FORMULATIONS OF ION CHANNEL MODULATORS AND METHODS OF PREPARATION AND USE OF ION CHANNEL MODULATORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Application No. 62/941,322, filed November 27, 2019; U.S. Provisional Patent Application No. 62/941,319, filed November 27, 2019; U.S. Provisional Patent Application No. 63/001,906, filed March 30, 2020; U.S. Provisional Patent Application No. 63/001,801, filed March 30, 2020; U.S. Provisional Patent Application No. 63/028,229, filed May 21, 2020; U.S. Provisional Patent Application No. 63/082,864, filed September 24, 2020; and U.S. Provisional Patent Application No. 63/082,857, filed September 24, 2020, the entire contents of each of which are incorporated by reference herein.

BACKGROUND

Sodium ion (Na+) channels primarily open in a transient manner and are quickly inactivated, thereby generating a fast Na+ current to initiate the action potential. The late or persistent sodium current (INaL) is a sustained component of the fast Na+ current of cardiac myocytes and neurons. Many common neurological and cardiac conditions are associated with abnormal INaL enhancement, which contributes to the pathogenesis of both electrical and contractile dysfunction in mammals (see, e.g., *Pharmacol Ther* (2008) 119:326-339). Accordingly, pharmaceutical compositions or dosage forms comprising compounds that selectively modulate sodium channel activity, e.g., abnormal INaL, are useful in treating such disease states.

SUMMARY

Described herein are compositions or dosage forms useful for preventing and/or treating a disease, disorder, or condition, e.g., a disease, disorder, or condition relating to aberrant function of a sodium ion channel, e.g., abnormal late sodium current (INaL). The present disclosure also comprises methods for modulating the sodium channel activity using a compound, composition, or dosage form described herein. Also provided herein is a method of preparing ion channel modulators.

In one aspect, the present disclosure provides a dosage form comprising: from about 0.1 mg to about 500 mg (e.g., from about 0.5 mg to about 200 mg, from about 1 mg to about 150 mg, from about 10 mg to about 120 mg) of Compound 1; and a pharmaceutically acceptable excipient.

In another aspect, the present disclosure provides a dosage form comprising: a plurality of particles of Compound 1; and a pharmaceutically acceptable excipient, wherein the amount of the plurality of particles of Compound 1 in the dosage form is from about 0.1 mg to about 500 mg (e.g., from about 0.5 mg to about 200 mg, from about 1 mg to about 150 mg, from about 10 mg to about 120 mg).

In one aspect, the present disclosure provides a composition in a dosage form comprising: from about 0.1 mg to about 500 mg (e.g., from about 0.5 mg to about 200 mg, from about 1 mg to about 150 mg, from about 10 mg to about 120 mg) of Compound 1; and a pharmaceutically acceptable excipient.

In another aspect, the present disclosure provides a composition in a dosage form comprising: a plurality of particles of Compound 1; and a pharmaceutically acceptable excipient, wherein the amount of the plurality of particles of Compound 1 in the composition is from about 0.1 mg to about 500 mg (e.g., from about 0.5 mg to about 200 mg, from about 1 mg to about 150 mg, from about 10 mg to about 120 mg).In another aspect, provided herein is a method of treating a condition relating to aberrant function of a sodium ion channel in a subject in need thereof, comprising administering to the subject a dosage form disclosed herein. Also provided herein is a method of treating a condition relating to aberrant function of a sodium ion channel in a subject in need thereof, comprising administering to the subject from about 2.5 mg to about 90 mg of Compound 1. In some embodiments, the condition is a neurological or psychiatric disorder In some embodiments, the condition is epilepsy or an epilepsy syndrome. In some embodiments, the condition is a genetic epilepsy or a genetic epilepsy syndrome. In some embodiments, the condition is a pediatric epilepsy or a pediatric epilepsy syndrome. In some embodiments, the condition is epileptic encephalopathy. In some embodiments, the condition is developmental. In some embodiments, the epileptic encephalopathy is selected from the group consisting of Dravet syndrome, infantile spasms, or Lennox-Gastaut syndrome. In other embodiments, the condition is selected from the group consisting of epileptic encephalopathy, epileptic encephalopathy with SCN1A, SCN2A, SCN8A mutations, early infantile epileptic encephalopathy, Dravet syndrome, Dravet syndrome with SCN1A mutation, generalized epilepsy with febrile seizures, intractable childhood epilepsy with generalized tonic-clonic seizures, infantile spasms, benign familial neonatal-infantile seizures, SCN2A epileptic encephalopathy, focal epilepsy with SCN3A mutation, cryptogenic pediatric partial epilepsy with SCN3A mutation, SCN8A epileptic encephalopathy, sudden unexpected death in epilepsy, Rasmussen encephalitis, malignant migrating partial seizures of infancy, autosomal dominant nocturnal frontal lobe

epilepsy, sudden expected death in epilepsy (SUDEP), KCNQ2 epileptic encephalopathy, and KCNT1 epileptic encephalopathy. In some embodiments, the condition is a cancer.

Also provided herein is a method of treating a neurological disorder or a psychiatric disorder in a subject in need thereof, wherein the method comprises administering to a subject in need thereof a dosage form disclosed herein.

The disclosure provides, in part, a method of treating a pain in a subject in need thereof, wherein the method comprises administering to the subject a dosage form disclosed herein.

Contemplated methods include a method of treating a cancer in a subject in need thereof, wherein the method comprises administering to the subject a dosage form disclosed herein.

In another aspect, provided herein is a method of treating or preventing a trigeminal autonomic cephalalgia (TAC) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a dosage form disclosed herein.

Also provided herein is a method of treating or preventing a trigeminal autonomic cephalalgia (TAC) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of Compound 1, e.g., from about 2.5 mg to about 90 mg of Compound 1.

In another aspect, provided herein is a method of treating or preventing a migraine in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a dosage form disclosed herein.

Provided herein, in part, is a method of treating or preventing a migraine in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of Compound 1, e.g., from about 2.5 mg to about 90 mg of Compound 1.

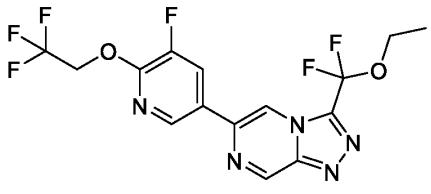
In another aspect, a method of treating or preventing cortical spreading depression (CSD) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a dosage form disclosed herein is provided.

A method of treating or preventing cortical spreading depression (CSD) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of Compound 1, e.g., from about 2.5 mg to about 90 mg is also provided.

Also provided herein is a method of treating or preventing a cranial neuropathy or multiple cranial neuropathies in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a dosage form described herein.

In another aspect, a method of treating or preventing a cranial neuropathy or multiple cranial neuropathies in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of Compound 1, e.g., from 2.5 mg to about 90 mg of Compound 1.

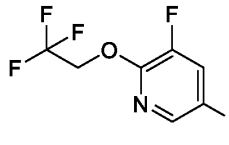
In another aspect, the present disclosure provides a method of making Compound 1:



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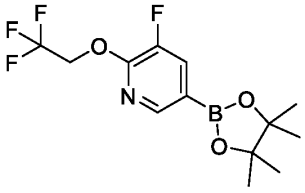
or a pharmaceutically acceptable salt thereof, the method comprising the steps of:

(i) contacting a solution of 2,2,2-trifluoroethanol with 5-bromo-2,3-difluoro-pyridine thereby providing a compound of formula (II):



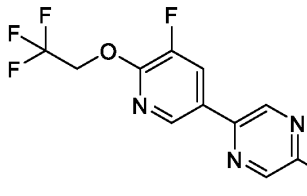
(II);

(ii) contacting the compound of formula (II) with a palladium catalyst and bis(pinacolato)diboron thereby providing a compound of formula (III):



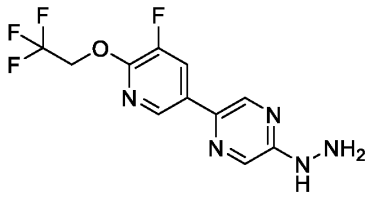
(III);

(iii) contacting the compound of formula (III) with a palladium catalyst and 2-bromo-5-chloro-pyrazine thereby providing a compound of formula (IV):

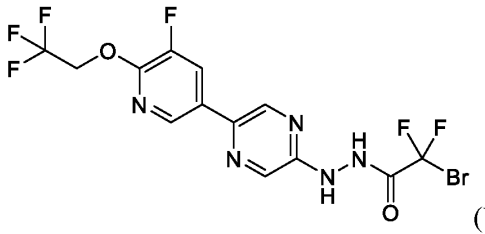


(IV);

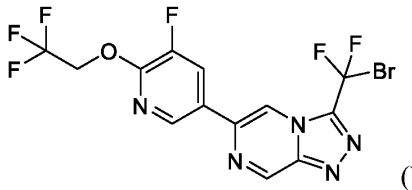
(iv) contacting the compound of formula (IV) with hydrazine thereby providing a compound of formula (V):


(V);

(v) contacting the compound of formula (V) with 2-bromo-2,2-difluoro-acetyl chloride thereby providing a compound of formula (VI):

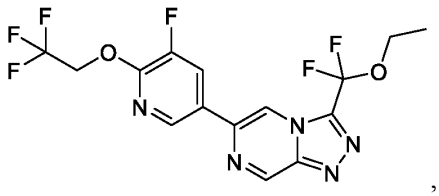

(VI);

(vi) contacting the compound of formula (VI) with an acid thereby providing a compound of formula (VII):

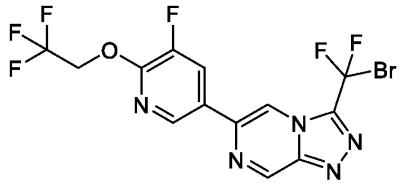

(VII); and

(vii) contacting the compound of formula (VII) with a silver catalyst and ethanol thereby providing Compound 1 or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure provides a method of making Compound 1:


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or a pharmaceutically acceptable salt thereof, wherein Compound 1 or a pharmaceutically acceptable salt thereof is provided by contacting the compound of formula (VII):



(VII)

with a silver catalyst and ethanol.

Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing **Brief Description of the Figures**, **Detailed Description**, **Examples**, and **Claims**.

BRIEF DESCRIPTION OF THE DRAWING

FIG. 1 shows the XRPD pattern of Compound 1 raw material and Compound 1 post jet-milling.

FIG. 2 shows dissolution result of ASD in capsule (2.5 mg and 10 mg active).

FIG. 3 shows dissolution result of 1:10 blend with MCC in capsule (1 and 10 mg active).

FIG. 4 shows dissolution result of 1:10 blend with MCC in capsule (2.5 mg active with 2% surfactant).

DETAILED DESCRIPTION

As generally described herein, the present disclosure provides, in part, compounds, compositions and dosage or dosage forms useful for preventing and/or treating a disease, disorder, or condition described herein, e.g., a disease, disorder, or condition relating to aberrant function of a sodium ion channel, such as abnormal late sodium current (INaL). Exemplary diseases, disorders, or conditions include a neurological disorder (e.g., epilepsy or an epilepsy syndrome, a neurodevelopmental disorder or a neuromuscular disorder), a psychiatric disorder, pain, a gastrointestinal disorder, trigeminal autonomic cephalalgia (TAC), migraine, cranial neuropathy or multiple cranial neuropathy, and cortical spreading depression (CSD). Also provided herein are methods of preparing ion channel modulators.

Definitions

As used herein, "pharmaceutically acceptable carrier" refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions described herein include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride

mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

As used herein, "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.*, describes pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences* (1977) 66:1–19. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p–toluenesulfonate, undecanoate, valerate salts, and the like. Pharmaceutically acceptable salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

As used herein, a "subject" to which administration is contemplated includes, but is not limited to, humans (i.e., a male or female of any age group, e.g., a pediatric subject (e.g,

infant, child, adolescent) or adult subject (e.g., young adult, middle–aged adult or senior adult)) and/or a non-human animal, e.g., a mammal such as primates (e.g., cynomolgus monkeys, rhesus monkeys), cattle, pigs, horses, sheep, goats, rodents, cats, and/or dogs. In certain embodiments, the subject is a human. In certain embodiments, the subject is a non-human animal. The terms "human," "patient," and "subject" are used interchangeably herein.

Disease, disorder, and condition are used interchangeably herein.

As used herein, and unless otherwise specified, the terms "treat," "treating," and "treatment" contemplate an action that occurs while a subject is suffering from the specified disease, disorder or condition, which reduces the severity of the disease, disorder or condition, or retards or slows the progression of the disease, disorder or condition (also "therapeutic treatment").

As used herein, the "effective amount" of a compound refers to an amount sufficient to elicit the desired biological response. As will be appreciated by those of ordinary skill in this art, the effective amount of a compound of the invention may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the disease being treated, the mode of administration, and the age, health, and condition of the subject. An effective amount encompasses therapeutic and prophylactic treatment.

As used herein, and unless otherwise specified, a "therapeutically effective amount" of a compound is an amount sufficient to provide a therapeutic benefit in the treatment of a disease, disorder or condition, or to delay or minimize one or more symptoms associated with the disease, disorder or condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the disease, disorder or condition. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of disease or condition, or enhances the therapeutic efficacy of another therapeutic agent.

As used herein, the term "amorphous" refers to a solid in a non-crystalline state. Amorphous solids generally possess crystal-like short range molecular arrangement, but no long range order of molecular packing as found in crystalline solids. The solid state form of a solid may be determined by polarized light microscopy, X-Ray powder diffraction ("XRPD"), differential scanning calorimetry ("DSC"), or other standard techniques known to those of skill in the art.

As used herein, "crystalline" refers to a solid having a highly regular chemical structure, i.e., having long range structural order in the crystal lattice. The molecules are

arranged in a regular, periodic manner in the 3-dimensional space of the lattice. In particular, a crystalline form may be produced as one or more single crystalline forms.

The term "peaks" when referring to the peaks in an XRPD pattern of a crystalline form of Compound 1 refers to a collection of certain peaks whose values of 2θ across a range of 0°-40° are, as a whole, uniquely assigned to one of the crystalline forms of Compound 1.

As used herein, the phrase "amorphous solid dispersion" refers to a solid comprising a drug substance (e.g., Compound 1) and a dispersion polymer.

The phrase "dispersion polymer" means a polymer that allows for the drug substance (e.g., Compound 1) to be dispersed throughout such that a solid dispersion may form. The dispersion polymer may contain a mixture of two or more polymers. Examples of dispersion polymers include, but are not limited to, vinyl polymers and copolymers, vinylpyrrolidine vinylacetate copolymer ("PVP-VA"), polyvinyl alcohols, polyvinyl alcohol polyvinyl acetate copolymers, polyvinyl pyrrolidine ("PVP"), acrylate and methacrylate copolymers, methylacrylic acid methyl methacrylate copolymer (such as Eudragit®), polyethylene polyvinyl alcohol copolymers, polyoxyethylene-polyoxypropylene block copolymers (also referred to as poloxamers), graft copolymer comprised of polyethylene glycol, polyvinyl caprolactam and polyvinyl acetate (such as Soluplus®), cellulosic polymers, such as hydroxypropyl methyl cellulose acetate ("HPMCA"), hydroxypropyl methyl cellulose ("HPMC"), hydroxypropyl cellulose ("HPC"), methyl cellulose, hydroxyethyl methyl cellulose, hydroxyethyl cellulose, hydroxyethyl cellulose acetate, and hydroxyethyl ethyl cellulose, hydroxypropyl methyl cellulose acetate succinate ("HPMCAS"), hydroxypropyl methyl cellulose phthalate ("HPMCP"), carboxymethylethyl cellulose ("CMEC"), cellulose acetate phthalate ("CAP"), cellulose acetate succinate ("CAS"), hydroxypropyl methyl cellulose acetate phthalate ("HPMCAP"), cellulose acetate trimellitate ("CAT"), hydroxypropyl methyl cellulose acetate trimellitate ("HPMCAT"), and carboxymethylcellulose acetate butyrate ("CMCAB"), and the like.

As used herein, the terms "stable" and "stability" refer to mean that the evolution of the drug substance (e.g., Compound 1) with time and/or under specific environmental conditions (e.g., temperature, humidity, etc.) has no significant effects on its quality, safety and/or efficacy for a given time period. It can be measured through the formation of degradation products (impurities), variation of pH, appearance, microbial growth, and/or color as exemplified in the experimental section. Typically, compositions according to the invention are considered as stable if at least 95% of the initial concentration of each of the drug substance is found after 4 weeks at 25° C, and/or if no substantial change in the

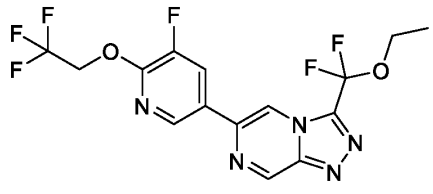
appearance of the solution is observed during such a period of time and under such temperature conditions. Stability may be assessed under a range of relative humidity (RH) conditions, typically between 60 and 75% RH.

As used herein, the term "particle size" is defined as the diameter of a particle as determined by Sympatec particle size analyzer.

Compounds

Described herein are pharmaceutical compositions or dosage forms comprising compounds that are useful for preventing and/or treating a disease, disorder, or condition, e.g., a disease, disorder, or condition relating to aberrant function of a sodium ion channel, e.g., abnormal late sodium current (INaL).

In one aspect, the present disclosure is directed to a dosage form comprising Compound 1 represented by:



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and a pharmaceutically acceptable excipient. In some embodiments, Compound 1 is crystalline. In some embodiments, the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 12.6±0.2, 15.8±0.2, and 18.6±0.2. In some embodiments, the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 10.7±0.2, 12.3±0.2, 12.6±0.2, 15.8±0.2, 18.6±0.2, and 22.6±0.2. In some embodiments, the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 10.7±0.2, 12.3±0.2, 12.6±0.2, 14.9±0.2, 15.8±0.2, 16.6±0.2, 16.8±0.2, 18.6±0.2, 21.0±0.2 and 22.6±0.2. In some embodiments, the crystalline form exhibits an X-ray powder diffraction pattern substantially the same as depicted in **FIG. 1**.

In some embodiments, Compound 1 is amorphous.

Dosage Forms and Compositions

In one aspect, the present disclosure features dosage forms or compositions useful for preventing and/or treating a disease, disorder, or condition described herein, e.g., a disease, disorder, or condition relating to aberrant function of a sodium ion channel, such as abnormal late sodium current (INaL).

This invention provides pharmaceutical compositions that contain, as the active ingredient, a compound described herein (e.g., Compound 1), or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients, carriers, including inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants. The pharmaceutical compositions may be administered alone or in combination with other therapeutic agents. Such compositions are prepared in a manner well known in the pharmaceutical art (see, e.g., Remington's Pharmaceutical Sciences, Mace Publishing Co., Philadelphia, Pa. 17th Ed. (1985); and Modern Pharmaceutics, Marcel Dekker, Inc. 3rd Ed. (G. S. Banker & C. T. Rhodes, Eds.)

The pharmaceutical compositions may be administered in either single or multiple doses by any of the accepted modes of administration of agents having similar utilities, for example as described in those patents and patent applications incorporated by reference, including rectal, buccal, intranasal and transdermal routes, by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, as an inhalant, or via an impregnated or coated device such as a stent, for example, or an artery-inserted cylindrical polymer.

One mode for administration is parenteral, particularly by injection. The forms in which the novel compositions of the present invention may be incorporated for administration by injection include aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles. Aqueous solutions in saline are also conventionally used for injection, but less preferred in the context of the present invention. Ethanol, glycerol, propylene glycol, liquid polyethylene glycol, and the like (and suitable mixtures thereof), cyclodextrin derivatives, and vegetable oils may also be employed. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like.

Sterile injectable solutions are prepared by incorporating a compound according to the present invention in the required amount in the appropriate solvent with various other ingredients as enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a

sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Oral administration is another route for administration of compounds in accordance with the invention. Administration may be via capsule or tablets, or the like. In making the pharmaceutical compositions that include at least one compound described herein, the active ingredient is usually diluted by an excipient and/or enclosed within such a carrier that can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be in the form of a solid, semi-solid, or liquid material (as above), which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, sterile injectable solutions, and sterile packaged powders.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl and propylhydroxy-benzoates; sweetening agents; and flavoring agents.

The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art. Controlled release drug delivery systems for oral administration include osmotic pump systems and dissolutional systems containing polymer-coated reservoirs or drug-polymer matrix formulations. Examples of controlled release systems are given in U.S. Pat. Nos. 3,845,770; 4,326,525; 4,902,514; and 5,616,345. Another formulation for use in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the

art. See, e.g., U.S. Pat. Nos. 5,023,252, 4,992,445 and 5,001,139. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

The compositions are preferably formulated in a unit dosage form. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient (e.g., a tablet, capsule, ampoule). The compounds are generally administered in a pharmaceutically effective amount. Preferably, for oral administration, each dosage unit contains from 1 mg to 2 g of a compound described herein, and for parenteral administration, preferably from 0.1 to 700 mg of a compound a compound described herein. It will be understood, however, that the amount of the compound actually administered usually will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered and its relative activity, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

The tablets or pills of the present invention may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action, or to protect from the acid conditions of the stomach. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer that serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. Preferably, the compositions are administered by the oral or nasal

respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a facemask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

In one aspect, provided herein is a dosage form or a composition in a dosage form comprising: from about 0.1 mg to about 500 mg (e.g., from about 0.5 mg to about 200 mg, from about 1 mg to about 150 mg, from about 10 mg to about 120 mg) of Compound 1; and a pharmaceutically acceptable excipient.

In some embodiments, the dosage form or a composition in a dosage form comprises from about 2.5 mg to about 150 mg (e.g., from about 10 mg to about 150 mg, from about 20 mg to about 150 mg, from about 40 mg to about 150 mg, from about 60 mg to about 150 mg, from about 80 mg to about 150 mg, from about 100 mg to about 150 mg, from about 10 mg to about 120 mg, from about 20 mg to about 120 mg, from about 40 mg to about 120 mg, from about 60 mg to about 120 mg, from about 80 mg to about 120 mg, from about 100 mg to about 120 mg, from about 10 mg to about 100 mg, from about 20 mg to about 100 mg, from about 40 mg to about 100 mg, from about 60 mg to about 100 mg, from about 80 mg to about 100 mg, from about 10 mg to about 80 mg, from about 20 mg to about 80 mg, from about 40 mg to about 80 mg, from about 60 mg to about 80 mg, from about 10 mg to about 60 mg, from about 20 mg to about 60 mg, from about 40 mg to about 60 mg, from about 70 mg to about 120 mg, from about 70 mg to about 100 mg, from about 50 mg to about 120 mg, from about 50 mg to 90 mg, from about 30 mg to about 120 mg, from about 30 mg to about 60 mg, from about 30 mg to about 80 mg, from about 30 mg to about 100 mg) of Compound 1.

In some embodiments, the dosage form or a composition in a dosage form comprises from about 1 mg to about 100 mg (e.g., 1 from about 1 mg to about 80 mg, from about 1 mg to about 50 mg, from about 1 mg to about 20 mg, from about 1 mg to about 10 mg, from about 1 mg to about mg, from about 5 mg to about 100 mg, from about 5 mg to about 80 mg, from about 5 mg to about 50 mg, from about 5 mg to about 20 mg) of Compound 1.

In some embodiments, the dosage form or a composition in a dosage form comprises about 200 mg, 190 mg, 180 mg, 170 mg, 160 mg, 150 mg, 140 mg, 130 mg, 120 mg, 110 mg, 100 mg, about 99 mg, about 98 mg, about 97 mg, about 96 mg, about 95 mg, about 94 mg, about 93 mg, about 92 mg, about 91 mg, about 90 mg, about 85 mg, about 80 mg, about 75

mg, about 70 mg, about 69 mg, about 68 mg, about 67 mg, about 66 mg, about 65 mg, about 64 mg, about 63 mg, about 62 mg, about 61 mg, about 60 mg, about 59 mg, about 58 mg, about 57 mg, about 56 mg, about 55 mg, about 54 mg, about 53 mg, about 52 mg, about 51 mg, about 50 mg, about 45 mg, about 40 mg, about 35 mg, about 30 mg, about 25 mg, about 20 mg, about 15 mg, about 10 mg, about 7 mg, about 5 mg, about 2.5 mg, about 2 mg, about 1.5 mg, or about 1 mg of Compound 1.

In another aspect, the present disclosure provides a dosage form or a composition in a dosage form comprising: a plurality of particles of Compound 1; and a pharmaceutically acceptable excipient, wherein the amount of the plurality of particles of Compound 1 in the dosage form is from about 0.1 mg to about 500 mg (e.g., from about 0.5 mg to about 200 mg, from about 1 mg to about 150 mg, from about 10 mg to about 120 mg).

In some embodiments, the plurality of particles of Compound 1 in the dosage form or composition is from about 2.5 mg to about 150 mg (e.g., from about 10 mg to about 150 mg, from about 20 mg to about 150 mg, from about 70 mg to about 120 mg, from about 30 mg to about 60 mg, about 100 mg, about 50 mg).

In certain embodiments, 10% of the plurality of particles of Compound 1 have a particle size of less than about 1 μm. In other embodiments, 50% of the plurality of particles of Compound 1 have a particle size of less than about 4 μm. In some embodiments, 50% of the plurality of particles of Compound 1 have a particle size of less than about 2 μm. In certain embodiments, 90% of the plurality of particles of Compound 1 have a particle size of less than about 30 μm (e.g., less than about 15 μM). In other embodiments, 90% of the plurality of particles of Compound 1 have a particle size of less than about 5 μm. In some embodiments, 90% of the plurality of particles of Compound 1 have a particle size of from about 4 μm to 15 μM.

In some embodiments, 10% of the plurality of particles of Compound 1 have a particle size of less than about 1 μm, 50% of the plurality of particles of Compound 1 have a particle size of less than about 4 μm and 90% of the plurality of particles of Compound 1 have a particle size of less than about 30 μm.

In some embodiments, the dosage form or the composition is configured for oral administration.

In some embodiments, the dosage form is a solid form.

In some embodiments, the dosage form is in the form of a capsule.

In some embodiments, the pharmaceutical excipient in the capsule is a filler (e.g., cellulose derivatives (e.g., microcrystalline cellulose), starches (e.g., hydrolyzed starches, and

partially pregelatinized starches), anhydrous lactose, lactose monohydrate, sugar alcohols (e.g., sorbitol, xylitol, and mannitol).

In some embodiments, the ratio of Compound 1 to the filler is about 1:10. In some embodiments, the ratio of Compound 1 to the filler is about 1:10. In some embodiments, the ratio of Compound 1 to the filler is about 1:5. In some embodiments, the ratio of Compound 1 to the filler is about 1:4. In some embodiments, the ratio of Compound 1 to the filler is about 1:3. In some embodiments, the ratio of Compound 1 to the filler is about 1:2.

In some embodiments, the capsule further comprises a lubricant (e.g., magnesium stearate, calcium stearate, stearic acid, talc, silica, and fats).

In some embodiments, the dosage form is in the form of a blend.

In some embodiments, the pharmaceutical excipient in the blend is a filler (e.g., microcrystalline cellulose or starch). In some embodiments, the ratio of Compound 1 to the filler is about 1:1. In some embodiments, the ratio of Compound 1 to the filler is about 1:10. In some embodiments, the ratio of Compound 1 to the filler is about 1:5. In some embodiments, the ratio of Compound 1 to the filler is about 1:4. In some embodiments, the ratio of Compound 1 to the filler is about 1:3. In some embodiments, the ratio of Compound 1 to the filler is about 1:2.

In some embodiments, the dosage form is a liquid form.

In some embodiments, the dosage form is in the form of a solution.

In some embodiments, the pharmaceutical excipient in the solution is selected from the group consisting of a filler (e.g., polymer (e.g., PEG 400)), an emulsifier (e.g., a castor oil derivative (e.g., Kolliphor RH40), a surfactant (e.g., a glyceride (e.g., Labrafil M2125 CS), a vitamin derivative (e.g., Vitamin ETPGS)), a solvent (e.g., propylene glycol, ethanol, diethylene glycol monoethyl ether (or Transcutol HP)).

In some embodiments, the concentration of Compound 1 in the solution is from about 0.1 mg/mL to about 10 mg/mL (e.g., from about 0.5 mg/mL to about 10 mg/mL, from about 1 mg/mL to about 10 mg/mL, from about 2 mg/mL to about 10 mg/mL, from about 3 mg/mL to about 10 mg/mL, from about 4 mg/mL to about 10 mg/mL, from about 5 mg/mL to about 10 mg/mL, from about 6 mg/mL to about 10 mg/mL, from about 0.1 mg/mL to about 8 mg/mL, from about 0.5 mg/mL to about 8 mg/mL, from about 1 mg/mL to about 8 mg/mL, from about 2 mg/mL to about 8 mg/mL, from about 3 mg/mL to about 8 mg/mL, from about 4 mg/mL to about 8 mg/mL, from about 5 mg/mL to about 8 mg/mL, from about 6 mg/mL to about 8 mg/mL, from about 0.5 mg/mL to about 6 mg/mL, from about 1 mg/mL to about 6 mg/mL, from about 2 mg/mL to about 6 mg/mL, from about 3 mg/mL to about 6 mg/mL,

from about 4 mg/mL to about 6 mg/mL, from about 0.5 mg/mL to about 4 mg/mL, from about 1 mg/mL to about 4 mg/mL, or from about 2 mg/mL to about 4 mg/mL).

In some embodiments, the concentration of Compound 1 in the solution is about 0.1 mg/mL, about 0.5 mg/mL, about 1 mg/mL, about 2 mg/mL, about 3 mg/mL, about 4 mg/mL, about 5 mg/mL, about 6 mg/mL, about 7 mg/mL, about 8 mg/mL, about 9 mg/mL, or about 10 mg/mL.

In some embodiments, the dosage form or the composition comprises:

from about 20% to about 60% (e.g., from about 25% to about 55%, from about 30% to about 50%, from about 35% to about 45%, from about 37% to about 42%, or about 40%) by weight a filler (e.g., a polymer (e.g., PEG 200, PEG 300, PEG 400, PEG 600, PEG 1000, PEG 2000, PEG 3000, PEG 4000, PEG 6000, or PEG 8000));

from about 3% to about 25% (e.g., from about 3% to about 20%, from about 5% to about 13%, from about 8% to about 13%, from about 5% to about 15%, or about 10%) by weight an emulsifier (e.g., a castor oil derivative (e.g., Kolliphor RH40, macrogol 25 cetostearyl ether (e.g., Cremophor® A25), macrogol 6 cetostearyl ether (e.g., Cremophor® A6), macrogol glycerol ricinoleate 35 (e.g., Cremophor® EL), macrogol-glycerol hydroxystearate 40 (e.g.,Cremophor® RH 40)); and

from about 30% to about 70% (e.g., from about 35% to about 65%, from about 40% to about 60%, from about 45% to about 55%, or about 50%) by weight water;

wherein the concentration of Compound 1 is about 0.5 mg/mL or about 0.25 mg/mL.

In certain embodiments, the dosage form or the composition comprises: from about 35% to about 45% by weight a filler (e.g., a polymer (e.g., PEG 400)); from about 5% to about 15% by weight an emulsifier (e.g., a castor oil derivative (e.g., Kolliphor RH40); and from about 40% to about 60% by weight water; wherein the concentration of Compound 1 is about 0.5 mg/mL or about 0.25 mg/mL.

In some embodiments, the dosage form or the composition comprises:

from about 40% to about 75% (e.g., from about 45% to about 70%, from about 50% to about 65%, from about 55% to about 60%, or about 58%) by weight an emulsifier (e.g., a castor oil derivative (e.g., Kolliphor RH40), macrogol 25 cetostearyl ether (e.g., Cremophor® A25), macrogol 6 cetostearyl ether (e.g., Cremophor® A6), macrogol glycerol ricinoleate 35 (e.g., Cremophor® EL), macrogol-glycerol hydroxystearate 40 (e.g.,Cremophor® RH 40));

from about 10% to about 35% (e.g., from about 10% to about 30%, from about 10% to about 25%, from about 15% to about 25%, or from about 15% to about 20%) by weight a surfactant (e.g., a glyceride (e.g., Labrafil M2125 CS), caprylocaproyl macrogolglycerides

(e.g., Labrasol), natural triglyceride-based oil (e.g., olive oil, sesame oil, coconut oil, palm kernel oil));

from about 3% to about 20% (e.g., from about 3% to about 15%, from about 5% to about 15%, or from about 5% to about 10%) by weight propylene glycol; and

10% to about 35% (e.g., from about 10% to about 30%, from about 10% to about 25%, from about 15% to about 25%, or from about 15% to about 20%) by weight ethanol;

wherein the concentration of Compound 1 is from about 5 mg/mL to about 10 mg/mL (e.g., about 5 mg/mL, about 7.5 mg/mL, or about 10 mg/mL) or from about 2.5 mg to about 5 mg/mL.

In certain embodiments, the dosage form or the composition comprises: from about 55% to about 60% by weight an emulsifier (e.g., a castor oil derivative (e.g., Kolliphor RH40); from about 15% to about 20% by weight a surfactant (e.g., a glyceride (e.g., Labrafil M2125 CS); from about 5% to about 10% by weight propylene glycol; and from about 15% to about 20% by weight ethanol; wherein the concentration of Compound 1 is from about 5 mg/mL to about 10 mg/mL or from about 2.5 mg to about 5 mg/mL.

In some embodiments, the dosage form comprises:

from about 50% to about 85% (e.g., from about 55% to about 80%, from about 60% to about 75%, or from about 65% to about 70%) by weight an emulsifier (e.g., a castor oil derivative (e.g., Kolliphor RH40) macrogol 25 cetostearyl ether (e.g., Cremophor® A25), macrogol 6 cetostearyl ether (e.g., Cremophor® A6), macrogol glycerol ricinoleate 35 (e.g., Cremophor® EL), macrogol-glycerol hydroxystearate 40 (e.g.,Cremophor® RH 40));

from about 10% to about 30% (e.g., from about 10% to about 25%, from about 15% to about 25%, or from about 18% to about 23%) by weight a surfactant (e.g., a glyceride (e.g., Labrafil M2125 CS), caprylocaproyl macrogolglycerides (e.g., Labrasol), natural triglyceride-based oil (e.g., olive oil, sesame oil, coconut oil, palm kernel oil)); and

from about 3% to about 20% (e.g., from about 3% to about 15%, from about 5% to about 15%, from about 5% to about 12%, or from about 7% to about 12%) by weight propylene glycol;

wherein the concentration of Compound 1 is from about 1 mg/mL to about 10 mg/mL (e.g., from about 2 mg/mL to about 8 mg/mL, about 2 mg/mL, about 5 mg/mL, about 7 mg/mL, or about 10 mg/mL) or from 0.5 mg/mL to about 5 mg/mL.

In certain embodiments, the dosage form or the composition comprises: from about 65% to about 70% by weight an emulsifier (e.g., a castor oil derivative (e.g., Kolliphor RH40); from about 18% to about 23% by weight a surfactant (e.g., a glyceride (e.g., Labrafil

M2125 CS); and from about 7% to about 12% by weight propylene glycol; wherein the concentration of Compound 1 is from about 1 mg/mL to about 10 mg/mL or from 0.5 mg/mL to about 5 mg/mL.

In some embodiments, the dosage form or the composition comprises:

from about 20% to about 60% (e.g., from about 25% to about 55%, from about 30% to about 50%, 35% to about 45%, about 35%, about 40%, or about 45%) by weight diethylene glycol monoethyl ether (e.g., Transcutol HP);

from about 1% to about 20% (e.g., from about 3% to about 18%, from about 5% to about 18%, from about 5% to about 15%, from about 8% to about 12%, or about 10%) by weight a surfactant (e.g., a vitamin derivative (e.g., Vitamin ETPGS)); and

from about 20% to about 80% (e.g., from about 25% to about 75%, from about 30% to about 70%, from about 35% to about 55%, from about 40% to about 60%, or from about 45% to about 55%) by weight water;

wherein the concentration of Compound 1 is from about 1 mg/mL to about 5 mg/mL (e.g., about 1 mg/mL, about 2 mg/mL, about 3 mg/mL, about 4 mg, or about 5 mg/mL) or from 0.5 mg/mL to about 2.5 mg/mL.

In certain embodiments, the dosage form or the composition comprises: from about 35% to about 45% by weight diethylene glycol monoethyl ether (Transcutol HP); from about 5% to about 15% by weight a surfactant (e.g., a glyceride (e.g., a vitamin derivative (e.g., Vitamin ETPGS)); and from about 40% to about 60% by weight water; wherein the concentration of Compound 1 is from about 1 mg/mL to about 5 mg/mL or from 0.5 mg/mL to about 2.5 mg/mL.

In some embodiments, the dosage form or the composition comprises: from about 30% to about 40% by weight an emulsifier (e.g., a castor oil derivative (e.g., Kolliphor RH40); from about 40% to about 50% by weight a surfactant (e.g., a glyceride (e.g., Capmul MCM C8); from about 5% to 15% by weight a plasticizer (e.g., triethyl citrate); and from about 5% to about 15% by weight a solvent (e.g., ethanol).

In other embodiments, the dosage form or the composition comprises: from about 35% to about 45% by weight a propylene glycol monocaprylate (e.g., Capryol 90); from about 15% to about 25% by weight a glyceride (e.g., caprylocaproyl macrogolglycerides (e.g., Labrasol)) and from about 35% to 45% by weight diethylene glycol monoethyl ether (e.g., Transcutol HP).

In some embodiments, the dosage form is in the form of a suspension.

In some embodiments, the concentration of Compound 1 in the suspension is about 0.1 mg/mL, about 0.5 mg/mL, about 1 mg/mL, about 1.5 mg/mL, about 2 mg/mL, about 2.5 mg/mL, about 3 mg/mL, about 3.5 mg/mL, about 4 mg/mL, about 4.5 mg/mL, about 5 mg/mL, about 6 mg/mL, about 7 mg/mL, about 8 mg/mL, about 9 mg/mL, about 10 mg/mL, about 11 mg/mL, about 12 mg/mL, about 13 mg/mL, about 14 mg/mL, about 15 mg/mL, about 20 mg/mL, about 25mg/mL.

In some embodiments, the disclosed suspension can be further diluted with a solvent (e.g., water), wherein the concentration of the diluted solution is from about 50% to about 90% of the solution before the dilution.

In some embodiments, the concentration of Compound 1 in the suspension is from about 0.1 mg/mL to about 10 mg/mL (e.g., from about 0.5 mg/mL to about 10 mg/mL, from about 1 mg/mL to about 10 mg/mL, from about 2 mg/mL to about 10 mg/mL, from about 3 mg/mL to about 10 mg/mL, from about 4 mg/mL to about 10 mg/mL, from about 5 mg/mL to about 10 mg/mL, from about 6 mg/mL to about 10 mg/mL, from about 0.1 mg/mL to about 8 mg/mL, from about 0.5 mg/mL to about 8 mg/mL, from about 1 mg/mL to about 8 mg/mL, from about 2 mg/mL to about 8 mg/mL, from about 3 mg/mL to about 8 mg/mL, from about 4 mg/mL to about 8 mg/mL, from about 5 mg/mL to about 8 mg/mL, from about 6 mg/mL to about 8 mg/mL, from about 0.5 mg/mL to about 6 mg/mL, from about 1 mg/mL to about 6 mg/mL, from about 2 mg/mL to about 6 mg/mL, from about 3 mg/mL to about 6 mg/mL, from about 4 mg/mL to about 6 mg/mL, from about 0.5 mg/mL to about 4 mg/mL, from about 1 mg/mL to about 4 mg/mL, or from about 2 mg/mL to about 4 mg/mL).

In some embodiments, the pharmaceutical excipient in the suspension comprises:

from about 0.1% to about 5% (e.g., from about 0.1% to about 3%, from about 0.1% to about 2%, from about 0.1% to about 1%, from about 0.5% to about 3%, from about 0.5% to about 2%, from about 0.5% to about 1%, about 0.1%, about 0.3%, about 0.5%, about 1%, about 2%, or about 3%) by weight a filler (e.g., ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, caboxymethylcellulose, sodium hydroxypropylmethylcellulose, methylcellulose (e.g., 400 cP MC), methylethylcellulose, sodium carboxymethylcellulose, Aerosil (silicon dioxide), cetostearyl alcohol, cetyl alcohol, stearyl alcohol, Gelucires 33/01, 39/01 and 43/01, glyceryl behenate (Compritol 888 A TO), glyceryl palmitostearate (Precirol AT05), Softisans 100, 142, 378 and 649, stearyl alcohol carbomer, xanthan gum, maltodextrin, acacia, tragacanth, povidone, or polyvinyl alcohol); and

from about 0.1% to about 3% (e.g., from about 0.1% to about 2%, from about 0.1% to about 1%, from about 0.1% to about 0.5%, from about 0.2% to about 2%, from about 0.2% to

about 1%, from about 0.2% to about 0.5%, from about 0.1% to about 0.3%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, or about 1%) by weight an emulsifier (e.g., polyoxyethylene sorbate (e.g., Tween®), sorbitan long chain carboxylic acid esters (e.g., Span®), ethylene or propylene oxide block copolymers (Pluronic®), polyglycolyzed glycerides Labrasol®, Labrafil® and Labrafac®), sorbitan esters of oleate, stearate, laurate or other long chain carboxylic acids, polyethylene-polypropylene glycol block copolymers (e.g., Poloxamer 188), other sorbitan or sucrose long chain carboxylic acid esters, mono and diglycerides, PEG derivatives of caprylic/capric triglycerides).

In certain embodiments, the pharmaceutical excipient comprises: about 0.5% by weight a filler (e.g., methylcellulose, e.g., 400 cP MC); and about 0.2% by weight an emulsifier (e.g., Tween, e.g, Tween 80, e.g., Poloxamer 188).

In some embodiments, the pharmaceutical excipient further comprises about 1% by weight a preservative solution (e.g., paraben solution).

In some embodiments, the dosage form is in the form of amorphous solid dispersion.

In some embodiments, the pharmaceutical excipient in the amorphous solid dispersion is a polymer (e.g., Soluplus, Eudragit, HPMCASMF, PVP-VA, methylacrylic acid methyl methacrylate copolymer, HPMCP, CAP, HPMCAS, HPMCP H-55).

In some embodiments, the dosage form or the composition is stable (e.g., chemically stable) at 25°C and 60% RH for 7 days, 14 days, 21 days, 28 days, 1 month, 3 months, 5 months, 6 months, 12 months, 24 months, or 36 months.

In some embodiments, the dosage form or the composition is stable (e.g., chemically stable) at 25°C and 60% RH for at least 7 days (e.g., at least 14 days, at 21 days, at least 28 days, at least 1 month, at least 2 months, at least 3 months, at least 5 months, at least 6 months, at least 12 months, at least 24 months, or at least 36 months).

Methods of Making Dosage Forms

In another aspect, the present disclosure provides methods of making dosage forms as disclosed herein. Such methods are, for example, described in the Example section. In some embodiments, the contemplated dosage forms may be in the form of capsule, blend, solution, suspension, or ASD.

Methods of Use

Formulations described herein are generally useful for the modulating the activity of sodium channels and are useful in treating conditions relating to aberrant function of a sodium channel ion channel, e.g., abnormal late sodium (INaL) current. In some embodiments, a formulation comprising Compound 1 as provided by the present disclosure is

effective in the treatment of epilepsy or an epilepsy syndrome, a neurodevelopmental disorder, pain, or a neuromuscular disorder. A provided formulation comprising Compound 1, or a pharmaceutically acceptable salt thereof, may also modulate all sodium ion channels, or may be specific to only one or a plurality of sodium ion channels, e.g., Na_V 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, and/or 1.9.

In one aspect, the present invention provides a method of treating a condition relating to aberrant function of a sodium ion channel in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of Compound 1, e.g., from about 2.5 mg to about 90 mg of Compound 1.

Epilepsy and Epilepsy Syndromes

The formulations described herein (e.g., a dosage form, a composition in a dosage form comprising Compound 1) are useful in the treatment of epilepsy and epilepsy syndromes. Epilepsy is a CNS disorder in which nerve cell activity in the brain becomes disrupted, causing seizures or periods of unusual behavior, sensations and sometimes loss of consciousness. Seizure symptoms will vary widely, from a simple blank stare for a few seconds to repeated twitching of their arms or legs during a seizure.

Epilepsy may involve a generalized seizure or a partial or focal seizure. All areas of the brain are involved in a generalized seizure. A person experiencing a generalized seizure may cry out or make some sound, stiffen for several seconds to a minute a then have rhythmic movements of the arms and legs. The eyes are generally open, the person may appear not to be breathing and may actually turn blue. The return to consciousness is gradual and the person maybe confused from minutes to hours. There are six main types of generalized seizures: tonic-clonic, tonic, clonic, myoclonic, absence, and atonic seizures. In a partial or focal seizure, only part of the brain is involved, so only part of the body is affected. Depending on the part of the brain having abnormal electrical activity, symptoms may vary.

Epilepsy, as described herein, includes a generalized, partial, complex partial, tonic clonic, clonic, tonic, refractory seizures, status epilepticus, absence seizures, febrile seizures, or temporal lobe epilepsy.

The formulations described herein (e.g., a dosage form, a composition in a dosage form comprising Compound 1) may also be useful in the treatment of epilepsy syndromes. Severe syndromes with diffuse brain dysfunction caused, at least partly, by some aspect of epilepsy, are also referred to as epileptic encephalopathies. These are associated with frequent seizures that are resistant to treatment and severe cognitive dysfunction, for instance West syndrome.

In some embodiments, the epilepsy syndrome comprises an epileptic encephalopathy, such as developmental and epileptic encephalopathy (DEE), Dravet syndrome, Angelman syndrome, CDKL5 disorder, frontal lobe epilepsy, infantile spasms, West's syndrome, Juvenile Myoclonic Epilepsy, Landau-Kleffner syndrome, Lennox-Gastaut syndrome, Ohtahara syndrome, PCDH19 epilepsy, or Glut1 deficiency.

In some embodiments, the epilepsy or epilepsy syndrome is a genetic epilepsy or a genetic epilepsy syndrome. In some embodiments, epilepsy or an epilepsy syndrome comprises epileptic encephalopathy, developmental and epileptic encephalopathy, epileptic encephalopathy with SCN1A, SCN2A, SCN8A mutations, early infantile epileptic encephalopathy, Dravet syndrome, Dravet syndrome with SCN1A mutation, generalized epilepsy with febrile seizures, intractable childhood epilepsy with generalized tonic-clonic seizures, infantile spasms, benign familial neonatal-infantile seizures, SCN2A epileptic encephalopathy, focal epilepsy with SCN3A mutation, cryptogenic pediatric partial epilepsy with SCN3A mutation, SCN8A epileptic encephalopathy, sudden unexpected death in epilepsy, Rasmussen encephalitis, malignant migrating partial seizures of infancy, autosomal dominant nocturnal frontal lobe epilepsy, sudden expected death in epilepsy (SUDEP), KCNQ2 epileptic encephalopathy, or KCNT1 epileptic encephalopathy.

In some embodiments, the methods described herein further comprise identifying a subject having epilepsy or an epilepsy syndrome (e.g., epileptic encephalopathy, developmental and epileptic encephalopathy, epileptic encephalopathy with SCN1A, SCN2A, SCN8A mutations, early infantile epileptic encephalopathy, Dravet syndrome, Dravet syndrome with SCN1A mutation, generalized Epilepsy with febrile seizures, intractable childhood epilepsy with generalized tonic-clonic seizures, infantile spasms, benign familial neonatal-infantile seizures, SCN2A epileptic encephalopathy, focal epilepsy with SCN3A mutation, cryptogenic pediatric partial epilepsy with SCN3A mutation, SCN8A epileptic encephalopathy, sudden unexpected death in epilepsy, Rasmussen encephalitis, malignant migrating partial seizures of infancy, autosomal dominant nocturnal frontal lobe epilepsy, sudden unexpected death in epilepsy (SUDEP), KCNQ2 epileptic encephalopathy, or KCNT1 epileptic encephalopathy) prior to administration of a formulation described herein.

In one aspect, the present invention features a method of treating epilepsy or an epilepsy syndrome (e.g., epileptic encephalopathy, developmental and epileptic encephalopathy, epileptic encephalopathy with SCN1A, SCN2A, SCN8A mutations, early infantile epileptic encephalopathy, Dravet syndrome, Dravet syndrome with SCN1A

mutation, generalized Epilepsy with febrile seizures, intractable childhood epilepsy with generalized tonic-clonic seizures, infantile spasms, benign familial neonatal-infantile seizures, SCN2A epileptic encephalopathy, focal epilepsy with SCN3A mutation, cryptogenic pediatric partial epilepsy with SCN3A mutation, SCN8A epileptic encephalopathy, sudden unexpected death in epilepsy, Rasmussen encephalitis, malignant migrating partial seizures of infancy, autosomal dominant nocturnal frontal lobe epilepsy, sudden expected death in epilepsy (SUDEP), KCNQ2 epileptic encephalopathy, or KCNT1 epileptic encephalopathy) comprising administering to a subject in need thereof a formulation described herein.

A formulation of the present invention (e.g., a dosage form, a composition in a dosage form comprising Compound 1) may also be used to treat an epilepsy or an epilepsy syndrome (e.g., epileptic encephalopathy), wherein the subject has a mutation in one or more of ALDH7A1, ALG13, ARHGEF9, ARX, ASAH1, CDKL5, CHD2, CHRNA2, CHRNA4, CHRNB2, CLN8, CNTNAP2, CPA6, CSTB, DEPDC5, DNM1, EEF1A2, EPM2A, EPM2B, GABRA1, GABRB3, GABRG2, GNAO1, GOSR2, GRIN1, GRIN2A, GRIN2B, HCN1, IER3IP1, KCNA2, KCNB1, KCNC1, KCNMA1, KCNQ2, KCNQ3, KCNT1, KCTD7, LGI1, MEF2C, NHLRC1, PCDH19, PLCB1, PNKP, PNPO, PRICKLE1, PRICKLE2, PRRT2, RELN, SCARB2, SCN1A, SCN1B, SCN2A, SCN8A, SCN9A, SIAT9, SIK1, SLC13A5, SLC25A22, SLC2A1, SLC35A2, SLC6A1, SNIP1, SPTAN1, SRPX2, ST3GAL3, STRADA, STX1B, STXBP1, SYN1, SYNGAP1, SZT2, TBC1D24, and WWOX.

In some embodiments, the methods described herein further comprise identifying a subject having a mutation in one or more of ALDH7A1, ALG13, ARHGEF9, ARX, ASAH1, CDKL5, CHD2, CHRNA2, CHRNA4, CHRNB2, CLN8, CNTNAP2, CPA6, CSTB, DEPDC5, DNM1, EEF1A2, EPM2A, EPM2B, GABRA1, GABRB3, GABRG2, GNAO1, GOSR2, GRIN1, GRIN2A, GRIN2B, HCN1, IER3IP1, KCNA2, KCNB1, KCNC1, KCNMA1, KCNQ2, KCNQ3, KCNT1, KCTD7, LGI1, MEF2C, NHLRC1, PCDH19, PLCB1, PNKP, PNPO, PRICKLE1, PRICKLE2, PRRT2, RELN, SCARB2, SCN1A, SCN1B, SCN2A, SCN8A, SCN9A, SIAT9, SIK1, SLC13A5, SLC25A22, SLC2A1, SLC35A2, SLC6A1, SNIP1, SPTAN1, SRPX2, ST3GAL3, STRADA, STX1B, STXBP1, SYN1, SYNGAP1, SZT2, TBC1D24, and WWOX prior to administration of a formulation described herein.

A formulation of the present invention may also be used to treat an epilepsy or an epilepsy syndrome (e.g., epileptic encephalopathy), wherein the subject has a mutation in one or more of HNRNPU, CACNA1A, CASK, FOXG1, GNB1, GPHN, IQSEC2, MBD5,

MECP2, PIGA, PURA, SLC6A8, SLC9A6, TSC1, TSC2, UBE3A, WDR45, ZEB2, SLC1A2, GRIN2D, DYRK1A, PURA, WDR45, HNRNPU, SMC1A, FOXG1, ARID1B, ASXL3, KCNH1, GABRB2, NEXMIF, MECP2, SNAP25, COL4A3BP, GABRA1, GABRA2, GABRA3, GABRA4, GABRA5, GABRA6, GABRB1, GABRB2, GABRD, GABRE, GABRG1, GABRG3, GABRP, GABRQ, GABRR1, GABRR2, GABRR3, ABAT, ADCY1, ADCY2, ADCY3, ADCY4, ADCY5, ADCY6, ADCY7, ADCY8, ADCY9, ANK2, ANK3, DISC1, DLC1, DLC2, DNAI1, FGF13, GABARAP, GABARAPL1, GABARAPL2, GABBR1, GAD1, GAD2, GLS, GLS2, GLUL, GNAI1, GNAI2, GNAI3, GNB1, GNB2, GNB3, GNB4, GNB5, GNG10, GNG11, GNG12, GNG13, GNG2, GNG3, GNG4, GNG5, GNG7, GNG8, GNGT1, GNGT2, GPHN, HAP1, KCNB2, KCNC2, KCNC3, KCNJ6, KIF5A, KIF5B, KIF5C, MAGI, MKLN1, MYO5A, NLGN2, NRXN1, NSF, PFN1, PLCL1, PRKACA, PRKACB, PRKACG, PRKCA, PRKCB, PRKCG, RAFT1, RDX, SCN2B, SCN3A, SEMA4D, SLC12A2, SLC12A5, SLC32A1, SLC38A1, SLC38A2, SLC38A3, SLC38A5, SLC6A11, SLC6A13, SRC, TRAK1, TRAK2, CHRNA1, CHRNA10, CHRNA3, CHRNA5, CHRNA6, CHRNA7, CHRNA9, CHRNB1, CHRNB3, CHRNB4, CHRND, CHRNE, CHRNG, GRIA1, GRIA2, GRIA3, GRIA4, GRIK1, GRIK2, GRIK3, GRIK4, GRIK5, GRIN2C, GRIN2D, GRIN3A, GRIN3B, GRID1, GRID2, SCN10A, SCN11A, SCN2B, SCN3B, SCN4A, SCN4B, SCN5A, SCN7A, CACNA1A, CACNA1B, CACNA1C, CACNA1D, CACNA1E, CACNA1F, CACNA1G, CACNA1H, CACNA1I, CACNA1S, CACNA2D1, CACNA2D2, CACNA2D3, CACNA2D4, CACNB1, CACNB2, CACNB3, CACNB4, KCNA1, KCNA10, KCNA3, KCNA4, KCNA5, KCNA6,KCNA7, KCNAB1, KCNAB2, KCNAB3, KCNB2, KCNC2, KCNC3, KCNC4, KCND1, KCND2, KCND3, KCNE1, KCNE1L, KCNE2, KCNE3, KCNE4, KCNF1, KCNG1, KCNG2, KCNG3, KCNG4, KCNH1, KCNH2, KCNH3, KCNH4, KCNH5, KCNH6, KCNH7, KCNH8, KCNQ1, KCNQ5, KCNQ4, KCNRG, KCNS1, KCNS2, KCNS3, KCNV1, KCNV2, HCN2, HCN3, and HCN4.

In some embodiments, the methods described herein further comprise identifying a subject having a mutation in one or more of HNRNPU, CACNA1A, CASK, FOXG1, GNB1, GPHN, IQSEC2, MBD5, MECP2, PIGA, PURA, SLC6A8, SLC9A6, TSC1, TSC2, UBE3A, WDR45, ZEB2, SLC1A2, GRIN2D, DYRK1A, PURA, WDR45, HNRNPU, SMC1A, FOXG1, ARID1B, ASXL3, KCNH1, GABRB2, NEXMIF, MECP2, SNAP25, COL4A3BP, GABRA1, GABRA2, GABRA3, GABRA4, GABRA5, GABRA6, GABRB1, GABRB2, GABRD, GABRE, GABRG1, GABRG3, GABRP, GABRQ, GABRR1, GABRR2, GABRR3, ABAT, ADCY1, ADCY2, ADCY3, ADCY4, ADCY5, ADCY6, ADCY7,

ADCY8, ADCY9, ANK2, ANK3, DISC1, DLC1, DLC2, DNAI1, FGF13, GABARAP, GABARAPL1, GABARAPL2, GABBR1, GAD1, GAD2, GLS, GLS2, GLUL, GNAI1, GNAI2, GNAI3, GNB1, GNB2, GNB3, GNB4, GNB5, GNG10, GNG11, GNG12, GNG13, GNG2, GNG3, GNG4, GNG5, GNG7, GNG8, GNGT1, GNGT2, GPHN, HAP1, KCNB2, KCNC2, KCNC3, KCNJ6, KIF5A, KIF5B, KIF5C, MAGI, MKLN1, MYO5A, NLGN2, NRXN1, NSF, PFN1, PLCL1, PRKACA, PRKACB, PRKACG, PRKCA, PRKCB, PRKCG, RAFT1, RDX, SCN2B, SCN3A, SEMA4D, SLC12A2, SLC12A5, SLC32A1, SLC38A1, SLC38A2, SLC38A3, SLC38A5, SLC6A11, SLC6A13, SRC, TRAK1, TRAK2, CHRNA1, CHRNA10, CHRNA3, CHRNA5, CHRNA6, CHRNA7, CHRNA9, CHRNB1, CHRNB3, CHRNB4, CHRND, CHRNE, CHRNG, GRIA1, GRIA2, GRIA3, GRIA4, GRIK1, GRIK2, GRIK3, GRIK4, GRIK5, GRIN2C, GRIN2D, GRIN3A, GRIN3B, GRID1, GRID2, SCN10A, SCN11A, SCN2B, SCN3B, SCN4A, SCN4B, SCN5A, SCN7A, CACNA1A, CACNA1B, CACNA1C, CACNA1D, CACNA1E, CACNA1F, CACNA1G, CACNA1H, CACNA1I, CACNA1S, CACNA2D1, CACNA2D2, CACNA2D3, CACNA2D4, CACNB1, CACNB2, CACNB3, CACNB4, KCNA1, KCNA10, KCNA3, KCNA4, KCNA5, KCNA6,KCNA7, KCNAB1, KCNAB2, KCNAB3, KCNB2, KCNC2, KCNC3, KCNC4, KCND1, KCND2, KCND3, KCNE1, KCNE1L, KCNE2, KCNE3, KCNE4, KCNF1, KCNG1, KCNG2, KCNG3, KCNG4, KCNH1, KCNH2, KCNH3, KCNH4, KCNH5, KCNH6, KCNH7, KCNH8, KCNQ1, KCNQ5, KCNQ4, KCNRG, KCNS1, KCNS2, KCNS3, KCNV1, KCNV2, HCN2, HCN3, and HCN4 prior to administration of a formulation described herein.

Neurodevelopmental Disorders

The formulations described herein (e.g., a dosage form, a composition in a dosage form comprising Compound 1) may be useful in the treatment of a neurodevelopmental disorder. In some embodiments, the neurodevelopmental disorder comprises autism, autism with epilepsy, tuberous sclerosis, Fragile X syndrome, Rett syndrome, Angelman syndrome, Dup15q syndrome, 22q13.3 Deletion syndrome, Prader-Willi syndrome, velocardiofacial syndrome, Smith-Lemli-Opitz syndrome, or a neurodevelopmental disorder with epilepsy. In some embodiments, the methods described herein further comprise identifying a subject having a neurodevelopmental disorder (e.g., autism, autism with epilepsy, tuberous sclerosis, Fragile X syndrome, Rett syndrome, Angelman syndrome, Dup15q syndrome, 22q13.3 Deletion syndrome, Prader-Willi syndrome, velocardiofacial syndrome, Smith-Lemli-Opitz

syndrome, or a neurodevelopmental disorder with epilepsy) prior to administration of a formulation described herein.

In one aspect, the present invention features a method of treating a neurodevelopmental disorder (e.g., autism, autism with epilepsy, tuberous sclerosis, Fragile X syndrome, Rett syndrome, Angelman syndrome, Dup15q syndrome, 22q13.3 Deletion syndrome, Prader-Willi syndrome, velocardiofacial syndrome, Smith-Lemli-Opitz syndrome, or a neurodevelopmental disorder with epilepsy) comprising administering to a subject in need thereof a formulation described herein (e.g., a dosage form, a composition in a dosage form comprising Compound 1).

Pain

The formulations described herein (e.g., a dosage form, a composition in a dosage form comprising Compound 1) may be useful in the treatment of pain. In some embodiments, the pain comprises neuropathic pain, trigeminal neuralgia, migraine, hemiplegic migraine, familial hemiplegic migraine, familial hemiplegic migraine type 3, cluster headache, trigeminal neuralgia, or a related headache disorder. In some embodiments, the methods described herein further comprise identifying a subject having pain (e.g., neuropathic pain, trigeminal neuralgia, migraine, hemiplegic migraine, familial hemiplegic migraine, familial hemiplegic migraine type 3, cluster headache, trigeminal neuralgia, or a related headache disorder) prior to administration of a formulation described herein (e.g., a dosage form, a composition in a dosage form comprising Compound 1).

In one aspect, the present invention features a method of treating pain (e.g., neuropathic pain, trigeminal neuralgia, migraine, hemiplegic migraine, familial hemiplegic migraine, familial hemiplegic migraine type 3, cluster headache, trigeminal neuralgia, or a related headache disorder) comprising administering to a subject in need thereof a formulation described herein (e.g., a dosage form, a composition in a dosage form comprising Compound 1).

Neuromuscular Disorders

The formulations described herein (e.g., a dosage form, a composition in a dosage form comprising Compound 1) may be useful in the treatment of a neuromuscular disorder. In some embodiments, the neuromuscular disorder comprises amyotrophic lateral sclerosis, multiple sclerosism, myotonia, paramyotonia congenita, potassium-aggravated myotonia, periodic paralysis, hyperkalemic periodic paralysis, hypokalemic periodic paralysis, or

laryngospasm with SCN4A mutation. In some embodiments, the methods described herein further comprise identifying a subject having a neuromuscular disorder (e.g., amyotrophic lateral sclerosis, multiple sclerosism, myotonia, paramyotonia congenita, potassium-aggravated myotonia, periodic paralysis, hyperkalemic periodic paralysis, hypokalemic periodic paralysis, or laryngospasm with SCN4A mutation) prior to administration of a formulation described herein.

In one aspect, the present invention features a method of treating a neuromuscular disorder (e.g., amyotrophic lateral sclerosis, multiple sclerosism, myotonia, paramyotonia congenita, potassium-aggravated myotonia, periodic paralysis, hyperkalemic periodic paralysis, hypokalemic periodic paralysis, or laryngospasm with SCN4A mutation) comprising administering to a subject in need thereof a formulation described herein (e.g., a dosage form, a composition in a dosage form comprising Compound 1).

Other Disorders

In some embodiments, a formulation of the present invention (e.g., a dosage form, a composition in a dosage form comprising Compound 1) may have appropriate pharmacokinetic properties such that they may be active with regard to the central and/or peripheral nervous system. In some embodiments, the formulations provided herein (e.g., a dosage form, a composition in a dosage form comprising Compound 1) are used to treat a cardiovascular disease such as atrial and ventricular arrhythmias, including atrial fibrillation, Prinzmetal's (variant) angina, stable angina, unstable angina, ischemia and reperfusion injury in cardiac, kidney, liver and the brain, exercise induced angina, pulmonary hypertension, congestive heart disease including diastolic and systolic heart failure, recurrent ischemia, cerebral ischemia, stroke, renal ischemia, ischemia associated with organ transplant, acute coronary syndrome, peripheral arterial disease, intermittent claudication, and myocardial infarction.

In some embodiments, the formulations provided herein (e.g., a dosage form, a composition in a dosage form comprising Compound 1) may be used in the treatment of diseases affecting the neuromuscular system resulting in itching, seizures, or paralysis, or in the treatment of diabetes or reduced insulin sensitivity, and disease states related to diabetes, such as diabetic peripheral neuropathy. In some embodiments, a disclosed method comprises administering the pharmaceutical composition.

In some embodiments, provided herein is a method of treating a neurological disorder or a psychiatric disorder, wherein the method comprises administering to a subject in need

thereof a formulation disclosed herein (e.g., a dosage form, a composition in a dosage form comprising Compound 1).

Oncology

In another aspect, the present disclosure provides a method of treating a cancer, wherein the method comprises administering to a subject in need thereof a dosage form or a composition in a dosage form disclosed in the present disclosure.

Trigeminal Autonomic Cephalalgia

The compounds, dosage forms, and compositions described herein (e.g., Compound 1, a dosage form or a composition comprising Compound 1) are useful in the treatment of trigeminal autonomic cephalalgias (TACs). TACs are a group of primary headaches characterized by unilaterality of pain, a relatively short duration of symptoms, and associated ipsilateral cranial autonomic signs. TACs may include cluster headache (CH), paroxysmal hemicrania (PH), hemicrania continua (HC), short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA), and long-lasting autonomic symptoms with hemicrania (LASH). Despite their common elements, the trigeminal autonomic cephalalgias differ, *e.g.*, in attack duration and frequency and in the response to therapy.

In some embodiments, the present invention provides a method of treating PH, HC, SUNCT, SUNA, and/or LASH using a dosage form described herein. In some embodiments, the present invention provides a method of treating SUNCT using a compound, dosage form, or a composition described herein (e.g., Compound 1, a dosage form or a composition comprising Compound 1). In some embodiments, the present invention provides a method of treating SUNA using a provided compound, a dosage form, or a composition described herein (e.g., Compound 1, a dosage form or a composition comprising Compound 1). In another aspect, provided herein is a method of treating or preventing a trigeminal autonomic cephalalgia (TAC) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound, a dosage form, or a composition disclosed herein (e.g., Compound 1, a dosage form or a composition comprising Compound 1).

In another aspect, the present invention provides a method of treating or preventing a trigeminal autonomic cephalalgia (TAC) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of Compound 1, e.g., from 2.5 mg to 90 mg of Compound 1.

In some embodiments, TAC is selected from the group consisting of paroxysmal hemicrania, hemicrania continua, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA), and long-lasting autonomic symptoms with hemicrania.

In other embodiments, the TAC is a short-lasting unilateral neuralgiform headache attack.

In certain embodiments, the TAC is SUNCT. In some embodiments, the TAC is SUNA.

In other embodiments, the subject has an inadequate response to at least one medication used for the treatment of a TAC.

Migraines

The compounds, dosage forms, and compositions described herein (e.g., Compound 1, a dosage form or a composition comprising Compound 1) are useful in the treatment of migraines. Migraine is a primary headache disorder characterized by recurrent headaches that are moderate to severe. As described herein, a migraine may be migraine without aura, migraine with aura, hemiplegic migraine, familial hemiplegic migraine (FHM), familial hemiplegic migraine type 1 (FHM1), familial hemiplegic migraine type 2 (FHM2), familial hemiplegic migraine type 3 (FHM3), familial hemiplegic migraine type 4 (FHM4), and sporadic hemiplegic migraine (SHM).

In some embodiments, the present invention provides a method of treating migraine without aura, migraine with aura, hemiplegic migraine, FHM, FHM1, FHM2, FHM3, FHM4, and/or SHM using a provided compound. In some embodiments, the present invention provides a method of treating migraine without aura, migraine with aura, FHM1, FHM2, FHM4, and/or SHM using a provided compound, dosage form, or composition (e.g., Compound 1, a dosage form or a composition comprising Compound 1). In some embodiments, the present invention provides a method of treating migraine without aura using a provided compound. In some embodiments, the present invention provides a method of treating migraine with aura using a provided compound, dosage form, or composition (e.g., Compound 1, a dosage form or a composition comprising Compound 1). In some embodiments, the present invention provides a method of treating FHM1, FHM2, and/or FHM4 using a provided compound. In some embodiments, the present invention provides a

method of treating SHM using a provided compound, dosage form, or composition (e.g., Compound 1, a dosage form or a composition comprising Compound 1).

In another aspect, provided herein is a method of treating or preventing a migraine in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound, a dosage form, a composition disclosed herein (e.g., Compound 1, a dosage form or a composition comprising Compound 1).

In another aspect, the present invention provides a method of treating or preventing a migraine in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of Compound 1, e.g., from about 2.5 mg to about 90 mg of Compound 1.

In some embodiments, the migraine is selected from the group consisting of migraine without aura, migraine with aura, familial hemiplegic migraine type 1 (FHM1), familial hemiplegic migraine type 2 (FHM2), familial hemiplegic migraine type 4 (FHM4), and sporadic hemiplegic migraine (SHM), In other embodiments, the migraine is migraine without aura. In certain embodiments, the migraine is migraine with aura. In some embodiments, the migraine is FHM1. In some embodiments, the migraine is FHM2. In other embodiments, the migraine is FHM4. In certain embodiments, the migraine is SHM. In some embodiments, the subject has an inadequate response to at least one medication used for the treatment of a migraine.

Cortical spreading depression

The compounds, dosage forms, and compositions described herein (e.g., Compound 1, a dosage form or a composition comprising Compound 1).are useful in the treatment of cortical spreading depression (CSD). CSD is a wave of sustained depolarization (neuronal inactivation) moving through intact brain tissue and involved in, for example, brain ischemia, migraine aura, and seizures.

In another aspect, a method of treating or preventing cortical spreading depression (CSD) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound, a dosage form, or a composition disclosed herein (e.g., Compound 1, a dosage form or a composition comprising Compound 1) is provided.

In another aspect, provided herein is a method of treating or preventing cortical spreading depression (CSD) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of Compound 1, e.g., from about 2.5 mg to about 90 mg of Compound 1.

Cranial Neuropathy

The compounds, dosage forms, and compositions described herein (e.g., Compound 1, a dosage form or a composition comprising Compound 1) are useful in the treatment of cranial neuropathy. Neuropathy is a disorder of nerve damage and affects the ability to feel and move. When nerves in the brain or brainstem are affected, it is called cranial neuropathy. The cranial nerves are those that arise directly from the brain or brainstem and often affect areas like the face and eyes. Cranial neuropathies include Bell's palsy, microvascular cranial nerve palsy, third nerve palsy, fourth nerve palsy, and sixth nerve palsy. When several different cranial nerves are affected, it is called multiple cranial neuropathies (MCN).

Also provided herein is a method of treating or preventing a cranial neuropathy or multiple cranial neuropathies in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound, a dosage form, or a composition described herein (e.g., Compound 1, a dosage form or a composition comprising Compound 1).

In another aspect, a method of treating or preventing a cranial neuropathy or multiple cranial neuropathy in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of Compound 1, e.g., from about 2.5 mg to about 90 mg of Compound 1, is provided herein.

In some embodiments, the cranial neuropathy is selected from the group consisting of bell palsy, microvascular cranial nerve palsy, third nerve palsy, fourth nerve palsy, and sixth nerve palsy. In other embodiments, the dosage form is administered orally. In certain embodiments, the dosage form is a capsule. In some embodiments, the patient is 18 to 65 years of age.

Combination Therapy

A formulation described herein (e.g., a dosage form or a composition comprising Compound 1), e.g., for use in modulating a sodium ion channel, e.g., the late sodium (INaL) current) may be administered in combination with another agent or therapy. A subject to be administered a formulation disclosed herein may have a disease, disorder, or condition, or a symptom thereof, that would benefit from treatment with another agent or therapy. These diseases or conditions can relate to epilepsy or an epilepsy syndrome, a neurodevelopmental disorder, pain, or a neuromuscular disorder.

Antiepilepsy Agents

Anti-epilepsy agents include brivaracetam, carbamazepine, clobazam, clonazepam, diazepam, divalproex, eslicarbazepine, ethosuximide, ezogabine, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, lorazepam, oxcarbezepine, permpanel, phenobarbital, phenytoin, pregabalin, primidone, rufinamide, tigabine, topiramate, valproic acid, vigabatrin, zonisamide, and cannabidiol.

Cardiovascular Agent Combination Therapy

Cardiovascular related diseases or conditions that can benefit from a combination treatment of the sodium channel blockers of the invention with other therapeutic agents include, without limitation, angina including stable angina, unstable angina (UA), exercised-induced angina, variant angina, arrhythmias, intermittent claudication, myocardial infarction including non-STE myocardial infarction (NSTEMI), pulmonary hypertension including pulmonary arterial hypertension, heart failure including congestive (or chronic) heart failure and diastolic heart failure and heart failure with preserved ejection fraction (diastolic dysfunction), acute heart failure, or recurrent ischemia.

Therapeutic agents suitable for treating cardiovascular related diseases or conditions include anti-anginals, heart failure agents, antithrombotic agents, antiarrhythmic agents, antihypertensive agents, and lipid lowering agents.

The co-administration of the sodium channel blockers of the invention with therapeutic agents suitable for treating cardiovascular related conditions allows enhancement in the standard of care therapy the patient is currently receiving.

Anti-Anginals

Anti-anginals include beta-blockers, calcium channel blockers, and nitrates. Beta blockers reduce the heart's need for oxygen by reducing its workload resulting in a decreased heart rate and less vigorous heart contraction. Examples of beta-blockers include acebutolol (Sectral), atenolol (Tenormin), betaxolol (Kerlone), bisoprolol/hydrochlorothiazide (Ziac), bisoprolol (Zebeta), carteolol (Cartrol), esmolol (Brevibloc), labetalol (Normodyne, Trandate), metoprolol (Lopressor, Toprol XL), nadolol (Corgard), propranolol (Inderal), sotalol (Betapace), and timolol (Blocadren).

Nitrates dilate the arteries and veins thereby increasing coronary blood flow and decreasing blood pressure. Examples of nitrates include nitroglycerin, nitrate patches, isosorbide dinitrate, and isosorbide-5-mononitrate.

Calcium channel blockers prevent the normal flow of calcium into the cells of the heart and blood vessels causing the blood vessels to relax thereby increasing the supply of blood and oxygen to the heart. Examples of calcium channel blockers include amlodipine (Norvasc, Lotrel), bepridil (Vascor), diltiazem (Cardizem, Tiazac), felodipine (Plendil), nifedipine (Adalat, Procardia), nimodipine (Nimotop), nisoldipine (Sular), verapamil (Calan, Isoptin, Verelan), and nicardipine.

Heart Failure Agents

Agents used to treat heart failure include diuretics, ACE inhibitors, vasodilators, and cardiac glycosides. Diuretics eliminate excess fluids in the tissues and circulation thereby relieving many of the symptoms of heart failure. Examples of diuretics include hydrochlorothiazide, metolazone (Zaroxolyn), furosemide (Lasix), bumetanide (Bumex), spironolactone (Aldactone), and eplerenone (Inspra).

Angiotensin converting enzyme (ACE) inhibitors reduce the workload on the heart by expanding the blood vessels and decreasing resistance to blood flow. Examples of ACE inhibitors include benazepril (Lotensin), captopril (Capoten), enalapril (Vasotec), fosinopril (Monopril), lisinopril (Prinivil, Zestril), moexipril (Univasc), perindopril (Aceon), quinapril (Accupril), ramipril (Altace), and trandolapril (Mavik).

Vasodilators reduce pressure on the blood vessels by making them relax and expand. Examples of vasodilators include hydralazine, diazoxide, prazosin, clonidine, and methyldopa. ACE inhibitors, nitrates, potassium channel activators, and calcium channel blockers also act as vasodilators.

Cardiac glycosides are compounds that increase the force of the heart's contractions. These compounds strengthen the pumping capacity of the heart and improve irregular heartbeat activity. Examples of cardiac glycosides include digitalis, digoxin, and digitoxin.

Antithrombotic Agents

Antithrombotics inhibit the clotting ability of the blood. There are three main types of antithrombotics--platelet inhibitors, anticoagulants, and thrombolytic agents.

Platelet inhibitors inhibit the clotting activity of platelets, thereby reducing clotting in the arteries. Examples of platelet inhibitors include acetylsalicylic acid (aspirin), ticlopidine, clopidogrel (plavix), dipyridamole, cilostazol, persantine sulfinpyrazone, dipyridamole, indomethacin, and glycoprotein IIb/IIIa inhibitors, such as abciximab, tirofiban, and eptifibatide (Integrelin). Beta blockers and calcium channel blockers also have a platelet-

inhibiting effect. Anticoagulants prevent blood clots from growing larger and prevent the formation of new clots. Examples of anticoagulants include bivalirudin (Angiomax), warfarin (Coumadin), unfractionated heparin, low molecular weight heparin, danaparoid, lepirudin, and argatroban.

Thrombolytic agents act to break down an existing blood clot. Examples of thrombolytic agents include streptokinase, urokinase, and tenecteplase (TNK), and tissue plasminogen activator (t-PA).

Antiarrhythmic Agents

Antiarrhythmic agents are used to treat disorders of the heart rate and rhythm. Examples of antiarrhythmic agents include amiodarone, dronedarone, quinidine, procainamide, lidocaine, and propafenone. Cardiac glycosides and beta blockers are also used as antiarrhythmic agents.

Combinations with amiodarone and dronedarone are of particular interest given the recently discovered synergistic effects of the sodium channel blocker ranolazine and amioarone and dronedarone.

Antihypertensive Agents

Antihypertensive agents are used to treat hypertension, a condition in which the blood pressure is consistently higher than normal. Hypertension is associated with many aspects of cardiovascular disease, including congestive heart failure, atherosclerosis, and clot for illation. Examples of antihypertensive agents include alpha-1-adrenergic antagonists, such as prazosin (Minipress), doxazosin mesylate (Cardura), prazosin hydrochloride (Minipress), prazosin, polythiazide (Minizide), and terazosin hydrochloride (Hytrin); beta-adrenergic antagonists, such as propranolol (Inderal), nadolol (Corgard), timolol (Blocadren), metoprolol (Lopressor), and pindolol (Visken); central alpha-adrenoceptor agonists, such as clonidine hydrochloride (Catapres), clonidine hydrochloride and chlorthalidone (Clorpres, Combipres), guanabenz Acetate (Wytensin), guanfacine hydrochloride (Tenex), methyldopa (Aldomet), methyldopa and chlorothiazide (Aldoclor), methyldopa and hydrochlorothiazide (Aldoril); combined alpha/beta-adrenergic antagonists, such as labetalol (Normodyne, Trandate), Carvedilol (Coreg); adrenergic neuron blocking agents, such as guanethidine (ismelin), reserpine (Serpasil); central nervous system-acting antihypertensives, such as clonidine (Catapres), methyldopa (Aldomet), guanabenz (Wytensin); anti-angiotensin II agents; ACE inhibitors, such as perindopril (Aceon) captopril (Capoten), enalapril (Vasotec), lisinopril

(Prinivil, Zestril); angiotensin-II receptor antagonists, such as Candesartan (Atacand), Eprosartan (Teveten), Irbesartan (Avapro), Losartan (Cozaar), Telmisartan (Micardis), Valsartan (Diovan); calcium channel blockers, such as verapamil (Calan, Isoptin), diltiazem (Cardizem), nifedipine (Adalat, Procardia); diuretics; direct vasodilators, such as nitroprusside (Nipride), diazoxide (Hyperstat IV), hydralazine (Apresoline), minoxidil (Loniten), verapamil; and potassium channel activators, such as aprikalim, bimakalim, cromakalim, emakalim, nicorandil, and pinacidil.

Lipid Lowering Agents

Lipid lowering agents are used to lower the amounts of cholesterol or fatty sugars present in the blood. Examples of lipid lowering agents include bezafibrate (Bezalip), ciprofibrate (Modalim), and statins, such as atorvastatin (Lipitor), fluvastatin (Lescol), lovastatin (Mevacor, Altocor), mevastatin, pitavastatin (Livalo, Pitava) pravastatin (Lipostat), rosuvastatin (Crestor), and simvastatin (Zocor).

In this invention, the patient presenting with an acute coronary disease event often suffers from secondary medical conditions such as one or more of a metabolic disorder, a pulmonary disorder, a peripheral vascular disorder, or a gastrointestinal disorder. Such patients can benefit from treatment of a combination therapy comprising administering to the patient ranolazine in combination with at least one therapeutic agent.

Pulmonary Disorders Combination Therapy

Pulmonary disorder refers to any disease or condition related to the lungs. Examples of pulmonary disorders include, without limitation, asthma, chronic obstructive pulmonary disease (COPD), bronchitis, and emphysema.

Examples of therapeutics agents used to treat pulmonary disorders include bronchodilators including beta2 agonists and anticholinergics, corticosteroids, and electrolyte supplements. Specific examples of therapeutic agents used to treat pulmonary disorders include epinephrine, terbutaline (Brethaire, Bricanyl), albuterol (Proventil), salmeterol (Serevent, Serevent Diskus), theophylline, ipratropium bromide (Atrovent), tiotropium (Spiriva), methylprednisolone (Solu-Medrol, Medrol), magnesium, and potassium.

Metabolic Disorders Combination Therapy

Examples of metabolic disorders include, without limitation, diabetes, including type I and type II diabetes, metabolic syndrome, dyslipidemia, obesity, glucose intolerance, hypertension, elevated serum cholesterol, and elevated triglycerides.

Examples of therapeutic agents used to treat metabolic disorders include antihypertensive agents and lipid lowering agents, as described in the section "Cardiovascular Agent Combination Therapy" above. Additional therapeutic agents used to treat metabolic disorders include insulin, sulfonylureas, biguanides, alpha-glucosidase inhibitors, and incretin mimetics.

Peripheral Vascular Disorders Combination Therapy

Peripheral vascular disorders are disorders related to the blood vessels (arteries and veins) located outside the heart and brain, including, for example peripheral arterial disease (PAD), a condition that develops when the arteries that supply blood to the internal organs, arms, and legs become completely or partially blocked as a result of atherosclerosis.

Gastrointestinal Disorders Combination Therapy

Gastrointestinal disorders refer to diseases and conditions associated with the gastrointestinal tract. Examples of gastrointestinal disorders include gastroesophageal reflux disease (GERD), inflammatory bowel disease (IBD), gastroenteritis, gastritis and peptic ulcer disease, and pancreatitis.

Examples of therapeutic agents used to treat gastrointestinal disorders include proton pump inhibitors, such as pantoprazole (Protonix), lansoprazole (Prevacid), esomeprazole (Nexium), omeprazole (Prilosec), rabeprazole; H2 blockers, such as cimetidine (Tagamet), ranitidine (Zantac), famotidine (Pepcid), nizatidine (Axid); prostaglandins, such as misoprostoL (Cytotec); sucralfate; and antacids.

Antibiotics, Analgesics, Antidepressants and Anti-anxiety Agents Combination Therapy

Patients presenting with an acute coronary disease event may exhibit conditions that benefit from administration of therapeutic agent or agents that are antibiotics, analgesics, antidepressant and anti-anxiety agents in combination with ranolazine.

Antibiotics

Antibiotics are therapeutic agents that kill, or stop the growth of, microorganisms, including both bacteria and fungi. Example of antibiotic agents include .beta.-Lactam antibiotics, including penicillins (amoxicillin), cephalosporins, such as cefazolin, cefuroxime, cefadroxil (Duricef), cephalexin (Keflex), cephradine (Velosef), cefaclor (Ceclor), cefuroxime axtel (Ceftin), cefprozil (Cefzil), loracarbef (Lorabid), cefixime (Suprax), cefpodoxime proxetil (Vantin), ceftibuten (Cedax), cefdinir (Omnicef), ceftriaxone (Rocephin), carbapenems, and monobactams; tetracyclines, such as tetracycline; macrolide

antibiotics, such as erythromycin; aminoglycosides, such as gentamicin, tobramycin, amikacin; quinolones such as ciprofloxacin; cyclic peptides, such as vancomycin, streptogramins, polymyxins; lincosamides, such as clindamycin; oxazolidinoes, such as linezolid; and sulfa antibiotics, such as sulfisoxazole.

Analgesics

Analgesics are therapeutic agents that are used to relieve pain. Examples of analgesics include opiates and morphinomimetics, such as fentanyl and morphine; paracetamol; NSAIDs, and COX-2 inhibitors. Given the ability of the sodium channel blockers of the invention to treat neuropathic pain via inhibition of the Na_V 1.7 and 1.8 sodium channels, combination with analgesics are particularly envisioned. See U.S. Patent Application Publication 20090203707.

Antidepressant and Anti-anxiety Agents

Antidepressant and anti-anxiety agents include those agents used to treat anxiety disorders, depression, and those used as sedatives and tranquillizers. Examples of antidepressant and anti-anxiety agents include benzodiazepines, such as diazepam, lorazepam, and midazolam; benzodiazepines; barbiturates; glutethimide; chloral hydrate; meprobamate; sertraline (Zoloft, Lustral, Apo-Sertral, Asentra, Gladem, Serlift, Stimuloton); escitalopram (Lexapro, Cipralex); fluoxetine (Prozac, Sarafem, Fluctin, Fontex, Prodep, Fludep, Lovan); venlafaxine (Effexor XR, Efexor); citalopram (Celexa, Cipramil, Talohexane); paroxetine (Paxil, Seroxat, Aropax); trazodone (Desyrel); amitriptyline (Elavil); and bupropion (Wellbutrin, Zyban). Antidepressant and anti-anxiety agents may include neuroactive steroid and ketamine and related NMDA receptor antagonists.

Accordingly, one aspect of the invention provides for a composition comprising the sodium channel blockers of the invention and at least one therapeutic agent. In an alternative embodiment, the composition comprises the sodium channel blockers of the invention and at least two therapeutic agents. In further alternative embodiments, the composition comprises the sodium channel blockers of the invention and at least three therapeutic agents, the sodium channel blockers of the invention and at least four therapeutic agents, or the sodium channel blockers of the invention and at least five therapeutic agents.

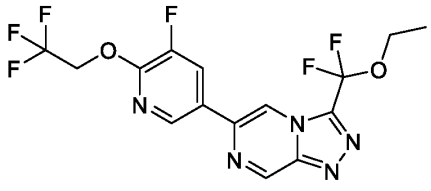
The methods of combination therapy include co-administration of a single formulation containing the sodium channel blockers of the invention and therapeutic agent or agents, essentially contemporaneous administration of more than one formulation comprising

the sodium channel blocker of the invention and therapeutic agent or agents, and consecutive administration of a sodium channel blocker of the invention and therapeutic agent or agents, in any order, wherein preferably there is a time period where the sodium channel blocker of the invention and therapeutic agent or agents simultaneously exert their therapeutic effect.

Methods of Preparation

Provided herein are methods of preparing compounds useful for preventing and/or treating a disease, disorder, or condition described herein, e.g., a disease, disorder, or condition relating to aberrant function of a sodium ion channel, such as abnormal late sodium current (INaL).

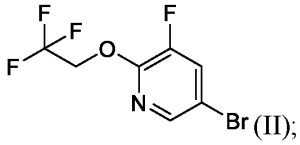
In one aspect, the present disclosure provides a method of making Compound 1:



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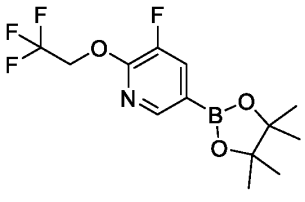
or a pharmaceutically acceptable salt thereof, the method comprising the steps of:

(i) contacting a solution of 2,2,2-trifluoroethanol with 5-bromo-2,3-difluoro-pyridine thereby providing a compound of formula (II):



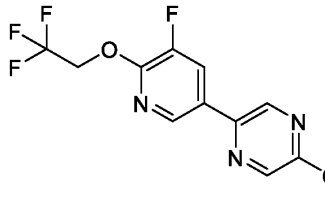
(II);

(ii) contacting the compound of formula (II) with a palladium catalyst and bis(pinacolato)diboron thereby providing a compound of formula (III):

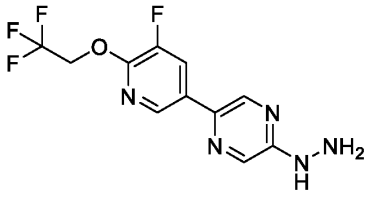


(III);

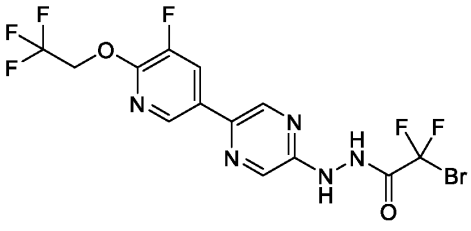
(iii) contacting the compound of formula (III) with a palladium catalyst and 2-bromo-5-chloro-pyrazine thereby providing a compound of formula (IV):


(IV);

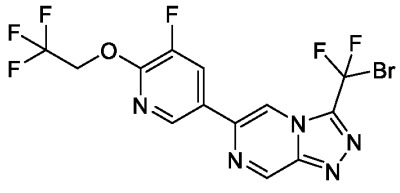
(iv) contacting the compound of formula (IV) with hydrazine thereby providing a compound of formula (V):


(V);

(v) contacting the compound of formula (V) with 2-bromo-2,2-difluoro-acetyl chloride thereby providing a compound of formula (VI):


(VI);

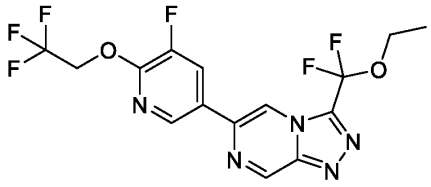
(vi) contacting the compound of formula (VI) with an acid thereby providing a compound of formula (VII):


(VII); and

(vii) contacting the compound of formula (VII) with a silver catalyst and ethanol thereby providing Compound 1 or a pharmaceutically acceptable salt thereof.

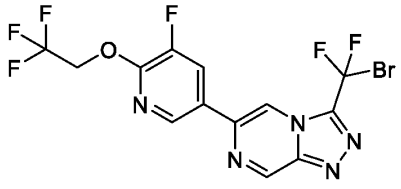
In some embodiments, the palladium catalyst in step (ii) or (iii) is [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride. In certain embodiments, the silver catalyst in step (vii) is silver tetrafluoroborate. In other embodiments, the acid in step (vi) is *p*-toluenesulfonic acid.

In another aspect, the present disclosure provides a method of making Compound 1:



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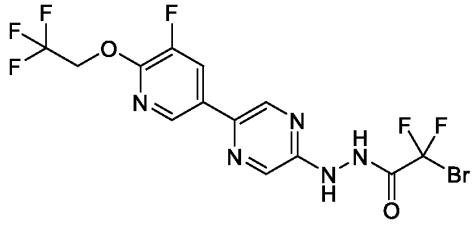
or a pharmaceutically acceptable salt thereof, wherein Compound 1 or a pharmaceutically acceptable salt thereof is provided by contacting the compound of formula (VII):



(VII)

with a silver catalyst and ethanol.

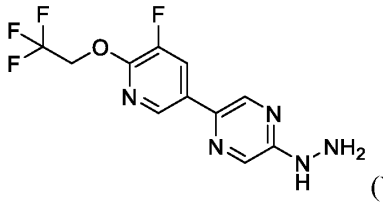
In some embodiments, the compound of formula (VII) is provided by contacting the compound of formula (VI):



(VI)

with an acid.

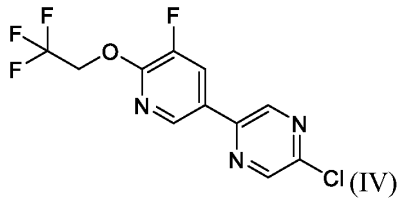
In other embodiments, the compound of formula (VI) is provided by contacting the compound of formula (V):



(V)

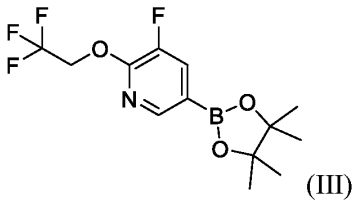
with 2-bromo-2,2-difluoro-acetyl chloride.

In certain embodiments, the compound of formula (V) is provided by contacting the compound of formula (IV):


(IV)

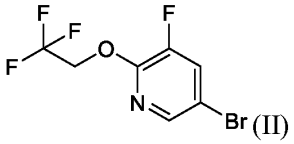
with hydrazine.

In some embodiments, the compound of formula (IV) is provided by contacting the compound of formula (III):


(III)

with a palladium catalyst and 2-bromo-5-chloro-pyrazine.

In other embodiments, the compound of formula (III) is provided by contacting the compound of formula (II):


(II)

with a palladium catalyst and bis(pinacolato)diboron.

In certain embodiments, the compound of formula (II) is provided by contacting a solution of 2,2,2-trifluoroethanol with 5-bromo-2,3-difluoro-pyridine. In other embodiments, the silver catalyst is silver tetrafluoroborate. In some embodiments, the acid is *p*-toluenesulfonic acid. In other embodiments, the palladium catalyst is [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride.

EXEMPLIFICATION

The representative examples that follow are intended to help illustrate the invention, and are not intended to, nor should they be construed to, limit the scope of the invention.

PSD	particle size distribution
XRPD	X-ray powder diffraction
NMR	nuclear magnetic resonance
LC-MS	liquid chromatography–mass spectrometry
PEG	polyethylene glycol
HPLC	high-performance liquid chromatography
MC	methylcellulose
RH	relative humidity
ASD	amorphous solid dispersion
PLM	polarized light microscopy
mDSC	modulated differential scanning calorimetry
FaSSIF	fasted state simulated intestinal fluid
UPLC	ultra performance liquid chromatography
API	active pharmaceutical ingredient
PVP	polyvinylpyrrolidone
HPMC	hydroxypropyl methylcellulose
SDS	sodium dodecyl sulfate
USP	United States pharmacopeia
TFA	trifluoroacetic acid
ACN	acetonitrile
PK	pharmacokinetic
MCC	microcrystalline cellulose
MgSt	magnesium stearate
rpm	revolutions per minute
RSD	relative standard deviation
HG	hard gelatin capsule
SLS	sodium laureth sulfate
AUC	area under the curve
C_{max}	maximum observed concentration
HPMCAS	hydroxypropylmethylcellulose acetate succinate
PG	propylene glycol

AE	adverse event
ECG	electrocardiogram
C-SSRS	Columbia-Suicide Severity Rating Scale
T_{max}	time to maximum observed concentration
$t_{1/2}$	apparent terminal elimination half-life
$AUC_{0\text{-last}}$	area under the concentration-time curve from time zero to the last measurable concentration
$AUC_{0\text{-inf}}$	area under the drug concentration-time curve from time zero to infinity
CL/F	clearance
V_d/F	volume of distribution
Clr	real clearance
fe	fraction of dose excreted unchanged in urine
$Ae_{0\text{-}72}$	amount excreted unchanged over 72 hours
EEG	electroencephalography
PD	pharmacodynamic
Rac (AUC)	time to steady state accumulation ratio based on AUC
Rac (C_{max})	accumulation ratio based on C_{max}
SAD	single ascending dose
QTcF	QT interval with Fridericia correction method
OTC	over-the-counter
BLQ	below the level of quantification
CV%	coefficient of variation

Example 1. Preparation and characterization of milled Compound 1

Compound 1 was milled by manual milling or jet milling to reduce particle size. For manual milling, Compound 1 was weighed into a ceramic motor and gentle milled for ~5 mins. Particle size distribution (PSD) of Compound 1 indicated D90 = 77.82 μm and D90 = 28.27 μm before and after manual milling of Compound 1. PSD via dry method was conducted by Sympatec HELOS particle size analyzer, and dispersing system and pressure were RODOS and 0.5 bar, respectively.

Table 1. Changes in particle size after manual milling

Compound 1	Before	After Manual Milling
D10	1.8 μm	0.8 μm
D50	22.2 μm	3.6 μm
D90	77.8 μm	28.3 μm

For jet milling, Compound 1 was micronized by jet milling with a yield of ~90%. Particle size of the jet-milled material was reduced to a D90 range of 4.7 to 13.5 μm.

Table 2. Changes in particle size after jet milling

Compound 1, batch 1	Before	After Jet Milling (51 g scale)
D10	1.8 μm	0.7 μm
D50	15.4 μm	1.8 μm
D90	80.9 μm	4.7 μm
Compound 1, batch 2	Before	After Jet Milling (95 g scale)
D10	13.2 μm	1.1 μm
D50	67.3 μm	3.7 μm
D90	162.1 μm	8.3 μm
Compound 1, batch 3	Before	After Jet Milling (104 g scale)
D10	14.6 μm	0.87 μm
D50	56.8 μm	5.58 μm
D90	104 μm	13.5 μm

X-ray powder diffraction (XRPD) data were collected using a Bruker D8 Advance powder diffractometer. The samples were irradiated with copper K-alpha X-rays (λ = 1.54179 Å) with the generator operating at 40kV/40 mA. The samples were scanned in continuous mode from 3° to 40° (2 θ) with a sample rotation speed of 15 rpm and a scanning rate of 10°/min. **FIG. 1** shows the XRPD pattern of raw material and jet-milled material, which indicates that there is no physical form change of Compound 1 after jet-milling.

Proton NMR (^{1}H-NMR), Florine NMR (^{19}F-NMR) and LC-MS analyses were also carried out on Compound 1 before jet milling and after jet milling. Both the NMR results and the LC-MS results all indicate there was no observed chemical or structural change to Compound 1 due to the jet milling.

Example 2. Preparation and stability of formulations comprising Compound 1

Solution Formulations

1) Prototype 1: 40% PEG 400 /10% Cremophor RH40/50% water

2400 µL PEG 400 was added to a 8 mL glass vial together with 3 mg of Compound 1 and mixed together by Vortex and sonicated for 5 min. Then 600 µL Cremophor RH40 was added to the container, mixed together by Vortex and sonicated for 5 min. Then 3000 µL water was added to the container, mixed together by Vortex and sonicated for 5 min. The compound was dissolved completely (0.5 mg/mL).

2) Prototype 2a: 58.1% Cremophor RH40 + 16.9% Labrafil M2125 CS + 8.3% Propylene glycol + 16.7% Ethanol

Vehicle preparation: 11.62 mL Cremophor RH40, 3.38 mL Labrafil M2125 CS, 1.66 mL Propylene glycol and 3.34 mL Ethanol were mixed together to get the vehicle of Prototype 2a.

About 15 mg compound were weighted to a 8 mL glass container and then 2 mL Prototype 2a was added to the glass container. The contents were mixed together by vortexing and sonication for 5 min. Compound 1 in Prototype 2a at 7.5 mg/mL was a clear solution.

3) Prototype 2b: 69.74% Cremophor RH40+20.28% Labrafil M2125 CS+9.98% Propylene glycol.

Preparation: 11.62 mL Cremophor RH40, 3.38 mL Labrafil M2125 CS and 1.66 mL propylene glycol were mixed together to get the vehicle of Prototype 2b.

About 15 mg compound was weighed to an 8 mL glass containers and then 2 mL of Prototype 2b was added to the container and mixed together by vortex and sonicated for 5 min. Compound 2 in Prototype 2b with 7.5 mg/mL was not clear. Then another 140 µL of Prototype 2b vehicle was added to the container and mixed together by vortex and sonicated for 5 min. Prototype 2b at 7 mg/mL was a clear solution.

4) Prototype 3: 40%Transcutol HP /10% Vitamin ETPGS/50% water

600µL PEG 400 was added to a 4 mL glass vial together with 3 mg of Compound 1 and mixed together by Vortex and sonicated for 5 min. Then 150µL Cremophor RH40 was added to the container and mixed together by Vortex and sonicated for 5 min. Then 750µL water was added to the container and mixed together by vortexing and sonicated for 5 min. The compound was dissolved completely (2 mg/mL).

5) Prototype 4: 36% Cremophor RH40 + 45% Capmul MCM C8 + 9% Triethylcitrate + 10% Ethanol

Cremophor RH40, Capmul MCM C8, Triethylcitrate and Ethanol were added together on a weight basis to a glass container and mixed together to form a solution mixture. Increasing amounts of Compound 1 was then added to the mixture and vortexed and sonicated to form a clear solution. Additional Compound 1 was added with vortexing and sonication until Compound 1 was no longer soluble. The resulting maximum solubility was visually determined to be between 25 and 50 mg/mL.

6) Prototype 5: 40% Capryol 90 + 20% Labrasol + 40% Transcutol HP

Capryol 90, Labrasol and Transcutol HP were added together on a volumetric basis to a glass container and mixed together to form a solution mixture. Increasing amounts of Compound 1 was then added to the mixture and vortexed and sonicated to form a clear solution. Additional Compound 1 was added with vortexing and sonication until Compound 1 was no longer soluble. The resulting maximum solubility was visually determined to be between 60 and 80 mg/mL.

Table 3 summarizes the prototypes used to prepare solution formulations of Compound 1 with their respective stability. **Table 4** shows detailed stability results.

Table 3. Solution formulations comprising Compound 1

Solution Formulation	**Target Concentration of Compound 1 (mg/mL)**	**Stability Observation (room temperature storage)**
Prototype 1 (40% PEG 400/10% Kolliphor RH40/50% water)	0.5	Stable for 7 days
Prototype 2a (58.1% KolliphorRH40 + 16.9% Labrafil M2125 CS + 8.3% Propylene glycol + 16.7% Ethanol)	7.5	Stable for 7 days
Prototype 2b (69.74% KolliphorRH40 + 20.28% Labrafil M2125 CS + 9.98% Propylene glycol	7	Stable for 7 days
	2.3 (diluted in water 3 fold)	Stable for 7 days
Prototype 3 (40% Transcutol HP/10% Vitamin ETPGS/50% water)	2	Stable for 7 days

For stability and purity testing of Compound 1 a high-performance liquid chromatography

(HPLC) method was developed. The HPLC method used for chemical stability and purity testing was as follows:

Column	Agilent Pursuit XRs C18 column (150 mm* 4.6 mm* 3 μm)		
Wavelength	245 nm		
Column Oven Temp.	45 °C		
Flow Rate	1.0 mL/min		
Injection Volume	2 μL		
Mobile Phases	A: 0.1% TFA in Water (v/v)		
	B: MeOH: ACN (80:20; v/v)		
Gradient Program	Time (min)	A%	B%
	0.00	50	50
	30.0	20	80
	35.0	20	80
	35.1	50	50
	40.0	50	50
Re-equilibration Time	5 min		
Run Time	40 min		
Needle Wash Solvent	ACN: Water (50:50; v/v)		
Diluent	ACN: Water (90:10; v/v)		

Table 4. Detailed stability test data for Prototype 1, 2a and 3 (storage was at room temperature, 15-25°C).

Target Conc. (mg/mL)	**Sample Time**	**Prototype 1 Appearance**	**Conc. (mg/mL)**	**Purity (%)**
0.5	1 hr	clear	0.53	98.58
	4 hrs	clear	0.52	98.58
	7 days	clear	0.43	97.78
Target Conc. (mg/mL)	**Sample Time**	**Prototype 2a Appearance**	**Conc. (mg/mL)**	**Purity (%)**
7.5	1 hr	clear	7.36	96.64
	4 hrs	clear	7.31	96.45
	7 days	clear	7.17	97.28
Target Conc. (mg/mL)	**Sample Time**	**Prototype 3 Appearance**	**Conc. (mg/mL)**	**Purity (%)**
1.0	1 hr	clear	1.11	96.87

	4 hrs	clear	1.11	97.01
	7 days	clear	1.06	97.59

About 24 mg compound of Compound 1 was added to a 8 mL glass bottle and dissolved by prototype 2b, then it was sonicated for 10 min to get a clear solution with concentration at 7 mg/mL. After that, the solution was diluted 3 times with water for stability test. Results are as showed in **Table 5** below.

Table 5: Detailed stability test data for Prototype 2b

Sample	**Time**	**Appearance**	**Target Conc. (mg/mL)**	**Conc. (mg/mL)**	**Purity (%)**
Prototype 2b diluted in water 3 times	initial	clear	2.33	-	-
	24 h	clear		2.19	99.56
	72 h	clear		2.23	99.83
	7 days	clear		2.45	99.65

Based on HPLC results and appearance, the Prototype 1, 2a, 2b and 3 formulations comprising Compound 1 was stable at ambient condition for at least 7 days.

Suspension Formulations

To prepare suspension formulations of Compound 1, about 0.5 mg, 5 mg and 10 mg of Compound 1 were weighted into separate vials and 1 mL 0.5% MC 400 cP/0.2% Tween 80 was added to each vial. The materials were mixed together by Vortex and stirred at room temperature overnight (24 hrs). The stability of the suspension formulations was measured by quantifying the purity of Compound 1 using high pressure liquid chromatography (HPLC). The suspensions remained as homogenous suspensions. **Table 6** summarizes the stability results.

To prepare a suspension formulation comprising jet-milled Compound 1, 15 mg of jet-milled Compound 1 was weighed into a glass vial and then 10 mL of vehicle (0.5% MC 400 cP /0.2% Tween 80) was added to disperse it to reach Compound 1 concentration of 1.5 mg/mL. The suspension was thoroughly dispersed by homogenization for ~30 seconds. The stability of the suspension was evaluated by HPLC and particle size distribution (PSD), and the results are summarized in **Table 7**. Based on HPLC and PSD, the suspension formulation comprising jet-milled Compound 1 was stable at ambient condition for 28 days.

Table 6. Stability of Compound 1 suspension formulations in 0.5% MC 400 cP/0.2% Tween 80.

Target Concentration (mg/mL)	Time point	Concentration (mg/mL)	Purity (%)
10	1 hr	9.69	96.86
	4 hrs	9.79	97.12
	7 days	9.72	96.71
5	1 hr	Not available	97.60
	4 hrs	4.72	97.84
	7 days	5.06	96.95
0.5	1 hr	0.58	97.46
	4 hrs	0.45	96.65
	7 days	0.49	97.85
1.5*	1 day	1.44	99.4
	6 days	1.43	99.5

Un-milled Compound 1 unless noted.

* designates jet milled material.

Table 7. Stability of suspension formulation in 0.5% MC 400 cP/0.2% Tween 80 comprising jet-milled Compound 1

Target Conc. (mg/mL)	Time point at RT (day)	Appearance	Conc. (mg/mL)	Purity (%)	PSD (D90, um)
1.5	Initial	Homogeneous suspension	1.61	99.43	-
	1	Homogeneous suspension	1.44	99.44	-
	2	Homogeneous suspension	1.38	99.52	-
	3	Homogeneous suspension	1.58	99.49	-
	6	Homogeneous suspension	1.43	99.51	-
	7	Homogeneous suspension	1.61	99.55	-
	14	Homogeneous suspension	1.61	99.36	-
	21	Homogeneous suspension	1.56	99.58	6.97
	28	Homogeneous suspension	1.64	98.96	6.80

As shown in **Tables 8-11, v**arious suspension formulations were tested for stability under different conditions.

To prepare a suspension weigh required amount of milled Compound 1 into a glass container and add corresponding volume of the vehicle. Thoroughly disperse the compound into a homogenous suspension using an overhead mixer at the final concentration target. Concentrations were prepared at 0.1 mg/mL and at 10mg/mL. The suspension products were physically evaluated on visual appearance, concentration, purity and PSD.

The vehicles are prepared by dissolving 0.5% by weight of either 400 cP methylcellulose or 4000 cP methylcellulose and 0.2% Poloxamer 188. For the preserved suspensions, additionally 1.0% by volume of paraben preservative solution was dissolved into vehicle using an overhead mixer. The paraben preservative solution was prepared by dissolving 0.10

g methyl paraben, 0.025 g propylparaben in 9.875 g propylene glycol dissolved by mixing with a stir bar at room temperature for 1 hour.

Table 8. Visual Stability Evaluation of suspension formulations comprising Compound 1 after 1, 4, and 24 hours at room temperature

Vehicle	Target Concentration (mg/mL)	Hours at RT	Visual Appearance (see reference key)
0.5% 400 cP MC, 0.2% Poloxamer 188 and 1.0% of paraben preservative solution	0.1	1	*
		4	*
		24	*
	10	1	*
		4	*
		24	*
0.5% 4000 cP MC, 0.2% Poloxamer 188 and 1.0% of paraben preservative solution	0.1	1	#
		4	#
		24	#
	10	1	#
		4	#
		24	#
0.5% 400 cP MC, 0.2% Poloxamer 188	0.1	1	*
		4	*
		24	*
	10	1	*
		4	*
		24	*
0.5% 4000 cP MC, 0.2% Poloxamer 188	0.1	1	#
		4	#
		24	#
	10	1	#
		4	#
		24	#

* homogeneous suspension initially, sedimentation occurred over time and returned to homogeneous after gentle agitation

viscous homogeneous suspension initially, sedimentation occurred over time and returned to homogeneous after gentle agitation

Table 9. Stability of suspension formulations comprising Compound 1 after 96 hours at room temperature

Vehicle	Target Conc. (mg/mL)	Hours at RT	Visual Appearance
0.5% 400 cP MC, 0.2% Poloxamer 188 and 1.0% of paraben preservative solution	0.1	96	*
	10	96	*
0.5% 4000 cP MC, 0.2% Poloxamer 188 and 1.0% of paraben preservative solution	0.1	96	#
	10	96	#
0.5% 400 cP MC, 0.2% Poloxamer 188	0.1	96	*
	10	96	*
0.5% 4000 cP MC, 0.2% Poloxamer 188	0.1	96	#
	10	96	#

* homogeneous suspension initially, sedimentation occurred over time and returned to homogeneous after gentle agitation for ~ 1 min

viscous homogeneous suspension initially, sedimentation occurred over time and returned to homogeneous after gentle agitation for ~ 2 mins

Table 10. Stability of suspension formulations comprising Compound 1 at 2-8°C

Vehicle	Target Conc. (mg/mL)	Time point at 2-8 °C	Appearance	Conc. (mg/mL)	Purity (%)	PSD (D90, µm)
0.5% 400 cP MC, 0.2% Poloxamer 188	0.1	0	*	0.11	100	19.9
		7D	*	0.12	100	18.2
		14D	*	0.11	100	14.2
		28D	*	0.11	100	15.4
		2M	*	0.11	95.87	9.1
		3M	*	0.11	93.20	12.7
	10	0	*	10.04	99.83	5.6
		7D	*	10.18	99.83	6.4
		14D	*	10.66	99.83	5.4
		28D	*	10.56	99.83	3.8
		2M	*	10.99	99.83	4.0
		3M	*	10.13	99.83	3.6

* homogeneous suspension initially, sedimentation occurred over time and returned to homogeneous after gentle agitation for ~ 1 min

Table 11. Stability of suspension formulations comprising Compound 1 at 25°C/60% RH

Vehicle	Target Conc. (mg/mL)	Time point at 25 °C/60%RH	Appearance	Conc. (mg/mL)	Purity (%)	PSD (D90, µm)
0.5% 400 cP MC, 0.2% Poloxamer 188	0.1	0	*	0.11	100.0	19.9
		7D	*	0.11	100.0	19.9
		14D	*	0.11	100	12.9
		28D	*	0.10	100	8.7
		2M	*	0.11	95.87	8.6
		3M	*	0.11	93.20	11.1
	10	0	*	10.04	99.83	5.6
		7D	*	10.48	99.83	6.3
		14D	*	9.85	99.83	5.2
		28D	*	10.00	99.83	4.6
		2M	*	10.47	99.83	4.3
		3M	*	10.16	99.83	3.5

* homogeneous suspension initially, sedimentation occurred over time and returned to homogeneous after gentle agitation for ~ 1 min

Amorphous Solid Dispersion (ASD)

Amorphous solid dispersion including Compound 1 was prepared with a mixture of Compound 1 and polymer. Nine ASD formulations were prepared using for screening 9 different polymers as the solid dispersant (PVPK30, PVPVA64, Soluplus, HPMC E5, HPMC ASMG, HPMC ASMF, HPMC ASHG, Eudragit EPO, Eudragit L100). About 10 mg of Compound 1 and 40 mg of corresponding polymer were weighed into 40-mL glass vials, and dissolved in 1 mL of MeOH/DCM (1:1, v/v) to prepare stock solution. The obtained clear solutions were stored under 70ºC to be fast evaporated to yield solid dispersion. The product after evaporation was dried under vacuum at 30°C overnight and further characterized by appearance, PLM, XRPD and mDSC.

The nine ASD formulations were tested for kinetic solubility in FaSSIF at the concentration of 2 mg/mL. The experiment was run at 37°C with the rate of 450 rpm. 0.5 mL of the mixture was taken out at each time point and centrifuged before running UPLC (a shortened runtime version of the described HPLC method was used to determine the

Compound 1 levels). The results are listed in Table 12. Solubility enhancement was observed for most polymer especially for Eudragit EPO.

Table 12. Summary of kinetic solubility of the ASDs

No.	SD formulation	Kinetic solubility in FaSSIF (µg/mL)				Final pH
		15 min	30 min	60 min	120 min	
0	Crystalline API (API = Compound 1)	5.7	8.1	7.1	11.6	6.54
1	API+ PVP K30	4.9	6.0	5.8	6.7	6.55
2	API+ PVP VA64	4.8	5.7	5.2	5.2	6.54
3	API+ Soluplus	12.9	19.1	17.5	18.7	6.56
4	API+ HPMC E5	8.8	8.2	7.9	7.6	6.57
5	API+ HPMC ASMG	21.7	24.7	26.9	22.1	5.92
6	API+ HPMC ASMF	20.3	26.2	24.4	31.4	5.96
7	API+ HPMC ASHG	28.4	24.2	21.9	20.9	6.49
8	API+ Eudragit EPO	111.0	207.0	273.3	327.2	7.21
9	API+ Eudragit L100	19.2	16.2	19.6	26.6	5.59

Based on kinetic solubility evaluation of the prototype ASD formulation. Three example prototype ASD formulations were then prepared for further evalautions using Soluplus, Eudragit L100, or HPMC ASMF and are summarized in **Table 13**. The stability test results of selected ASD formulations are shown in **Tables 14** and **15**.

Table 13. Summary of selected ASD formulations

Compound 1		**ASD + Soluplus**	**ASD + Eudragit L100**	**ASD + HPMC ASMF**
Appearance		White powder	White powder	White powder
PLM		No birefringence and spherical shape		
XRPD		Amorphous	Amorphous	Amorphous
Tg by mDSC (°C)		91.65	90.83	91.34
HPLC test	Drug load (w %)	18.9	19.3	18.1
	Purity (A %)	99.01	98.71	97.61
Kinetic SolKinetic Sol in FASSIF (ug/mL) at 120 min		19	21	31

Table 14. Stability results after 1 week of selected ASD formulations

SD Formulation	Initial drug load (%)	Initial purity (%)	Storage condition	After 1 week		
				XRPD	HPLC results	
					Drug load (%)	Purity (%)
ASD_Soluplus	18.9	98.68	25 °C /60%RH, open	Partially crystalline	20.80	96.40
			40 °C /75%RH, open	Partially crystalline	19.82	95.81
	18.86	97.81	25 °C /60%RH, closed	Partially crystalline	18.69	97.49
			60 °C, closed	Partially crystalline	18.65	96.86
ASD_Eudragit L100	19.1	97.58	25 °C /60%RH, open	Amorphous	19.86	96.79
			40 °C /75%RH, open	Amorphous	20.00	96.35
	19.12	97.31	25 °C /60%RH, closed	Amorphous	18.62	96.86
			60 °C, closed	Amorphous	18.63	96.48
ASD_HPMC ASMF	18.1	96.42	25 °C /60%RH, open	Amorphous	17.44	94.40
			40 °C /75%RH, open	Partially crystalline	17.33	94.74
	17.81	95.17	25 °C /60%RH, closed	Amorphous	17.32	95.44
			60 °C, closed	Amorphous	17.38	94.93

Table 15. Stability results after 2 weeks

SD Formulation	Initial drug load (%)	Initial purity (%)	Storage condition	After 2 weeks		
				XRPD	HPLC results	
					Drug load (%)	Purity (%)
ASD_Soluplus	18.9	98.68	25 ℃ /60%RH, open	Partially crystalline	21.29	97.24
			40 ℃ /75%RH, open	Partially crystalline	20.43	95.23
	18.86	97.81	25 ℃ /60%RH, closed	Partially crystalline	17.92	94.01
			60 ℃, closed	Partially crystalline	18.69	93.41
ASD_Eudragit L100	19.1	97.58	25 ℃ /60%RH, open	Amorphous	19.57	97.21
			40 ℃ /75%RH, open	Amorphous	19.99	95.84
	19.12	97.31	25 ℃ /60%RH, closed	Amorphous	18.89	96.53
			60 ℃, closed	Partially crystalline	18.54	96.09
ASD_HPMC ASMF	18.1	96.42	25 ℃ /60%RH, open	Amorphous	17.69	94.32
			40 ℃ /75%RH, open	Partially crystalline	17.77	95.70
	17.81	95.17	25 ℃ /60%RH, closed	Amorphous	17.93	94.01
			60 ℃, closed	Partially crystalline	17.33	94.54

Scale up of three ASDs with a spray dryer

ASD-1 preparation: About 300 mg Compound 1 and about 1200 mg Soluplus were weighed into a 250 mL glass, then 150 mL acetone was added into to make a clear solution before spray drying. After spray drying, the powder was collected and dried under vacuum condition at 30°C for 12 hrs (yield of 80.2%).

ASD-2 preparation: About 300 mg Compound 1 and about 1200 mg Eudragit L100 were weighed into a 250 mL glass, then 150 mL acetone was added into to make a clear

solution before spray drying. After spray drying, the powder was collected and dried under vacuum condition at 30°C for 12 hrs (yield of 74.5%).

ASD-3 preparation: About 300 mg Compound 1 and about 1200 mg HPMC ASMF were weighed into a 250 mL glass, then 150 mL acetone was added into to make a clear solution before spray drying. After spray drying, the powder was collected and dried under vacuum condition at 30°C for 12 hrs (yield of 70.0%).

The ASD-3 prototype was also evaluated in an *in vitro* dissolution study. The ASD-3 spray dried powder which was collected was hand-weighed on an analytical balance directly into a size #4 hard-gelatin capsules at two dose strengths: 2.5 and 10 mg of active (13.7 and 54.8 mg of ASD).

The dissolution method used the following conditions:

Parameters	**Setting**
Instrument	Agilent 708-DS
Media	0.1 N HCl with 2%SDS
Apparatus	USP Apparatus 2 (paddle)
Rotation Speed	75 rpm (200 rpm for infinity spin)
Media Volume	900 mL
Temperature	37.0 ±0.5°C
Sampling time point	15, 30, 45, 60 mins and infinity at 120 mins

For the dissolution analysis a HPLC method was used for quantifying Compound 1 levels in the dissolution media. The same HPLC method was used for both dissolution and content uniformity testing. The HPLC method used is as follows:

Column	Agilent Pursuit XRs C18 column (150 mm* 4.6 mm* 3 μm)		
Wavelength	245 nm		
Column Oven Temp.	45°C		
Flow Rate	1.0 mL/min		
Injection Volume	2 μL		
Mobile Phases	A: 0.1% TFA in Water (v/v)		
	B: MeOH: ACN (80:20; v/v)		
Gradient Program	Time (min)	A%	B%
	0.00	70	30
	10.00	0	100

Re-equilibration Time	2 min
Run Time	10 min
Needle Wash Solvent	ACN: Water (50:50; v/v)
Diluent	ACN: Water (90:10; v/v)

The dissolution results are shown in Figure 2, where the release of two dose strengths were 29.76% and 17.64% for the 2.5 mg and 10 mg dose strengths, respectively.

The ASD-3 prototype was also evaluated in a pharmacokinetic (PK) study in cynomolgus monkeys using a cross-over study design. The ASD-3 spray dried powder which was collected was hand-weighed on an analytical balance directly into a size #4 hard-gelatin capsules. Three male monkeys were orally administered 0.5 mg/kg of body weight in a fasted state and plasma samples were analyzed for Compound 1 levels.

Capsule Formulations

Exemplary capsule formulations include 2.5 mg, 10 mg, or 100 mg of Compound 1 per capsule. For the 2.5 mg dose capsule, a formulation includes 1:10 blend of Compound 1 to microcrystalline cellulose (MCC) with 2% magnesium stearate (MgSt) in a gelatin capsule, and another formulation includes 2.5 mg neat Compound 1 in a gelatin capsule (with no additional excipients).

Milled Compound 1 and filler (MCC or starch) were weighed separately and blended for 15 mins to get a homogenous mixture. A required amount of magnesium stearate was added and blended together. Blend was hand filled in appropriately sized hard gelatin capsules. Samples were then subjected to stability at different conditions and analyzed for appearance, assay at different time points.

Blend Formulations

Blend 1 and 2 (1:10 Blending)

1 g of milled Compound 1 and 9 g of MCC or starch were weighed into a container. The two components were blended by Turbula for about 15 mins at a speed of 36 rpm to obtain homogeneous phase. 0.2 g of MgSt was added and mixed for another 3 mins to obtain homogeneous blend 1 (Table 16). Dose uniformity was assessed by measuring 10 capsules assay (Tables 18 and 19).

Table 16. Composition of Blend 1 and 2

Blend 1		
Components	**Function**	**Percentage (w/w %)**
Compound 1	Active	10
MCC	Filler	90
MgSt	Lubricant	2
Blend 2		
Components	**Function**	**Percentage (w/w %)**
Compound 1	Active	10
Starch	Filler	90
MgSt	Lubricant	2

Blend 3 and 4 (1:1 Blending)

5 g of milled Compound 1 and 5 g of MCC or starch were weighed into a container. The two components were blended by Turbula for about 15 mins at a speed of 36 rpm to obtain homogeneous phase. 0.2 g of MgSt was added and mixed for another 3 mins to obtain homogeneous blend 1 (Table 17). Dose uniformity was assessed by measuring 10 capsules assay (Table 20 and 21).

Table 17. Composition of Blend 3 and 4

Blend 3		
Components	**Function**	**Percentage (w/w %)**
Compound 1	Active	50
MCC	Filler	50
MgSt	Lubricant	2
Blend 4		
Components	**Function**	**Percentage (w/w %)**
Compound 1	Active	50
Starch	Filler	50
MgSt	Lubricant	2

Tables 18-21 summarize blend uniformity results for 4 exemplary blends (blends 1-4 as described above) comprising Compound 1.

Table 18. 1:10 blend uniformity results of **blend 1**

Sampling location	**Sample weight (mg)**	**Label claim (%)**	**Average (%)**	**RSD (%)**
Top-1	7.79	97.95	94.18	3.97
Top-2	7.36	92.36		
Top-3	9.16	95.09		
Middle-1	7.89	86.96		
Middle-2	10.69	88.58		
Middle-3	7.58	96.55		
Middle-4	6.79	94.81		
Bottom-1	7.86	96.96		
Bottom-2	7.62	95.47		
Bottom-3	6.62	97.1		

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Table 19. 1:10 blend uniformity results of **blend 2**

Sampling location	**Sample weight (mg)**	**Label claim (%)**	**Average (%)**	**RSD (%)**
Top-1	11.83	88.66	93.21	4.34
Top-2	11.47	96.28		
Top-3	6.91	93.45		
Middle-1	8.51	94.50		
Middle-2	7.66	96.34		
Middle-3	11.95	91.53		
Middle-4	8.54	87.87		
Bottom-1	10.45	99.85		
Bottom-2	8.49	88.20		
Bottom-3	11.13	95.44		

Table 20. 1:1 blend uniformity results of **blend 3**

Sampling location	**Sample weight (mg)**	**Label claim (%)**	**Average (%)**	**RSD (%)**
Top-1	15.15	93.46	93.88	3.13
Top-2	15.05	94.84		
Top-3	16.92	99.64		
Middle-1	12.89	89.67		
Middle-2	14.96	94.61		
Middle-3	16.38	91.61		
Middle-4	17.46	92.68		
Bottom-1	18.32	95.81		
Bottom-2	16.61	90.56		
Bottom-3	16.63	95.89		

Table 21. 1:1 blend uniformity results of **blend 4**

Sampling location	**Sample weight (mg)**	**Label claim (%)**	**Average (%)**	**RSD (%)**
Top-1	20.62	95.48	94.26	3.83
Top-2	18.01	95.94		
Top-3	22.95	87.41		
Middle-1	14.98	88.62		
Middle-2	21.74	95.24		
Middle-3	17.47	92.89		
Middle-4	14.34	94.80		
Bottom-1	17.35	96.73		
Bottom-2	15.16	98.25		
Bottom-3	22.29	97.25		

Tables 21.1, 21.2, 21.3 and 21.4 show the stability results of Blend 1 capsules and Blend 2 capsules at dose strengths of 1 mg per capsule (1:10 blend ratio), 10 mg per capsule (1:10 and 50:50 blend ratios), and 100 mg per capsule (50:50 blend ratio).

Table **21.1: Stability of 1 mg active blend in capsule at 25°C/60%RH**

1 mg dose in 1:10 blend 1 (MCC) at 25C/60%RH				
Capsule	**Time**	**Appearance**	**Assay (%)**	**Purity (%)**
Size #0 HG	0	Blend in opaque white capsule	100.00	99.83
	7D	Blend in opaque white capsule	98.50	99.83
	14D	Blend in opaque white capsule	99.00	99.83
	28D	Blend in opaque white capsule	102.76	99.83
	2M	Blend in opaque white capsule	100.69	99.83
	3M	Blend in opaque white capsule	100.58	99.83
1 mg dose in 1:10 blend 2 (Starch) at 25°C/60% RH				
Capsule	**Time**	**Appearance**	**Assay (%)**	**Purity (%)**
Size #0 HG	0	Blend in opaque white capsule	100.00	99.83
	7D	Blend in opaque white capsule	99.78	99.83
	14D	Blend in opaque white capsule	97.60	99.83
	28D	Blend in opaque white capsule	98.56	99.83
	2M	Blend in opaque white capsule	98.50	99.83
	3M	Blend in opaque white capsule	97.97	99.83

Table **21.2: Stability of 10 mg active 1:10 blend in capsule at 25°C/60%RH**

10 mg dose in 1:10 blend 1 (MCC) at 25°C/60% RH				
Capsule	**Time**	**Appearance**	**Assay (%)**	**Purity (%)**
Size #0 HG	0	Blend in opaque white capsule	100.00	99.83
	7D	Blend in opaque white capsule	99.70	99.83
	14D	Blend in opaque white capsule	96.58	99.83
	28D	Blend in opaque white capsule	101.47	99.83
	2M	Blend in opaque white capsule	99.14	99.83
	3M	Blend in opaque white capsule	102.19	99.83
10 mg dose in 1:10 blend 2 (Starch) at 25°C/60% RH				
Capsule	**Time**	**Appearance**	**Assay (%)**	**Purity (%)**
Size #0 HG	0	Blend in opaque white capsule	100.00	99.83
	7D	Blend in opaque white capsule	99.23	99.83
	14D	Blend in opaque white capsule	98.70	99.83
	28D	Blend in opaque white capsule	99.45	99.83
	2M	Blend in opaque white capsule	100.29	99.83
	3M	Blend in opaque white capsule	99.99	99.83

Table **21.3: Stability of 10 mg active 50:50 blend in capsule at 25°C/60%RH**

10 mg dose in 50:50 blend 1 (MCC) at 25°C/60% RH				
Capsule	**Time**	**Appearance**	**Assay (%)**	**Purity (%)**
Size #0 HG	0	Blend in opaque white capsule	100.00	99.83
	7D	Blend in opaque white capsule	98.90	99.83
	14D	Blend in opaque white capsule	101.36	99.83
	28D	Blend in opaque white capsule	100.42	99.83
	2M	Blend in opaque white capsule	101.94	99.83
	3M	Blend in opaque white capsule	100.97	99.83
10 mg dose in 50:50 blend 2 (Starch) at 25°C/60% RH				
Capsule	**Time**	**Appearance**	**Assay (%)**	**Purity (%)**
Size #0 HG	0	Blend in opaque white capsule	100.00	99.83
	7D	Blend in opaque white capsule	99.78	99.83
	14D	Blend in opaque white capsule	98.42	99.83
	28D	Blend in opaque white capsule	98.98	99.83
	2M	Blend in opaque white capsule	101.14	99.83
	3M	Blend in opaque white capsule	102.01	99.83

Table **21.4 Stability of 100 mg active 50:50 blend in capsule at 25°C/60% RH**

100 mg dose in 50:50 blend 1 (MCC) at 25°C/60% RH				
Capsule	**Time**	**Appearance**	**Assay (%)**	**Purity (%)**
Size #0 HG	0	Blend in opaque white capsule	100.00	99.83
	7D	Blend in opaque white capsule	102.11	99.83
	14D	Blend in opaque white capsule	101.52	99.83
	28D	Blend in opaque white capsule	99.93	99.83
	2M	Blend in opaque white capsule	101.54	99.83
	3M	Blend in opaque white capsule	101.33	99.83
100 mg dose in 50:50 blend 2 (Starch) at 25°C/60% RH				
Capsule	**Time**	**Appearance**	**Assay (%)**	**Purity (%)**
Size #0 HG	0	Blend in opaque white capsule	100.00	99.83
	7D	Blend in opaque white capsule	100.70	99.83
	14D	Blend in opaque white capsule	102.06	99.83
	28D	Blend in opaque white capsule	98.13	99.83
	2M	Blend in opaque white capsule	100.85	99.83
	3M	Blend in opaque white capsule	103.63	99.83

The dissolution of Blend 1 at the 1:10 Compound 1 to MCC ratio in size #0 HG capsules was evaluated at both 1 and 10 mg of active (10 and 100 mg of blend with MCC, respectively). The dissolution method used the following conditions:

Parameters	**Setting**
Instrument	Agilent 708-DS
Media	0.1 N HCl with 2%SDS
Apparatus	USP Apparatus 2 (paddle)
Rotation Speed	75 rpm (200 rpm for infinity spin)
Media Volume	900 mL
Temperature	37.0 ±0.5°C
Sampling time point	15, 30, 45, 60 mins and infinity at 120 mins

The results are showing in Figure 3, where 50.3% of the 1 mg dose strength capsule released after 120 minutes, and 20.5% of the 10 mg dose strength capsule released after 120 minutes.

A further prototype blend capsule formulation was prepared to evaluate the effect of adding surfactant to the 1:10 MCC capsule blend (Blend 1). A 1:10 Compound 1:MCC with 2% SLS (25 mg of blend and 0.5 mg SLS) was hand filled into size #4 hard gelatin capsules (dose level was 2.5 mg of active per capsule) for evaluation in a stability study (Table 21.3), cross-over monkey PK study and dissolution test.

Table **21.5 Stability of 2.5 mg active 1:10 blend with 2% surfactant**

2.5 mg dose in blend MCC with 2% SLS at RT for monkey PK study				
Capsule	**Time (Day)**	**Appearance**	**Assay (%)**	**Purity (%)**
Size #4 HG	0	Blend in opaque white capsule	100.00	99.83
	7	Blend in opaque white capsule	101.98	99.83
2.5 mg dose in blend MCC with 2% Poloxamer 188 at RT for monkey PK study				
Capsule	**Time**	**Appearance**	**Assay (%)**	**Purity (%)**
Size #4 HG	0	Blend in opaque white capsule	100.00	99.83
	7	Blend in opaque white capsule	97.39	99.83

Three male monkeys were orally administered 0.5 mg/kg of body weight in a fasted state and plasma samples were analyzed for Compound 1 levels. The resulting Compound 1

levels in the plasma showed no significant increase in exposure for the MCC blend capsule with surfactant (area-under the curve from 0 to infinity, AUC[0-inf] = 1,004 ng-hr/mL) compared to without surfactant (AUC[0-inf] = 994 ng-hr/mL).

The Blend 1 MCC capsules with and without surfactant were also evaluated in an *in vitro* dissolution study at a dose strength of 2.5 mg Compound 1.

The dissolution method used the following conditions:

Parameters	**Setting**
Instrument	Agilent 708-DS
Media	0.1 N HCl with 2%SDS
Apparatus	USP Apparatus 2 (paddle)
Rotation Speed	75 rpm (200 rpm for infinity spin)
Media Volume	900 mL
Temperature	37.0 ±0.5°C
Sampling time point	15, 30, 45, 60 mins and infinity at 120 mins

The dissolution results are shown in Figure 4, where the addition of 2% SDS to the formulation significantly increased the in vitro dissolution release, from 38% release after 120 minutes with Poloxamer 188 to 54% release after 120 minutes with SLS.

Table 22 provides other exemplified formulations for blend capsules (prototypes 1-12).

Table 22. Exemplified formulations

Ingredient	**Trade Example (supplier)**	**Function**	**Amount (weight in grams) in Capsule**											
			1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
			1:10 Blend	*1:10 Blend*	*1:10 Blend*	*1:10 Blend*	*1:1 Blend*	*1:1 Blend*	*1:1 Blend*	*1:1 Blend*				
Compound 1	Pharmaceutical Active	Pharmaceutical Active	1.0	1.0	10.0	10.0	10.0	10.0	100.0	100.0	1.0	1.0	10.0	100.0
Starch	Starch 1500 (Colorcon)	Filler, Dispersant	10.0		100.0		10.0		100.0		5.0	2.5	2.5	25.0
Microcrystalline Cellulose (MCC)	Avicel (FMC)	Filler, Dispersant		10.0		100.0		10.0		100.0	5.0	2.5	2.5	25.0
Lactose	Lactose (FMC)	Filler, Dispersant										2.5	2.5	25.0
Mannitol	Mannitol (FMC)	Filler, Dispersant										2.5	2.5	25.0
Magnesium Stearate	Mangesium Stearate (FMC)	Lubricant, Flow Aid	0.22	0.22	2.2	2.2	0.40	2.2	2.2	2.2	0.1	0.1	0.2	1.0

Fumed silica	Glidant (Specialty Minerals)	Lubricant, Flow Aid									0.1	0.1	0.2	1.0
TOTAL			11.22	11.22	112.2	112.2	20.4	22.2	202.2	202.2	11.2	11.2	20.4	202.0

Examples of excipients that may be used in preparation of the formulations as disclosed in this application are shown in **Table 23**.

Table 23. Exemplified excipients

Drug Product	**Excipient**	**Example Trade Name (Supplier)**	**Function**
Capsule or Tablet	Cellulose, Microcrystalline	Cellulose, Microcrystalline, Compendial PH101 (DuPont)	Filler, Dispersant
	Croscarmellose Sodium	Croscarmellose Sodium SD-711 (DuPont)	Dispersant, Disintegrant
	Crospovidone	Crospovidone XL-10 (Ashland)	Dispersant, Disintegrant
	Mannitol	Mannitol 100SD (Roquette)	Filler, Dispersant
	Magnesium Stearate	Magnesium Stearate LIGAMED MF-2-V	Lubricant
	Poloxamer 188	Poloxamer 188 (FMC)	Surfactant, Dispersant
	Tween 80	Tween 80 (Spectrum Chemical)	Surfactant, Dispersant
	Sodium Lauryl Sulfate	Sodium Lauryl Sulfate SLS Fine (BASF)	Surfactant, Dispersant
	Colloidal Silicon Dioxide	Colloidal Silicon Dioxide Aerosil 200 Pharm (Evonik)	Lubricant
	Starch	Starch 1500 Partially Pregelatinized Maize starch 2001-NEC (Colorcon)	Filler, Dispersant
Suspension	Polysorbate 80	Tween 80 (Spectrum Chemical)	Surfactant, Wetting Agent
	Poloxamer 188	Pluronic F-68 (FMC)	Surfactant, Wetting Agent
	Methyl cellulose (MC)	Methyl cellulose, 400 cP, USP (Alpha Chemical)	Suspension aid, thickener
	Methyl cellulose (MC)	Methyl cellulose, 4000 cP, USP (Alpha Chemical)	Suspension aid, thickener
	Hydroxypropyl methyl cellulose (HPMC)	Hypermellose HPMC E-464 (Orison Chemicals)	Suspension aid, thickener
	Methyl Paraben	Methyl Paraben (Sigma Chemical)	Anti-microbial preservative
	Propyl Paraben	Propyl Paraben (Sigma Chemical)	Anti-microbial preservative
	Propylene Glycol (PG)	Propylene Glycol (Sigma Chemical)	Solubilizer, Co-Solvent
ASD	Hydroxypropylmethylcellulose acetate succinate (HPMCAS)	AquaSolve HPMC-AS (Ashland)	Polymer matrix, amorphous dispersant
	Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft co-polymer	Soluplus (BASF)	Polymer matrix, amorphous dispersant

	Poly(deoxyadenylic-thymidylic) acid sodium salt	Eudragit L100	Polymer matrix, amorphous dispersant
Solution	Polyethylene glycol 400 (PEG 400)	Kollisolv PEG 400 (BASF)	Solubilizer, Co-Solvent
	Polyethylene glycol 300 (PEG 300)	Kollisolv PEG 300 (BASF)	Solubilizer, Co-Solvent
	Hydrogenated castor oil	Kolliphor RH40 (BASF)	Solubilizer, Co-Solvent
	Linoleoyl Polyoxyl-6 glycerides	Labrafil M2125 CS (Gattefossé)	Solubilizer, Co-Solvent
	Diethylene glycol monoethyl ether	Transcutol HP (Gattefossé)	Solubilizer, Co-Solvent
	d-α-Tocopheryl polyethylene glycol 1000 succinate	Vitamin E TPGS (Parchem)	Solubilizer, Co-Solvent
	Ethanol	Ethanol (Cargill)	Solubilizer, Co-Solvent
	Propylene Glycol (PG)	Propylene Glycol (Sigma Chemical)	Solubilizer, Co-Solvent

Example 3. Pharmacokinetic studies of formulations comprising Compound 1

Pharmacokinetic (PK) studies were performed on animals with formulations as described in Example 2. Compound 1 was formulated to achieve desired dose (**Table 24**) and administered to a group of three fasted animals by single oral gavage. A minimum of 7 time points were used to collect blood samples and then prepared plasma samples for bio-analysis. PK parameters were then obtain after non-compartmental pharmacokinetic analysis by using the Phoenix WinNonlin software (version 6.3, Pharsight, Mountain View, CA). The linear/log trapezoidal rule was applied in obtaining the PK parameters. The nominal dose levels and nominal sampling times were used in the calculation of all pharmacokinetic parameters. **Table 24** summarizes the PK data. Results are summarized in the below table. Studies 14-17 were conducted under a crossover design. In the table, Prototype 2a solution is 58.1% KolliphorRH40 + 16.9% LabrafilM2125 CS + 8.3% Propylene glycol + 16.7% Ethanol. MC is methyl cellulose 400 cP, Tween 80 is Polyoxyethylene (80) sorbitan monooleate, HPMC-ASMF, soluplus, and Eudragit are polymers, and Poloxamer is co-polymer.

Table 24. Selected PK data of formulations tested in animals

Study	Dose (mg/kg)	Formulation	Species	Auc0-inf (ng/ml*hr)	(ng/mL)
1	5	(0.5%MC 400 cP,0.2% Tween 80) suspension	Rat	1094	A
2	5	(0.5%MC 400 cP,0.2% Tween 80) suspension	Rat	3015	B
3	5	Prototype 2a solution	Rat	3024*	B
4	5	(HPMC-ASMF) - ASD	Rat	5534	C
5	5	(Soluplus) - ASD	Rat	6728	D
6	5	(Eudragit L100) - ASD	Rat	6936	D
7	15	(0.5%MC 400 cP,0.2% Tween 80) suspension	Rat	5172*	C
8	15	(0.5%MC 400 cP,0.2% Tween 80) suspension - milled	Rat	13436	D
9	1	(Prototype 2a) solution	Dog	406	A
10	1	(0.5%MC 400 cP,0.2% Tween 80) suspension	Dog	174	A
11	1	(0.5%MC 400 cP,0.2% Tween 80) suspension - milled	Dog	303	A
12	0.5	(0.5% 400 cP MC, 0.2% Poloxamer 188) suspension - milled	C. Monkey	997	B
13	0.5	(0.5%MC 400 cP,0.2% Tween 80) suspension	C. Monkey	762	A
14	0.5	Size #4 hard gelatin capsule (1:10 blend with MCC)	C. Monkey	994	A
15	0.5	Size #4 hard gelatin capsule (ASD-3 HPMCASMF, Drug load (w%)= 18.22%)	C. Monkey	1358	B
16	0.5	Size #4 hard gelatin capsule (1:10 blend with MCC and 2%SLS)	C. Monkey	1004	A
17	1.0	Size #4 hard gelatin capsule (1:10 blend with MCC)	C. Monkey	1749	B

*Auc(0-Last)

For Cmax values in Table 24, A indicates greater than 50 ng/mL and up to 150 ng/mL, B indicates greater than 150 ng/mL and up to 300 ng/mL, C denotes indicates greater than 300 mg/mL and up to 600 mg/mL, and D indicates greater than 600 ng/mL and up to 900 ng/mL.

In addition, human PK and efficacious dose are estimated. Based on calculations, human efficacious dose for a neurological disorder (e.g., epilepsy) is about 2.5 to 100 mg (e.g., 60 mg), once a day.

Example 4. A Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Safety, Tolerability and Pharmacokinetics of Single and Multiple Ascending Doses and Food Effect of Compound 1 in Healthy Volunteers

This is a three-part clinical trial to evaluate the safety, tolerability, PK, and food effect of Compound 1 in healthy volunteers aged 18 to 55 years inclusive. The clinical trial is comprised of the following 3 parts:

- Part A is randomized, double-blinded and placebo-controlled. Part A is designed to investigate the safety and PK of single ascending doses of Compound 1.
- Part B is randomized, double-blinded and placebo-controlled. Part B is designed to investigate the safety and PK of multiple ascending doses of Compound 1 (selected based on the results from Part A).
- Part C is a randomized, open-label, crossover design to investigate the PK of a single dose of Compound 1 in the fasted and fed state.

OBJECTIVES AND ENDPOINTS:

Part A

Objective	Endpoint
Primary	
• To assess the safety and tolerability of single oral doses of Compound 1	• Incidence and severity of adverse events (AEs) • Changes in vital sign measurements • Changes in clinical laboratory results • Changes in electrocardiogram (ECG) parameters • Incidence of Columbia-Suicide Severity Rating Scale (C-SSRS) measured suicidal ideation or behavior
Secondary	
• To evaluate the pharmacokinetics (PK) of single oral doses of Compound 1	The following PK parameters will be calculated: • Maximum observed concentration (C_{max}) • Time to maximum observed concentration (t_{max}) • Apparent terminal elimination half-life ($t_{1/2}$) • Area under the concentration-time curve from time zero to the last measurable concentration ($AUC_{0\text{-last}}$) • Area under the drug concentration-time curve from time zero to infinity ($AUC_{0\text{-inf}}$) • Clearance (CL/F) • Volume of distribution (V_d/F) • Renal clearance (Clr) • Fraction of dose excreted unchanged in urine (fe)

	• Amount excreted unchanged over 72 hours (Ae_{0-72})
Exploratory	
• To evaluate the pharmacodynamic (PD) effect of Compound 1 on stimulated electroencephalography (EEG) endpoints using auditory stimulation	• Electroencephalography (EEG) measurement of auditory evoked responses (e.g., (auditory steady state response (ASSR))

Part B

Objective	Endpoint
Primary	
• To assess the safety and tolerability of 7-day repeat oral doses of Compound 1	• Incidence and severity of AEs • Changes in vital sign measurements • Changes in clinical laboratory results • Changes in electrocardiogram (ECG) parameters • Incidence of C-SSRS measured suicidal ideation or behavior
Secondary	
• To assess the pharmacokinetics (PK) of 7-day repeat oral doses of Compound 1	The following PK parameters will be calculated on Day 1 and Day 7: • C_{max} • t_{max} • AUC_{0-last} • Area under the concentration-time curve from time zero during a dosing interval (AUC_{tau}) • Time to steady state Accumulation ratio based on AUC (Rac (AUC)) Accumulation ratio based on C_{max} (Rac (C_{max}))
Exploratory	
• To evaluate the PD effect of Compound 1 on stimulated EEG endpoints using auditory stimulation.	• EEG measurement of auditory evoked responses (e.g., (auditory steady state response (ASSR)) • circulating metabolites profiling

Part C

Objective	Endpoint
Primary	
• To evaluate the effect of food on the pharmacokinetics (PK) of single oral doses of Compound 1	The following PK parameters, in fasted and fed states, will be calculated: • C_{max} • t_{max} • $AUC_{0\text{-last}}$, • $AUC_{0\text{-inf}}$
Secondary	
• To assess the safety and tolerability of oral doses of Compound 1 in the fasted and fed states	• Incidence and severity of AEs • Changes in vital sign measurements • Changes in clinical laboratory results • Changes in electrocardiogram (ECG) parameters • Incidence of C-SSRS measured suicidal ideation or behavior

Based on emerging safety and PK data from Part A, the SRC may select a starting dose for Part B prior to completion of all dose level cohorts in Part A. Part C may commence after the last SAD cohort. Parts A and B are double blinded, including participant and investigator; sponsor is unblinded to facilitate safety review. Each part consists of 3 periods: Screening, Intervention, and Safety Follow-up.

Screening/ Baseline Period

The Screening Period for all three parts will be up to 27 days in duration (Day-28 to Day-2).

Intervention Period

Following confirmation of continued eligibility, participants check-in to the clinic on Day -1 (the day before study drug administration) and assessments are performed. Participants remain in the unit from Baseline (Day -1) to Discharge (Day 6 in Part A, Day 12 in Part B, and Day 13 in Part C).

Part A

Healthy volunteers are enrolled to receive single ascending doses of Compound 1 or placebo on Day 1. Dose escalation in Part A is conducted in a total of 6 planned cohorts (Cohorts A1 to A6). Up to 3 additional cohorts may be studied at planned or intermediate dose levels. Eight participants are enrolled in each cohort and will be randomized to receive either Compound 1 or placebo (ratio 3:1). Compound 1 is administered to Cohort A1 participants at the starting dose of 2.5 mg. Dosing in all cohorts is under fasted conditions.

Dosing in each dose level cohort starts with 2 sentinel participants with one of the 2 participants randomized to receive Compound 1 and the other participant randomized to receive placebo. The safety and tolerability of each sentinel participant are monitored until Day 6 and reviewed prior to dosing the remainder of participants in each cohort.

Cohorts are dosed in an escalating order. After each dose cohort in Part A has completed dosing, blinded cumulative safety data collected up to Day 6 and available blinded PK data are reviewed by the Safety Review Committee (SRC) to determine the safety and tolerability of the study drug.

If the current dose level is determined to be safe and tolerated, the next dose cohort is enrolled and randomized to receive the selected dose of active Compound 1 or placebo. EEG to assess the effect of Compound 1 on auditory evoked responses may be performed in one or more cohorts, as determined based on the safety and PK profile.

Part A Dosing Regimen

Cohort	Study Drug	Dose and Route of Administration
A1	Compound 1	2.5 mg, oral, fasted
A2	Compound 1	Up to 10 mg, oral, fasted
A3	Compound 1	Up to 30 mg, oral, fasted
A4	Compound 1	Up to 60 mg, oral, fasted
A5	Compound 1	Up to 90 mg, oral, fasted
A6	Compound 1	Up to 120 mg, oral, fasted

Part B

The starting dose level in Part B is determined by the SRC based on safety, tolerability and PK data obtained in Part A. The SRC may select a starting dose for Part B prior to completion of all dose level cohorts in Part A.

A dose level is evaluated in Part B if determined to be safe and tolerable in Part A. It is anticipated that 3 dose levels are evaluated in Part B in a total of 3 cohorts (Cohorts B1-B3). One additional cohort may be added to repeat a dose level or study an intermediate dose. Eight participants are enrolled in each cohort and randomized to receive either Compound 1 or placebo (ratio 3:1).

Compound 1 dose levels to be evaluated in Part B do not exceed doses studied in part A. Dosing commences on Day 1 and continue until Day 7. The last dose is administered on

the morning of Day 7. Dosing in all cohorts in Part B is under fasted conditions. Two sentinel participants are planned for each dose cohort in Part B.

Part B Dosing Regimen

Cohort	Study Drug	Daily Dose and Route of Administration
B1	Compound 1	Up to 60 mg, oral, fasted
B2	Compound 1	Up to 90 mg, oral, fasted
B3	Compound 1	Up to 120 mg, oral, fasted

After each dose cohort in Part B has completed dosing with study drug, the SRC reviews blinded safety data (including safety assessments performed on Day 9) and available PK data to determine the safety and tolerability of the study drug, following the same procedures in Part A.

EEG to assess the effect of Compound 1 on auditory evoked responses may be performed in one or more cohorts, as determined by Sponsor based on the safety and PK profile.

Part C

Part C may commence once the safety and PK have been adequately evaluated in the last cohort of Part A. Up to 16 participants receive two doses of Compound 1, one dose after a minimum of 10 hours fasting and one after consumption of a high-fat, high calorie meal in a randomized crossover design, with a 7 day washout in between periods. Up to 3 additional days of washout may be added between fasted and fed dosing based on the observed half-life in Part A.

The dose to be used in Part C does not exceed those used in Part A and is approved by the SRC based on the accrued safety and PK data. Sentinel dosing may be used in Part C if considered appropriate by the SRC. Part C is not blinded.

Safety Assessments and Monitoring

Safety and tolerability assessments include vital signs, 12-lead ECGs, physical examinations, clinical laboratory tests, and the C-SSRS as outlined in the SoAs.

NUMBER OF PARTICIPANTS:

- Part A: Up to 72 are planned to be administered Compound 1 or placebo.
- Part B: Up to 32 are planned to be administered Compound 1 or placebo.
- Part C: Up to 16 are planned to be administered Compound 1.

Exclusion Criteria

A participant who meets any of the following criteria, among other things, at Screening is excluded from this clinical trial:

- Any abnormal ECG finding assessed as clinically significant by the Investigator, including a QT interval with Fridericia correction method (QTcF) >450 msec, confirmed with 1 repeat testing as needed, at Screening or Day 1.
- Use of systemic prescription medications or over-the-counter (OTC) medication, including multivitamins, and dietary and herbal supplement within 2 weeks or 5 times the terminal half-lives of the medication prior to first dose of study drug, whichever is longer and for the duration of the study.

TEST PRODUCT, REFERENCE THERAPY, ADMINISTRATION:

- Part A: Compound 1 capsules or matching placebo are administered orally.
- Part B: Compound 1 capsules or matching placebo are administered orally.
- Part C: Compound 1 capsules are administered orally.

STATISTICAL METHODS:

PK Analyses: A validated bioanalytical method is utilized for the determination of plasma and urine concentrations of Compound 1. Plasma and urine concentrations are summarized by dose group/condition and timepoint using descriptive statistics. In addition to descriptive statistics specified in General Conditions above, plasma concentrations are also summarized using number and percentage of concentrations below the level of quantification (BLQ) and coefficient of variation (CV%).

Pharmacokinetic parameters are estimated from concentration-time data using standard non-compartmental methods. Urine PK parameters are estimated from urine concentration and urine volume data. PK parameters are summarized by dose group/condition using descriptive statistics. In addition to descriptive statistics specified in General Conditions above, PK parameters are summarized using CV%, geometric mean, and geometric coefficient of variation. PK parameters are assessed for linearity and dose proportionality using the power model where feasible. To test for a food effect in Part C, the geometric mean ratio (ln transformed) of the test treatment (ie, fed condition) relative to the reference treatment (ie, fasted condition) are estimated with the 90% CIs calculated for C_{max} and $AUC_{0\text{-}inf}$. Absence of a food effect are concluded if the 90% CIs for the ratios of both C_{max} and $AUC_{0\text{-}inf}$ are completely contained within the interval of 0.80 to 1.25. If there is

unexpected difficulty in determining the terminal half-life, $AUC_{0\text{-last}}$ may be used in place of $AUC_{0\text{-inf}}$.

Example 5. A Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Safety, Tolerability and Pharmacokinetics of Single and Multiple Ascending Doses and Food Effect of Compound 1 in Healthy Volunteers

This is a three-part clinical trial to evaluate the safety, tolerability, PK, and food effect of Compound 1 in healthy volunteers aged 18 to 55 years inclusive. The clinical trial is comprised of the following 3 parts:

- Part A is randomized, double-blinded and placebo-controlled. Part A is designed to investigate the safety, tolerability, and PK of single ascending doses of Compound 1 from 2.5 mg to 90 mg.
- Part B is randomized, double-blinded and placebo-controlled. Part B is designed to investigate the safety, tolerability, and PK of multiple ascending doses of Compound 1 (doses selected based on the results from Part A).
- Part C is a randomized, open-label, crossover design to investigate the PK, safety and tolerability of a single dose of Compound 1 in the fasted and fed state (dose selected based on the results from Part A).

OBJECTIVES AND ENDPOINTS:

Part A

Objective	Endpoint
Primary	
• To assess the safety and tolerability of single oral doses of Compound 1	• Incidence and severity of adverse events (AEs) • Changes in vital sign measurements • Changes in clinical laboratory results • Changes in electrocardiogram (ECG) parameters • Incidence of Columbia-Suicide Severity Rating Scale (C-SSRS) measured suicidal ideation or behavior
Secondary	
• To evaluate the pharmacokinetics (PK) of single oral doses of Compound 1	The following PK parameters will be calculated: • Maximum observed concentration (C_{max}) • Time to maximum observed concentration (t_{max})

	• Apparent terminal elimination half-life ($t_{1/2}$) • Area under the concentration-time curve from time zero to the last measurable concentration (AUC_{last}) • Area under the drug concentration-time curve from time zero to infinity (AUC_{inf}) • Clearance (CL/F) • Volume of distribution (V_d/F) • Renal clearance (Clr) • Fraction of dose excreted unchanged in urine (fe) • Amount excreted unchanged over hours (Ae_{0-72})
Exploratory	
• To evaluate the pharmacodynamic (PD) effect of Compound 1 on stimulated electroencephalography (EEG) endpoints using auditory stimulation	• Electroencephalography (EEG) measurement of auditory evoked responses (e.g., (auditory steady state response (ASSR))

Part B

Objective	Endpoint
Primary	
• To assess the safety and tolerability of 7-day repeat oral doses of Compound 1	• Incidence and severity of AEs • Changes in vital sign measurements • Changes in clinical laboratory results • Changes in electrocardiogram (ECG) parameters • Incidence of C-SSRS measured suicidal ideation or behavior
Secondary	
• To assess the pharmacokinetics (PK) of 7-day repeat oral doses of Compound 1	The following PK parameters will be calculated: • C_{max} • t_{max} • AUC_{last} • Area under the concentration-time curve from time zero during a dosing interval (AUC_{tau}) • Time to steady state • Accumulation ratio based on AUC (Rac (AUC)) • Accumulation ratio based on C_{max} (Rac (C_{max}))
Exploratory	

• To evaluate the PD effect of Compound 1 on stimulated EEG endpoints using auditory stimulation.	• EEG measurement of auditory evoked responses (e.g., (auditory steady state response (ASSR))

Part C

Objective	Endpoint
Primary	
• To evaluate the effect of food on the pharmacokinetics (PK) of single oral doses of Compound 1	The following PK parameters, in fasted and fed states, will be calculated: • C_{max} • t_{max} • AUC_{last} • AUC_{inf}
Secondary	
• To assess the safety and tolerability of oral doses of Compound 1 in the fasted and fed states	• Incidence and severity of AEs • Changes in vital sign measurements • Changes in clinical laboratory results • Changes in electrocardiogram (ECG) parameters • Incidence of C-SSRS measured suicidal ideation or behavior

Based on emerging safety and PK data from Part A, the SRC may select a starting dose for Part B prior to completion of all dose level cohorts in Part A. Part C may commence after the last SAD cohort. Parts A and B are double blinded, including participant and investigator; sponsor is unblinded to facilitate safety review. Each part consists of 3 periods: Screening, Intervention, and Safety Follow-up.

Following confirmation of continued eligibility, participants check-in to the clinic on Day -1 (the day before study drug administration) and assessments are performed. Participants remain in the unit from Baseline (Day -1) to Discharge (Day 6 in Part A, Day 12 in Part B, and Day 13 in Part C).

Part A

Healthy volunteers are enrolled to receive single ascending doses of Compound 1 or placebo on Day 1. Dose escalation in Part A is conducted in a total of 6 planned cohorts (Cohorts A1 to A6). Up to 3 additional cohorts may be studied at planned or intermediate dose levels. Eight participants are enrolled in each cohort and will be randomized to receive either Compound 1 or placebo (ratio 3:1). Compound 1 is administered to Cohort A1 participants at the starting dose of 2.5 mg. Dosing in all cohorts is under fasted conditions.

Dosing in each dose level cohort starts with 2 sentinel participants with one of the 2 participants randomized to receive Compound 1 and the other participant randomized to receive placebo. The safety and tolerability of each sentinel participant are monitored until Day 6 and reviewed prior to dosing the remainder of participants in each cohort.

Cohorts are dosed in an escalating order. After each dose cohort in Part A has completed dosing, blinded cumulative safety data collected up to Day 6 and available blinded PK data are reviewed by the Safety Review Committee (SRC) to determine the safety and tolerability of the study drug.

If the current dose level is determined to be safe and tolerated, the next dose cohort is enrolled and randomized to receive the selected dose of active Compound 1 or placebo. EEG to assess the effect of Compound 1 on auditory evoked responses may be performed in one or more cohorts, as determined based on the safety and PK profile.

Part A Dosing Regimen

Cohort	Study Drug	Dose and Route of Administration
A1	Compound 1	2.5 mg, oral, fasted
A2	Compound 1	Up to 7.5 mg, oral, fasted
A3	Compound 1	Up to 15 mg, oral, fasted
A4	Compound 1	Up to 30 mg, oral, fasted
A5	Compound 1	Up to 60 mg, oral, fasted
A6	Compound 1	Up to 90 mg, oral, fasted

Part B

The starting dose level in Part B is determined by the SRC based on safety, tolerability and PK data obtained in Part A. The SRC may select a starting dose for Part B prior to completion of all dose level cohorts in Part A.

A dose level is evaluated in Part B if determined to be safe and tolerable in Part A. It is anticipated that 3 dose levels are evaluated in Part B in a total of 3 cohorts (Cohorts B1-B3). One additional cohort may be added to repeat a dose level or study an intermediate dose. Participants are enrolled in each cohort and randomized to receive either Compound 1 or placebo (ratio 3:1).

Compound 1 dose levels to be evaluated in Part B do not exceed doses studied in part A. Dosing commences on Day 1 and continue until Day 7. The last dose is administered on

the morning of Day 7. Dosing in all cohorts in Part B is under fasted conditions. Two sentinel participants are planned for each dose cohort in Part B.

Part B Dosing Regimen

Cohort	Study Drug	Daily Dose and Route of Administration
B1	Compound 1	Up to 30 mg, oral, fasted
B2	Compound 1	Up to 60 mg, oral, fasted
B3	Compound 1	Up to 90 mg, oral, fasted

After each dose cohort in Part B has completed dosing with study drug, the SRC reviews blinded safety data (including safety assessments performed on Day 9) and available PK data to determine the safety and tolerability of the study drug, following the same procedures in Part A.

EEG to assess the effect of Compound 1 on auditory evoked responses may be performed in one or more cohorts, as determined by Sponsor based on the safety and PK profile.

Part C

Part C may commence once the safety and PK have been adequately evaluated in the last cohort of Part A. Participants receive two doses of Compound 1, one dose after a minimum of 10 hours fasting and one after consumption of a high-fat, high calorie meal in a randomized crossover design, with a 7 day washout in between periods. Up to 3 additional days of washout may be added between fasted and fed dosing based on the observed half-life in Part A.

The dose to be used in Part C does not exceed those used in Part A and is approved by the SRC based on the accrued safety and PK data. Sentinel dosing may be used in Part C if considered appropriate by the SRC. Part C is not blinded.

Safety Assessments and Monitoring

Safety and tolerability assessments include vital signs, 12-lead ECGs, physical examinations, clinical laboratory tests, and the C-SSRS.

Exclusion Criteria

A participant who meets any of the following criteria, among other things, at Screening is excluded from this clinical trial:

- Any abnormal ECG finding assessed as clinically significant by the Investigator, including a QT interval with Fridericia correction method (QTcF) >450 msec, confirmed with 1 repeat testing as needed, at Screening or Day 1.
- Use of systemic prescription medications or over-the-counter (OTC) medication, including multivitamins, and dietary and herbal supplement within 2 weeks or 5 times the terminal half-lives of the medication prior to first dose of study drug, whichever is longer and for the duration of the study.

TEST PRODUCT, REFERENCE THERAPY, ADMINISTRATION:

- Part A: Compound 1 capsules or matching placebo are administered orally.
- Part B: Compound 1 capsules or matching placebo are administered orally.
- Part C: Compound 1 capsules are administered orally.

STATISTICAL METHODS:

PK Analyses: A validated bioanalytical method (e.g., Liquid chromatography–mass spectrometry (LC-MS)) is utilized for the determination of plasma and urine concentrations of Compound 1. Plasma and urine concentrations are summarized by dose group/condition and timepoint using descriptive statistics. In addition to descriptive statistics specified in General Conditions above, plasma concentrations are also summarized using number and percentage of concentrations below the level of quantification (BLQ) and coefficient of variation (CV%).

Pharmacokinetic parameters are estimated from concentration-time data using standard non-compartmental methods. Urine PK parameters are estimated from urine concentration and urine volume data. PK parameters are summarized by dose group/condition using descriptive statistics. In addition to descriptive statistics specified in General Conditions above, PK parameters are summarized using CV%, geometric mean, and geometric coefficient of variation. PK parameters are assessed for linearity and dose proportionality using the power model where feasible. To test for a food effect in Part C, the geometric mean ratio (ln transformed) of the test treatment (i.e., fed condition) relative to the reference treatment (i.e., fasted condition) are estimated with the 90% CIs calculated for C_{max} and AUC_{inf}. Absence of a food effect are concluded if the 90% CIs for the ratios of both C_{max} and AUC_{inf} are

completely contained within the interval of 0.80 to 1.25. If there is unexpected difficulty in determining the terminal half-life, AUC_{last} may be used in place of AUC_{inf}.

Results

Preliminary analysis of the first four of six planned cohorts of the study in Part A indicate that Compound 1 appears to be well tolerated at the doses tested. Safety data reviewed included adverse events, vital signs, ECG, C-SSRS, physical examination, and safety laboratory data. In the first three cohorts tested there have been no reported Serious Adverse Events, severe Adverse Events, or any Adverse Events leading to study withdrawal or discontinuation.

Based on the preliminary data, exposure appears to increase proportionate to dose level and maximal concentrations are achieved in 2-3 hours. Terminal elimination half-life averages 114 hours (~4-5 days) across groups. 90% of steady-state should be achieved in approximately 2 weeks with once daily dosing.

Example 5. A Randomized Double-Blind Comparison of the Efficacy and Safety of Compound 1 to Placebo for the Acute and Prophylactic Treatment of Chronic SUNCT and SUNA

This multi-center clinical trial will assess the efficacy, safety, tolerability, and pharmacokinetics of Compound 1 in participants, for example, aged 18 to 65 years with chronic SUNCT or chronic SUNA. This is a double-blind, placebo-controlled study. Participants will be randomized to receive 1 of 3 blinded treatments [Compound 1 high dose mg by mouth daily, Compound 1 low dose mg by mouth daily, or placebo by daily] in a 1:1:1 ratio. Participants will self-administer study drug once daily with weekly clinic visits. Participants will also be asked to respond to questions in an electronic diary (eDiary), for example, 3 times daily (pre-dose or approximately 24 hours after the previous dose, approximately 4 hours post-dose, and approximately 10 hours post-dose).

Objective	Endpoint
Primary	
To evaluate the effects of Compound 1 for the treatment of SUNCT and SUNA headaches	• Change in average daily frequency of SUNCT and SUNA headache attacks from baseline to Day 21 as recorded by eDiary • Change in average peak intensity of SUNCT and SUNA headache severity from baseline to Day 21 as measured by the Stanford Pain Scale

Secondary	
• To evaluate the effects of Compound 1 on the treatment of SUNCT and SUNA headaches	• Change in average daily frequency of attacks from baseline to average daily frequency throughout the study treatment period as recorded by eDiary • Change in average peak intensity of SUNCT and SUNA headache severity from baseline throughout the study period as measured by the Stanford Pain Scale
• To evaluate the safety and tolerability of Compound 1 in SUNCT and SUNA participants	• Incidence and severity of adverse events • Changes in vital sign measurements • Changes in clinical laboratory results • Changes in ECG parameters • Incidence of Columbia-Suicide Severity Rating Scale (C-SSRS) measured suicidal ideation or behavior
• To characterize the PK profile of Compound 1 in SUNCT and SUNA participants	• Plasma concentrations of Compound 1 and its potential metabolites • Primary PK parameters: C_{max}, t_{max}, and $AUC_{0\text{-}tau}$
Exploratory	
• To evaluate the effects of Compound 1 on other measures associated with SUNCT and SUNA	• Change in SUNCT and SUNA headache duration calculated as number of minutes of pain per day recorded by eDiary • Change in average daily frequency of autonomic symptoms as assessed by the participant • Change in autonomic symptoms as assessed by facial imaging • Change in response to triggering factors • Proportion of participants able to perform their usual daily activities • Changes in SF-36 total and factor scores • Patient satisfaction with treatment as measured by visual analog scale (VAS) • Change in Level of Disability from baseline to Day 21 • Proportion of patients in remission (defined as no headache for the observation interval) • Duration of remission

The clinical trial consists of 3 periods: Screening/Baseline, Intervention, and Safety Follow-up. An optional Washout period is also available for participants on preventative medications.

Screening/Baseline Period

The Screening period will be up to, e.g., 28 days (Day -28 to Day -1). An optional Washout period of up to, e.g., 14 days prior to Screening will be allowed for participants who

are discontinuing SUNCT or SUNA preventative medications (eg, carbamazepine, lamotrigine).

During Screening, participants will complete daily eDiary entries during e.g., a 14-day observation period to assess the stability, severity, and frequency of SUNCT and SUNA headaches.

Intervention Period

Following confirmation of eligibility during Screening, participants will complete baseline assessments (Day 1).

On Day 1, participants will return to the clinic to be randomized to 1 of 3 treatment groups and receive the first dose of study drug. Participants will remain in a clinical setting under medical observation for at least e.g., 6 hours. Headache logs will be completed via eDiary daily pre-dose (e.g., approximately 24 hours after the previous dose), and e.g., approximately 4 hours and 10 hours post-dose. After the first dose, participants will continue daily dosing at home through Day 21. Participants will return to the clinic on e.g., Day 7 (±1 day), Day 14 (±1 day), and Day 21 (±1 day) to complete assessments. At select sites, intensive PK sampling will be obtained in the clinic on e.g., Day 1, Day 7 (±1 day), Day 14 (±1 day), and Day 21 (±1 day).

Key safety measures will include clinical laboratory evaluations, 12-lead ECG, C-SSRS, and vital signs. Key efficacy assessments will include the Headache log via eDiary (see schedule of assessment for additional details). Blood samples will be obtained for the determination of Compound 1 plasma concentrations using a validated bioanalytical method and may also be used for exploratory method development and/or metabolite characterization.

Safety Follow-up Period

The Safety Follow-up period will take place from e.g., Day 22 to e.g., Day 36. At the end of the Safety Follow-up period, participants will return to the clinic on e.g., Day 57 (±1 day) for the end of study assessments. During this visit the following assessments will be performed: vital signs, physical examination, clinical laboratory tests, ECG, C-SSRS assessment, and efficacy assessments.

Adverse events and concomitant medication use and procedures will be monitored from the time of informed consent to Day 36 (±1 day). At that time, participants will have completed the clinical trial.

Inclusion/Exclusion Criteria

Participants are a female or male e.g., 18 to 65 years of age (inclusive) at screening and has greater than e.g., 1-year history of chronic SUNCT and SUNA headache with onset prior to 50 years of age and demonstrated of a minimum of e.g., 100 SUNCT and SUNA headaches over 14 days during the clinical trial observation period.

Test Product, Reference Therapy, Administration

High dose mg Compound 1 capsules, low dose mg Compound 1 capsules or placebo will be administered orally and provided in pre-packaged containers to participants.

Dose/Route/Regimen

Dose TBD with PK data. Route will be oral.

Statistical Methods

Safety, tolerability, PK, and efficacy variables will be summarized using descriptive statistics. Descriptive summaries for categorical variables will include counts and percentage. Descriptive summaries for continuous variables will include number of participants (n), mean, standard deviation (SD), median, minimum, and maximum. Where appropriate, 95% confidence intervals (CIs) may be reported. Summaries will be presented by time point, where appropriate.

Standard PK parameters will be estimated using non-compartmental methods based on the concentration-time data. These parameters will include, where possible, Cmax, tmax, and AUC0-tau Exploratory analyses examining the relationship between PK and efficacy parameters may be performed for the PK analysis set.

Primary and Secondary Efficacy Measures

Headache Log completed via eDiary

An electronic tablet application for collecting information about a participant's headache activity before dosing (or approximately 24 hours after the previous dose) and approximately 4 hours and 10 hours post-dose. Information collected at all timepoints will include the following: frequency of headaches, duration of headaches, and severity of headaches (measured by Stanford Pain Scale). Information collected at 10 hours post-dose only will include the following: types of attacks, associated symptoms, and triggering factors, autonomic symptoms. Other information that will be collected via eDiary at 10 hours post-dose will include the following: Visual Analog Scale (VAS), activities of daily living, and level of disability.

Stanford Pain Scale

The Stanford Pain Scale is a comparative pain scale with descriptions assigned to each of the scale values, which range from 0 (No pain) to 10 (Unimaginable unspeakable).

Pain rated from 0 through 3 is considered "Minor", pain rated from 4 through 6 is considered "Moderate", and pain rated from 7 through 10 is considered "Severe." The Stanford Pain Scale is completed by the participant.

Triggering Factors

Participants will be asked to rate whether their response to triggering factors (eg, brushing hair, touching face, chewing, etc.) has changed using a 5-point scale 0=no change 1=mild improvement 2=moderate improvement 3=significant improvement 4=resolution of triggering factors.

Visual Analog Scale

The visual analog scale will ask participants to rate their satisfaction with treatment using a Likert scale with categories ranging from 0=very poor effect to 10=very good effect.

Level of Disability

The participant's level of disability will be measured by the participant using a Goal Attainment Scale with the following categories: 0=no disability, 1= mild, 2=moderate, 3=severe, 4=unbearable.

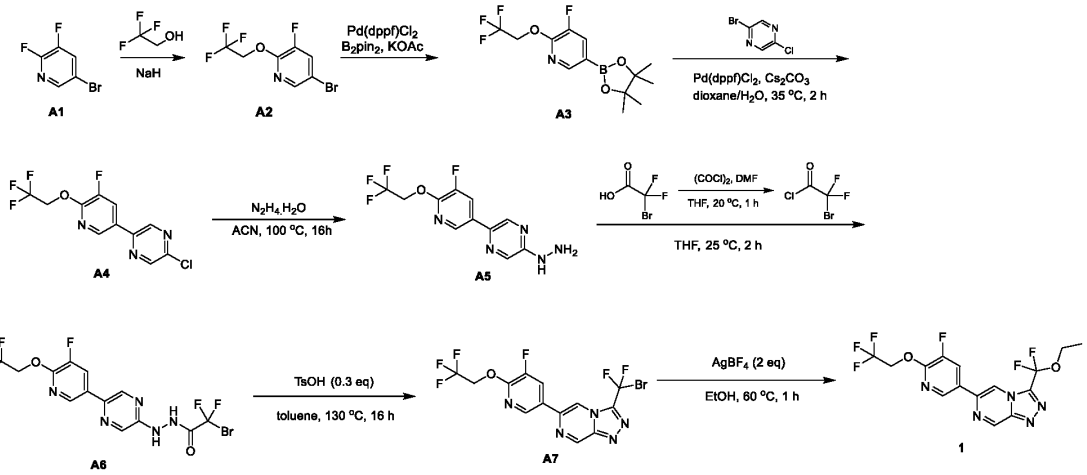
36-Item Short Form Health Survey (v2 Acute)

The SF-36 is a 36-item survey that measures the overall health status of a participant (McHorney et al., 1994). The SF-36 assesses 8 health concepts. The scores are weighted sums of the questions in each section. Scores range from 0 to 100 where lower scores indicate greater disability. The acute version of the SF-36 will be completed by the participant where indicated in the SoA. The acute version asks participants about their health status in the previous week.

Activities of Daily Living

The participant will be asked to assess change in their ability to complete activities of daily living.

Example 6. Synthesis of (3-[cyclopropylmethoxy(difluoro)methyl]-6-[5-fluoro-6-(2,2,2-trifluoroethoxy)-3-pyridyl]-[1,2,4]triazolo[4,3-a]pyrazine) (Compound 1)



Synthesis of A2: To a stirred solution of 2,2,2-trifluoroethanol (5.67 g, 56.71 mmol) in THF (200 mL) at 0 °C was added NaH (60% in mineral oil, 2.26 g, 56.71 mmol) in small portions. The reaction mixture was stirred for 15 min and 5-bromo-2,3-difluoro-pyridine (10.0 g, 51.55 mmol) was added drop-wise. The reaction mixture was slowly warmed to room temperature and stirred for 2 hours. The reaction mixture was cooled to 10 °C and treated with ice water (100 mL). The reaction mixture was extracted with ethyl acetate (2 x 100 mL). The organic layer was washed with brine (80 mL), dried over anhydrous Na_2SO_4 and concentrated. The crude compound was purified by column chromatography on silica gel with 2% ethyl acetate/PE to afford the product (10.5 g, 38.1 mmol, 73% yield). **LCMS**: 273.9 (M+H) and 276.0 (M+2+H), Rt 2.53 min Column: ZORBAX XDB C-18 (50 X 4.6 mm), 3.5 µm Mobile Phase: A: 0.1% HCOOH in water : ACN (95:5), B: ACN; Flow Rate: 1.5 mL/min.

Synthesis of A3: To a stirred solution of 5-bromo-3-fluoro-2-(2,2,2-trifluoroethoxy)pyridine (3.0 g, 10.95 mmol) and bis(pinacolato)diboron (3.61 g, 14.23 mmol) in 1,4-dioxane (30.0 mL) was added potassium acetate (2.15 g, 21.9 mmol). $Pd(dppf)Cl_2$·DCM (0.89 g, 1.09 mmol) was added to the reaction mixture under nitrogen atmosphere and heated at 80 °C for 12 hours. The reaction mixture was cooled to room temperature, filtered through Celite and concentrated under reduced pressure. The crude compound was purified by column chromatography on silica gel with 15% ethyl acetate/PE to afford the product (2.0 g, 6.2 mmol, 56% yield). **LCMS**: 322.1 (M+H), Rt 2.97 min Column: Atlantis dC18(50 X 4.6 mm), 5 µm Mobile Phase: A: 0.1% HCOOH in water : ACN (95:5), B: ACN; Flow Rate: 1.5 mL/min.

Synthesis of A4: A mixture of $Pd(dppf)Cl_2$ (15.13 g, 20.68 mmol), Cs_2CO_3 (269.49 g, 827.17 mmol), 3-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(2,2,2-trifluoroethoxy)pyridine (141.18 g, 439.69 mmol) and 2-bromo-5-chloro-pyrazine (80 g, 413.59 mmol) in 1,4-Dioxane (1 L) and Water (150 mL) under N_2 was stirred at 35 °C for 2 hours. After cooling to room temperature, to the mixture was added water (300 mL) and the mixture was filtered through Celite. After separating, the organic phase was washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product. The crude product was re-dissolved in EA/PE = 1/3 (500 mL) and then filtered through silica gel mat. The cake was washed with EA/PE = 1/3 (500 mL). The combined organic phase was concentrated to give a residue as oil. To the oil was added PE (500 mL) slowly and some solid was obtained. The solid was collected and dried in oven to give the product (100 g, 242.4 mmol, 58% yield) as a solid. **LCMS** R_t = 1.28 min in 2.0 min chromatography, 10-80AB, MS ESI calcd. for $C_{11}H_7ClF_4N_3O$ $[M+H]^+$ 308.0, found 307.9.

Synthesis of A5: A mixture of 2-chloro-5-[5-fluoro-6-(2,2,2-trifluoroethoxy)-3-pyridyl]pyrazine (140 g, 339.36 mmol) and hydrazine hydrate (169.88 g, 3393.6 mmol) in MeCN (1.4 L) was stirred at 100 °C for 16 hours. After cooling to room temperature, the mixture was poured into water (4.5 L). Some solid was observed and the solid was collected by filtered. The cake was washed with water (500 mL x 2). The solid was re-dissolved in EtOAc (3 L), washed with brine (500 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product (100 g, 329.8 mmol, 97% yield) as a solid. **LCMS** R_t = 0.74 min in 1.5 min chromatography, 5-95AB, MS ESI calcd. for $C_{11}H_{10}F_4N_5O$ $[M+H]^+$ 304.1, found 303.9.

Synthesis of A6: To a solution of 2-bromo-2,2-difluoro-acetic acid (87 g, 497.34 mmol) in THF (1 L) was added one drop of DMF and $(COCl)_2$ (50.5 mL, 596.81 mmol). The resulting mixture was stirred at 20 °C for 1 hour. The resulting solution was used into next step directly. To the solution of 2-bromo-2,2-difluoro-acetyl chloride (95.66 g, 494.69 mmol) in THF (1 L) was added [5-[5-fluoro-6-(2,2,2-trifluoroethoxy)-3-pyridyl]pyrazin-2-yl]hydrazine (100 g, 329.79 mmol). The resulting mixture was stirred at 20 °C for 2 hours. To the solution was added water (1 L), extracted with EtOAc (1L x 2). The combined organic phase was washed with brine (500 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product (150 g, 326.0 mmol, 98% yield, mixture of mono- and bis-alkylated products) as a solid. **LCMS** R_t = 0.92 min in 1.5 min chromatography, 5-95AB, MS ESI calcd. for $C_{13}H_9BrF_6N_5O_2$ $[M+H]^+$ 460.1, found 459.8.

Synthesis of A7: A solution of 2-bromo-2,2-difluoro-N'-[5-[5-fluoro-6-(2,2,2-trifluoroethoxy)-3-pyridyl]pyrazin-2-yl]acetohydrazide (150 g, 325.99 mmol) and TsOH (16.84 g, 97.8 mmol) in Toluene (1.5 L) was stirred at 130 °C for 16 hours. After cooling to room temperature, the mixture was poured into water (2 L), extracted with EtOAc (2L x 2). The combined organic phase was washed with brine (1 L x 2), dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product. The crude product was purified by chromatography flash on siliga gel (EtOAc in PE = 0% to 15% to 30%) to give the product (80 g, 181.0 mmol, 55% yield) as oil. **^{1}H NMR** ($CDCl_3$, 400MHz) δ_H = 9.60 (d, 1H), 8.55 (d, 1H), 8.45 (s, 1H), 8.09 (dd, 1H), 4.93 (q, 2H).

Synthesis of Compound 1: A mixture of 3-[bromo(difluoro)methyl]-6-[5-fluoro-6-(2,2,2-trifluoroethoxy)-3-pyridyl]-[1,2,4]triazolo[4,3-a]pyrazine (76 g, 171.9 mmol) and $AgBF_4$ (66.93 g, 343.81 mmol) in Ethanol (760 mL) was stirred at 60 °C for 1 hour. After cooling to room temperature, the mixture was poured into saturated aqueous NaCl (1 L) and EtOAc (2 L). The mixture was filtered through Celite. After separating, the aqueous layer was extracted with EtOAc (500 mL x 2). The combined organic phase was washed with brine (500 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product. The crude product was purified by chromatography flash column on silica gel (EtOAc in PE = 0% to 30% to 50%) and then triturated from EtOH (50 mL) to give the product (44.45 g, 109.01 mmol, 63% yield) as a solid. **^{1}H NMR** ($CDCl_3$ 400MHz) δ_H = 9.52 (d, 1H), 8.49 (dd, 2H), 8.07 (dd, 1H), 4.93 (q, 2H), 4.37 (q, 2H), 1.51 (t, 3H). **LCMS** R_t = 1.25 min in 2.0 min chromatography, 10-80AB, MS ESI calcd. for $C_{15}H_{12}F_6N_5O_2$ $[M+H]^+$ 408.1, found 408.0.

Equivalents and Scope

In the claims articles such as “a,” “an,” and “the” may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include “or” between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

Furthermore, the invention encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Where elements are presented as lists, e.g., in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should it be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements and/or features, certain embodiments of the invention or aspects of the invention consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth *in haec verba* herein. It is also noted that the terms "comprising" and "containing" are intended to be open and permits the inclusion of additional elements or steps. Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub–range within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the invention can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

CLAIMS

1. A dosage form comprising:

from about 0.1 mg to about 500 mg (e.g., from about 0.5 mg to about 200 mg, from about 1 mg to about 150 mg, from about 10 mg to about 120 mg) of Compound 1; and

a pharmaceutically acceptable excipient.

2. The dosage form of claim 1, wherein the dosage form comprises from about 2.5 mg to about 150 mg (e.g., from about 10 mg to about 150 mg, from about 20 mg to about 150 mg, from about 70 mg to about 120 mg, from about 30 mg to about 60 mg, about 100 mg, about 50 mg) of Compound 1.

3. A dosage form comprising:

a plurality of particles of Compound 1; and

a pharmaceutically acceptable excipient,

wherein the amount of the plurality of particles of Compound 1 in the dosage form is from about 0.1 mg to about 500 mg (e.g., from about 0.5 mg to about 200 mg, from about 1 mg to about 150 mg, from about 10 mg to about 120 mg).

4. The dosage form of claim 3, wherein the plurality of particles of Compound 1 in the dosage form is from about 2.5mg to about 150 mg (e.g., from about 10 mg to about 150 mg, from about 20 mg to about 150 mg, from about 70 mg to about 120 mg, from about 30 mg to about 60 mg, about 100 mg, about 50 mg).

5. The dosage form of claim 3 or 4, wherein 10% of the plurality of particles of Compound 1 have a particle size of less than about 1 μm.

6. The dosage form of any one of claims 3-5, wherein 50% of the plurality of particles of Compound 1 have a particle size of less than about 4 μm.

7. The dosage form of claim 6, wherein 50% of the plurality of particles of Compound 1 have a particle size of less than about 2 μm.

8. The dosage form of any one of claims 3-7, wherein 90% of the plurality of particles of Compound 1 have a particle size of less than about 30 μm (e.g., less than about 15 μM).

9. The dosage form of claim 8, wherein 90% of the plurality of particles of Compound 1 have a particle size of less than about 5 μm.

10. The dosage form of claim 9, wherein 10% of the plurality of particles of Compound 1 have a particle size of less than about 1 μm, 50% of the plurality of particles of Compound 1 have a particle size of less than about 4 μm and 90% of the plurality of particles of Compound 1 have a particle size of less than about 30 μm.

11. The dosage form of any one of claims 1-10, wherein the dosage form is for oral administration.

12. The dosage form of any one of claims 1-11, wherein the dosage form is a solid form.

13. The dosage form of any one of claims 1-12, wherein Compound 1 is crystalline.

14. The dosage form of any one of claims 1-13, wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 12.6±0.2, 15.8±0.2, and 18.6±0.2.

15. The dosage form of any one of claims 1-14, wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 10.7±0.2, 12.3±0.2, 12.6±0.2, 15.8±0.2, 18.6±0.2, and 22.6±0.2.

16. The dosage form of any one of claims 1-15, wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 10.7±0.2, 12.3±0.2, 12.6±0.2, 14.9±0.2, 15.8±0.2, 16.6±0.2, 16.8±0.2, 18.6±0.2, 21.0±0.2 and 22.6±0.2.

17. The dosage form of any one of claims 1-16, wherein the crystalline form exhibits an X-ray powder diffraction pattern substantially the same as depicted in FIG. 1.

18. The dosage form of any one of claims 1-17, wherein the dosage form is in the form of a capsule.

19. The dosage form of any one of claims 1-18, wherein the dosage form is in the form of a blend.

20. The dosage form of claim 18 or 19, wherein the pharmaceutical excipient is a filler (e.g., microcrystalline cellulose or starch).

21. The dosage form of any one of claims 18-20, wherein the ratio of Compound 1 to the filler is about 1:1.

22. The dosage form of any one of claims 18-20, wherein the ratio of Compound 1 to the filler is about 1:10.

23. The dosage form of any one of claims 18-20, wherein the pharmaceutical excipient is a filler or a lubricant.

24. The dosage form of any one of claims 18-23, wherein the dosage form comprises:
from about 50% to 90% by weight filler and
from 0% to about 5% by weight lubricant.

25. The dosage form of any one of claims 18-23, wherein the dosage form comprises:
from about 1% to about 50% by weight Compound 1;
from about 50% to about 90% by weight filler; and

from 0% to about 4% by weight lubricant.

26. The dosage form of any one of claims 1, 2, and 11, wherein the dosage form is a liquid form.

27. The dosage form of claim 26, wherein the dosage form is in the form of a solution.

28. The dosage form of claim 27, wherein the pharmaceutical excipient is selected from the group consisting of a co-solubilizer/co-solvent (e.g., polymer (e.g., PEG 400)), an emulsifier (e.g., a castor oil derivative, e.g., Kolliphor RH40), a surfactant (e.g., a glyceride (e.g., Labrafil M2125 CS), a vitamin derivative (e.g., Vitamin ETPGS)), a solvent (e.g., propylene glycol, ethanol, diethylene glycol monoethyl ether (or Transcutol HP)).

29. The dosage form of any one of claims 26-28, wherein the concentration of Compound 1 is from about 0.1 mg/mL to about 10 mg/mL.

30. The dosage form of any one of claims 26-28, wherein the dosage form comprises:

from about 35% to about 45% by weight a filler (e.g., a polymer (e.g., PEG 400));

from about 5% to about 15% by weight an emulsifier (e.g., a castor oil derivative (e.g., Kolliphor RH40); and

from about 40% to about 60% by weight water;

wherein the concentration of Compound 1 is about 0.5 mg/mL or about 0.25 mg/mL.

31. The dosage form of any one of claims 26-28, wherein the dosage form comprises:

from about 55% to about 60% by weight an emulsifier (e.g., a castor oil derivative (e.g., Kolliphor RH40);

from about 15% to about 20% by weight a surfactant (e.g., a glyceride (e.g., Labrafil M2125 CS);

from about 5% to about 10% by weight propylene glycol; and

from about 15% to about 20% by weight ethanol;

wherein the concentration of Compound 1 is from about 5 mg/mL to about 10 mg/mL, or from about 2.5 mg/mL to about 5 mg/mL.

32. The dosage form of any one of claims 26-28, wherein the dosage form comprises:

from about 65% to about 70% by weight an emulsifier (e.g., a castor oil derivative (e.g., Kolliphor RH40);

from about 18% to about 23% by weight a surfactant (e.g., a glyceride (e.g., Labrafil M2125 CS); and

from about 7% to about 12% by weight propylene glycol;

wherein the concentration of Compound 1 is from about 1 mg/mL to about 10 mg/mL or from about 0.5 mg/mL to about 5 mg/mL.

33. The dosage form of any one of claims 26-28, wherein the dosage form comprises:

from about 35% to about 45% by weight diethylene glycol monoethyl ether (Transcutol HP);

from about 5% to about 15% by weight a surfactant (e.g., a glyceride (e.g., a vitamin derivative (e.g., Vitamin ETPGS)); and

from about 40% to about 60% by weight water;

wherein the concentration of Compound 1 is from about 1 mg/mL to about 5 mg/mL or from about 0.5 mg/mL to about 2.5 mg/mL.

34. The dosage form of any one of claims 26-28, wherein the dosage form comprises:

from about 30% to about 40% by weight an emulsifier (e.g., a castor oil derivative (e.g., Kolliphor RH40);

from about 40% to about 50% by weight a surfactant (e.g., a glyceride (e.g., Capmul MCM C8);

from about 5% to 15% by weight a plasticizer (e.g., triethyl citrate); and

from about 5% to about 15% by weight a solvent (e.g., ethanol).

35. The dosage form of any one of claims 26-28, wherein the dosage form comprises:

from about 35% to about 45% by weight a propylene glycol monocaprylate (e.g., Capryol 90);

from about 15% to about 25% by weight a glyceride (e.g., caprylocaproyl macrogolglycerides (e.g., Labrasol)) and

from about 35% to 45% by weight diethylene glycol monoethyl ether (e.g., Transcutol HP).34. The dosage form of any one of claims 26-33, wherein the solution can be further diluted with a solvent (e.g., water), wherein the concentration of the diluted solution is from about 50% to about 90% of the solution before the dilution.

36. The dosage form of any one of claims 1, 2, 11, and 26, wherein the dosage form is in the form of a suspension.

37. The dosage form of claim 35, wherein the concentration of Compound 1 is about 0.1 mg/mL, about 0.5 mg, about 1 mg/mL, about 5 mg/mL, about 10 mg/mL, or about 15 mg/mL of Compound 1.

38. The dosage form of claim 36 or 37, wherein the pharmaceutical excipient comprises:

about 0.5% by weight a filler (e.g., methylcellulose, e.g., 400 cP MC); and

about 0.2% by weight an emulsifier (e.g., Tween 80, e.g., Poloxamer 188).

39. The dosage form of claim 38, wherein the pharmaceutical excipient further comprises about 1% by weight a preservative solution (e.g., paraben solution).

40. The dosage form of any one of claims 1, 2, and 11, wherein Compound 1 is amorphous.

41. The dosage form of any one of claims 1, 2, 11, and 40, wherein the dosage form is in the form of amorphous solid dispersion.

42. The dosage form of claim 41, wherein the pharmaceutical excipient is a polymer (e.g., soluplus, Eudragit, and HPMC ASMF).

43. The dosage form of any one of claims 1-42, wherein the dosage form is stable (e.g., chemically stable) at 25°C and 60% RH for 7 days, 14 days, 21 days, 28 days, 1 month, 3 months, or 6 months.

44. A composition in a dosage form comprising:

from about 0.1 mg to about 500 mg (e.g., from about 0.5 mg to about 200 mg, from about 1 mg to about 150 mg, from about 10 mg to about 120 mg) of Compound 1; and

a pharmaceutically acceptable excipient.

45. The composition of claim 44, wherein the composition comprises from about 2.5 mg to about 150 mg (e.g., from about 10 mg to about 150 mg, from about 20 mg to about 150 mg, from about 70 mg to about 120 mg, from about 30 mg to about 60 mg, about 100 mg, about 50 mg) of Compound 1.

46. A composition in a dosage form comprising:

a plurality of particles of Compound 1; and

a pharmaceutically acceptable excipient,

wherein the amount of the plurality of particles of Compound 1 in the composition is from about 0.1 mg to about 500 mg (e.g., from about 0.5 mg to about 200 mg, from about 1 mg to about 150 mg, from about 10 mg to about 120 mg).

47. The composition of claim 46, wherein the plurality of particles of Compound 1 in the composition is from about 2.5 mg to about 150 mg (e.g., from about 10 mg to about 150 mg, from about 20 mg to about 150 mg, from about 70 mg to about 120 mg, from about 30 mg to about 60 mg, about 100 mg, about 50 mg).

48. The composition of claim 46 or 47, wherein 10% of the plurality of particles of Compound 1 have a particle size of less than about 1 μm.

49. The composition of any one of claims 46-48, wherein 50% of the plurality of particles of Compound 1 have a particle size of less than about 4 μm.

50. The composition of claim 49, wherein 50% of the plurality of particles of Compound 1 have a particle size of less than about 2 μm.

51. The composition of any one of claims 46-50, wherein 90% of the plurality of particles of Compound 1 have a particle size of less than about 30 μm (e.g., less than about 15 μM).

52. The composition of claim 51 wherein 90% of the plurality of particles of Compound 1 have a particle size of less than about 5 μm.

53. The composition of claim 52, wherein 10% of the plurality of particles of Compound 1 have a particle size of less than about 1 μm, 50% of the plurality of particles of Compound 1 have a particle size of less than about 4 μm and 90% of the plurality of particles of Compound 1 have a particle size of less than about 30 μm.

54. The composition of any one of claims 44-53, wherein the composition is for oral administration.

55. The composition of any one of claims 44-54, wherein the dosage form is a solid form.

56. The composition of any one of claims 44-55, wherein Compound 1 is crystalline.

57. The composition of any one of claims 44-56, wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 12.6±0.2, 15.8±0.2, and 18.6±0.2.

58. The composition of any one of claims 44-57, wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 10.7±0.2, 12.3±0.2, 12.6±0.2, 15.8±0.2, 18.6±0.2, and 22.6±0.2.

59. The composition of any one of claims 44-58, wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 10.7±0.2, 12.3±0.2, 12.6±0.2, 14.9±0.2, 15.8±0.2, 16.6±0.2, 16.8±0.2, 18.6±0.2, 21.0±0.2 and 22.6±0.2.

60. The composition of any one of claims 44-59, wherein the crystalline form exhibits an X-ray powder diffraction pattern substantially the same as depicted in FIG. 1.

61. The composition of any one of claims 44-60, wherein the dosage form is in the form of a capsule.

62. The composition of any one of claims 44-61, wherein the dosage form is in the form of a blend.

63. The composition of claim 61 or 62, wherein the pharmaceutical excipient is a filler (e.g., microcrystalline cellulose or starch).

64. The composition of any one of claims 61-63, wherein the ratio of Compound 1 to the filler is about 1:1.

65. The composition of any one of claims 61-63, wherein the ratio of Compound 1 to the filler is about 1:10.

66. The composition of any one of claims 61-63, wherein the pharmaceutical excipient is a filler or a lubricant.

67. The composition of any one of claims 61-66, wherein the composition form comprises:

from about 50% to 90% by weight filler and

from 0% to about 5% by weight lubricant.

68. The composition of any one of claims 61-67, wherein the composition comprises:

from about 1% to about 50% by weight Compound 1;

from about 50% to about 90% by weight filler; and

from 0% to about 4% by weight lubricant.

69. The composition of any one of claims 44, 45, or 54, wherein the dosage form is a liquid form.

70. The composition of claim 69, wherein the dosage form is in the form of a solution.

71. The composition of claim 70, wherein the pharmaceutical excipient is selected from the group consisting of a co-solubilizer/co-solvent (e.g., polymer (e.g., PEG 400)), an emulsifier (e.g., a castor oil derivative, e.g., Kolliphor RH40), a surfactant (e.g., a glyceride (e.g., Labrafil M2125 CS), a vitamin derivative (e.g., Vitamin ETPGS)), a solvent (e.g., propylene glycol, ethanol, diethylene glycol monoethyl ether (or Transcutol HP)).

72. The composition of any one of claims 69-71, wherein the concentration of Compound 1 is from about 0.1 mg/mL to about 10 mg/mL.

73. The composition of any one of claims 69-71, wherein the compositon comprises:

from about 35% to about 45% by weight a filler (e.g., a polymer (e.g., PEG 400));

from about 5% to about 15% by weight an emulsifier (e.g., a castor oil derivative (e.g., Kolliphor RH40); and

from about 40% to about 60% by weight water;

wherein the concentration of Compound 1 is about 0.5 mg/mL or about 0.25 mg/mL.

74. The composition of any one of claims 69-71, wherein the composition comprises:

from about 55% to about 60% by weight an emulsifier (e.g., a castor oil derivative (e.g., Kolliphor RH40);

from about 15% to about 20% by weight a surfactant (e.g., a glyceride (e.g., Labrafil M2125 CS);

from about 5% to about 10% by weight propylene glycol; and

from about 15% to about 20% by weight ethanol;

wherein the concentration of Compound 1 is from about 5 mg/mL to about 10 mg/mL, or from about 2.5 mg/mL to about 5 mg/mL.

75. The composition of any one of claims 69-71, wherein the composition comprises:

from about 65% to about 70% by weight an emulsifier (e.g., a castor oil derivative (e.g., Kolliphor RH40);

from about 18% to about 23% by weight a surfactant (e.g., a glyceride (e.g., Labrafil M2125 CS); and

from about 7% to about 12% by weight propylene glycol;

wherein the concentration of Compound 1 is from about 1 mg/mL to about 10 mg/mL or from about 0.5 mg/mL to about 5 mg/mL.

76. The composition of any one of claims 69-71, wherein the composition comprises:

from about 35% to about 45% by weight diethylene glycol monoethyl ether (Transcutol HP);

from about 5% to about 15% by weight a surfactant (e.g., a glyceride (e.g., a vitamin derivative (e.g., Vitamin ETPGS)); and

from about 40% to about 60% by weight water;

wherein the concentration of Compound 1 is from about 1 mg/mL to about 5 mg/mL or from about 0.5 mg/mL to about 2.5 mg/mL.

77. The composition of any one of claims 69-71, wherein the composition comprises:

from about 30% to about 40% by weight an emulsifier (e.g., a castor oil derivative (e.g., Kolliphor RH40);

from about 40% to about 50% by weight a surfactant (e.g., a glyceride (e.g., Capmul MCM C8);

from about 5% to 15% by weight a plasticizer (e.g., triethyl citrate); and

from about 5% to about 15% by weight a solvent (e.g., ethanol).

78. The composition of any one of claims 69-71, wherein the composition comprises:

from about 35% to about 45% by weight a propylene glycol monocaprylate (e.g., Capryol 90);

from about 15% to about 25% by weight a glyceride (e.g., caprylocaproyl macrogolglycerides (e.g., Labrasol)) and

from about 35% to 45% by weight diethylene glycol monoethyl ether (e.g., Transcutol HP).

79. The composition of any one of claims 44, 45, 54, and 69, wherein the dosage form is in the form of a suspension.

80. The composition of claim 79, wherein the concentration of Compound 1 is about 0.1 mg/mL, about 0.5 mg, about 1 mg/mL, about 5 mg/mL, about 10 mg/mL, or about 15 mg/mL of Compound 1.

81. The composition of claim 79 or 80, wherein the pharmaceutical excipient comprises:

about 0.5% by weight a filler (e.g., methylcellulose, e.g., 400 cP MC); and

about 0.2% by weight an emulsifier (e.g., Tween 80, e.g., Poloxamer 188).

82. The composition of claim 81, wherein the pharmaceutical excipient further comprises about 1% by weight a preservative solution (e.g., paraben solution).

83. The composition of any one of claims 44, 45, and 54, wherein Compound 1 is amorphous.

84. The composition of any one of claims 44, 45, 54, and 83, wherein the dosage form is in the form of amorphous solid dispersion.

85. The composition of claim 84, wherein the pharmaceutical excipient is a polymer (e.g., soluplus, Eudragit, and HPMC ASMF).

86. The composition of any one of claims 44-85, wherein the composition is stable (e.g., chemically stable) at 25°C and 60% RH for 7 days, 14 days, 21 days, 28 days, 1 month, 3 months, or 6 months.

87. A method of treating a condition relating to aberrant function of a sodium ion channel in a subject in need thereof, comprising administering to the subject a dosage form or a composition of any one of claims 1-86.

88. A method of treating a condition relating to aberrant function of a sodium ion channel in a subject in need thereof, comprising administering to the subject from about 2.5 mg to about 90 mg of Compound 1.

89. The method of claim 87 or 88, wherein the condition is a neurological or psychiatric disorder.

90. The method of any one of claims 87-89, wherein the condition is epilepsy or an epilepsy syndrome.

91. The method of any one of claims 87-90, wherein the condition is a genetic epilepsy or a genetic epilepsy syndrome.

92. The method of any one of claims 87-91, wherein the condition is a pediatric epilepsy or a pediatric epilepsy syndrome.

93. The method of any one of claims 87-92, wherein the condition is developmental or epileptic encephalopathy.

94. The method of claim 93, wherein the developmental or epileptic encephalopathy is selected from the group consisting of Dravet syndrome, infantile spasms, or Lennox-Gastaut syndrome.

95. The method of any one of claims 87-94, wherein the condition is selected from the group consisting of epileptic encephalopathy, developmental and epileptic encephalopathy, epileptic encephalopathy with SCN1A, SCN2A, SCN8A mutations, early infantile epileptic encephalopathy, Dravet syndrome, Dravet syndrome with SCN1A mutation, generalized epilepsy with febrile seizures, intractable childhood epilepsy with generalized tonic-clonic seizures, infantile spasms, benign familial neonatal-infantile seizures, SCN2A epileptic encephalopathy, focal epilepsy with SCN3A mutation, cryptogenic pediatric partial epilepsy with SCN3A mutation, SCN8A epileptic encephalopathy, sudden unexpected death in epilepsy, Rasmussen encephalitis, malignant migrating partial seizures of infancy, autosomal dominant nocturnal frontal lobe epilepsy, sudden expected death in epilepsy (SUDEP), KCNQ2 epileptic encephalopathy, and KCNT1 epileptic encephalopathy.

96. The method of any one of claims 87-89, wherein the condition is a cancer.

97. A method of treating a neurological disorder or a psychiatric disorder in a subject in need thereof, wherein the method comprises administering to a subject in need thereof a dosage form of any one of claims 1-86.

98. A method of treating a pain in a subject in need thereof, wherein the method comprises administering to the subject a dosage form or a composition of any one of claims 1-86.

99. A method of treating a cancer in a subject in need thereof, wherein the method comprises administering to the subject a dosage form or a composition of any one of claims 1-86.

100. A method of treating or preventing a trigeminal autonomic cephalalgia (TAC) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a dosage form or a composition of any one of claims 1-86.

101. A method of treating or preventing a trigeminal autonomic cephalalgia (TAC) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of Compound 1, e.g., from 2.5 mg to 90 mg of Compound 1.

102. The method of claim 100 or 101, wherein the TAC is selected from the group consisting of paroxysmal hemicrania, hemicrania continua, short-lasting unilateral

neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA), and long-lasting autonomic symptoms with hemicrania.

103. The method of claim 102, wherein the TAC is a short-lasting unilateral neuralgiform headache attack.

104. The method of claim 102, wherein the TAC is SUNCT.

105. The method of claim 102, wherein the TAC is SUNA.

106. The method of any one of claims 100-105, wherein the subject has an inadequate response to at least one medication used for the treatment of a TAC.

107. A method of treating or preventing a migraine in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a dosage form or a composition of any one of claims 1-86.

108. A method of treating or preventing a migraine in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of Compound 1, e.g., from about 2.5 mg to about 90 mg of Compound 1.

109. The method of claim 107 or 108, wherein the migraine is selected from the group consisting of migraine without aura, migraine with aura, familial hemiplegic migraine type 1 (FHM1), familial hemiplegic migraine type 2 (FHM2), familial hemiplegic migraine type 4 (FHM4), and sporadic hemiplegic migraine (SHM),

110. The method of claim 109, wherein the migraine is migraine without aura.

111. The method of claim 109, wherein the migraine is migraine with aura.

112. The method of claim 109, wherein the migraine is FHM1.

113. The method of claim 109, wherein the migraine is FHM2.

114. The method of claim 109, wherein the migraine is FHM4.

115. The method of claim 109, wherein the migraine is SHM.

116. The method of any one of claims 107-115, wherein the subject has an inadequate response to at least one medication used for the treatment of a migraine.

117. A method of treating or preventing cortical spreading depression (CSD) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a dosage form or a composition of any one of claims 1-86.

118. A method of treating or preventing cortical spreading depression (CSD) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of Compound 1, e.g., from about 2.5 mg to about 90 mg of Compound 1.

119. A method of treating or preventing a cranial neuropathy or multiple cranial neuropathy in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a dosage form or a composition of any one of claims 1-86.

120. A method of treating or preventing a cranial neuropathy or multiple cranial neuropathy in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of Compound 1, e.g., from about 2.5 mg to about 90 mg of Compound 1.

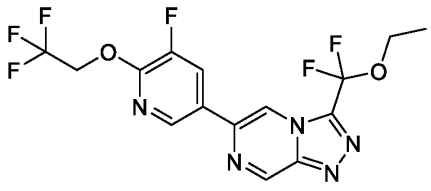
121. The method of claim 119 or 120, wherein the cranial neuropathy is selected from the group consisting of bell palsy, microvascular cranial nerve palsy, third nerve palsy, fourth nerve palsy, and sixth nerve palsy.

122. The method of any one of claims 87-121, wherein the dosage form is administered orally.

123. The method of any one of claims 87-122, wherein the dosage form is a capsule.

124. The method of any one of claims 87-123, wherein the subject is 18 to 65 years of age.

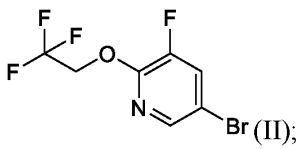
125. A method of making Compound 1:



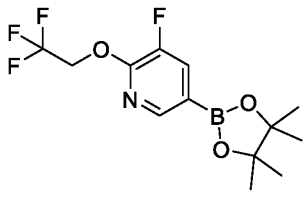
,

or a pharmaceutically acceptable salt thereof, the method comprising the steps of:

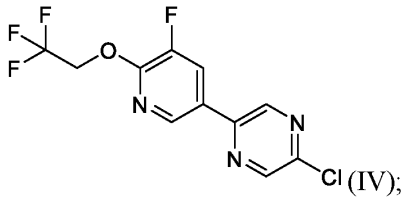
(i) contacting a solution of 2,2,2-trifluoroethanol with 5-bromo-2,3-difluoro-pyridine thereby providing a compound of formula (II):


(II);

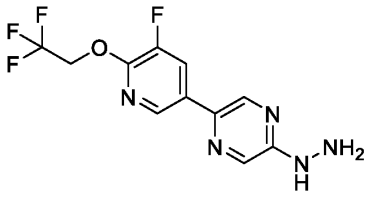
(ii) contacting the compound of formula (II) with a palladium catalyst and bis(pinacolato)diboron thereby providing a compound of formula (III):


(III);

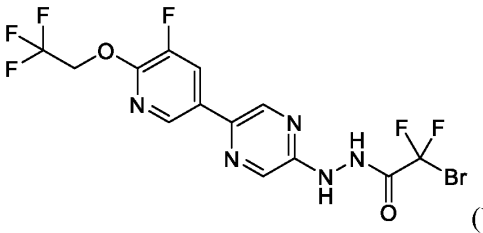
(iii) contacting the compound of formula (III) with a palladium catalyst and 2-bromo-5-chloro-pyrazine thereby providing a compound of formula (IV):


(IV);

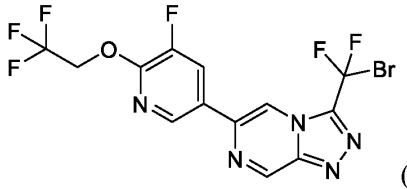
(iv) contacting the compound of formula (IV) with hydrazine thereby providing a compound of formula (V):


(V);

(v) contacting the compound of formula (V) with 2-bromo-2,2-difluoro-acetyl chloride thereby providing a compound of formula (VI):


(VI);

(vi) contacting the compound of formula (VI) with an acid thereby providing a compound of formula (VII):


(VII); and

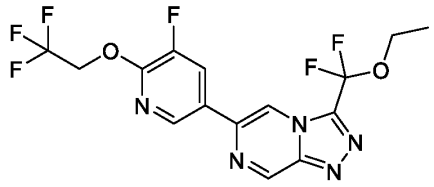
(vii) contacting the compound of formula (VII) with a silver catalyst and ethanol thereby providing Compound 1 or a pharmaceutically acceptable salt thereof.

126. The method of claim 125, wherein the palladium catalyst in step (ii) or (iii) is [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride.

127. The method of claim 125 or 126, wherein the silver catalyst in step (vii) is silver tetrafluoroborate.

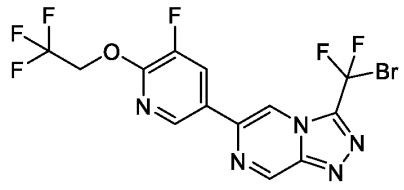
128. The method of any one of claims 125-127, wherein the acid in step (vi) is *p*-toluenesulfonic acid.

129. A method of making Compound 1:



(I)

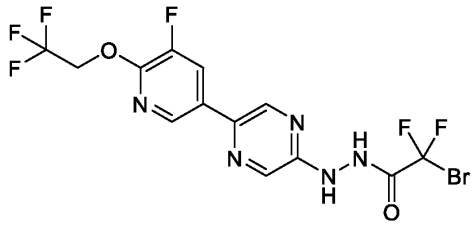
or a pharmaceutically acceptable salt thereof, wherein Compound 1 or a pharmaceutically acceptable salt thereof is provided by contacting the compound of formula (VII):



(VII)

with a silver catalyst and ethanol.

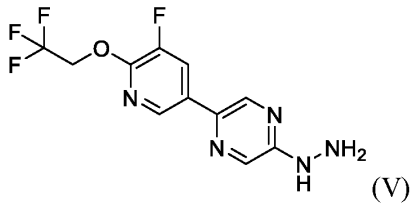
130. The method of claim 129, wherein the compound of formula (VII) is provided by contacting the compound of formula (VI):



(VI)

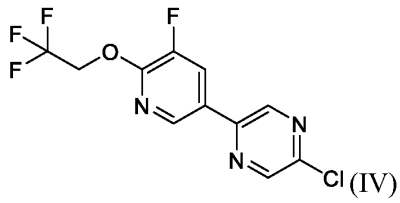
with an acid.

131. The method of claim 130, wherein the compound of formula (VI) is provided by contacting the compound of formula (V):


(V)

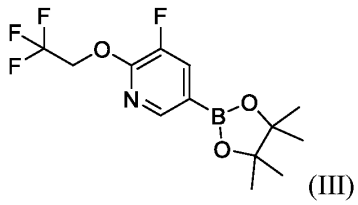
with 2-bromo-2,2-difluoro-acetyl chloride.

132. The method of claim 131, wherein the compound of formula (V) is provided by contacting the compound of formula (IV):


(IV)

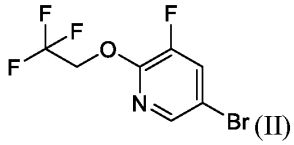
with hydrazine.

133. The method of claim 132, wherein the compound of formula (IV) is provided by contacting the compound of formula (III):


(III)

with a palladium catalyst and 2-bromo-5-chloro-pyrazine.

134. The method of claim 133, wherein the compound of formula (III) is provided by contacting the compound of formula (II):


(II)

with a palladium catalyst and bis(pinacolato)diboron.

135. The method of claim 134, wherein the compound of formula (II) is provided by contacting a solution of 2,2,2-trifluoroethanol with 5-bromo-2,3-difluoro-pyridine.

136. The method of any one of claims 125-135, wherein the silver catalyst is silver tetrafluoroborate.

137. The method of any one of claims 125-136, wherein the acid is *p*-toluenesulfonic acid.

138. The method of any one of claims 125-137, wherein the palladium catalyst is [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride.