In some embodiments, the present disclosure provides a method of treating an infection of a diabetic foot ulcer in a patient in need thereof. In some embodiments, the method comprises
20 administering an effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, to the patient. In some embodiments, the patient is suffering from Type I

diabetes or Type II diabetes. As used herein, the term “diabetic foot ulcer” refers to an open wound located anywhere on the foot of a patient. In some embodiments, the wound is located on the heel, mid-foot, and/or forefoot of the patient’s foot. As used herein, the term “treating,” in the context of a diabetic foot ulcer, also includes without limitation reducing or eliminating infection in a patient, which, in some embodiments, results in limiting the progression in size, area, and/or depth of the foot ulcer; reducing the size, area, and/or depth of the foot ulcer; increasing the rate of healing and/or reducing time to healing; healing of the foot ulcer (about 100% epithelialization with no drainage); and/or decreased incidence of amputation or slowing in time to amputation.

In some embodiments, the patient is a human. In some embodiments, the administration is topical administration. In some embodiments, the administration is carried out using the compound, or a pharmaceutically acceptable salt thereof, in a lotion, paste, gel, cream, ointment, oil or other viscous composition. In some embodiments, the patient is administered at least one additional active ingredient. In some embodiments, the administration is carried out as a multiple dose regimen. In some embodiments, the multiple dose regimen is a time period of up to about one month. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about two months. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about three months. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about four months. Other time periods may be used herein.

In some embodiments, the administration is carried out one or more times per day. In some embodiments, the administration is carried out one time per day. In some embodiments, the

administration is carried out two times per day. In some embodiments, the administration is carried out three times per day. In some embodiments, the administration is carried out four times per day.

The present disclosure also provides a method of treating a urinary tract infection in a patient in need thereof. In some embodiments, the method comprises administering an effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, to the patient. As used herein, the term “urinary tract” refers to the organs of a patient’s body that produce, store, and discharge urine and includes without limitation the kidneys, ureters, bladder, and urethra. As used herein, the term “urinary tract infection” refers to an infection of the urinary tract of a patient and includes without limitation an uncomplicated urinary tract infection and a complicated urinary tract infection. As used herein, the term “uncomplicated urinary tract infection” refers to an infection by a microbe of a structurally and functionally normal urinary tract of a patient. As used herein, the term “complicated urinary tract infection” refers to an infection by a microbe of an abnormal structural and functional urinary tract of a patient. In some embodiments, the complicated urinary tract infection is a catheter-associated urinary tract infection. As used herein, the term “catheter-associated urinary tract infection” refers to a complicated urinary tract infection that occurs in a patient having an indwelling urinary catheter.

In some embodiments, the patient is a human. In some embodiments, the administration is intravesical administration. In some embodiments, the administration is carried out using a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, in a liquid solution or suspension. In some embodiments, the patient is administered at least one additional

active ingredient. In some embodiments, the administration is carried out as a multiple dose regimen. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 2 days. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 3 days. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 4 days. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 5 days. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 6 days. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 7 days. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 14 days. In some embodiments of the present disclosure, the administration is carried out as a chronic treatment regimen. Other time periods may be used herein.

In some embodiments, the administration is carried out one or more times per day. In some embodiments, the administration is carried out one time per day. In some embodiments, the administration is carried out two times per day. In some embodiments, the administration is carried out three times per day. In some embodiments, the administration is carried out four times per day.

The present disclosure also provides a method of treating a lung infection in a patient in need thereof. In some embodiments, the method comprises administering an effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, to the patient. As used herein, the term “lung infection” refers to an infection of one or both of a patient’s lungs.

In some embodiments, the lung infection arises from a pulmonary condition. As used herein, the term “pulmonary condition” refers to both infection and non-infection induced disease and dysfunction of the respiratory system.

Non-limiting examples of pulmonary conditions include without limitation genetic
5 conditions, acquired conditions, primary conditions, secondary conditions, asthma, chronic obstructive pulmonary disease, cystic fibrosis, bronchiolitis, pneumonia, bronchitis, emphysema, adult respiratory distress syndrome, allergies, lung cancer, small cell lung cancer, primary lung cancer, metastatic lung cancer, bronchiectasis, bronchopulmonary dysplasia, chronic bronchitis, chronic lower respiratory diseases, croup, high altitude pulmonary edema, pulmonary fibrosis,
10 interstitial lung disease, reactive airway disease, lymphangioleiomyomatosis, neonatal respiratory distress syndrome, parainfluenza, pleural effusion, pleurisy, pneumothorax, primary pulmonary hypertension, psittacosis, pulmonary edema secondary to various causes, pulmonary embolism, pulmonary hypertension secondary to various causes, respiratory failure secondary to various causes, sleep apnea, sarcoidosis, smoking, stridor, acute respiratory distress syndrome, infectious
15 diseases, SARS, tuberculosis, psittacosis infection, Q fever, parainfluenza, respiratory syncytial virus, combinations thereof, and conditions caused by any one or combination of the above.

In some embodiments, the pulmonary condition is caused by a coronavirus. In some embodiments, the coronavirus is selected from the group consisting of an alphacoronavirus, a betacoronavirus, a gammacoronavirus, a deltacoronavirus, and an omicroncoronavirus, or
20 combinations thereof.

In some embodiments, the coronavirus is selected from the group consisting of porcine epidemic diarrhea virus (PEDv), scotophilus bat coronavirus 512, bat coronavirus CDPHE15, BtRF-Alpha-CoV HuB-2013, bat coronavirus HKU10, miniopterus bat coronavirus HKU8, miniopterus bat coronavirus 1, *Nyctalus velutinus* alphacoronavirus SC-2013, *Pipistrellus kuhlii* coronavirus 3398, *Myotis ricketti* alphacoronavirus Sax-2011, HumCoV 229E, 229E-related bat coronavirus, camel alphacoronavirus, alpaca respiratory coronavirus, HumCoV NL63, NL63-related Bat-CoV BtKYNL63-9b, HKU2, SADSr-CoV, SADS-CoV, Lucheng Rn rat coronavirus2, FIPV, TGEV, PRCV, alphacoronavirus 1, mink coronavirus 1, FRCoV-NL-2010, *Sorex araneus* coronavirus T14, *Suncus murinus* coronavirus X74, HumCoV OC43, HumCoV OC43 isolate TNP F1778_2, HKU23, BovCoV, SACoV, GiCoV, bovine coronavirus isolate alpaca, canine respiratory coronavirus K37, PHEV, equine coronavirus, HKU14, HKU24, myodes coronavirus 2JL14, HKU1, MHV, rat coronavirus Parker, HKU4, HKU5, human MERS-CoV, camel MERS-CoV, hedgehog coronavirus 1, HKU9, rousettus bat coronavirus GCCDC1, eidolon bat coronavirus C704, human SARS-CoV, palm civet SARS-CoV, badger SARS-CoV, bat-SL-CoV RsSHC014, bat-SL-CoV Rs3367, bat-SL-CoV WIV1, HKU3, bat-SL-CoV ZC45, bat-SL-CoV ZXC21, bat-CoV RaTG13, bat-CoV RmYN02, human SARS-CoV-2, cat-CoV, tiger-CoV, dog-CoV, mink-CoV, GD pangolin-CoV, bat Hp-betacoronavirus Zhejiang2013, peafowl IBV, avian coronavirus 9203, fowl IBV, avian coronavirus, duck-CoV, partridge IBV, goose coronavirus CB17, beluga whale coronavirus SW1, HKU22, HKU19, HKU20, HKU21, HKU11, HKU12, HKU16, HKU27, HKU28, HKU29, HKU18, HKU13, HKU30-UAE, HKU30-Poland, HKU17-USA, HKU17-China, AlCCoV, and HKU15, or combinations thereof.

In some embodiments, the coronavirus is a betacoronavirus selected from the group consisting of HumCoV OC43 isolate TNP F1778_2, HKU23, BovCoV, SACoV, GiCoV, bovine coronavirus isolate alpaca, canine respiratory coronavirus K37, PHEV, equine coronavirus, HKU14, HKU24, myodes coronavirus 2JL14, HKU1, MHV, rat coronavirus Parker, HKU4, HKU5, human MERS-CoV, camel MERS-CoV, hedgehog coronavirus 1, HKU9, rousettus bat coronavirus GCCDC1, eidolon bat coronavirus C704, human SARS-CoV, palm civet SARS-CoV, badger SARS-CoV, bat-SL-CoV RsSHC014, bat-SL-CoV Rs3367, bat-SL-CoV WIV1, HKU3, bat-SL-CoV ZC45, bat-SL-CoV ZXC21, bat-CoV RaTG13, bat-CoV RmYN02, human SARS-CoV-2, cat-CoV, tiger-CoV, dog-CoV, mink-CoV, GD pangolin-CoV, and bat Hp-
10 betacoronavirus Zhejiang2013, or combinations thereof.

In some embodiments of the present disclosure, a method of treating a lung infection arising from cystic fibrosis in a patient in need thereof is provided. In some embodiments, the method comprises administering an effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, to the patient. As used herein, the term “cystic fibrosis”
15 refers to a genetic disease that causes the production of abnormally thick mucus resulting in lung infections and damage to the lungs, digestive system, and other organs in a patient’s body.

In some embodiments, the administration is inhalation administration. In some embodiments, the patient is administered at least one additional active ingredient. In some embodiments, the patient is a human. In some embodiments, the administration is carried out
20 using a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, in a liquid solution, suspension or dry powder. In some embodiments, the administration is carried out

as a multiple dose regimen. In some embodiments, the multiple dose regimen is a time period of up to about one month. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about two months. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about three months. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about four months. In some
5 embodiments of the present disclosure, the multiple dose regimen is a time period of up to about five months. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about six months. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about seven months. In some
10 disclosure, the multiple dose regimen is a time period of up to about eight months. Other time periods may be used herein.

In some embodiments, the administration is carried out one or more times per day. In some embodiments, the administration is carried out one time per day. In some embodiments, the administration is carried out two times per day. In some embodiments, the administration is carried
15 out three times per day. In some embodiments, the administration is carried out four times per day.

In some embodiments of the present disclosure, a method of treating pneumonia in a patient in need thereof is provided. In some embodiments, the method comprises administering an effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt
20 thereof, to the patient. As used herein, the term “pneumonia” refers to an infection by a microbe of one or both lungs of a patient resulting in inflammation of lung tissue. In some embodiments,

the pneumonia is ventilator acquired pneumonia. As used herein, the term “ventilator acquired pneumonia” refers to pneumonia arising from a patient being connected to a mechanical ventilation machine. Ventilator acquired pneumonia includes pneumonia occurring more than about 48 hours after a patient has been intubated and received mechanical ventilation.

5 In some embodiments, the administration is inhalation administration. In some
embodiments, the patient is administered at least one additional active ingredient. In some
embodiments, the patient is a human. In some embodiments, the administration is carried out
using a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, in a
liquid solution, suspension or dry powder. In some embodiments, the administration is carried out
10 as a multiple dose regimen. In some embodiments of the present disclosure, the multiple dose
regimen is a time period of up to about 7 days. In some embodiments of the present disclosure,
the multiple dose regimen is a time period of up to about 14 days. In some embodiments of the
present disclosure, the multiple dose regimen is a time period of up to about 21 days. In some
embodiments, the multiple dose regimen is a time period of up to about one month. In some
15 embodiments of the present disclosure, the multiple dose regimen is a time period of up to about
two months. Other time periods may be used herein.

 In some embodiments, the administration is carried out one or more times per day. In some
embodiments, the administration is carried out one time per day. In some embodiments, the
administration is carried out two times per day. In some embodiments, the administration is carried
20 out three times per day. In some embodiments, the administration is carried out four times per
day.

The present disclosure also provides a method of treating an infection in a burn wound in a patient in need thereof. In some embodiments, the method comprises administering an effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, to the patient. As used herein, the term “burn wound” refers to a burn injury to a patient’s body
5 involving damage to a patient’s skin and possibly tissues underlying the patient’s skin. There are three primary types of burn levels known to one of skill in the art, including without limitation first-, second-, and third-degree burns. In some embodiments, the method of treating an infection in a burn wound contemplated by the present disclosure is used to treat a first-, second-, and/or third-degree burn.

10 In some embodiments, the patient is a human. In some embodiments, the administration is topical administration. In some embodiments, the administration is carried out using a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, in lotion, cream, ointment, oil, solution, suspension, emulsion or other viscous composition. In some embodiments, the patient is administered at least one additional active ingredient. In some embodiments, the
15 administration is carried out as a multiple dose regimen. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 2 days. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 3 days. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 4 days. In some embodiments of the present disclosure, the multiple dose regimen is a time period
20 of up to about 5 days. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 6 days. In some embodiments of the present disclosure, the multiple

dose regimen is a time period of up to about 7 days. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 14 days. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 21 days. In some embodiments, the multiple dose regimen is a time period of up to about one
5 month. In some embodiments, the multiple dose regimen is a time period of up to about two months. Other time periods may be used herein.

In some embodiments, the administration is carried out one or more times per day. In some embodiments, the administration is carried out one time per day. In some embodiments, the administration is carried out two times per day. In some embodiments, the administration is carried
10 out three times per day. In some embodiments, the administration is carried out four times per day.

The present disclosure also provides a method of treating otitis externa in a patient in need thereof. In some embodiments, the method comprises administering an effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, to the patient.
15 As used herein, the term “otitis externa” refers to an infection of the external ear canal of a patient.

In some embodiments, the patient is a human. In some embodiments, the administration is topical administration directly into the patient’s external ear canal. In some embodiments, the administration is carried out using a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, in a liquid solution, suspension, lotion, paste, gel, cream, ointment, oil or
20 other viscous composition. In some embodiments, the patient is administered at least one additional active ingredient. In some embodiments, the administration is carried out as a multiple

dose regimen. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 7 days. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 14 days. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 21 days. In some embodiments, the multiple dose regimen is a time period of up to about one month. Other time periods may be used herein.

In some embodiments, the administration is carried out one or more times per day. In some embodiments, the administration is carried out one time per day. In some embodiments, the administration is carried out two times per day. In some embodiments, the administration is carried out three times per day. In some embodiments, the administration is carried out four times per day.

The present disclosure also provides a method of treating bacterial vaginosis in a patient in need thereof. In some embodiments, the method comprises administering an effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, to the patient. As used herein, the term “bacterial vaginosis” refers to an infection of the vagina of a patient caused by an overgrowth of bacteria naturally found in the vagina.

In some embodiments, the patient is a female human. In some embodiments, the administration is topical administration. In some embodiments, the administration is carried out using a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, in a lotion, gel, cream, ointment, oil, solution, suspension, emulsion or other viscous composition. In some embodiments, the patient is administered at least one additional active ingredient. In some

embodiments, the administration is carried out as a multiple dose regimen. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 7 days. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 14 days. In some embodiments of the present disclosure, the multiple dose regimen is a time
5 period of up to about 21 days. In some embodiments, the multiple dose regimen is a time period of up to about one month. Other time periods may be used herein.

In some embodiments, the administration is carried out one or more times per day. In some embodiments, the administration is carried out one time per day. In some embodiments, the administration is carried out two times per day. In some embodiments, the administration is carried
10 out three times per day. In some embodiments, the administration is carried out four times per day.

The present disclosure also provides a method of treating impetigo in a patient in need thereof. In some embodiments, the method comprises administering an effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, to the patient.
15 As used herein, the term “impetigo” refers an infection of the skin of a patient that results in vesicles, pustules, yellowish crusts, and the like.

In some embodiments, the patient is a human. In some embodiments, the administration is topical administration. In some embodiments, the administration is carried out using a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, in a lotion, gel,
20 cream, ointment, oil, solution, suspension, emulsion or other viscous composition. In some embodiments, the patient is administered at least one additional active ingredient. In some

embodiments, the administration is carried out as a multiple dose regimen. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 2 days. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 3 days. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 4 days. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 5 days. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 6 days. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 7 days. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 14 days. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 21 days. In some embodiments, the multiple dose regimen is a time period of up to about one month. Other time periods may be used herein.

In some embodiments, the administration is carried out one or more times per day. In some embodiments, the administration is carried out one time per day. In some embodiments, the administration is carried out two times per day. In some embodiments, the administration is carried out three times per day. In some embodiments, the administration is carried out four times per day.

The present disclosure also provides a method of treating oral mucositis in a patient in need thereof. In some embodiments, the method comprises administering an effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, to the patient. As used herein, the term “oral mucositis” refers to inflammation and ulceration in the mouth. Oral

mucositis is a common complication experienced by patients receiving cancer chemotherapy or radiation treatment. Oral mucositis can lead to several problems, including pain, nutritional problems as a result of inability to eat, and increased risk of infection due to open sores in the mucosa. Oral mucositis may also have a significant effect on a cancer patient's quality of life and
5 can limit the effectiveness of certain treatment options (i.e., requiring a reduction in subsequent chemotherapy doses). Oral mucositis is also a significant side effect of bone marrow transplantation.

In some embodiments, the patient is a human. In some embodiments, the administration is topical administration directly into the patient's oral cavity. In some embodiments, the
10 administration is carried out using a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, in a liquid solution, suspension, lotion, paste, gel, cream, ointment, oil or other viscous composition. In some embodiments, the administration is carried out using the compound of the present disclosure in a mouthwash. In some embodiments, the compound of the present disclosure is present in the pharmaceutical composition in an amount from about 1% to
15 about 20% (weight/weight). In some embodiments, the compound of the present disclosure is present in the pharmaceutical composition in an amount from about 5% to about 15% (weight/weight). In some embodiments, the compound of the present disclosure is present in the pharmaceutical composition in an amount from about 30% to about 50% (weight/weight).

In some embodiments, the patient is administered at least one additional active ingredient.
20 In some embodiments, the administration is carried out as a multiple dose regimen. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about

7 days. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 14 days. In some embodiments of the present disclosure, the multiple dose regimen is a time period of up to about 21 days. In some embodiments, the multiple dose regimen is a time period of up to about one month. Other time periods may be used herein.

5 In some embodiments, the administration is carried out one or more times per day. In some embodiments, the administration is carried out one time per day. In some embodiments, the administration is carried out two times per day. In some embodiments, the administration is carried out three times per day. In some embodiments, the administration is carried out four times per day.

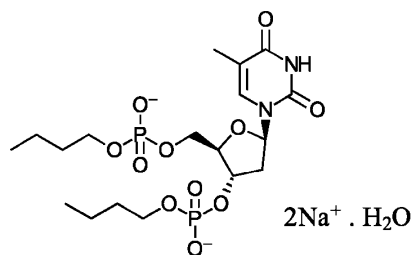
10 The present disclosure also provides a kit. In some embodiments, the kit comprises a compound according to the present disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to the present disclosure. As used herein, the term “kit” refers to any manufacture, such as, for example, a package, container, and the like, containing a compound according to the present disclosure, or a pharmaceutically acceptable salt thereof, or a
15 pharmaceutical composition according to the present disclosure. In some embodiments, a compound according to the present disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to the present disclosure is packaged in a vial, bottle, tube, flask or patch, which may be further packaged within a box, envelope, bag, or the like. In some
20 embodiments, a compound according to the present disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to the present disclosure is approved by the U.S. Food and Drug Administration or similar regulatory agency in the U.S. or a jurisdiction

or territory outside the U.S. for administration to a patient. In some embodiments, the kit includes written instructions for use and/or other indication that a compound according to the present disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to the present disclosure is suitable or approved for administration to a patient. In some
5 embodiments, a compound or composition of the present disclosure is packaged in unit dose or single unit dose form, such as, for example, single unit dose pills, capsules or the like. In some embodiments, the kit includes a dispenser.

The present disclosure also provides the use of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament. As used herein,
10 the term “medicament” refers to a pharmaceutical composition according to the present disclosure. In some embodiments, the pharmaceutical composition is contained in any manufacture, such as, for example, a package, container, and the like.

In addition to the aspects and embodiments described and provided elsewhere in the present disclosure, the following non-limiting list of embodiments are also contemplated.

15 1. A crystalline form of Nu-3 having the formula:



Formula (I)

or a pharmaceutically acceptable salt thereof.

2. A crystalline disodium monohydrate form of 1-[(2*R*,4*S*,5*R*)-4-(Hydroxybutoxyphosphoryloxy)-5-[(hydroxybutoxyphosphoryloxy)methyl]tetrahydro-2-furyl]-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione.
- 5 3. The crystalline form of clause 1 or clause 2, characterized by an X-ray powder diffraction (XRPD) pattern having one or more peaks at about 4.1° to about 4.3°, about 5.4° to about 5.7°, about 6.2° to about 6.4°, or about 7.6° to about 7.8°, each peak being ±0.2, ±0.1, ±0.05, ±0.02, or ±0.01 °2θ.
4. The crystalline form of any of clauses 1-3, wherein the XRPD pattern includes one or more
10 peaks at about 7.8° to about 8.1°, about 10.4° to about 10.7°, about 11.2° to about 11.4°, or about 12.1° to about 12.5°, each peak being ±0.2, ±0.1, ±0.05, ±0.02, or ±0.01 °2θ.
5. The crystalline form of any of clauses 1-4, wherein the XRPD pattern includes one or more peaks at about 15.0° to about 15.5°, about 15.6° to about 15.9°, about 16.6° to 16.8°, about 17.2° to about 17.3°, or about 17.4° to about 17.6°, each peak being ±0.2, ±0.1, ±0.05, ±0.02,
15 or ±0.01 °2θ.
6. The crystalline form of any of clauses 1-5, wherein the XRPD pattern includes one or more peaks at about 18.1° to about 18.7°, about 18.9° to about 19.5°, about 19.6° to about 19.7°, about 20° to about 20.2°, or about 21.2° to about 21.4°, each peak being ±0.2, ±0.1, ±0.05, ±0.02, or ±0.01 °2θ.

7. The crystalline form of any of clauses 1-6, wherein the XRPD pattern includes one or more peaks at about 21.9° to about 22°, about 22.5° to about 23.0°, or about 23.2° to about 23.8°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .
8. The crystalline form of any of clauses 1-7, characterized by an X-ray powder diffraction (XRPD) pattern having one or more peaks at about 24.0° to about 24.3°, about 25.3° to about 25.6°, about 27.4° to about 27.5°, or about 28.2° to about 28.4°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .
9. The crystalline form of any of clauses 1-8 characterized by an X-ray powder diffraction (XRPD) pattern includes one or more peaks at about 5.4°, about 5.6°, about 7.7°, about 12.4°, about 15.0°, about 15.7°, about 16.7°, about 17.2°, about 17.5°, about 18.5°, about 18.6°, about 18.9°, about 19.3°, about 21.3°, about 22.9°, about 24.0°, about 24.2°, or about 27.7°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .
10. The crystalline form of any of clauses 1-9, wherein the XRPD pattern includes one or more peaks at about 4.1° to about 4.3°, about 5.4° to about 5.7°, about 6.2° to about 6.4°, about 7.6° to about 7.8°, about 7.8° to about 8.1°, about 10.4° to about 10.7°, about 11.2° to about 11.4°, about 12.1° to about 12.5°, about 15.0° to about 15.5°, about 15.6° to about 15.9°, about 16.6° to about 16.8°, about 17.2° to about 17.3°, about 17.4° to about 17.6°, about 18.1° to about 18.7°, about 18.9° to about 19.5°, about 19.6° to about 19.7°, about 20° to about 20.2°, about 21.2° to about 21.4°, about 21.9° to about 22°, about 22.5° to about 23.0°, about 23.2° to about 23.8°, about 24.0° to about 24.3°, about 25.3° to about 25.6°, about 27.4° to about 27.5°, or about 28.2° to about 28.4°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .

11. The crystalline form of any of clauses 1-10 characterized by an XRPD pattern having one or more peaks at about 5.4° , about 7.7° , or about 17.2° , each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^{\circ} 2\theta$.
12. The crystalline form of any of clauses 1-11 characterized by an XRPD pattern having one or more peaks at about 5.4° , about 7.7° , about 12.1° , about 15.4° , or about 17.2° , each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^{\circ} 2\theta$.
13. The crystalline form of clauses 1-12 characterized by an XRPD pattern having one or more peaks at about 5.472° , about 7.714° , or about 17.252° , each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^{\circ} 2\theta$.
14. The crystalline form of any of clauses 1-13 characterized by an XRPD pattern having one or more peaks at about 18.1° , about 18.9° , about 19.6° , about 21.9° , about 22.5° , about 23.2° , or about 27.4° , each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^{\circ} 2\theta$.
15. The crystalline form of any of clauses 1-14 characterized by an XRPD pattern having one or more peaks at about 5.4° , about 7.7° , about 12.1° , about 15.4° , about 17.2° , about 18.1° , about 18.9° , about 19.6° , about 21.9° , about 22.5° , about 23.2° , or about 27.4° , each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^{\circ} 2\theta$.
16. The crystalline form of any of clauses 1-15 characterized by an XRPD pattern having peaks at about 5.4° , about 7.7° , about 12.1° , about 15.4° , about 17.2° , about 18.1° , about 18.9° , about 19.6° , about 21.9° , about 22.5° , about 23.2° , and about 27.7° , each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^{\circ} 2\theta$.

17. The crystalline form of any of clauses 1-16 characterized by an XRPD pattern having peaks at about 5.472° , about 7.714° , about 12.190° , about 15.413° , about 17.252° , about 18.116° , about 18.972° , about 19.674° , about 21.947° , about 22.598° , about 23.235° , and about 27.41° , with each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^{\circ} 2\theta$.
- 5 18. The crystalline form of clauses 1 and 2, characterized by an XRPD pattern having a peak at about $5.5^{\circ} 2\theta \pm 0.2$, ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^{\circ} 2\theta$.
19. The crystalline form of any of clauses 1 and 2 characterized by an XRPD pattern having a peak at $5.472^{\circ} 2\theta \pm 0.2$, ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^{\circ} 2\theta$.
20. The crystalline form of any of clauses 1-10 characterized by an XRPD pattern having one or
10 more peaks at about 7.9° , about 16.7° , about 18.5° , about 22.7° , and about 24.2° , each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^{\circ} 2\theta$.
21. The crystalline form of any of clauses 1-10 and clause 20 characterized by an XRPD pattern having one or more peaks at about 7.989° , about 16.717° , about 18.529° , about 22.770° , and about 24.228° , each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^{\circ} 2\theta$.
- 15 22. The crystalline form of any of clauses 1-10 and 20-21 characterized by an XRPD pattern having one or more peaks at about 7.9° , about 16.7° , about 18.5° , about 22.7° , about 23.6° , about 24.2° , or about 25.4° , each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^{\circ} 2\theta$.
23. The crystalline form of any of clauses 1-10 and 21-22 characterized by an XRPD pattern having peaks at about 7.989° , about 16.717° , about 18.529° , about 22.770° , about 23.682° ,
20 about 24.228° , and about 25.494° , each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^{\circ} 2\theta$.

24. The crystalline form of any of clauses 1-10 characterized by an XRPD pattern having one or more peaks at about 4.3° , about 15.1° or about 19.4° , each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^{\circ} 2\theta$.
25. The crystalline form of any of clauses 1-10 or 24 characterized by an XRPD pattern having one or more peaks at about 4.290° , about 15.069° , or about 19.356° , each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^{\circ} 2\theta$.
26. The crystalline form of any of clauses 1-10 characterized by an XRPD pattern having one or more peaks at about 7.9° , 12.4° or about 20.1° , each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^{\circ} 2\theta$.
27. The crystalline form of any of clauses 1-10 and clause 26 characterized by an XRPD pattern having one or more peaks at about 7.924° , 12.424° or about 20.081° , each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^{\circ} 2\theta$.
28. The crystalline form of any of clauses 1-10 characterized by an XRPD pattern having one or more peaks at about at about 5.7° , about 10.6° , about 15.8° , about 17.6° , about 18.6° , or about 21.3° , each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^{\circ} 2\theta$.
29. The crystalline form of any of clauses 1-10 and 28 characterized by an XRPD pattern having one or more peaks at about 5.692° , about 10.590° , about 15.759° , about 17.554° , about 18.640° , or about 21.302° , each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^{\circ} 2\theta$.
30. The crystalline form of any of clauses 1-10 or 28-29 characterized by an XRPD pattern having one or more peaks at about 23° or about 24° , each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or $\pm 0.01^{\circ} 2\theta$.

31. The crystalline form of any of clauses 1-10 or 28-30 characterized by an XRPD pattern having one or more peaks at about 22.958° or about 24.041°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .
32. The crystalline form of any of clauses 1-10 or 28-31 characterized by an XRPD pattern having
5 one or more peaks at about 5.7°, about 10.6°, about 15.8°, about 17.6°, about 18.6°, about 21.3°, about 23°, about 24°, or about 28.3°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .
33. The crystalline form of any of clauses 1-10 or 28-32, characterized by an XRPD pattern having
10 peaks at about 5.692°, about 6.331°, about 10.590°, about 11.314°, about 15.759°, about 17.554°, about 18.640°, about 21.302°, about 22.958°, about 24.041°, and 28.301°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .
34. The crystalline form of any of clauses 3-33, wherein the peaks of the XRPD pattern have a deviation of ± 0.2 °2 θ .
35. The crystalline form of any of clauses 3-33, wherein the peaks of the XRPD pattern have a
15 deviation of ± 0.1 °2 θ .
36. The crystalline form of any of clauses 3-33, wherein the peaks of the XRPD pattern have a deviation of ± 0.05 °2 θ .
37. A crystalline disodium monohydrate form of 1-[(2*R*,4*S*,5*R*)-4-(Hydroxybutoxyphosphoryloxy)-5-[(hydroxybutoxyphosphoryloxy)methyl]tetrahydro-2-furyl]-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione comprising less than about 0.5 wt. % of residual
20 organic solvent.

38. A crystalline disodium monohydrate form of 1-[(2*R*,4*S*,5*R*)-4-(Hydroxybutoxyphosphoryloxy)-5-[(hydroxybutoxyphosphoryloxy)methyl]tetrahydro-2-furyl]-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione comprising less than about 0.2 wt. % of residual organic solvent.
- 5 39. A crystalline disodium monohydrate form of 1-[(2*R*,4*S*,5*R*)-4-(Hydroxybutoxyphosphoryloxy)-5-[(hydroxybutoxyphosphoryloxy)methyl]tetrahydro-2-furyl]-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione comprising less than about 0.1 wt. % of residual organic solvent.
40. A crystalline disodium monohydrate form of 1-[(2*R*,4*S*,5*R*)-4-
10 (Hydroxybutoxyphosphoryloxy)-5-[(hydroxybutoxyphosphoryloxy)methyl]tetrahydro-2-furyl]-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione comprising less than about 0.05 wt. % of residual organic solvent.
41. A crystalline disodium monohydrate form of 1-[(2*R*,4*S*,5*R*)-4-
15 furyl]-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione comprising less than about 0.001 wt. % of residual organic solvent.
42. A crystalline disodium monohydrate form of 1-[(2*R*,4*S*,5*R*)-4-
20 (Hydroxybutoxyphosphoryloxy)-5-[(hydroxybutoxyphosphoryloxy)methyl]tetrahydro-2-furyl]-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione comprising less than about 0.0001 wt. % of residual organic solvent.

43. A pharmaceutical composition comprising the crystalline form according to any of clauses 1 to 36, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients, or diluents.
44. A pharmaceutical composition comprising the crystalline form according to any of clauses 37 to 42, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, excipients, or diluents.
45. A method of treating an infection in a patient in need thereof, the method comprising administering an effective amount of a compound comprising the crystalline form according to any one of clauses 1 to 36, or a pharmaceutically acceptable salt thereof, to the patient.
46. A method of treating an infection of at least one of a wound or an ulcer in a patient in need thereof, the method comprising administering an effective amount of a compound comprising the crystalline form according to any one of clauses 1 to 36, or a pharmaceutically acceptable salt thereof, to the patient.
47. A method of treating an infection of a diabetic foot ulcer in a patient in need thereof, the method comprising administering an effective amount of a compound comprising the crystalline form according to any one of clauses 1 to 36, or a pharmaceutically acceptable salt thereof, to the patient.
48. A method of treating a bladder and/or a urinary tract infection in a patient in need thereof, the method comprising administering an effective compound comprising the crystalline form according to any one of clauses 1 to 36, or a pharmaceutically acceptable salt thereof, to the patient.

49. A method of treating a lung infection in a patient in need thereof, the method comprising administering an effective amount of a compound comprising the crystalline form according to any one of clauses 1 to 36, or a pharmaceutically acceptable salt thereof, to the patient.
50. The method of clause 49, wherein the lung infection arises from a pulmonary condition.
- 5 51. The method of clause 50, wherein the pulmonary condition is selected from the group consisting of genetic conditions, acquired conditions, primary conditions, secondary conditions, asthma, chronic obstructive pulmonary disease, cystic fibrosis, bronchiolitis, pneumonia, bronchitis, emphysema, adult respiratory distress syndrome, allergies, lung cancer, small cell lung cancer, primary lung cancer, metastatic lung cancer, bronchiectasis, bronchopulmonary dysplasia, chronic bronchitis, chronic lower respiratory diseases, croup, 10 high altitude pulmonary edema, pulmonary fibrosis, interstitial lung disease, reactive airway disease, lymphangioleiomyomatosis, neonatal respiratory distress syndrome, parainfluenza, pleural effusion, pleurisy, pneumothorax, primary pulmonary hypertension, psittacosis, pulmonary edema secondary to various causes, pulmonary embolism, pulmonary hypertension 15 secondary to various causes, respiratory failure secondary to various causes, sleep apnea, sarcoidosis, smoking, stridor, acute respiratory distress syndrome, infectious diseases, SARS, tuberculosis, psittacosis infection, Q fever, parainfluenza, respiratory syncytial virus, combinations thereof, and conditions caused by any one or combination thereof.
52. The method of clause 51, wherein the pulmonary condition arises from a coronavirus.

53. The method of clause 52, wherein the coronavirus is selected from the group consisting of an alphacoronavirus, a betacoronavirus, a gammacoronavirus, a deltacoronavirus, and an omicroncoronavirus, or combinations thereof.
54. The method of clause 52, wherein the coronavirus is selected from the group consisting of
- 5 porcine epidemic diarrhea virus (PEDv), scotophilus bat coronavirus 512, bat coronavirus CDPHE15, BtRF-Alpha-CoV HuB-2013, bat coronavirus HKU10, miniopterus bat coronavirus HKU8, miniopterus bat coronavirus 1, *Nyctalus velutinus* alphacoronavirus SC-2013, *Pipistrellus kuhlii* coronavirus 3398, *Myotis ricketti* alphacoronavirus Sax-2011, HumCoV 229E, 229E-related bat coronavirus, camel alphacoronavirus, alpaca respiratory
- 10 coronavirus, HumCoV NL63, NL63-related Bat-CoV BtKYNL63-9b, HKU2, SADSr-CoV, SADS-CoV, Lucheng Rn rat coronavirus2, FIPV, TGEV, PRCV, alphacoronavirus 1, mink coronavirus 1, FRCoV-NL-2010, *Sorex araneus* coronavirus T14, *Suncus murinus* coronavirus X74, HumCoV OC43, HumCoV OC43 isolate TNP F1778_2, HKU23, BovCoV, SACoV, GiCoV, bovine coronavirus isolate alpaca, canine respiratory coronavirus K37, PHEV, equine
- 15 coronavirus, HKU14, HKU24, myodes coronavirus 2JL14, HKU1, MHV, rat coronavirus Parker, HKU4, HKU5, human MERS-CoV, camel MERS-CoV, hedgehog coronavirus 1, HKU9, rousettus bat coronavirus GCCDC1, eidolon bat coronavirus C704, human SARS-CoV, palm civet SARS-CoV, badger SARS-CoV, bat-SL-CoV RsSHC014, bat-SL-CoV Rs3367, bat-SL-CoV WIV1, HKU3, bat-SL-CoV ZC45, bat-SL-CoV ZXC21, bat-CoV RaTG13, bat-CoV RmYN02, human SARS-CoV-2, cat-CoV, tiger-CoV, dog-CoV, mink-
- 20 CoV, GD pangolin-CoV, bat Hp-betacoronavirus Zhejiang2013, peafowl IBV, avian

coronavirus 9203, fowl IBV, avian coronavirus, duck-CoV, partridge IBV, goose coronavirus CB17, beluga whale coronavirus SW1, HKU22, HKU19, HKU20, HKU21, HKU11, HKU12, HKU16, HKU27, HKU28, HKU29, HKU18, HKU13, HKU30-UAE, HKU30-Poland, HKU17-USA, HKU17-China, AICCoV, and HKU15, or combinations thereof.

- 5 55. The method of clause 52, wherein the coronavirus is a betacoronavirus selected from the group consisting of HumCoV OC43 isolate TNP F1778_2, HKU23, BovCoV, SACoV, GiCoV, bovine coronavirus isolate alpaca, canine respiratory coronavirus K37, PHEV, equine coronavirus, HKU14, HKU24, myodes coronavirus 2JL14, HKU1, MHV, rat coronavirus Parker, HKU4, HKU5, human MERS-CoV, camel MERS-CoV, hedgehog coronavirus 1, 10 HKU9, rousettus bat coronavirus GCCDC1, eidolon bat coronavirus C704, human SARS-CoV, palm civet SARS-CoV, badger SARS-CoV, bat-SL-CoV RsSHC014, bat-SL-CoV Rs3367, bat-SL-CoV WIV1, HKU3, bat-SL-CoV ZC45, bat-SL-CoV ZXC21, bat-CoV RaTG13, bat-CoV RmYN02, human SARS-CoV-2, cat-CoV, tiger-CoV, dog-CoV, mink-CoV, GD pangolin-CoV, and bat Hp-betacoronavirus Zhejiang2013, or combinations thereof.
- 15 56. A method of treating cystic fibrosis in a patient in need thereof, the method comprising administering an effective amount of a compound comprising the crystalline form according to any one of clauses 1 to 36, or a pharmaceutically acceptable salt thereof, to the patient.
57. A method of treating pneumonia in a patient in need thereof, the method comprising administering an effective amount of a compound comprising the crystalline form according 20 to any one of clauses 1 to 36, or a pharmaceutically acceptable salt thereof, to the patient.
58. The method of clause 57, wherein the pneumonia is ventilator acquired pneumonia.

59. A method of treating an infection in a burn wound in a patient in need thereof, the method comprising administering an effective amount of a compound comprising the crystalline form according to any one of clauses 1 to 36, or a pharmaceutically acceptable salt thereof, to the patient.
- 5 60. A method of treating otitis externa in a patient in need thereof, the method comprising administering an effective amount of a compound comprising the crystalline form according to any one of clauses 1 to 36, or a pharmaceutically acceptable salt thereof, to the patient.
61. A method of treating bacterial vaginosis in a patient in need thereof, the method comprising administering an effective amount of a compound comprising the crystalline form according to any one of clauses 1 to 36, or a pharmaceutically acceptable salt thereof, to the patient.
- 10 62. A method of treating impetigo in a patient in need thereof, the method comprising administering an effective amount of a compound comprising the crystalline form according to any one of clauses 1 to 36, or a pharmaceutically acceptable salt thereof, to the patient.
63. A method of treating oral mucositis in a patient in need thereof, the method comprising administering an effective amount of a compound comprising the crystalline form according to any one of clauses 1 to 36, or a pharmaceutically acceptable salt thereof, to the patient.
- 15 64. A crystalline form according to any of clauses 1 to 36, or a pharmaceutically acceptable salt thereof, for use in therapy.
65. The use of a crystalline form according to any of clauses 1 to 36, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating an infection
- 20 66. The use of clause 65, wherein the infection is an infection of a diabetic foot ulcer.

67. The use of clause 65, wherein the infection is an infection of a burn wound.
68. The use of clause 65, wherein the infection is an infection of a complicated venous leg ulcer.
69. The use of clause 65, wherein the infection is an otitis externa infection.
70. The use of clause 65, wherein the infection is acne vulgaris.
- 5 71. The use of clause 65, wherein the infection is conjunctivitis.
72. The use of clause 65, wherein the infection onychomycosis.
73. The use of clause 65, wherein the infection is a wound or an ulcer.
74. The use of clause 65, wherein the infection is a bladder infection.
75. The use of clause 65, wherein the infection is a urinary tract infection.
- 10 76. The use of clause 65, wherein the infection is a lung infection.
77. The use of clause 76, wherein the lung infection arises from a pulmonary condition.
78. The use of clause 77, wherein the pulmonary condition is selected from the group consisting
of genetic conditions, acquired conditions, primary conditions, secondary conditions, asthma,
chronic obstructive pulmonary disease, cystic fibrosis, bronchiolitis, pneumonia, bronchitis,
15 emphysema, adult respiratory distress syndrome, allergies, lung cancer, small cell lung cancer,
primary lung cancer, metastatic lung cancer, bronchiectasis, bronchopulmonary dysplasia,
chronic bronchitis, chronic lower respiratory diseases, croup, high altitude pulmonary edema,
pulmonary fibrosis, interstitial lung disease, reactive airway disease,
lymphangiomyomatosis, neonatal respiratory distress syndrome, parainfluenza, pleural
20 effusion, pleurisy, pneumothorax, primary pulmonary hypertension, psittacosis, pulmonary
edema secondary to various causes, pulmonary embolism, pulmonary hypertension secondary

to various causes, respiratory failure secondary to various causes, sleep apnea, sarcoidosis, smoking, stridor, acute respiratory distress syndrome, infectious diseases, SARS, tuberculosis, psittacosis infection, Q fever, parainfluenza, respiratory syncytial virus, combinations thereof, and conditions caused by any one or combination thereof.

- 5 79. The use of clause 77, wherein the pulmonary condition is a genetic condition.
- 80. The use of clause 77, wherein the pulmonary condition is an acquired condition.
- 81. The use of clause 77, wherein the pulmonary condition is a primary condition.
- 82. The use of clause 77, wherein the pulmonary condition is a secondary condition.
- 83. The use of clause 77, wherein the pulmonary condition is asthma.
- 10 84. The use of clause 77, wherein the pulmonary condition is chronic obstructive pulmonary disease.
- 85. The use of clause 77, wherein the pulmonary condition is cystic fibrosis.
- 86. The use of clause 77, wherein the pulmonary condition is bronchiolitis.
- 87. The use of clause 77, wherein the pulmonary condition is pneumonia.
- 15 88. The use of clause 87, wherein the pneumonia is ventilator acquired pneumonia.
- 89. The use of clause 77, wherein the pulmonary condition is bronchitis.
- 90. The use of clause 78, wherein the pulmonary condition is emphysema.
- 91. The use of clause 77, wherein the pulmonary condition is adult respiratory distress syndrome.
- 92. The use of clause 77, wherein the pulmonary condition is allergies.
- 20 93. The use of clause 77, wherein the pulmonary condition is lung cancer.
- 94. The use of clause 77, wherein the pulmonary condition is small cell lung cancer.

95. The use of clause 77, wherein the pulmonary condition is primary lung cancer.
96. The use of clause 77, wherein the pulmonary condition is metastatic lung cancer.
97. The use of clause 77, wherein the pulmonary condition is bronchiectasis.
98. The use of clause 77, wherein the pulmonary condition is bronchopulmonary dysplasia.
- 5 99. The use of clause 77, wherein the pulmonary condition is chronic bronchitis.
100. The use of clause 77, wherein the pulmonary condition is chronic lower respiratory diseases.
101. The use of clause 77, wherein the pulmonary condition is croup.
102. The use of clause 77, wherein the pulmonary condition is high altitude pulmonary edema.
- 10 103. The use of clause 77, wherein the pulmonary condition is pulmonary fibrosis.
104. The use of clause 77, wherein the pulmonary condition is interstitial lung disease.
105. The use of clause 77, wherein the pulmonary condition is reactive airway disease.
106. The use of clause 77, wherein the pulmonary condition is lymphangioleiomyomatosis.
107. The use of clause 77, wherein the pulmonary condition is neonatal respiratory distress
- 15 syndrome.
108. The use of clause 77, wherein the pulmonary condition is parainfluenza.
109. The use of clause 77, wherein the pulmonary condition is pleural effusion.
110. The use of clause 77, wherein the pulmonary condition is pleurisy.
111. The use of clause 77, wherein the pulmonary condition is pneumothorax.
- 20 112. The use of clause 77, wherein the pulmonary condition is primary pulmonary hypertension.
113. The use of clause 77, wherein the pulmonary condition is psittacosis.

114. The use of clause 77, wherein the pulmonary condition is pulmonary edema secondary to various causes.
115. The use of clause 77, wherein the pulmonary condition is pulmonary embolism.
116. The use of clause 77, wherein the pulmonary condition is pulmonary hypertension
5 secondary to various causes.
117. The use of clause 77, wherein the pulmonary condition is respiratory failure secondary to various causes.
118. The use of clause 77, wherein the pulmonary condition is sleep apnea.
119. The use of clause 77, wherein the pulmonary condition is sarcoidosis.
- 10 120. The use of clause 77, wherein the pulmonary condition is smoking.
121. The use of clause 77, wherein the pulmonary condition is stridor.
122. The use of clause 77, wherein the pulmonary condition is acute respiratory distress syndrome.
123. The use of clause 77, wherein the pulmonary condition is infectious diseases.
- 15 124. The use of clause 77, wherein the pulmonary condition is SARS.
125. The use of clause 77, wherein the pulmonary condition is tuberculosis.
126. The use of clause 77, wherein the pulmonary condition is psittacosis infection.
127. The use of clause 77, wherein the pulmonary condition is Q fever.
128. The use of clause 77, wherein the pulmonary condition is parainfluenza.
- 20 129. The use of clause 77, wherein the pulmonary condition is respiratory syncytial virus.
130. The use of clause 77, wherein the pulmonary condition arises from a coronavirus.

131. The use of clause 130, wherein the coronavirus is selected from the group consisting of porcine epidemic diarrhea virus (PEDv), scotophilus bat coronavirus 512, bat coronavirus CDPHE15, BtRF-Alpha-CoV HuB-2013, bat coronavirus HKU10, miniopterus bat coronavirus HKU8, miniopterus bat coronavirus 1, *Nyctalus velutinus* alphacoronavirus SC-2013, *Pipistrellus kuhlii* coronavirus 3398, *Myotis ricketti* alphacoronavirus Sax-2011, HumCoV 229E, 229E-related bat coronavirus, camel alphacoronavirus, alpaca respiratory coronavirus, HumCoV NL63, NL63-related Bat-CoV BtKYNL63-9b, HKU2, SADSr-CoV, SADS-CoV, Lucheng Rn rat coronavirus2, FIPV, TGEV, PRCV, alphacoronavirus 1, mink coronavirus 1, FRCoV-NL-2010, *Sorex araneus* coronavirus T14, *Suncus murinus* coronavirus X74, HumCoV OC43, HumCoV OC43 isolate TNP F1778_2, HKU23, BovCoV, SACoV, GiCoV, bovine coronavirus isolate alpaca, canine respiratory coronavirus K37, PHEV, equine coronavirus, HKU14, HKU24, myodes coronavirus 2JL14, HKU1, MHV, rat coronavirus Parker, HKU4, HKU5, human MERS-CoV, camel MERS-CoV, hedgehog coronavirus 1, HKU9, rousettus bat coronavirus GCCDC1, eidolon bat coronavirus C704, human SARS-CoV, palm civet SARS-CoV, badger SARS-CoV, bat-SL-CoV RsSHC014, bat-SL-CoV Rs3367, bat-SL-CoV WIV1, HKU3, bat-SL-CoV ZC45, bat-SL-CoV ZXC21, bat-CoV RaTG13, bat-CoV RmYN02, human SARS-CoV-2, cat-CoV, tiger-CoV, dog-CoV, mink-CoV, GD pangolin-CoV, bat Hp-betacoronavirus Zhejiang2013, peafowl IBV, avian coronavirus 9203, fowl IBV, avian coronavirus, duck-CoV, partridge IBV, goose coronavirus CB17, beluga whale coronavirus SW1, HKU22, HKU19, HKU20, HKU21, HKU11, HKU12,

HKU16, HKU27, HKU28, HKU29, HKU18, HKU13, HKU30-UAE, HKU30-Poland, HKU17-USA, HKU17-China, AICCoV, and HKU15, or combinations thereof.

132. The use of clause 131, wherein the coronavirus is selected from the group consisting of an alphacoronavirus, a betacoronavirus, a gammacoronavirus, a deltacoronavirus, and an omicroncoronavirus, or combinations thereof.

133. The use of clause 132, wherein the betacoronavirus is selected from the group consisting of HumCoV OC43 isolate TNP F1778_2, HKU23, BovCoV, SACoV, GiCoV, bovine coronavirus isolate alpaca, canine respiratory coronavirus K37, PHEV, equine coronavirus, HKU14, HKU24, myodes coronavirus 2JL14, HKU1, MHV, rat coronavirus Parker, HKU4, HKU5, human MERS-CoV, camel MERS-CoV, hedgehog coronavirus 1, HKU9, rousettus bat coronavirus GCCDC1, eidolon bat coronavirus C704, human SARS-CoV, palm civet SARS-CoV, badger SARS-CoV, bat-SL-CoV RsSHC014, bat-SL-CoV Rs3367, bat-SL-CoV WIV1, HKU3, bat-SL-CoV ZC45, bat-SL-CoV ZXC21, bat-CoV RaTG13, bat-CoV RmYN02, human SARS-CoV-2, cat-CoV, tiger-CoV, dog-CoV, mink-CoV, GD pangolin-CoV, and bat Hp-betacoronavirus Zhejiang2013, or combinations thereof.

134. The use of clause 65, wherein the infection is a bacterial vaginosis.

135. The use of clause 65, wherein the infection is impetigo.

136. The use of clause 65, wherein the infection is oral mucositis.

137. A crystalline form according to any of clauses 1 to 36, or a pharmaceutically acceptable salt thereof, for use in treating a diabetic foot ulcer.

138. A crystalline form according to any of clauses 1 to 36, or a pharmaceutically acceptable salt thereof, for use in treating a burn wound.
139. A crystalline form according to any of clauses 1 to 36, or a pharmaceutically acceptable salt thereof, for use in treating a complicated venous leg ulcer.
- 5 140. A crystalline form according to any of clauses 1 to 36, or a pharmaceutically acceptable salt thereof, for use in treating an otitis externa infection.
141. A crystalline form according to any of clauses 1 to 36, or a pharmaceutically acceptable salt thereof, for use in treating acne vulgaris.
142. A crystalline form according to any of clauses 1 to 36, or a pharmaceutically acceptable
10 salt thereof, for use in treating conjunctivitis.
143. A crystalline form according to any of clauses 1 to 36, or a pharmaceutically acceptable salt thereof, for use in treating onychomycosis.
144. A crystalline form according to any of clauses 1 to 36, or a pharmaceutically acceptable salt thereof, for use in treating an ulcer.
- 15 145. A crystalline form according to any of clauses 1 to 36, or a pharmaceutically acceptable salt thereof, for use in treating a bladder infection.
146. A crystalline form according to any of clauses 1 to 36, or a pharmaceutically acceptable salt thereof, for use in treating a urinary tract infection.
147. A crystalline form according to any of clauses 1 to 36, or a pharmaceutically acceptable
20 salt thereof, for use in treating a lung infection.

148. A crystalline form according to any of clauses 1 to 36, or a pharmaceutically acceptable salt thereof, for use in treating a pulmonary condition.
149. The crystalline form according to clause 148, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is selected from the group consisting of genetic conditions, acquired conditions, primary conditions, secondary conditions, asthma, chronic obstructive pulmonary disease, cystic fibrosis, bronchiolitis, pneumonia, bronchitis, emphysema, adult respiratory distress syndrome, allergies, lung cancer, small cell lung cancer, primary lung cancer, metastatic lung cancer, bronchiectasis, bronchopulmonary dysplasia, chronic bronchitis, chronic lower respiratory diseases, croup, high altitude pulmonary edema, pulmonary fibrosis, interstitial lung disease, reactive airway disease, lymphangiomyomatosis, neonatal respiratory distress syndrome, parainfluenza, pleural effusion, pleurisy, pneumothorax, primary pulmonary hypertension, psittacosis, pulmonary edema secondary to various causes, pulmonary embolism, pulmonary hypertension secondary to various causes, respiratory failure secondary to various causes, sleep apnea, sarcoidosis, smoking, stridor, acute respiratory distress syndrome, infectious diseases, SARS, tuberculosis, psittacosis infection, Q fever, parainfluenza, respiratory syncytial virus, combinations thereof, and conditions caused by any one or combination thereof.
150. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is a genetic condition.
151. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is an acquired condition.

152. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is a primary condition.
153. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is a secondary condition.
- 5 154. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is asthma.
155. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is chronic obstructive pulmonary disease.
156. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt
10 thereof, wherein the pulmonary condition is cystic fibrosis.
157. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is bronchiolitis.
158. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is pneumonia.
- 15 159. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pneumonia is ventilator acquired pneumonia.
160. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is bronchitis.
161. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt
20 thereof, wherein the pulmonary condition is emphysema.

162. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is adult respiratory distress syndrome.
163. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is allergies.
- 5 164. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is lung cancer.
165. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is small cell lung cancer.
166. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt
10 thereof, wherein the pulmonary condition is primary lung cancer.
167. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is metastatic lung cancer.
168. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is bronchiectasis.
- 15 169. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is bronchopulmonary dysplasia.
170. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is chronic bronchitis.
171. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt
20 thereof, wherein the pulmonary condition is chronic lower respiratory diseases.

172. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is croup.
173. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is high altitude pulmonary edema.
- 5 174. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is pulmonary fibrosis.
175. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is interstitial lung disease.
176. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt
10 thereof, wherein the pulmonary condition is reactive airway disease.
177. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is lymphangioleiomyomatosis.
178. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is neonatal respiratory distress syndrome.
- 15 179. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is parainfluenza.
180. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is pleural effusion.
181. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt
20 thereof, wherein the pulmonary condition is pleurisy.

182. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is pneumothorax.
183. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is primary pulmonary hypertension.
- 5 184. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is psittacosis.
185. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is pulmonary edema secondary to various causes.
186. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt
10 thereof, wherein the pulmonary condition is pulmonary embolism.
187. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is pulmonary hypertension secondary to various causes.
188. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt
15 thereof, wherein the pulmonary condition is respiratory failure secondary to various causes.
189. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is sleep apnea.
190. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is sarcoidosis,.
- 20 191. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is smoking.

192. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is stridor.
193. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is acute respiratory distress syndrome.
- 5 194. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is infectious diseases.
195. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is SARS.
196. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt
10 thereof, wherein the pulmonary condition is tuberculosis.
197. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is psittacosis infection.
198. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is Q fever.
- 15 199. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is parainfluenza.
200. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the pulmonary condition is respiratory syncytial virus.
201. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt
20 thereof, wherein the pulmonary condition arises from a coronavirus.

202. The crystalline form according to any of clause 149, or a pharmaceutically acceptable salt thereof, wherein the coronavirus is selected from the group consisting of porcine epidemic diarrhea virus (PEDv), scotophilus bat coronavirus 512, bat coronavirus CDPHE15, BtRF-Alpha-CoV HuB-2013, bat coronavirus HKU10, miniopterus bat coronavirus HKU8, 5 miniopterus bat coronavirus 1, Nyctalus velutinus alphacoronavirus SC-2013, Pipistrellus kuhlii coronavirus 3398, Myotis ricketti alphacoronavirus Sax-2011, HumCoV 229E, 229E-related bat coronavirus, camel alphacoronavirus, alpaca respiratory coronavirus, HumCoV NL63, NL63-related Bat-CoV BtKYNL63-9b, HKU2, SADSr-CoV, SADS-CoV, Lucheng Rn rat coronavirus2, FIPV, TGEV, PRCV, alphacoronavirus 1, mink coronavirus 1, FRCoV-NL-10 2010, Sorex araneus coronavirus T14, Suncus murinus coronavirus X74, HumCoV OC43, HumCoV OC43 isolate TNP F1778_2, HKU23, BovCoV, SACoV, GiCoV, bovine coronavirus isolate alpaca, canine respiratory coronavirus K37, PHEV, equine coronavirus, HKU14, HKU24, myodes coronavirus 2JL14, HKU1, MHV, rat coronavirus Parker, HKU4, HKU5, human MERS-CoV, camel MERS-CoV, hedgehog coronavirus 1, HKU9, rousettus bat 15 coronavirus GCCDC1, eidolon bat coronavirus C704, human SARS-CoV, palm civet SARS-CoV, badger SARS-CoV, bat-SL-CoV RsSHC014, bat-SL-CoV Rs3367, bat-SL-CoV WIV1, HKU3, bat-SL-CoV ZC45, bat-SL-CoV ZXC21, bat-CoV RaTG13, bat-CoV RmYN02, human SARS-CoV-2, cat-CoV, tiger-CoV, dog-CoV, mink-CoV, GD pangolin-CoV, bat Hp-betacoronavirus Zhejiang2013, peafowl IBV, avian coronavirus 9203, fowl IBV, avian 20 coronavirus, duck-CoV, partridge IBV, goose coronavirus CB17, beluga whale coronavirus SW1, HKU22, HKU19, HKU20, HKU21, HKU11, HKU12, HKU16, HKU27, HKU28,

HKU29, HKU18, HKU13, HKU30-UAE, HKU30-Poland, HKU17-USA, HKU17-China, AICCoV, and HKU15, or combinations thereof.

203. The crystalline form according to clause 202, or a pharmaceutically acceptable salt thereof, wherein the coronavirus is selected from the group consisting of an alphacoronavirus, a
5 betacoronavirus, a gammacoronavirus, a deltacoronavirus, and an omicroncoronavirus, or combinations thereof.

204. The crystalline form according to clause 203, or a pharmaceutically acceptable salt thereof, wherein the betacoronavirus is selected from the group consisting of HumCoV OC43 isolate TNP F1778_2, HKU23, BovCoV, SACoV, GiCoV, bovine coronavirus isolate alpaca, canine
10 respiratory coronavirus K37, PHEV, equine coronavirus, HKU14, HKU24, myodes coronavirus 2JL14, HKU1, MHV, rat coronavirus Parker, HKU4, HKU5, human MERS-CoV, camel MERS-CoV, hedgehog coronavirus 1, HKU9, rousettus bat coronavirus GCCDC1, eidolon bat coronavirus C704, human SARS-CoV, palm civet SARS-CoV, badger SARS-CoV, bat-SL-CoV RsSHC014, bat-SL-CoV Rs3367, bat-SL-CoV WIV1, HKU3, bat-SL-CoV
15 ZC45, bat-SL-CoV ZXC21, bat-CoV RaTG13, bat-CoV RmYN02, human SARS-CoV-2, cat-CoV, tiger-CoV, dog-CoV, mink-CoV, GD pangolin-CoV, and bat Hp-betacoronavirus Zhejiang2013, or combinations thereof.

205. A crystalline form according to any of clauses 1 to 36, or a pharmaceutically acceptable salt thereof, for use in treating a bacterial vaginosis.

20 206. A crystalline form according to any of clauses 1 to 36, or a pharmaceutically acceptable salt thereof, for use in treating impetigo.

207. A crystalline form according to any of clauses 1 to 36, or a pharmaceutically acceptable salt thereof, for use in treating oral mucositis.
208. A composition comprising the crystalline form according to any one of clauses 1 to 43.
209. The composition of clause 208, wherein the crystalline form is formulated to be
- 5 administered orally, topically, intravenously, intraperitoneally, intradermally, intraocularly, inhalation (and intrapulmonary), intranasally, transdermally, epicutaneously, subdermally, mucosally, nasally, ophthalmically, impression into skin, intravaginally, intrauterinely, intracervically, or rectally.
210. A kit comprising a composition according to clause 209.
- 10 211. The crystalline form of any of clauses 3-36 and 43-209, wherein the peak of the XRPD pattern has a deviation of $\pm 0.02^\circ 2\theta$.
212. The crystalline form of any of clauses 3-36 and 43-209, or 211, wherein the peak of the XRPD pattern has a deviation of $\pm 0.01^\circ 2\theta$.

15

EXAMPLES

Examples related to the present disclosure are described below. In most cases, alternative techniques can be used. The examples are intended to be illustrative and are not limiting or restrictive of the scope of the invention as set forth in the claims.

EXAMPLE 1

Physicochemical and physical characterization of di-Na monohydrate crystalline salt of Nu-3
(Form 1).

Prior to the start of solid form screening, Form 1 was characterized by ¹H NMR, PXRD,
5 DSC, GC, KF, TGA and mDSC (Figure 1-6).

The purity and crystallinity of the salt were confirmed by ¹H-NMR and PXRD studies,
respectively. The ¹H-NMR is shown in FIG. 1 and the powder X-ray diffraction (PXRD)
pattern is shown in FIG. 2. The powder X-ray diffraction analysis was performed using the
Malvern Panalytical EMPYREAN instrument with data analysis performed by the software
10 Highscore plus version 4.8 (4.8.0.25518). Briefly, sample powder was placed in a zero-
background holder of Pan analytical (X-ray Cu/40kV/30mA) and made surface smooth using a
glass slide. The sample powder was placed in the sample holder in the holder cabin on the
goniometer and measured in the scan range of 3 to 40°2θ in a continuous scan mode. X-ray
diffraction patterns were processed and the peak positions were marked.

15 Multiple thermal events were observed in differential scanning calorimetry (DSC)
thermogram. All thermal events captured in DSC were also seen in mDSC (modulated DSC).
Results are shown in FIG. 3 and FIG. 4. However, the kinetics of the thermal events moved
to lower temperatures due to sinusoidal heating patterns. The first endotherm may be associated
with solvent/water loss. A 3.492% weight loss was observed up to 150°C in thermogravimetric
20 analysis (TGA). Results from the TGA are shown in FIG. 5. There were no residual process
solvents (EtOH, Acetone, DCM, and 1-butanol) found in a gas chromatography (GC) analysis

in significant amounts. Results from the GC analysis are shown in FIG. 6. 4.578% of water (by Karl Fischer (KF) titration, see FIG. 7) was found in the salt. Acicular crystals of Form 1 were observed under optical microscopy (see FIG. 8).

EXAMPLE 2

5 Thermal Behaviour of Form 1

To understand the thermal behavior of Form 1, the below experiments were designed based on the mDSC data results in FIG. 4:

1. Heat-cool-heat DSC analysis.
2. Heating Form 1 at 180°C followed by PXRD and ¹H-NMR.
- 10 3. Heating Form 1 at 220°C followed by PXRD and ¹H-NMR.

A heat-cool-heat DSC analysis was planned to understand the nature of the first endotherm event observed in DSC and mDSC thermogram as shown in FIG. 3 and FIG. 4. The heat-cool-heat cycle demonstrated that the first endothermic peak was associated with de-solvation. During the second heating cycle, the first endothermic event did not appear, but other events were reproduced (FIG. 9). To understand the nature of the compound after de-solvation, it was heated 15 up to 180°C (in a TGA pan) and then subjected to PXRD and ¹H-NMR analysis. Post de-solvation at 180°C, the compound became amorphous (FIG. 10A). However, no sign of degradation was observed in ¹H-NMR (FIG. 10B). While the compound was heated at 220°C, the amorphous material was found to be recrystallized (FIG. 11A) at around 200°C followed by melting at 243.97 20 °C (as shown FIG. 3). The PXRD pattern of FIG. 11A is different than Form 1. However, no sign of degradation was observed in ¹H-NMR (FIG. 11B).

From the above set of experiments, it was evident that Form 1 undergoes de-solvation (between about 125°C to about 160°C) and becomes an amorphous material. Post de-solvation/amorphization, Form 1 went through an *in-situ* crystallization process (cold crystallization; at around 200°C) and then melted at about 243.97 °C.

5

EXAMPLE 3

Hydrate level of di-sodium salt of Nu-3 (Form 1)

A series of dehydration studies were performed to understand the level of hydrates of Form 1 (molecular weight: 558.36). The calculated water content (weight %) for the stoichiometric monohydrate, hemi-hydrate, sesqui-hydrate, and di-hydrate of di-Na salt of Nu-3 are 3.1%, 1.6%,
10 4.6% and 6.2%, respectively.

Disodium crystalline solid Form 1 was exposed to 22% relative humidity (RH) at room temperature (RT) (using saturated potassium acetate solution) for 72 hrs. PXRD and TGA were performed on the dried material after 72 hrs. The dehydrated sample did not show any change in crystallinity by PXRD (FIG. 12A) compared to the Form 1 sample input. A weight loss of 4.531%
15 was observed up to 150°C in TGA (FIG. 12B). The isohume conditions did not lead to loss of water below stoichiometric monohydrate.

Crystalline solid Form 1 was then heated at 100°C for 24 hrs. After 24 hrs., PXRD, TGA and NMR were performed on the dried material. The dehydrated sample did not show any change in PXRD pattern (FIG. 13A). There was no change observed in the ¹H-NMR spectra of Form 1
20 after heating (FIG. 13B). 3.212% weight loss was observed up to 150°C in TGA which was close

to the theoretical weight loss for a monohydrate TGA (FIG. 13C). It strongly suggests that Form 1 is a monohydrate.

As described above, Form 1 was extensively characterized by PXRD, DSC, mDSC, TGA, GC, microscopy, and NMR. Form 1 of Nu-3 was found to be a crystalline material with acicular morphology (as seen in FIG. 8). The compound was found to be a hydrate as there were no significant process solvents present in it (confirmed by GC) except water (confirmed by KF). A series of studies were executed to understand the hydrate level of Form 1, which suggests that Form 1 of Nu-3 sodium salt is a stoichiometric monohydrate. Form 1 may undergo a kinetic de-solvation (suggested by heat-cool-heat DSC) that is dependent on the ramp rate and appears as an endotherm in DSC/mDSC thermogram. De-solvation of Form 1 leads to the formation of an amorphous material due to the collapse of the crystal lattice (reflected in the PXRD pattern as shown in FIG. 10A). The resulting amorphous intermediate was then cold-crystallized (at around 200°C) to another form *in situ*. The compound remained stable throughout the heating cycle. The crystalline form, obtained after heating Form 1 up to 220°C, could possibly be a new anhydrous crystalline solid form (referred to as Form 6 (having unique 2 θ peaks of about 5.5°, about 7.7°, and about 12.2° with the relative intensities of 100%, 15.4% and 6.9% respectively, see Table 2) or Form 6' – see EXAMPLE 8).

EXAMPLE 4

Solubility of Form 1 di-Na monohydrate salt of Nu-3 and selection of crystallization modes

Solubility of crystalline salt Form 1 was assessed in sixteen different solvents of diverse classes (ICH class 2 & 3) to facilitate the selection of solvent systems and corresponding strategies

for the subsequent crystallization experiments (Table 3). The solubility was visually estimated at 25°C and also at higher temperatures up to 50°C, by dosing small aliquots of the solvent into a fixed amount of Nu-3 (5 mg) until the dissolution point or a maximum volume of 1000 mL was reached.

5 Table 3: Selection of crystallization modes based on solvent screening data

S. No	Solvent	Solubility (mg/mL) at 25°C	Solvent volume at 25°C	Solvent class	Solubility (mg/mL) at 50°C	Solvent volume at 50°C	Crystallization modes			
							Cooling crystallization	Slurry crystallization	Anti-solvent crystallization	Evaporative crystallization
1	MeOH	>200	>20	2	>400	>2.5	√	-	√ (co-solvent)	√
2	Ethanol	7.1	141	3	10	100	√	√	-	√
3	IPA	<1	>1000	3	<1	>1000	-	√	√	-
4	1-propanol	<1	>1000	3	2.5	400	√	√	-	√
5	Acetone	<1	>1000	2	<1	>1000	-	√	√	-
6	Acetonitrile	<1	>1000	2	<1	>1000	-	√	√	-
7	Ethylacetate	<1	>1000	3	<1	>1000	-	√	√	-
8	THF	<1	>1000	2	<1	>1000	-	√	√	-
9	1,4-Dioxane	<1	>1000	2	<1	>1000	-	√	√	-
10	DCM	<1	>1000	2	<1	>1000	-	√	√	-
11	MTBE	<1	>1000	3	<1	>1000	-	√	√	-
12	Toluene	<1	>1000	2	<1	>1000	-	√	√	-
13	NMP	5	200	2	7	143	√	√	-	√
14	DMF	1.25	800	2	5	200	√	√	-	√

15	DMSO	>50	>20	3	>200	>5	√	-	√ (co-solvent)	√
16	Water	>200	>40	3	>900	>1.1	√	-	√ (co-solvent)	√

This solubility information was used to design the crystallization experiments. Solubility of Form 1 of the Nu-3 salt was evaluated at 25°C and 50°C in solvents having diverse functionality, such as alcohol, ketone, ester, ether, etc. Disodium monohydrate Nu-3 salt (i.e., Form 1) was found to be soluble in MeOH, DMSO, and water and slightly soluble in EtOH, NMP, and DMF. Solubility of the salt was improved only in MeOH, DMSO, and water at 50°C. Form 1 remained insoluble in most of the other solvents even at 50°C.

EXAMPLE 5

Solid form screening with Form 1: Anti-solvent crystallization

For anti-solvent crystallization, co-solvents (in which solubility of the Nu-3 $\geq$ 50 mg/mL) and anti-solvent (in which solubility of the Nu-3 $<$ 1 mg/mL) were selected based on the solubility data shown in Table 3. Crystalline Form 1 of Nu-3 salt was initially dissolved in different co-solvents and then an anti-solvent was added slowly into the solution under stirring conditions, at RT. The crystallized-out material in dispersion was stirred for about 4 days at RT. Results are summarized in the table below (Table 4).

Table 4: Crystal polymorphs isolated from Form 1 using anti-solvent crystallization

S.No	Batch size (mg)	Co-solvent	Volume (mL)	Anti-solvent	Volume (mL)	Observation	Results
1	50	MeOH	0.15	ACN	1.5	White suspension	Crystalline; mixture of solid forms
2	50	MeOH	0.15	Acetone	2	White suspension	Crystalline; Form 1
3	50	MeOH	0.15	MTBE	1.5	White suspension	Crystalline; Form 5

4	50	MeOH	0.15	THF	3	White suspension	Crystalline; Form 2
5	50	Water	0.15	ACN	2	Oiling out/bi-phasic mixture	NA
6	50	Water	0.15	Acetone	2	Oiling out/bi-phasic mixture	NA
7	50	Water	0.15	IPA	3	White suspension	Crystalline; Form 3
8	50	Water	0.15	THF	3	Oiling out/bi-phasic mixture	NA
9	50	MeOH	0.15	Ethylacetate	1.5	White suspension	Crystalline; Form 1
10	50	MeOH	0.15	1,4-Dioxane	1.5	White suspension	Crystalline; Form 5
11	50	MeOH	0.15	DCM	1.5	White suspension	Crystalline; Form 1

Besides Form 1, three more crystalline solid forms, Form 2, 3, and 5, were identified during the anti-solvent crystallization (see FIG. 14 for the XRPD peaks).

EXAMPLE 6

5 Solid Form Screening of Form 1: Slurry Crystallization

The crystalline Form 1 of Nu-3 salt was slurried in solvents with relatively less to poor solubility (EtOH, n-propanol, DMF, NMP and Toluene) under stirring at about 50°C. Then the mixtures continued to stir at 50°C for about 6 days. Results are summarized in the below Table

10 Table 5: Crystal polymorphs isolated from Form 1 using slurry crystallization

S.No	Batch size (mg)	Solvents	Concentration (mg/mL)	Observation after 7 days	Results
1	50	EtOH	50	White suspension	Crystalline; Form 1
2	100	n-propanol	50	White suspension	Crystalline; Form 2
3	50	DMF	50	Gel formation observed	NA
4	50	NMP	50	Gel formation observed	NA
5	50	Toluene	50	White suspension	Crystalline; Form 5

Apart from input Form 1, crystalline solid Form 2 and 5 were also identified during slurry crystallization (See FIG. 15 for XRPD peaks).

EXAMPLE 7

Solid Form Screening of Form 1: Cooling Crystallization

5 Based on the solubility data, MeOH, EtOH, 1-propanol, and water were selected as solvents for cooling crystallization. Crystalline Form 1 of Nu-3 salt was dissolved in different solvents at 50°C and then their volumes were reduced by heating the clear solutions. Then the solutions were divided into two parts. Crystallization at ambient conditions and crash cooling were performed for each set of solutions. Material was isolated in MeOH, 1-propanol and EtOH
10 after ambient cooling and from EtOH after crash cooling. Solutions that were clear after cooling at 5°C for 24 hrs. were allowed to continue to cool at 5°C for 6 more days. After 7 days at 5°C, gel formation was observed in all samples. Solids were isolated from the gels after constant nitrogen flow. Results are summarized in the Table 6 below.

Table 6: No crystal polymorphs were isolated from Form 1 using cooling crystallization

S.No	Batch size (mg)	Solvents	Concentration (mg/mL)	Initial Observation	Final Observation	Results
1	200	MeOH	400	Ambient cooling: White suspension Crash cooling: Clear solution	Ambient cooling: White suspension Crash cooling: Gel (solid isolated after N ₂ flow)	Crystalline: Form 1 Amorphous
2	300	Water	882	Ambient cooling: Clear solution Crash cooling: Clear solution	Ambient cooling: Gel (solid isolated after N ₂ flow) Crash cooling: Gel (solid isolated after N ₂ flow)	Amorphous In both cases

3	50	EtOH	10	Ambient cooling: White suspension Crash cooling: White suspension	Ambient cooling: White suspension Crash cooling: White suspension	Mixture of solids In both cases
4	25	n-propanol	2.5	Ambient cooling: White suspension	Ambient cooling: White suspension	Crystalline; Form 1

While Form 1 was recovered, no new crystalline solid forms were identified after cooling crystallization processes (See FIG. 16 for the XRPD pattern).

EXAMPLE 8

5

De-hydration of Form 1

Attempts were made to isolate an anhydrous solid form from hydrated Form 1 after heating Form 1 at a higher temperature (between about 200-220°C). Two de-hydration batches were formed in the oven at 220°C and 200°C, respectively. The PXRD patterns from the isolated crystalline solids from both batches were found to be similar to the PXRD pattern of the solid obtained post TGA at 220°C (EXAMPLE 3) with an additional two 2θ peaks of high intensity on the left side of the spectra. (FIG. 17). The de-hydrated solid was designated as Form 6. Results are summarized in the table below (Table 7).

Table 7: Results of dehydration experiments of Form 1

S.No	Batch size (mg)	De-hydration process	Observation	Results
1	200	Heated at 220°C for 5 minutes in an oven	Off-white solid was formed	Crystalline; Form 6
2	200	Heated at 200°C for 5 minutes in an oven	Off-white solid was formed	Crystalline; Form 6

For EXAMPLES 5 through 8, three crystalline solid forms (i.e., Forms 2, 3, and 5) were identified during the screening trials apart from input solid Form 1. Besides these solid forms, another anhydrous crystalline solid form (Form 6) was identified *in situ* by heating Form 1.

EXAMPLE 9

5 Preparation of Amorphous Form 4 from Form 1

An amorphous solid form (Form 4) was prepared from an aqueous solution of crystalline Form 1 by lyophilization. Briefly, solid Form 1 was dissolved in water and then subjected to lyophilization. Three different batches (0.5 g, 1 g, 2 g) were lyophilized according to details in Table 8. PXRD analysis was performed on the resulting powders and the results suggest an
10 amorphous form (FIG. 18), with a broad diffraction peak at a low 2-theta value (~5.0). Results are summarized in the table below (Table 8).

Table 8: Preparation of amorphous Form 4

S.No	Batch size (g)	Lyophilization process	Observation	Results
1	0.5	500 mg of the NU-3 salt was dissolved in 20 mL of water and filtered it. The resultant clear solution was freeze at -70°C and then subjected to lyophilization overnight with collector temperature of -80°C and at 0.9 mbar pressure. After 2 days under vacuum, material was taken out from lyophilizer and submitted for PXRD.	White solid was formed	Amorphous; Form 4
2	1.0	1 g of the NU-3 salt was dissolved in 40 mL of water and filtered it. The resultant clear solution was freeze at -70°C and then subjected to lyophilization overnight with collector temperature of -80°C and	White solid was formed	Amorphous; Form 4

		at 0.9 mbar pressure. After 2 days under vacuum, material was taken out from lyophilizer and submitted for PXRD.		
3	2.0	2 g of the NU-3 salt was dissolved in 80 mL of water and filtered it. The resultant clear solution was freeze at -70°C and then subjected to lyophilization overnight with collector temperature of -80°C and at 0.9 mbar pressure. After 2 days under vacuum, material was taken out from lyophilizer and submitted for PXRD.	White solid was formed	Amorphous; Form 4

EXAMPLE 10

Solubility Studies of Amorphous Form 4

The solubility of amorphous Form 4 was assessed in nine different solvents of diverse classes (ICH class 2 & 3) to facilitate the selection of solvent systems and corresponding strategies for the subsequent crystallization experiments. Results are shown in Table 9. The solubility was visually estimated at 50°C, by dosing small aliquots of the solvent into a fixed amount of Nu-3 (20 mg) until the dissolution point or a maximum volume of 1000 mL was reached.

Table 9: Solubility data for amorphous Form 4

S.No	Solvent	Solvent class	Solubility (mg/mL) at 50°C	Solvent volume at 50°C
1	Acetone	2	<1	>1000
2	Acetonitrile	2	<1	>1000
3	THF	2	<1	>1000
4	Dioxane	2	<1	>1000
5	l-propanol	3	10	100
6	Toluene	2	5	200
7	Ethyl acetate	3	2.5	400
8	NMP	2	>40	500
9	Ethanol	3	>40	500

This solubility information was used to design the following slurry crystallization experiments. Amorphous Nu-3 salt (Form 4) was found to be soluble in NMP, EtOH, 1-propanol and slightly soluble in ethylacetate and toluene. Salt remained insoluble in acetone, acetonitrile, THF and dioxane at 50°C.

EXAMPLE 11

Slurry Crystallization

The amorphous Form 4 of Nu-3 salt was slurried in solvents with relatively less to poor solubility (EtOH, n-propanol, DMF, NMP and toluene) under stirring. Slurry continued for 4 hrs. at 50°C followed by 16 hrs. stirring at RT. This process continued for the next 7 days. Results are summarized in the below Table 10. Crystalline solid Form 3 and 5 were identified during slurry crystallization (FIG. 19).

Table 10 shows slurry crystallization data of amorphous Form 4

S.No	Batch size (mg)	Solvents	Concentration (mg/mL)	Observation after 7 days	Results
1	100	Toluene	100	White suspension	Crystalline; Form 5
2	50	DMF	50	White suspension	Crystalline; Form 3
3	50	Ethylacetate	50	White suspension	Crystalline; Form 5
4	50	THF	50	White suspension	Sticky solid, PXRD not performed
5	50	1,4-dioxane	50	White suspension	Sticky solid, PXRD not performed

Crystalline solid Form 3 (from DMF) and 5 (from toluene and ethylacetate) were isolated during the slurry crystallization trials with amorphous Form 4.

EXAMPLE 12

Characterization of Form 2

Crystalline Form 2 was thoroughly characterized by powder diffraction, thermal screenings, specifically differential scanning calorimetry, and thermogravimetric analysis. Further GC analysis, KF and ¹H-NMR studies were also conducted. The results are described below and further illustrated in FIGs. 20 to 26. The diffraction peaks are different than Form 1 as shown in PXRD pattern in FIG. 20. In DSC thermogram, two broad peaks were observed at around 100°C (exotherm) and 262.02°C (endotherm) as shown in FIG. 21. Similar events were observed in mDSC thermogram also as shown in FIG. 22. No thermal degradation was observed in ¹H-NMR as shown in FIG. 23. A heat-cool-heat DSC was performed to understand the thermal events associated with the first exotherm as shown in FIG. 24. In form 2, the heat-cool-heat cycle clearly demonstrates that the first exothermic peak was associated with de-solvation. Post re-heating, the first exothermic event did not appear, however, post de-solvation other events (FIG. 24) were reproduced. A continuous weight loss was observed (20.293% weight loss up to 150°C) in TGA as shown in FIG. 25. From DSC and TGA, it was evident that Form 2 is a crystalline solvate/hydrate.

Turning to FIG. 26, GC analysis was performed to check the presence of crystallization solvents (MeOH and THF) in Form 2. 1.95% of THF (19512 ppm) was found in Form 2. The amount of MeOH in Form 2 was found to be insignificant. Along with THF, 5.297% of water (by KF, see FIG. 27) was also found in Form 2. The existence of THF was also observed in ¹H-NMR. From TGA, GC, NMR and KF, it was evident that non-stoichiometric THF and water are associated with Form 2. However, the total amount of THF and water did not correlate with

the weight loss observed in TGA. Isothermal heating of Form 2 in TGA followed by PXRD and ¹H-NMR showed that after 190°C crystallinity was induced in the compound, but it did not match with the anhydrous solid Form 6. Irregular-shaped crystals of Form 2 were observed under optical microscopy.

5

EXAMPLE 13

Characterization of Form 3

Crystalline Form 3 was initially isolated from IPA/water mixture following anti-solvent crystallization. Form 3, obtained from IPA/Water, was characterized by PXRD (FIG. 28) and DSC (FIG. 29). Multiple thermal events were observed in DSC.

10 Form 3 was successfully reproduced in DMF following slurry crystallization. The isolated compound was thoroughly characterized by powder diffraction (FIG. 30), thermal screenings, specifically differential scanning calorimetry (FIG. 31 and FIG. 32), and thermogravimetric analysis (FIG. 33). Further GC analysis (FIG. 34), KF (FIG. 35) and ¹H-NMR (FIG. 36) studies were also conducted. Multiple thermal events were observed both in DSC and mDSC. A
15 continuous weight loss was observed (13.524% weight loss up to 105°C) in TGA. From DSC and TGA, it was evident that Form 3 is a crystalline solvate/hydrate.

GC analysis was performed to check the presence of crystallization solvents (DMF) in Form 3. 14.90% of DMF was found in Form 3. 1.165% of water (by KF, see FIG. 34) was found in Form 3. The existence of DMF was also observed in ¹H-NMR. From TGA, GC, NMR
20 and KF, it was evident that Form 3 could be a potential DMF solvate.

EXAMPLE 14

Characterization of Form 4

Amorphous Form 4 was prepared by lyophilization and then characterized by PXRD (FIG. 37), mDSC (FIG. 38), and NMR (FIG. 39). Generally, PXRD pattern resembled that of an amorphous structure; however, there was a broad diffraction peak at a low 2θ value (~ 5.0).
5 Surprisingly, the mDSC did not corroborate a clear T_g event to conclude that form 4 is an amorphous material. The mDSC captures multiple thermal events that were difficult to interpret and conclude. There was no degradation observed in ^1H -NMR.

EXAMPLE 15

Characterization of Form 5

10 Crystalline Form 5 was initially isolated from a MeOH/MTBE mixture following anti-solvent crystallization and subsequently characterized by PXRD (FIG. 40), DSC (FIG. 41), and mDSC (FIG. 42). Multiple thermal events were observed in DSC. Form 5 was also identified in a MeOH/1,4-dioxane mixture following anti-solvent crystallization. The isolated compound was characterized by PXRD, DSC, TGA and mDSC. Further GC analysis was also conducted.
15 The obtained results from the MeOH/1,4-dioxane are mentioned below (and shown in FIGs. 43 to 47). Multiple thermal events were observed both in DSC and mDSC. A non-congruent two step weight loss was observed (3.569% weight loss up to 105°C) in TGA. From DSC and TGA, it was evident that Form 5 is a crystalline solvate/hydrate. GC analysis was performed to check the presence of crystallization solvents (1,4-dioxane) in Form 5. 2.28% of 1,4-dioxane was
20 found in Form 5. From TGA and GC, it was evident that Form 5 could be a non-stoichiometric solvate. Isothermal heating of Form 5 in TGA followed by PXRD and ^1H -NMR showed that

after 220°C Form 5 was converted into the anhydrous solid Form 6 (See FIG. 48). Irregular-shaped crystals of Form 5 were observed under optical microscopy (see FIG. 49).

EXAMPLE 16

Characterization of Form 6

5 Most forms upon de-solvation show the tendency to form *in-situ* anhydrous form 6, which unfortunately could not be isolated using any crystallization process. Form 6 was characterized by PXRD (FIG. 50), DSC (FIG. 51), mDSC (FIG. 52), TGA (FIG. 53), ¹H-NMR (FIG. 54), and KF (FIG. 55). The chemical purity of the form was confirmed by ¹H-NMR (FIG. 11B). Single endotherm (melting) was observed at 255.92°C (onset) in DSC. The same peak
10 was also observed at 242.89°C (onset) in mDSC. No de-solvation/solid form transformation was observed before melting. Only 1.173% water content was found (by KF, see FIG. 55) in Form 6 i.e., theoretically less than hemihydrate. Although, there was no de-solvation event observed in DSC/mDSC, 2.979% weight loss was observed in TGA. The above data suggests that Form 6 is an anhydrous crystalline solid.

15

EXAMPLE 17

Notes from Characterizing Polymorph Forms 2, 3, 5, and 6

Out of four crystalline solid forms, Form 2, 3 and 5 were identified during solvent mediated screening experiments. Form 2 and 5 were not reproducible. Despite several trials for Form 2 and 5, only Form 1 was isolated suggesting the Form 1 is a stable structure of the
20 disodium monohydrate crystalline salt of Nu-3. Form 3 was successfully reproduced in DMF.

However, Form 2, 3 and 5 were found to be either a solvate/binary solvate with an organic solvent and/or water associated with the crystal unit.

Form 6 was only isolated after de-solvation of Form 1, 3, and 5 at higher temperatures and was found to be anhydrous in nature. It was not isolated in any of the solvent mediated crystallization trials. Without being limited by theory, one potential reason for its not being isolated is the propensity of Nu-3 to sorb water/solvent of crystallization during the efforts of its isolation using any feasible method of solid form screening. Based on the PXRD pattern, Form 4 was found to be amorphous except for one broad diffraction peak.

EXAMPLE 18

10 Recovery of pure Form 1

After completion of all crystallization and characterization experiments, the materials remaining from the crystallization trials (mixture of all solid forms) were collected and subjected to re-crystallization. The crystallization process of pure Form 1 was followed. The compound was initially dissolved in an EtOH/water mixture. Pure Form 1 was crystallized following anti-solvent crystallization by adding acetone (Table 11). The re-crystallized Form 1 (see FIG. 56 for comparison with original Form 1 input) was characterized by PXRD (FIG. 57), TGA (FIG. 58), NMR (FIG. 59), GC (FIG. 60), and KF (FIG. 61). 3.495% weight loss was observed up to 150°C in TGA. There was no residual solvent (acetone: 1.7 ppm, EtOH: not detected) observed in the purified and recrystallized Form 1. Chemical purity was confirmed by ¹H-NMR. 5.155% of water content was found in the KF analysis (see FIG. 61).

Table 11: procedure to recover Form 1 and results

S.No	Batch size (g)	Anti-solvent crystallization	Crystallization process	Observation	Results
1	5.0	Solvent: EtOH/Water (24 mL/6 mL) Anti-solvent: Acetone (150 mL)	Compound was dissolved in EtOH/Water at RT and then slowly Acetone was added into it under stirring. The mixture was continued to stir for 24 hours.	White solid was formed	Crystalline; Form 1

EXAMPLE 19

Solubility Studies of Nu-3 di-Na salt

- Solubility of all the solid forms were evaluated in Mili-Q water at RT. Solubility of
- 5 Form 1 was assessed in different buffer medium (pH-1.2 HCl buffer, pH-4.5 acetate buffer, pH-6.8 Phosphate buffer) at RT. Solubility data are summarized in the tables below (Table 12 and 13).

Table 12: Solubility of Nu-3 disodium salt solids in MQ-water

Mili-Q water	Solubility (mg/mL)					
	Form 1	Form 2	Form 3	Form 4	Form 5	Form 6
Initial	91.043	98.483	74.911	105.386	Not performed	100.934
1 Hr.	91.209	94.495	75.146	105.996	90.479	102.855
24 Hrs.	95.086	76.476	71.225	116.446	103.157	100.791
Observation	Clear solution	Clear solution	Clear solution	Clear solution	Turbid solution	Clear solution

- 10 Note: Compounds are highly soluble in water. Since the samples were not saturated, the solubility may be higher than provided in the table.

Table 13: Solubility of Form 1 in buffers

	Solubility of Form 1 (mg/mL)		
	pH-1.2 buffer	pH-4.5 buffer	pH-6.8 buffer
Initial	91.752	90.749	100.624
1 Hr.	94.553	87.946	95.432
24 Hrs.	89.057	82.866	85.650
Observation	Clear solution	Clear solution	Clear solution

Form 1 was found to be highly soluble in water irrespective of different solid forms. Solubility of Form 1 was found to be pH independent. Since the samples were not saturated, the solubility could be higher than provided in the table.

5

EXAMPLE 20

Stability studies of disodium monohydrate Nu-3 crystalline and amorphous salt

Stability of the solid forms (Form 1, 4, and 6) were evaluated at different humidity conditions to understand their tendency to form a lower or a higher hydrate. Solids were exposed to different relative humidity conditions and kept for 7 days at RT. Crystallinity of the solids were evaluated by PXRD (FIG. 62). Results are summarized below table (Table 14).

10

Table: 14: Stability studies at variable humidity conditions

Solid forms	Relative humidity conditions	Results
Form 1	8-10% RH (saturated KOH solution)	Solid: Form 1
	84% RH (saturated KCl solution)	Became deliquescent after 48 Hrs.
Form 4	8-10% RH (saturated KOH solution)	Solid: Form 4
	84% RH (saturated KCl solution)	Became deliquescent after 48 Hrs.
Form 6	8-10% RH (saturated KOH solution)	Solid: Form 6
	84% RH (saturated KCl solution)	Became deliquescent after 48 Hrs.

No solid form transformation to another polymorph was observed at about 8-10% RH for Form 1, 4, and 6 after 1 week. Form 1, 4, and 6 became deliquescent after 48 hrs. and exposure to 84% RH. Nu-3 has not shown any tendency to form lower than a monohydrate. However, the existence of the higher hydrate could not be established due to its hygroscopic nature.

5

EXAMPLE 21

Relative stability studies: non-competitive slurry and water activity studies

To understand the slurry-mediated transformation under non-competitive conditions, solids were suspended in acetone:water mixtures with varying water activity (a_w) at RT for 7 days. Relative humidity can be calculated from the following formula:

10 $a_w = (\text{ERH}\%/100\%)$, where ERH% = equilibrium relative humidity %.

Solids were isolated, dried, and subjected to PXRD to check solid state transformation (FIG. 63 and FIG. 64). Results are summarized in the table below (Table 15).

Table 15: Relative stability studies under non-competitive conditions

Solid forms	Relative humidity conditions	Results
Form 1	Acetone: Water (98:2), $a_w=0.27$	Form 1
	Acetone: Water (95:5), $a_w=0.51$	Form 1
	Acetone: Water (85:15), $a_w=0.75$	Solid could not be isolated (PXRD not performed)
Form 4	Acetone: Water (98:2), $a_w=0.27$	Form 1
	Acetone: Water (95:5), $a_w=0.51$	Form 1
	Acetone: Water (85:15), $a_w=0.75$	Solid could not be isolated (PXRD not performed)
Form 6	Acetone: Water (98:2), $a_w=0.27$	Form 1
	Acetone: Water (95:5), $a_w=0.51$	Form 1
	Acetone: Water (85:15), $a_w=0.75$	Solid could not be isolated (PXRD not performed)
Form 2	Acetone: Water (98:2), $a_w=0.27$	Form 1'
	Acetone: Water (95:5), $a_w=0.51$	Form 1'
	Acetone: Water (85:15), $a_w=0.75$	Solid could not be isolated (PXRD not performed)

Form 3	Acetone: Water (98:2), aw=0.27	Form 1'
	Acetone: Water (95:5), aw=0.51	Form 1'
	Acetone: Water (85:15), aw=0.75	Solid could not be isolated (PXRD not performed)
Form 5	Acetone: Water (98:2), aw=0.27	Form 1'
	Acetone: Water (95:5), aw=0.51	Form 1'
	Acetone: Water (85:15), aw=0.75	Solid could not be isolated (PXRD not performed)

There was no change in the PXRD pattern of solid form 1 after 1 week at a_w 0.27 and 0.51. Form 6 and 4 were found to be converted into solid Form 1 (monohydrate). Form 2, 3 and 5 were found to be converted Form 1'. In Form 1', some additional peaks were found to be emerged along with the typical diffraction peaks of Form 1. Without intending to be bound by theory Form 1' appears to be an intermediate between Form 1 and Form 7, and Form 7 appears to be a polymorph of Form 1 (i.e., a disodium salt monohydrate form).

EXAMPLE 22

Competitive slurry studies

Investigations were aimed to understand the relative stability of different solid forms to select a suitable solid form for further development. The crystalline solid(s) were subjected to the slurry transformation under competitive conditions, in different solvent systems (acetone and THF) at RT and 40°C. Solvents were selected such that the compound has relatively lower solubility and heat was applied to expedite the phase-transformations. Results are summarized in the table below (Table 16).

Table 16: Relative stability studies under competitive conditions

Sr. No.	Batch size (mg)	Solvent system	Input solid form(S)	Initial observation	Results
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1	60	Acetone	From 1 to 6	White suspension at 25°C	Mixture of solid Forms
2	60	Acetone	From 1 to 6	White suspension at 40°C	Form 1'
3	60	THF	From 1 to 6	White suspension at 25°C	Mixture of solid Forms
4	60	THF	From 1 to 6	White suspension at 40°C	Form 1'

At 25°C, mixture of solid forms was observed (both in acetone and THF) after 1 week during slurry-mediated transformation under competitive condition. All the forms were found to be converted into Form 1' after 1 week at 40°C.

5

EXAMPLE 23

Physical stability studies of impure Form 1 under stress conditions

Investigations were planned to understand the physical stability of Form 1 under the influence of varying temperatures and humidity conditions prior to recommending it for further development. For that, Form 1 was subjected to the below temperatures and humidity conditions for up to 4 weeks.

10

1. 40°C and 75%RH.
2. 25°C and 60% RH

Any changes in their physical appearance and crystallinity was monitored at each time point.

The results are summarized in the table below (Table 17).

15 Table 17: Physical stability studies under competitive conditions

	Initial	25°C and 60% RH			40°C and 75% RH		
Time points	Day zero	1 week	2 weeks	4 weeks	1 week	2 weeks	4 weeks

Physical appearance	White crystalline solid	White crystalline solid	White crystalline solid	White crystalline solid	Deliquescent	Deliquescent	Deliquescent
PXRD results	Crystalline Form 1	Crystalline Form 1'	Crystalline (Form 7)	Crystalline (Form 7)	NA	NA	NA

Form 1 was found to be converted into Form 1' after 1 week at 25°C and 60% RH. Form 1 became deliquescent after 1 week at 40°C and 75% RH. Form 1 appeared to be physically less stable at higher temperatures and higher humidity. After 2 weeks at 25°C and 60% RH, Form 1 was converted into a potential new solid form (Form 7). In Form 7, there were some additional peaks observed along with the standard Form 1 diffraction peaks. There were no new peaks observed in 4-week sample compared to 2-week stability sample (FIG. 65).

EXAMPLE 24

Stability of Nu-3 di-Na salt (Form 1) at 2-8°C

Upon storage of Form 1 at 2-8°C for more than a month, some additional PXRD diffraction peaks (same as observed earlier in relative stability studies of EXAMPLE 23) were observed indicating transformation to Form 1'. In Form 1' (with additional peaks), 10 new PXRD peaks appeared compared to input Form 1 (FIG. 66). This could be attributed to the crystalline phase impurity that is generated over time.

Form 7 was further characterized by DSC, TGA, and NMR (FIG. 67 and FIG. 68). There was no significant change in weight loss observed in TGA thermogram compared to input Form 1. An additional endotherm was observed at 43.70°C (onset) in DSC. No chemical change was observed in ¹H-NMR (FIG. 69) as compared to Form 1. Based on the above studies, it was suggested that potential solid Form 1 and 7 are isomorphous solids.

Initially, crystalline Form 1 was selected based on the preliminary stability data and subjected to physical stability studies. During its storage at 25°C and 60%RH for 2 weeks, Form 1 was found to be converted into a potential new solid Form 7. Form 1 appeared to be less stable (deliquescent) at higher temperatures and higher humidity conditions (40°C and 75%
5 RH). However, Form 1 appears stable and the preferred crystalline form when stored at a relative humidity of about 51% or less and at a temperature of about RT or less.

An extensive solid form screening was performed on the Nu-3 di-Na salt. The crystallization methods (anti-solvent, cooling, and slurry crystallization) were selected based on the solubility of the salt. Besides input solid Form 1, a total of six different solid forms were
10 identified during this study. Five of them were crystalline and one was amorphous in nature. The isolated solid forms were extensively characterized by PXRD, DSC, mDSC, TGA, NMR, KF, and GC. Crystalline Form 1 appeared to be a monohydrate of Nu-3 di-Na salt. Form 2, 3, and 5 were identified as crystalline solvates of Nu-3 di-Na salt. Form 4 was found to be a
PXRD amorphous material but, there was no typical glass transition temperature found in the
15 mDSC thermogram. Crystalline Form 6 was characterized as an anhydrous solid form of the salt. Form 6 was only isolated after de-solvation of Form 1, 3, and 5 at higher temperatures. Further, Form 2, 3, and 5 crystal structures were irregular and tended to transition to Form 1 or Form 1'.

All the solid forms were subjected to solubility studies. They were all found to be highly
20 soluble in water. Form 1 showed pH independent solubility in different buffer mediums. After solubility studies, relative stability studies were performed both under competitive and non-

competitive conditions. In relative stability studies, all the solid forms were found to be converted into either Form 1 or Form 1' (with additional diffraction peaks).

The physical stability of solid Form 1 was then investigated at different temperatures and humidity conditions. At 40°C and 75% RH, Form 1 was found to be unstable. Form 1 was initially (after 1 week) converted into Form 1' and finally to Form 7 (after 2 weeks) at 25°C and 60% RH. It was also noticed that Form 1 transformed into Form 1' upon storage at 2-8°C over a month period. These data suggest that there is a tendency for Form 1 to convert into Form 7 with time through an intermediate Form 1'.

The new solid Form 7 was characterized by PXRD, DSC, TGA, and ¹H-NMR. Additional PXRD peaks were observed in Form 7. There was no significant change observed in the thermal profile of Form 7 suggesting that it is most likely an isomorphic monohydrate of Nu-3 di-Na salt.

EXAMPLE 25

Crystalline Form 1 of Nu-3 Treatment of Human Patient Having Complicated Urinary Tract Infection

A human patient is identified as having a complicated urinary tract infection. A pharmaceutical composition containing an effective amount of Crystalline Form 1 of Nu-3 is administered intravesically to the patient via a catheter. The patient is monitored until symptoms are alleviated or ameliorated, and the pharmaceutical composition may be administered one or more additional times if it is determined that such administration is necessary or helpful for treatment.

EXAMPLE 26

Crystalline Form 1 of Nu-3 Treatment of Human Patient Having a Lung Infection
arising from Cystic Fibrosis

A human patient is identified as having a lung infection arising from cystic fibrosis. A
5 pharmaceutical composition containing an effective amount of Crystalline Form 1 of Nu-3 is
administered via inhalation to the patient via a nebulizer. The patient is monitored until
symptoms are alleviated or ameliorated, and the pharmaceutical composition may be
administered one or more additional times if it is determined that such administration is
necessary or helpful for treatment.

10

EXAMPLE 27

Crystalline Form 1 of Nu-3 Treatment of Human Patient Having an Infection of a
Diabetic Foot Ulcer

A human patient is identified as having a diabetic foot ulcer. A pharmaceutical
composition in the form of a gel containing an effective amount of Crystalline Form 1 of Nu-3
15 is administered topically to the patient at the location of the diabetic foot ulcer. The patient is
monitored until symptoms are alleviated or ameliorated, and the pharmaceutical composition
may be administered one or more additional times if it is determined that such administration is
necessary or helpful for treatment.

EXAMPLE 28

20 Crystalline Form 1 of Nu-3 Treatment of Human Patient Having Ventilator Acquired
Pneumonia

A human patient is identified as having ventilator acquired pneumonia. A pharmaceutical composition containing an effective amount of Crystalline Form 1 of Nu-3 is administered via inhalation to the patient via a nebulizer. The patient is monitored until symptoms are alleviated or ameliorated, and the pharmaceutical composition may be

5 administered one or more additional times if it is determined that such administration is necessary or helpful for treatment.

EXAMPLE 29

Crystalline Form 1 of Nu-3 Treatment of Human Patient Having an Infection in a Burn Wound

10 A human patient is identified as having an infection in a burn wound. A pharmaceutical composition in the form of a gel containing an effective amount of Crystalline Form 1 of Nu-3 is administered topically to the patient at the location of the burn wound. The patient is monitored until symptoms are alleviated or ameliorated, and the pharmaceutical composition may be administered one or more additional times if it is determined that such administration

15 is necessary or helpful for treatment.

EXAMPLE 30

Crystalline Form 1 of Nu-3 Treatment of Human Patient Having Impetigo

A human patient is identified as having impetigo. A pharmaceutical composition in the form of a gel containing an effective amount of Crystalline Form 1 of Nu-3 is administered

20 topically to the patient at the location of the vesicles, pustules and/or yellowish crusts. The patient is monitored until symptoms are alleviated or ameliorated, and the pharmaceutical

composition may be administered one or more additional times if it is determined that such administration is necessary or helpful for treatment.

EXAMPLE 31

Crystalline Form 1 of Nu-3 Treatment of Human Patient Having Otitis Externa

5 A human patient is identified as having otitis externa. A pharmaceutical composition containing an effective amount of Crystalline Form 1 of Nu-3 is administered topically directly into the patient's external ear canal. The patient is monitored until symptoms are alleviated or ameliorated, and the pharmaceutical composition may be administered one or more additional times if it is determined that such administration is necessary or helpful for treatment.

10

EXAMPLE 32

Crystalline Form 1 of Nu-3 Treatment of Female Human Patient Having Bacterial Vaginosis

A female human patient is identified as having bacterial vaginosis. A pharmaceutical composition in the form of a gel containing an effective amount of Crystalline Form 1 of Nu-3
15 is administered topically onto or into the patient's vagina. The patient is monitored until symptoms are alleviated or ameliorated, and the pharmaceutical composition may be administered one or more additional times if it is determined that such administration is necessary or helpful for treatment.

EXAMPLE 33

20

Crystalline Form 1 of Nu-3 Treatment of Human Patient Having Lung Infection

A human patient is identified as having a lung infection. A pharmaceutical composition containing an effective amount of Crystalline Form 1 of Nu-3 is administered via inhalation to the patient via a nebulizer. The patient is monitored until symptoms are alleviated or ameliorated, and the pharmaceutical composition may be administered one or more additional
5 times if it is determined that such administration is necessary or helpful for treatment.

EXAMPLE 34

Crystalline Form 1 of Nu-3 Treatment of Human Patient Having a Pulmonary Condition Arising from a Coronavirus

A human patient is identified as having a coronavirus. A pharmaceutical composition
10 containing an effective amount of Crystalline Form 1 of Nu-3 is administered via inhalation to the patient via a nebulizer. The patient is monitored until symptoms are alleviated or ameliorated, and the pharmaceutical composition may be administered one or more additional times if it is determined that such administration is necessary or helpful for treatment.

EXAMPLE 35

Crystalline Form 1 of Nu-3 Treatment of Human Patient Having Acne Vulgaris

A human patient is identified as having acne vulgaris. A pharmaceutical composition in the form of a gel containing an effective amount of Crystalline Form 1 of Nu-3 is administered topically to the patient at the location of the skin lesion. The patient is monitored until symptoms are alleviated or ameliorated, and the pharmaceutical composition may be administered one or
20 more additional times if it is determined that such administration is necessary or helpful for treatment.

EXAMPLE 36

Crystalline Form 1 of Nu-3 Treatment of Human Patient Having Conjunctivitis

A human patient is identified as having conjunctivitis. A pharmaceutical composition containing an effective amount of Crystalline Form 1 of Nu-3 is administered in a liquid form
5 to the patient via a dropper. The patient is monitored until symptoms are alleviated or ameliorated, and the pharmaceutical composition may be administered one or more additional times if it is determined that such administration is necessary or helpful for treatment.

EXAMPLE 37

Crystalline Form 1 of Nu-3 Treatment of Human Patient Having Onychomycosis

10 A human patient is identified as having onychomycosis. A pharmaceutical composition in the form of a gel containing an effective amount of Crystalline Form 1 of Nu-3 is administered topically to the patient at the location of the infected nail. The patient is monitored until symptoms are alleviated or ameliorated, and the pharmaceutical composition may be administered one or more additional times if it is determined that such administration is
15 necessary or helpful for treatment.

EXAMPLE 38

Crystalline Form 1 of Nu-3 Treatment of Human Patient Having Oral Mucositis

A human patient is identified as having oral mucositis. A pharmaceutical composition in the form of a gel containing an effective amount of Crystalline Form 1 of Nu-3 is
20 administered topically to the patient at the location to coat the inflamed mucosa. The patient is monitored until symptoms are alleviated or ameliorated, and the pharmaceutical composition

may be administered one or more additional times if it is determined that such administration is necessary or helpful for treatment.

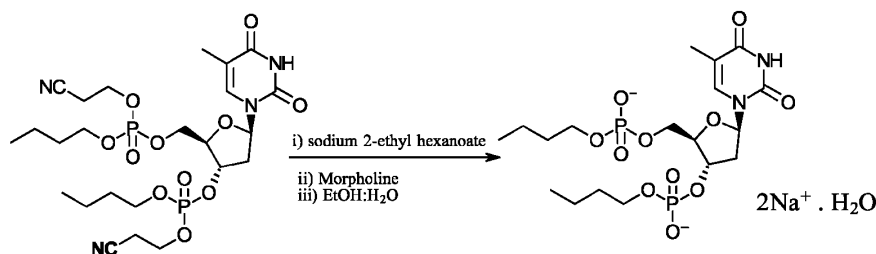
EXAMPLE 39

Crystalline Form 1 of Nu-3 Treatment of Human Patient Having an Infection in a Wound or an Ulcer

A human patient is identified as having an infection in a wound or an ulcer. A pharmaceutical composition in the form of a gel containing an effective amount of Crystalline Form 1 of Nu-3 is administered topically to the patient at the location of the wound or ulcer. The patient is monitored until symptoms are alleviated or ameliorated, and the pharmaceutical composition may be administered one or more additional times if it is determined that such administration is necessary or helpful for treatment.

EXAMPLE 40

Preparation of disodium salt monohydrate Nu-3 Form 1.



A solution of 3-{[(2*R*,3*S*,5*R*)-3-(2-cyanoethoxybutoxyphosphoryloxy)-5-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)tetrahydro-2-furyl]methoxybutoxyphosphoryloxy}propiononitrile (100 g, 0.16 mol) in ethanol (405 ml) and water (45 ml) was charged to a large vessel. Sodium 2 ethyl hexanoate (58 g, 0.336 mol and

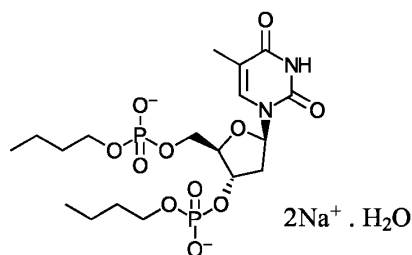
morpholine (30.1 ml, 0.336 mol) were added at 20 °C and the solution was heated to reflux for 20 hours. The solution was cooled to 20 °C and filtered through a glass fiber filter, washing the filter with 9:1 ethanol:water (50 ml). The clarified solution was charged to a large vessel and diluted with acetone (90 ml). The solution was stirred, and a seed of crystalline Nu-3 disodium salt added
5 as a slurry in acetone (10 ml). The seed was stirred for 2 hours. Additional acetone (900 ml) was added over 5 hours and the suspension was filtered through filter paper, washed with (1:9:20) water:ethanol:acetone (200 ml) 1 time then acetone (200 ml) 2 times, and dried at 50 °C under vacuum for 21 hours to yield disodium (2*R*,4*S*,5*R*) butoxy({3-[butoxy(oxido)(oxo)-λ⁵-phosphanyloxy]-5-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)tetrahydro-2-
10 furyl}methoxy)(oxo)-λ⁵-phosphanolate monohydrate (82.1 g).

Recrystallisation of the sodium salt was achieved by redissolving the Nu-3 disodium salt monohydrate (82.1 g, 0.142 mol in 9:1 ethanol:water (530 ml) at 80 °C, cooling to 20 °C, clarifying through a glass fiber filter, washing the filter with 9:1 ethanol:water (41 ml), addition of acetone (74 ml) followed by a seed of crystalline Nu-3 disodium salt added as a slurry in acetone (8 ml),
15 stirring of the seed for 1 hour, addition of acetone (739 mL) over 5 hours to induce crystallization of the disodium salt monohydrate. The crystallized solid was filtered through filter paper, washed with (1:9:20) water:ethanol:acetone (164 ml) 1 time then acetone (164 ml) 2 times, and dried at 50 °C under vacuum for 45 hours to yield disodium (2*R*,4*S*,5*R*) butoxy({3-[butoxy(oxido)(oxo)-λ⁵-phosphanyloxy]-5-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)tetrahydro-2-
20 furyl}methoxy)(oxo)-λ⁵-phosphanolate monohydrate (76.5 g, 82.4% yield).

While embodiments have been disclosed hereinabove, the present invention is not limited to the disclosed embodiments. Instead, this application is intended to cover any variations, uses, or adaptations of the invention using its general principles. Further, this application is intended to cover such departures from the present disclosure as come within
5 known or customary practice in the art to which this invention pertains and which fall within the limits of the appended claims.

What is claimed is:

1. A crystalline form of Nu-3 having the formula:



Formula (I)

or a pharmaceutically acceptable salt thereof.

2. A crystalline disodium monohydrate form of 1-[(2*R*,4*S*,5*R*)-4-(Hydroxybutoxyphosphoryloxy)-5-[(hydroxybutoxyphosphoryloxy)methyl]tetrahydro-2-furyl]-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione.
3. The crystalline form of claim 1 or claim 2, characterized by an X-ray powder diffraction (XRPD) pattern having one or more peaks at about 4.1° to about 4.3°, about 5.4° to about 5.7°, about 6.2° to about 6.4°, or about 7.6° to about 7.8°, each peak being ±0.2, ±0.1, ±0.05, ±0.02, or ±0.01 °2θ.
4. The crystalline form of any of claims 1-3, wherein the XRPD pattern includes one or more peaks at about 7.8° to about 8.1°, about 10.4° to about 10.7°, about 11.2° to about 11.4°, or about 12.1° to about 12.5°, each peak being ±0.2, ±0.1, ±0.05, ±0.02, or ±0.01 °2θ.
5. The crystalline form of any of claims 1-4, wherein the XRPD pattern includes one or more peaks at about 15.0° to about 15.5°, about 15.6° to about 15.9°, about 16.6° to 16.8°, about

17.2° to about 17.3°, or about 17.4° to about 17.6°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .

6. The crystalline form of any of claims 1-5, wherein the XRPD pattern includes one or more peaks at about 18.1° to about 18.7°, about 18.9° to about 19.5°, about 19.6° to about 19.7°, about 20° to about 20.2°, or about 21.2° to about 21.4°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .
7. The crystalline form of any of claims 1-6, wherein the XRPD pattern includes one or more peaks at about 21.9° to about 22°, about 22.5° to about 23.0°, or about 23.2° to about 23.8°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .
8. The crystalline form of any of claims 1-7, characterized by an X-ray powder diffraction (XRPD) pattern having one or more peaks at about 24.0° to about 24.3°, about 25.3° to about 25.6°, about 27.4° to about 27.5°, or about 28.2° to about 28.4°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .
9. The crystalline form of any of claims 1-8 characterized by an X-ray powder diffraction (XRPD) pattern includes one or more peaks at about 5.4°, about 5.6°, about 7.7°, about 12.4°, about 15.0°, about 15.7°, about 16.7°, about 17.2°, about 17.5°, about 18.5°, about 18.6°, about 18.9°, about 19.3°, about 21.3°, about 22.9°, about 24.0°, about 24.2°, or about 27.7°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .
10. The crystalline form of any of claims 1-9, wherein the XRPD pattern includes one or more peaks at about 4.1° to about 4.3°, about 5.4° to about 5.7°, about 6.2° to about 6.4°, about 7.6° to about 7.8°, about 7.8° to about 8.1°, about 10.4° to about 10.7°, about 11.2° to about 11.4°,

about 12.1° to about 12.5°, about 15.0° to about 15.5°, about 15.6° to about 15.9°, about 16.6° to 16.8°, about 17.2° to about 17.3°, about 17.4° to about 17.6°, about 18.1° to about 18.7°, about 18.9° to about 19.5°, about 19.6° to about 19.7°, about 20° to about 20.2°, about 21.2° to about 21.4°, about 21.9° to about 22°, about 22.5° to about 23.0°, about 23.2° to about 23.8°, about 24.0° to about 24.3°, about 25.3° to about 25.6°, about 27.4° to about 27.5°, or about 28.2° to about 28.4°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .

11. The crystalline form of any of claims 1-10 characterized by an XRPD pattern having one or more peaks at about 5.4°, about 7.7°, or about 17.2°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .
12. The crystalline form of any of claims 1-11 characterized by an XRPD pattern having one or more peaks at about 5.4°, about 7.7°, about 12.1°, about 15.4°, or about 17.2°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .
13. The crystalline form of claims 1-12 characterized by an XRPD pattern having one or more peaks at about 5.472°, about 7.714°, or about 17.252°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .
14. The crystalline form of any of claims 1-13 characterized by an XRPD pattern having one or more peaks at about 18.1°, about 18.9°, about 19.6°, about 21.9°, about 22.5°, about 23.2°, or about 27.4°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .
15. The crystalline form of any of claims 1-14 characterized by an XRPD pattern having one or more peaks at about 5.4°, about 7.7°, about 12.1°, about 15.4°, about 17.2°, about 18.1°, about

18.9°, about 19.6°, about 21.9°, about 22.5°, about 23.2°, or about 27.4°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .

16. The crystalline form of any of claims 1-15 characterized by an XRPD pattern having peaks at about 5.4°, about 7.7°, about 12.1°, about 15.4°, about 17.2°, about 18.1°, about 18.9°, about 19.6°, about 21.9°, about 22.5°, about 23.2°, and about 27.7°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .
17. The crystalline form of any of claims 1-16 characterized by an XRPD pattern having peaks at about 5.472°, about 7.714°, about 12.190°, about 15.413°, about 17.252°, about 18.116°, about 18.972°, about 19.674°, about 21.947°, about 22.598°, about 23.235°, and about 27.41°, with each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .
18. The crystalline form of claims 1 and 2, characterized by an XRPD pattern having a peak at about 5.5° 2 θ ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 ° 2 θ .
19. The crystalline form of any of claims 1 and 2 characterized by an XRPD pattern having a peak at 5.472° 2 θ ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 ° 2 θ .
20. The crystalline form of any of claims 1-10 characterized by an XRPD pattern having one or more peaks at about 7.9°, about 16.7°, about 18.5°, about 22.7°, and about 24.2°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .
21. The crystalline form of any of claims 1-10 and claim 20 characterized by an XRPD pattern having one or more peaks at about 7.989°, about 16.717°, about 18.529°, about 22.770°, and about 24.228°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .

22. The crystalline form of any of claims 1-10 and 20-21 characterized by an XRPD pattern having one or more peaks at about 7.9°, about 16.7°, about 18.5°, about 22.7°, about 23.6°, about 24.2°, or about 25.4°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .
23. The crystalline form of any of claims 1-10 and 21-22 characterized by an XRPD pattern having peaks at about 7.989°, about 16.717°, about 18.529°, about 22.770°, about 23.682°, about 24.228°, and about 25.494°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .
24. The crystalline form of any of claims 1-10 characterized by an XRPD pattern having one or more peaks at about 4.3°, about 15.1° or about 19.4°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .
25. The crystalline form of any of claims 1-10 or 24 characterized by an XRPD pattern having one or more peaks at about 4.290°, about 15.069°, or about 19.356°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .
26. The crystalline form of any of claims 1-10 characterized by an XRPD pattern having one or more peaks at about 7.9°, 12.4° or about 20.1°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .
27. The crystalline form of any of claims 1-10 and claim 26 characterized by an XRPD pattern having one or more peaks at about 7.924°, 12.424° or about 20.081°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .
28. The crystalline form of any of claims 1-10 characterized by an XRPD pattern having one or more peaks at about at about 5.7°, about 10.6°, about 15.8°, about 17.6°, about 18.6°, or about 21.3°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .

29. The crystalline form of any of claims 1-10 and 28 characterized by an XRPD pattern having one or more peaks at about 5.692°, about 10.590°, about 15.759°, about 17.554°, about 18.640°, or about 21.302°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .
30. The crystalline form of any of claims 1-10 or 28-29 characterized by an XRPD pattern having one or more peaks at about 23° or about 24°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .
31. The crystalline form of any of claims 1-10 or 28-30 characterized by an XRPD pattern having one or more peaks at about 22.958° or about 24.041°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .
32. The crystalline form of any of claims 1-10 or 28-31 characterized by an XRPD pattern having one or more peaks at about 5.7°, about 10.6°, about 15.8°, about 17.6°, about 18.6°, about 21.3°, about 23°, about 24°, or about 28.3°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .
33. The crystalline form of any of claims 1-10 or 28-32, characterized by an XRPD pattern having peaks at about 5.692°, about 6.331°, about 10.590°, about 11.314°, about 15.759°, about 17.554°, about 18.640°, about 21.302°, about 22.958°, about 24.041°, and 28.301°, each peak being ± 0.2 , ± 0.1 , ± 0.05 , ± 0.02 , or ± 0.01 °2 θ .
34. The crystalline form of any of claims 3-33, wherein the peaks of the XRPD pattern have a deviation of ± 0.2 °2 θ .
35. The crystalline form of any of claims 3-33, wherein the peaks of the XRPD pattern have a deviation of ± 0.1 °2 θ .

36. The crystalline form of any of claims 3-33, wherein the peaks of the XRPD pattern have a deviation of $\pm 0.05^\circ 2\theta$.