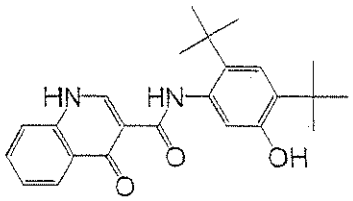
**[0014]** Accordingly, there is a need for stable bioavailable pharmaceutical compositions of N-[2,4-bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide useful for treating patients suffering from CF and methods of administering the same.

## SUMMARY ~~OF THE INVENTION~~

**[0015]** In general, the ~~invention~~disclosure relates to pharmaceutical compositions comprising a solid dispersion of N-[2,4-bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide ("Compound 1"). The pharmaceutical compositions may also include one or more of the following excipients: a filler, a disintegrant, a glidant, a lubricant, a binder, and a surfactant.

**[0015a]** In one aspect, there is provided a pharmaceutical composition consisting of a tablet comprising

a. 34.1 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises 80 wt% of substantially amorphous N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide (Compound 1)




Compound 1

by weight of the dispersion, 19.5 wt% of HPMCAS by weight of the dispersion, and 0.5 wt% SLS by weight of the dispersion;

b. 30.5 wt% of microcrystalline cellulose by weight of the composition;

c. 30.4 wt% of lactose by weight of the composition;

d. 3 wt% of sodium croscarmellose by weight of the composition;

e. 0.5 wt% of SLS by weight of the composition;

f. 0.5 wt% of colloidal silicon dioxide by weight of the composition; and

g. 1.0 wt% of magnesium stearate by weight of the composition,

wherein the term "substantially amorphous" refers to Compound 1 having less than 15% crystallinity.

**[0015b]** In another aspect, there is provided the pharmaceutical composition as defined above for use in treating or lessening the severity of a disease in a patient, wherein said disease is selected from cystic fibrosis, asthma, smoke induced COPD, chronic bronchitis, rhinosinusitis, constipation, pancreatitis, pancreatic insufficiency, male infertility caused by congenital bilateral absence of the vas deferens (CBAVD), mild pulmonary disease, idiopathic pancreatitis, allergic bronchopulmonary aspergillosis (ABPA), liver disease, hereditary emphysema, hereditary hemochromatosis, coagulation-fibrinolysis deficiencies, such as protein C deficiency, Type 1 hereditary angioedema, lipid processing deficiencies, such as familial hypercholesterolemia, Type 1 chylomicronemia, abetalipoproteinemia, lysosomal storage diseases, such as I-cell disease/pseudo-Hurler, mucopolysaccharidoses, Sandhof/Tay-Sachs, Crigler-Najjar type II, polyendocrinopathy/hyperinsulinemia, Diabetes mellitus, Laron dwarfism, myeloperoxidase deficiency, primary hypoparathyroidism, melanoma, glycanosis CDG type 1, congenital hyperthyroidism, osteogenesis imperfecta, hereditary hypofibrinogenemia, ACT deficiency, Diabetes insipidus (DI), neurohypophyseal DI, nephrogenic DI, Charcot-Marie Tooth syndrome, Pelizaeus-Merzbacher disease, neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, progressive supranuclear palsy, Pick's disease, several polyglutamine neurological disorders such as Huntington's, spinocerebellar ataxia type I, spinal and bulbar muscular atrophy, dentatorubral pallidoluysian atrophy, and myotonic dystrophy, as well as spongiform encephalopathies, such as hereditary Creutzfeldt-Jakob disease (due to prion protein processing defect), Fabry disease, Gerstmann-Sträussler-Scheinker syndrome, COPD, dry-eye disease, or Sjogren's disease, Osteoporosis, Osteopenia, Gorham's Syndrome, chloride channelopathies such as myotonia congenita (Thomson and Becker forms), Bartter's syndrome type III, Dent's disease, hyperekplexia, epilepsy, lysosomal storage disease, Angelman syndrome, and Primary Ciliary Dyskinesia (PCD), a term for inherited disorders of the structure and/or function of cilia, including PCD with situs inversus (also known as Kartagener syndrome), PCD without situs inversus and ciliary aplasia.

[0016] In one embodiment, the present ~~invention~~disclosure provides a pharmaceutical composition comprising a solid dispersion of amorphous Compound 1, wherein the solid dispersion comprises about 25 mg of amorphous Compound 1. In certain embodiments, the solid dispersion comprises about 25 mg of substantially amorphous Compound 1.

[0017] In one embodiment, the present ~~invention~~disclosure provides a pharmaceutical composition comprising a solid dispersion of amorphous Compound 1, wherein the solid dispersion comprises about 50 mg of amorphous Compound 1. In certain embodiments, the solid dispersion comprises about 50 mg of substantially amorphous Compound 1.

[0018] In one embodiment, the present ~~invention~~disclosure provides a pharmaceutical composition comprising a solid dispersion of amorphous Compound 1, wherein the solid dispersion comprises about 75 mg of amorphous Compound 1. In certain embodiments, the solid dispersion comprises about 75 mg of substantially amorphous Compound 1.

[0019] In one embodiment, the present ~~invention~~disclosure provides a pharmaceutical composition comprising a solid dispersion of amorphous Compound 1, wherein the solid dispersion comprises about 100 mg of amorphous Compound 1. In certain embodiments, the solid dispersion comprises about 100 mg of substantially amorphous Compound 1.

[0020] In one embodiment, the present ~~invention~~disclosure provides a pharmaceutical composition comprising a solid dispersion of amorphous Compound 1, wherein the solid dispersion comprises about 150 mg of amorphous Compound 1. In certain embodiments, the solid dispersion comprises about 150 mg of substantially amorphous Compound 1.

[0021] In one embodiment, the present ~~invention~~disclosure provides a pharmaceutical composition comprising a solid dispersion of amorphous Compound 1, wherein the solid dispersion comprises about 250 mg of amorphous Compound 1. In certain embodiments, the solid dispersion comprises about 250 mg of substantially amorphous Compound 1.

[0022] In one ~~aspect~~embodiment, the solid form of Compound 1 in the pharmaceutical composition is a solid dispersion comprising substantially amorphous or amorphous Compound 1 and a polymer, such as hydroxypropylmethylcellulose (HPMC), hydroxypropylmethylcellulose acetate succinate (HPMCAS), vinylpyrrolidone/vinyl acetate copolymer (PVP/VA), polyvinylpyrrolidone (PVP), methacrylic acid/methacrylate copolymers, hydroxypropyl cellulose (HPC), or any combination thereof. Embodiments ~~of this aspect~~ include one or more of the following: The solid dispersion is a powder having mean particle diameter of greater than about 5 μm or the solid dispersion has a bulk density of about 0.10 g/cc or greater.

**[0023]** In some instances, the solid dispersion has a concentration of at least 20 wt% of Compound 1, by weight of the solid dispersion. In other instances, the solid dispersion comprises 80 wt% or less of HPMCAS or PVP/VA. Some solid dispersions comprise from about 40 wt% to about 60 wt% of substantially amorphous or amorphous Compound 1 by weight of the solid dispersion and from about 60 wt% to about 40 wt% of polymer by weight of the solid dispersion. Other solid dispersions comprise from about 65 wt% to about 95 wt% of substantially amorphous or amorphous Compound 1 by weight of the solid dispersion and from about 45 wt% to about 5 wt% of polymer by weight of the solid dispersion.

**[0024]** Solid dispersions can also optionally comprise additives such as a surfactant (e.g., sodium lauryl sulfate (SLS)), which can be present in a concentration of less than 10 wt% of surfactant by weight of solid dispersion.

**[0025]** Still other solid dispersions comprise from about 45 wt% to about 85 wt% of substantially amorphous or amorphous Compound 1, from about 0.45 wt% to about 0.55 wt% of SLS, and from about 14.45 wt% to about 55.55 wt% of HPMCAS or PVP/VA by weight of the solid dispersion.

**[0026]** In still further embodiments, the pharmaceutical compositions also comprise a filler (e.g., lactose, sorbitol, celluloses, calcium phosphates, starches, sugars (e.g., mannitol, sucrose, or the like) or any combination thereof) in concentrations of at least about 10 wt% by weight of the composition; a disintegrant (e.g., sodium croscarmellose, sodium starch glycolate, or a combination thereof) in concentrations of about 10 wt% or less by weight of the composition; a surfactant (e.g., sodium lauryl sulfate, sodium stearyl fumarate (SSF), polyoxyethylene 20 sorbitan mono-oleate, or any combination thereof) in concentrations of about 10 wt% or less by weight of the composition; a binder (e.g., microcrystalline cellulose, dibasic calcium phosphate, sucrose, corn (maize) starch, modified cellulose (e.g., hydroxymethyl cellulose), or any combination thereof) in concentrations of at least about 1

wt% by weight of the composition; a glidant (e.g., colloidal silicon dioxide, talc, or a combination thereof) in concentrations of about 2 wt% or less by weight of the composition; and a lubricant (e.g., magnesium stearate, stearic acid, hydrogenated oil, sodium stearyl fumarate, or any combination thereof) in concentrations of about 2 wt% or less by weight of the composition.

**[0027]** Such pharmaceutical compositions can optionally comprise one or more colorants, fragrances, and/or flavors to enhance its visual appeal, taste, and scent.

**[0028]** Another ~~aspect~~embodiment of the present ~~invention~~disclosure provides a pharmaceutical composition consisting of a tablet that comprises a solid dispersion, a filler, a disintegrant, a surfactant, a binder, a glidant, and a lubricant, wherein the tablet has a dissolution of at least about 50% in about 30 minutes, and the solid dispersion comprises substantially amorphous Compound 1. As noted below, dissolution is measured with a standard USP Type II apparatus that employs a dissolution media of 0.6% sodium lauryl sulfate dissolved in 900 mL of DI water (or a volume of media having the same ratio of SLS to DI water) at a temperature of about 37 °C. A single experimental tablet is tested in each test vessel of the apparatus. Dissolution can also be measured with a standard USP Type II apparatus that employs a dissolution media of 0.7% sodium lauryl sulfate dissolved in 900 mL of 50 mM sodium phosphate buffer (pH 6.8) at a temperature of about 37 °C. Dissolution can also be measured with a standard USP Type II apparatus that employs a dissolution media of 0.5% sodium lauryl sulfate dissolved in 900 mL of 50 mM sodium phosphate buffer (pH 6.8) at a temperature of about 37 °C. A single experimental tablet is tested in each test vessel of the apparatus.

**[0029]** Another ~~aspect~~embodiment of the present ~~invention~~disclosure provides a pharmaceutical composition consisting of a tablet that comprises a solid dispersion comprising amorphous or substantially amorphous Compound 1 and HPMCAS or PVP/VA; and, a filler, a disintegrant, a surfactant, a binder, a glidant, and a lubricant, wherein the tablet has a hardness of at least about 5 Kp.

**[0030]** In yet another ~~aspect~~embodiment, the tablets described herein are coated.

**[0031]** In another ~~aspect~~embodiment, the coated tablets described herein are colored.

**[0032]** In still another ~~aspect~~embodiment, the colored, coated tablets include text or images. For instance, the text or images can be printed on the colored, coated tablet.

In still other ~~aspects~~embodiments, the colored, coated tablets include about 3 wt% of a film coating comprising a blue colorant, such as OPADRY® II. In some embodiments, the colored tablets can be labeled with a logo and text indicating the strength of the active ingredient in the tablet using a black ink, such as Opacode® WB or Opacode® S-1-17823. In still further embodiments, the colored, coated tablets are coated with a colorant, waxed, and then labeled

with a logo, other image, and/or text using a suitable ink. In some embodiments, the tablets are coated with about 3 wt% of colorant, and waxed with Carnauba wax powder weighed out in the amount of about 0.01% w/w of the starting tablet core weight. The waxed tablets can be labeled with a logo and text indicating the strength of the active ingredient in the tablet using a suitable ink.

[0033] Another ~~aspect~~embodiment of the present ~~invention~~disclosure provides a method of producing a pharmaceutical composition comprising the steps of providing an admixture of a solid dispersion of amorphous Compound 1, a binder, a glidant, a surfactant, a lubricant, a disintegrant, and a filler, and compressing the admixture into a tablet having a dissolution of at least about 50% in about 30 minutes. In one example, the admixture is compressed to a hardness of at least about 5 Kp.

[0034] Another ~~aspect~~embodiment of the present ~~invention~~disclosure provides a method of producing a pharmaceutical composition comprising the steps of providing an admixture of a solid dispersion of amorphous Compound 1, a binder, a glidant, a surfactant, a lubricant, a disintegrant, and a filler, and compressing the admixture into a tablet having a dissolution of at least about 70% in about 30 minutes.

[0035] Another ~~aspect~~embodiment of the present ~~invention~~disclosure provides a method of administering a pharmaceutical composition by orally administering to a patient at least once per day at least one tablet comprising a solid dispersion of substantially amorphous or amorphous Compound 1, a filler, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, in which the solid dispersion comprises at least about 25 mg of substantially amorphous or amorphous Compound 1. In some embodiments, the tablet is orally administered to the patient once per day. Other tablets useful in this method comprise a solid dispersion containing at least about 50 mg of substantially amorphous or amorphous Compound 1. Some tablets useful in this method comprise a solid dispersion containing at least about 75 mg of substantially amorphous or amorphous Compound 1. Other tablets useful in this method comprise a solid dispersion containing at least about 100 mg of substantially amorphous or amorphous Compound 1. Yet other tablets useful in this method comprise a solid dispersion containing at least about 150 mg of substantially amorphous or amorphous Compound 1. In another method, the administration comprises orally administering to a patient at least once per day at least one tablet comprising a solid dispersion of substantially amorphous or amorphous Compound 1, a filler, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, in which the solid dispersion contains at least about 250 mg of substantially amorphous or amorphous Compound 1.

In some embodiments, the present ~~invention~~disclosure provides for a method of orally administering the pharmaceutical compositions described herein at least once a day. In other embodiments, the present ~~invention~~disclosure provides for a method of orally administering the pharmaceutical composition described herein once a day. hi some embodiments, the present ~~invention~~disclosure provides for a method of orally administering the pharmaceutical composition described herein twice a day.

**[0036]** In one ~~aspect~~embodiment, the ~~invention~~disclosure also provides a method of treating or lessening the severity of a disease in a patient comprising administering to said patient one of the compositions as defined herein, and said disease is selected from cystic fibrosis, asthma, smoke induced COPD, chronic bronchitis, rhinosinusitis, constipation, pancreatitis, pancreatic insufficiency, male infertility caused by congenital bilateral absence of the vas deferens (CBAVD), mild pulmonary disease, idiopathic pancreatitis, allergic bronchopulmonary aspergillosis (ABPA), liver disease, hereditary emphysema, hereditary hemochromatosis, coagulation-fibrinolysis deficiencies, such as protein C deficiency, Type 1 hereditary angioedema, lipid processing deficiencies, such as familial hypercholesterolemia, Type 1 chylomicronemia, abetalipoproteinemia, lysosomal storage diseases, such as I-cell disease/pseudo-Hurler, mucopolysaccharidoses, Sandhof/Tay-Sachs, Crigler-Najjar type II, polyendocrinopathy/hyperinsulemia, Diabetes mellitus, Laron dwarfism, myleoperoxidase deficiency, primary hypoparathyroidism, melanoma, glycanosis CDG type 1, congenital hyperthyroidism, osteogenesis imperfecta, hereditary hypofibrinogenemia, ACT deficiency, Diabetes insipidus (DI), neurophyseal DI, neprogenic DI, Charcot-Marie Tooth syndrome, Perlizaeus-Merzbacher disease, neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, progressive supranuclear plasy, Pick's disease, several polyglutamine neurological disorders such as Huntington's, spinocerebullar ataxia type I, spinal and bulbar muscular atrophy, dentatorubal pallidoluysian, and myotonic dystrophy, as well as spongiform encephalopathies, such as hereditary Creutzfeldt-Jakob disease (due to prion protein processing defect), Fabry disease, Straussler-Scheinker syndrome, COPD, dry-eye disease, Sjogren's disease, Osteoporosis, Osteopenia, Gorham's Syndrome, chloride channelopathies such as myotonia congenita (Thomson and Becker forms), Bartter's syndrome type III, Dent's disease, hyperekplexia, epilepsy, hyperekplexia, lysosomal storage disease, Angelman syndrome, and Primary Ciliary Dyskinesia (PCD), a term for inherited disorders of the structure and/or function of cilia, including PCD with situs inversus (also known as Kartagener syndrome), PCD without situs inversus and ciliary aplasia.