FORMULATIONS OF T-TYPE CALCIUM CHANNEL MODULATORS AND METHODS OF USE THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to and the benefit of U.S. Provisional Patent Application Numbers 62/873,022, filed July 11, 2019, 62/934,820, filed November 13, 2019, and 62/958,923, filed January 9, 2020, each of which is incorporated herein by reference in its entirety.

BACKGROUND

T-type calcium channels are low-voltage activated ion channels that mediate the influx of calcium into cells. Aberrant function of these ion channels is associated with several diseases or conditions, including psychiatric disorder (e.g., mood disorder (e.g., major depressive disorder)), pain, tremor (e.g., essential tremor), epilepsy, or an epilepsy syndrome (e.g., absence seizures and juvenile myoclonic epilepsy). Accordingly, compounds that selectively modulate T-type calcium channel in mammals may be useful in treatment of such disease states.

SUMMARY ~~OF THE INVENTION~~

Described herein are compositions and dosage forms useful for preventing and/or treating a disease or condition relating to aberrant function of a T-type calcium channel, such as epilepsy and epilepsy syndromes (e.g., absence seizures, juvenile myoclonic epilepsy, or a genetic epilepsy) and mood disorders (e.g., major depressive disorder). The present ~~invention~~disclosure further comprises methods for modulating the function of a T-type calcium channel.

In one aspect of the present disclosure, there is provided an oral dosage form comprising:

the compound of formula (I) or a pharmaceutically acceptable salt thereof; and

a modified-release polymer.

In another aspect of the present disclosure, there is provided a crystalline form of the compound of formula (II), wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ):

(i) 16.2±0.2, 17.4±0.2, and 26.6±0.2; or

(ii) 11.5±0.2, 16.2±0.2, 17.4±0.2, 22.6±0.2, and 26.6±0.2; or

(iii) 11.5±0.2, 16.2±0.2, 17.4±0.2, 18.3±0.2, 18.5±0.2, 19.2±0.2, 20.0±0.2, 22.6±0.2, 23.9±0.2, and 26.6±0.2.

In a further aspect of the present disclosure, there is provided a crystalline form of the compound of formula (II), wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ):

(i) 21.9±0.2, 18.5±0.2, and 17.8±0.2; or

(ii) 21.9±0.2, 18.5±0.2, 17.8±0.2, 10.2±0.2, and 20.5±0.2; or

(iii) 21.9±0.2, 18.5±0.2, 17.8±0.2, 10.2±0.2, 20.5±0.2, 25.2±0.2, 16.9±0.2, 24.2±0.2, 28.6±0.2, and 21.2±0.2.

In another aspect of the present disclosure, there is provided a use of the oral dosage form disclosed herein, or the crystalline form disclosed herein, in the manufacture of a medicament for treating a neurological disorder in a subject in need thereof.

In a further aspect of the present disclosure, there is provided a use of the oral dosage form disclosed herein, or the crystalline form disclosed herein, in the manufacture of a medicament for treating a psychiatric disorder in a subject in need thereof.

In another aspect of the present disclosure, there is provided a use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, or the oral dosage form disclosed herein, or the crystalline form disclosed herein, in the manufacture of a medicament that results in reduction of the essential tremor as assessed by The Essential Tremor Rating Assessment Scale (TETRAS) score; or as assessed by accelerometer-based upper limb score; or that results in reduction of sigma frequency band.

In a further aspect of the present disclosure, there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof, or the oral dosage form disclosed herein, or the crystalline form disclosed herein, for use in therapy.

In one ~~aspect~~example, the present ~~invention~~disclosure provides a pharmaceutical composition comprising the compound of formula (I) or a pharmaceutically acceptable salt thereof, and an excipient that functions to modify the release rate of the compound of formula (I) or a pharmaceutically acceptable salt thereof.

In one ~~aspect~~example, the present ~~invention~~disclosure provides an oral dosage form comprising: the compound of formula (I) or a pharmaceutically acceptable salt thereof; and a modified-release polymer (e.g., a controlled-release polymer, hydrophilic matrix polymers, e.g., an HPMC polymer as a hydrophilic matrix polymer, hydrophobic matrix polymers (e.g., ethyl cellulose, ethocel), or polyacrylate polymers (e.g., Eudragit RL100, Eudragit RS100)). In some ~~embodiment~~examples, the dosage form comprises from about 0.9 % by weight to about 40 % by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)). In other ~~embodiment~~examples, the dosage form comprises from about 1 mg to about 40

mg (e.g., about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg) of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)).

The dosage form disclosed herein may comprise from about 10% by weight to about 70% by weight of the modified-release polymer. The dosage form disclosed herein may comprise a diluent (e.g., microcrystalline cellulose).

In another ~~aspect~~example, the present ~~invention~~disclosure discloses an oral dosage form comprising: from about 15 mg to 25 mg of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)); and from about 55 mg to 65 mg of an HPMC polymer.

In another ~~aspect~~example, the present ~~invention~~disclosure provides an oral dosage form comprising: from about 14% by weight to about 25% by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)); and from about 53% by weight to about 64% by weight of an HPMC polymer.

Also provided herein is an oral dosage form comprising: from about 3 mg to 8 mg of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)); and from about 55 mg to 65 mg of an HPMC polymer.

In one ~~aspect~~example, provided herein is an oral dosage form comprising: from about 3% by weight to about 8% by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)); and from about 53% to about 64% by weight of an HPMC polymer.

The present ~~invention~~disclosure provides, in part, an oral (e.g., particulate) composition comprising: the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)); and a modified-release polymer (e.g., a controlled-release polymer, hydrophilic matrix polymers, e.g., an HPMC polymer , hydrophobic matrix polymers (e.g., ethyl cellulose, ethocel), or polyacrylate polymers (e.g., Eudragit RL100, Eudragit RS100)).

In some ~~embodiment~~examples, the composition comprises from about 0.9 % by weight to about 40 % by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)). In certain ~~embodiment~~examples, the composition comprises from about 1 mg to about 40 mg (e.g., about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg) of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)).

Also provided herein is an oral (e.g., particulate) composition comprising: from about 15 mg to 25 mg of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)); and from about 55 mg to 65 mg HPMC.

In another ~~aspect~~example, the present ~~invention~~disclosure provides an oral (e.g., particulate) composition comprising: from about 14% by weight to about 25% by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)); and from about 53% to about 64% by weight of an HPMC polymer.

Provided herein, in part, is an oral (e.g., particulate) composition comprising: from about 3 mg to 8 mg of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)); and from about 55 mg to 65 mg HPMC.

The present ~~invention~~disclosure discloses, in part, an oral (e.g., particulate, swellable core) composition comprising: from about 3% by weight to about 8% by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)); and from about 53% to about 64% by weight of an HPMC polymer.

In one ~~aspect~~example, the present ~~invention~~disclosure provides a crystalline form of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)), wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 16.2±0.2, 17.4±0.2, and 26.6±0.2.

In another ~~aspect~~example, the present ~~invention~~disclosure provides a crystalline form of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II), wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 21.9±0.2, 18.5±0.2, and 17.8±0.2.

The present ~~invention~~disclosure provides, in part, a method of treating a neurological disorder in a subject in need thereof, wherein the method comprises administering to the subject the oral dosage, the composition, or the crystalline form disclosed herein. In some ~~embodiment~~examples, the neurological disorder is epilepsy. In other ~~embodiment~~examples, the epilepsy is juvenile epilepsy. In certain ~~embodiment~~examples, the epilepsy is genetic epilepsy (e.g., CACNA1G related genetic generalized epilepsy). In some ~~embodiment~~examples, the neurological disorder is absence seizure. In other ~~embodiment~~examples, the neurological disorder is absence epilepsy (e.g., CACNA1H related absence epilepsy). In certain ~~embodiment~~examples, the neurological disorder is epilepsy related to CACNA1G, H or I. In some ~~embodiment~~examples, the epilepsy is childhood absence epilepsy (CAE). In other ~~embodiment~~examples, the epilepsy is juvenile absence epilepsy (JAE). In certain ~~embodiment~~examples, the epilepsy is Lenox-Gastaut Syndrome. In some ~~embodiment~~examples, the neurological disorder is

pain (e.g., acute pain, chronic pain, neuropathic pain, inflammatory pain, nociceptive pain, central pain; e.g., thalamic pain; or migraine). In other ~~embodiment~~examples, the neurological disorder is tremor (e.g., essential tremor, Parkinson's tremor, or cerebellar tremor, CACNA1G related tremor). In certain ~~embodiment~~examples, the neurological disorder is ataxia (e.g., spinocerebellar ataxia, or spinocerebellar ataxia with CACNA1G mutations). In other ~~embodiment~~examples, the neurological disorder is tinnitus. In some ~~embodiment~~examples, the neurological disorder is a disorder of wakefulness.

In another ~~aspect~~example, provided herein is a method of treating a psychiatric disorder in a subject in need thereof, wherein the method comprises administering to the subject the oral dosage, the composition, or the crystalline form disclosed herein. In some ~~embodiment~~examples, the psychiatric disorder is a mood disorder. In other ~~embodiment~~examples, the mood disorder is major depressive disorder.

In certain ~~embodiment~~examples of the methods described herein, the dosage form is administered to the subject once a day. The dosage form may be administered to the subject twice a day. The dosage form may be administered to the subject every other day.

In some ~~embodiment~~examples of the methods described herein, about 15 mg to 25 mg (e.g., about 20 mg) of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) may be administered to the subject daily or about 30 mg to 50 mg (e.g., about 40 mg) of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) is administered to the subject daily.

In certain ~~embodiment~~examples of the methods described herein, the dosage form, upon administration to the subject, may have a reduced C_{max} value than a reference oral dosage form (e.g., a dosage form with any intended release rate profile e.g., modified release rate profile, a dosage form that does not have a modified release rate profile, a dosage form that does not have a modified-release polymer, e.g., an HPMC polymer). In other ~~embodiment~~examples of the methods disclosed herein, the dosage form, upon administration to the subject, may have a greater t_{max} value than a reference oral dosage form (e.g., a dosage form with any intended release rate profile e.g., modified release rate profile, a dosage form that does not have a modified release rate profile, a dosage form that does not have a modified-release polymer, e.g., an HPMC polymer).

Also provided herein is a method of treating a generalized epileptic syndrome with absence seizures in a patient in need thereof, comprising administering to the patient a sufficient amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the

compound of formula (II)) (e.g., the oral dosage form, the composition, or the crystalline form disclosed herein) that results in reduction of the number of seizures.

In one ~~aspect~~example, provided herein is a method of treating a generalized epileptic syndrome with absence seizures in a patient in need thereof, comprising administering to the patient a sufficient amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) (e.g., the oral dosage form, the composition, or the crystalline form disclosed herein) that results in reduction of the seizure density as measured by Electroencephalogram (EEG).

Provided herein, in part, is a method of treating a generalized epileptic syndrome with absence seizures in a patient in need thereof, comprising administering to the patient a sufficient amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) (e.g., the oral dosage form, the composition, or the crystalline form disclosed herein) that results in reduction of the mean seizure duration as measured by EEG.

In another ~~aspect~~example, disclosed herein is a method of treating a generalized epileptic syndrome with absence seizures in a patient in need thereof, comprising administering to the patient a sufficient amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II) (e.g., the oral dosage form, the composition, or the crystalline form disclosed herein) that results in reduction of the cumulative seizure duration as measured by EEG.

Provided herein, in part, is a method of treating a generalized epileptic syndrome with absence seizures in a patient in need thereof, comprising administering to the patient a sufficient amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) (e.g., the oral dosage, the composition, or the crystalline described herein) that results in reduction of the total time with 2.5-4Hz spike wave discharges after hyperventilation and photic stimulation challenges as measured by EEG.

In another ~~aspect~~example, a method of treating a generalized epileptic syndrome with absence seizures in a patient in need thereof, comprising administering to the patient a sufficient amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) (e.g., the oral dosage form, the composition, or the crystalline form) that results in reduction of global severity as measured by Clinical Global Impression-Severity (CGI-S) or Clinical Global Impression-Improvement (CGI-I) scores is provided herein.

Also provided herein is a method of treating an essential tremor in a patient in need thereof, comprising administering to the patient a sufficient amount of the compound of formula

(I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) (e.g., the oral dosage form, the composition, or the crystalline form disclosed herein) that results in reduction of the essential tremor as assessed by The Essential Tremor Rating Assessment Scale (TETRAS) score. In some ~~embodiment~~examples, the reduction of the essential tremor is assessed by The Essential Tremor Rating Assessment Scale (TETRAS) upper limb score. In other ~~embodiment~~examples, the reduction of the essential tremor is assessed by TETRAS-ADL (activities of daily living). the reduction of the essential tremor is assessed by TETRAS performance subscale score or TETRAS performance individual items.

Also provided herein is a method of treating an essential tremor in a patient in need thereof, comprising administering to the patient a sufficient amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) (e.g., the oral dosage, the composition, or the crystalline form disclosed herein) that results in reduction of the essential tremor as assessed by accelerometer-based upper limb score.

In another ~~aspect~~example, provided herein is a method of treating an essential tremor in a patient in need thereof, comprising administering to the patient a sufficient amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) (e.g., the oral dosage form, the composition, or the crystalline form disclosed herein) that results in reduction of sigma frequency band. In some ~~embodiment~~examples, the essential tremor is upper limb tremor.

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 FIGURES

FIG. 1 is a powder X-ray diffractogram of form C of the compound of formula (II).

FIG. 2 is a differential scanning calorimetry (DSC) thermogram of form C of the compound of formula (II).

FIG. 3 is a thermogravimetric analysis (TGA) thermogram of form C of the compound of formula (II).

FIG. 4 is a hot stage microscopy (HSM) photomicrographs of form C of the compound of formula (II).

CLAIMS

1. An oral dosage form comprising:

the compound of formula (I) or a pharmaceutically acceptable salt thereof; and

a modified-release polymer ~~(e.g., a controlled-release polymer, hydrophilic matrix polymers, e.g., an HPMC polymer, hydrophobic matrix polymers (e.g., ethyl cellulose, ethocel), or polyacrylate polymers (e.g., Eudragit RL100, Eudragit RS100))~~.

2. The dosage form of claim 1, wherein the dosage form comprises from about 0.9 % by weight to about 40 % by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof ~~(e.g., the compound of formula (II))~~.

~~3. The dosage form of claim 1 or 2, wherein the dosage form comprises from about 14% by weight to about 25% by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)).~~

~~4. The dosage form of any one of claims 1-3, wherein the dosage form comprises from about 19% by weight to about 20% by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)).~~

~~5. The dosage form of any one of claims 1-3, wherein the dosage form comprises from about 21% by weight to about 22% by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)).~~

~~6. The dosage form of claim 1 or 2, wherein the dosage form comprises from about 4% by weight to about 15% by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)).~~

~~7. The dosage form of any one of claim 1, 2, or 6, wherein the dosage form comprises from about 4% by weight to about 10% by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)).~~

~~8. The dosage form of any one of claim 1, 2, 6, or 7, wherein the dosage form comprises from about 4% by weight to about 5% by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)).~~

~~9. The dosage form of any one of claim 1, 2, 6, or 7, wherein the dosage form comprises from about 5% by weight to about 6% by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)).~~

~~10. The dosage form of any one of claim 1, 2, 6, or 7, wherein the dosage form comprises from about 9% by weight to about 10% by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)).~~

~~11~~3. The dosage form of claim 1 ~~any one of claims 1-10~~, wherein the dosage form comprises from about 1 mg to about 40 mg ~~(e.g., about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg)~~ of the compound of formula (I) or a pharmaceutically acceptable salt thereof ~~(e.g., the compound of formula (II))~~.

~~12. The dosage form of any one of claims 1-11, wherein the dosage form comprises from about 4 mg to about 6 mg (e.g., about 5 mg) of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)).~~

~~13. The dosage form of any one of claims 1-11, wherein the dosage form comprises from about 15 mg to about 25 mg (e.g., about 20 mg) of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)).~~

~~14~~4. The dosage form of claim 1 or 3 ~~any one of claims 1-13~~, wherein the compound of formula (I) or a pharmaceutically acceptable salt thereof ~~(e.g., the compound of formula (II))~~ is in a crystalline form.

~~15~~5. The dosage form of claim ~~1~~4, wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ):

(i) 16.2±0.2, 17.4±0.2, and 26.6±0.2~~.~~; or

~~16. The dosage form of claim 14 or 15, wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ):~~ (ii) 11.5±0.2, 16.2±0.2, 17.4±0.2, 22.6±0.2, and 26.6±0.2~~.~~; or

~~17. The dosage form of any one of claims 14-16, wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ):~~ (iii) 11.5±0.2, 16.2±0.2, 17.4±0.2, 18.3±0.2, 18.5±0.2, 19.2±0.2, 20.0±0.2, 22.6±0.2, 23.9±0.2, and 26.6±0.2.

~~18~~6. The dosage form of claim 4 or 5 ~~any one of claims 14-17~~, wherein the crystalline form has a X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern depicted in FIG. 1.

~~19. The dosage form of any one of claims 14-18, wherein the powder X-ray diffraction pattern was obtained using Cu Kα radiation.~~

~~20~~7. The dosage form of any one of claims 4-6~~14-19~~, wherein the crystalline form has a melting point onset as determined by differential scanning calorimetry at about 226.6 °C.

~~21~~8. The dosage form of any one of claims 1 and 3-6~~1-20~~, wherein the dosage form comprises from about 55 mg to 65 mg of the modified-release polymer.

~~22~~9. The dosage form of any one of claims 1 and 3-6~~1-21~~, wherein the dosage form comprises from about 10% by weight to about 70% by weight of the modified-release polymer.

~~23. The dosage form of any one of claims 1-22, wherein the dosage form comprises from about 50% by weight to about 60% by weight of the modified-release polymer.~~

~~24~~10. The dosage form of any one of claims 1 and 3-9~~1-23~~, wherein the dosage form further comprises a diluent.

~~25~~11. The dosage form of claim ~~24~~10, wherein the diluent comprises microcrystalline cellulose.

~~26~~12. The dosage form of claim ~~25~~11, wherein the dosage form comprises from about 15 mg to 40 mg ~~(e.g., from about 15 mg to about 25 mg, from about 20 mg to about 25 mg, from about 25 mg to about 30 mg, from about 30 mg to about 40 mg)~~ microcrystalline cellulose~~.~~; or

~~27. The dosage form of claim 25,~~ wherein the dosage form comprises from about 15% by weight to about 35% by weight ~~(e.g., from about 15% by weight to about 20% by weight, from about 20% by weight to about 25 % by weight, from 25% by weight to about 30% by weight, from 30% by weight to about 35% by weight)~~ microcrystalline cellulose.

~~28~~13. The dosage form of any one of claims 1 and 3-12~~1-27~~, wherein the dosage form further comprises a glidant.

~~29~~14. The dosage form of claim ~~28~~13, wherein the glidant comprises colloidal silicon dioxide.

~~30~~15. The dosage form of any one of claims 1 and 3-14~~1-29~~, wherein the dosage form further comprises a lubricant.

~~31~~16. The dosage form of claim ~~30~~15, wherein the lubricant comprises magnesium stearate.

~~32~~17. The dosage form of any one of claims 1 and 3-16~~1-31~~, wherein the dosage form further comprises a coating.

~~33. The dosage form of any one of claims 1-32, wherein about 80% of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) is released within 7 hours upon administration to a subject.~~

~~34. The dosage form of claim 33, wherein about 80% of the compound of formula (I) is released in 7 hours using USP apparatus type I, media containing 900 mL 0.1 M HCl, and a paddle speed of 100 rpm.~~

~~35. The dosage form of any one of claims 1-34, wherein the dosage form, upon administration to a subject, has a reduced C_{max} value than a reference oral dosage form (e.g., a dosage form with any intended release rate profile e.g., modified release rate profile, a dosage form that does not have a modified release rate profile, a dosage form that does not have a modified release polymer, e.g., an HPMC polymer).~~

~~36. The dosage form of any one of claims 1-35, wherein the dosage form, upon administration to a subject, has a greater t_{max} value than a reference oral dosage form (e.g., a dosage form with any intended release rate profile e.g., modified release rate profile, a dosage form that does not have a modified release rate profile, a dosage form that does not have a modified release polymer, e.g., an HPMC polymer).~~

~~37~~18. The dosage form of any one of claims 1 and 3-17~~1-36~~, wherein the dosage form is administered to a patient once daily or twice daily.

~~38. The dosage form of any one of claims 1-36, wherein the dosage form is administered to a patient twice daily.~~

~~39. An oral dosage form comprising:~~

~~from about 15 mg to 25 mg of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)); and~~

~~from about 55 mg to 65 mg of an HPMC polymer.~~

~~40. An oral dosage form comprising:~~

~~from about 14% by weight to about 25% by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)); and~~

~~from about 53% by weight to about 64% by weight of an HPMC polymer.~~

~~41. An oral dosage form comprising:~~

~~from about 3 mg to 8 mg of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)); and~~

~~from about 55 mg to 65 mg of an HPMC polymer.~~

~~42. An oral dosage form comprising:~~

~~from about 3% by weight to about 8% by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)); and~~

~~from about 53% to about 64% by weight of an HPMC polymer.~~

~~43~~19. The dosage form of any one of claims 1 and 3-18~~1-42~~, wherein the dosage form is a tablet, a capsule or a suspension.

~~44. The dosage form of any one of claims 1-42, wherein the dosage form is a capsule.~~

~~45. The dosage form of any one of claims 1-42, wherein the dosage form is a suspension.~~

~~46. An oral (e.g., particulate) composition comprising:~~

~~the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)); and~~

~~a modified release polymer (e.g., a controlled release polymer, hydrophilic matrix polymers, e.g., an HPMC polymer , hydrophobic matrix polymers (e.g., ethyl cellulose, ethocel), or polyacrylate polymers (e.g., Eudragit RL100, Eudragit RS100)).~~

~~47. The composition of claim 46, wherein the composition comprises from about 0.9 % by weight to about 40 % by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)).~~

~~48. The composition of claim 46 or 47, wherein the composition comprises from about 14% by weight to about 25% by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)).~~

~~49. The composition of any one of claims 46-48, wherein the composition comprises about 19% by weight to about 20% by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)).~~

~~50. The composition of any one of claims 46-48, wherein the composition comprises about from 21% by weight to about 22% by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)).~~

~~51. The composition of claim 46 or 47, wherein the composition comprises from about 4% by weight to about 15% by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)).~~

~~52. The composition of any one of claim 46, 47, or 51, wherein the composition comprises from about 4% by weight to about 10% by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)).~~

~~53. The composition of any one of claim 46, 47, 51, or 52, wherein the composition comprises about 4% by weight to about 5% by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)).~~

~~54. The composition of any one of claim 46, 47, 51, or 52, wherein the composition comprises about 5% by weight to about 6% by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)).~~

~~55. The composition of any one of claim 46, 47, 51, or 52, wherein the composition comprises about 9% by weight to about 10% by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)).~~

~~56. The composition of any one of claims 46-55, wherein the composition comprises from about 1 mg to about 40 mg (e.g., about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg) of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)).~~

~~57. The composition of any one of claims 46-55, wherein the composition comprises from about 4 mg to about 6 mg (e.g., about 5 mg) of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)).~~

~~58. The composition of any one of claims 46-55, wherein the composition comprises from about 15 mg to about 25 mg (e.g., about 20 mg) of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)).~~

~~59. The composition of any one of claims 46-55, wherein the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) is a crystalline form.~~

~~60. The composition of claim 59, wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 16.2±0.2, 17.4±0.2, and 26.6±0.2.~~

~~61. The composition of claim 59 or 60, wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 11.5±0.2, 16.2±0.2, 17.4±0.2, 22.6±0.2, and 26.6±0.2.~~

~~62. The composition of any one of claims 59-61, wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 11.5±0.2, 16.2±0.2, 17.4±0.2, 18.3±0.2, 18.5±0.2, 19.2±0.2, 20.0±0.2, 22.6±0.2, 23.9±0.2, and 26.6±0.2.~~

~~63. The composition of any one of claims 59-62, wherein the crystalline form has an X-ray powder diffraction pattern substantially the same as depicted in FIG. 1.~~

~~64. The composition of any one of claims 59-63, wherein the powder X-ray diffraction pattern was obtained using Cu Kα radiation.~~

~~65. The composition of any one of claims 59-64, wherein the crystalline form has a melting point onset as determined by differential scanning calorimetry at about an onset at about 226.6 °C.~~

~~66. The composition of any one of claims 59-65, wherein the crystalline form has a differential scanning calorimetry curve substantially the same as shown in FIG. 2.~~

~~67. The composition of any one of claims 46-66, wherein the composition comprises from about 55 mg to 65 mg of the modified-release polymer.~~

~~68. The composition of any one of claims 42-62, wherein the composition comprises from about 10% by weight to about 70% by weight of the modified-release polymer.~~

~~69. The composition of any one of claims 42-63, wherein the composition comprises from about 50% by weight to about 60% by weight of the modified-release polymer.~~

~~70. The composition of any one of claims 42-64, wherein the dosage form comprises a diluent.~~

~~71. The composition of claim 65, wherein the diluent comprises microcrystalline cellulose.~~

~~72. The composition of claim 66, wherein the composition comprises from about 15 mg to 40 mg (e.g., from about 15 mg to about 25 mg, from about 20 mg to about 25 mg, from about 25 mg to about 30 mg, from about 30 mg to about 40 mg), microcrystalline cellulose.~~

~~73. The composition of claim 66, wherein the composition comprises from about 15% to about 35% by weight (e.g., from about 15% to about 20%, from about 20% to about 25 %, from 25% to about 30%, from 30% to about 35% by weight)microcrystalline cellulose.~~

~~74. The composition of any one of claims 42-68, wherein the composition further comprises a glidant.~~

~~75. The composition of claim 69, wherein the glidant comprises colloidal silicon dioxide.~~

~~76. The composition of any one of claims 42-70, wherein the composition further comprises a lubricant.~~

~~77. The composition of claim 71, wherein the lubricant comprises magnesium stearate.~~

78. The composition of any one of claims 42-72, wherein the composition further comprises a coating.

79. The composition of any one of claims 42-73, wherein the compound is stable at about 25 °C at 60 % relative humidity for at least 24 months.

80. The composition of any one of claims 42-74, wherein the compound is stable at about 25 °C at 60 % relative humidity for at least 36 months.

81. The composition of any one of claims 42-75, wherein the compound is stable at about 25 °C at 60 % relative humidity for at least 48 months.

82. The composition of any one of claims 42-76, wherein the compound is stable at about 25 °C at 60 % relative humidity for at least 60 months.

83. The composition of any one of claims 42-77, wherein the compound is stable at about 40 °C at 75 % relative humidity for at least 6 months.

84. An oral (e.g., particulate) composition comprising:

from about 15 mg to 25 mg of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)); and

from about 55 mg to 65 mg HPMC.

85. An oral (e.g., particulate) composition comprising:

from about 14% by weight to about 25% by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)); and

from about 53% to about 64% by weight of an HPMC polymer.

86. An oral (e.g., particulate) composition comprising:

from about 3 mg to 8 mg of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)); and

from about 55 mg to 65 mg HPMC.

87. An oral (e.g., particulate, swellable core) composition comprising:

from about 3% by weight to about 8% by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)); and

from about 53% to about 64% by weight of an HPMC polymer.

~~88~~20. A crystalline form of the compound of formula (II), wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ):

(i) 16.2±0.2, 17.4±0.2, and 26.6±0.2~~.~~; or

~~89. The crystalline form of claim 88, wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ):~~ (ii) 11.5±0.2, 16.2±0.2, 17.4±0.2, 22.6±0.2, and 26.6±0.2~~.~~; or

~~90. The crystalline form of claim 88 or 89, wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ):~~ (iii) 11.5±0.2, 16.2±0.2, 17.4±0.2, 18.3±0.2, 18.5±0.2, 19.2±0.2, 20.0±0.2, 22.6±0.2, 23.9±0.2, and 26.6±0.2.

~~91~~21. The crystalline form of claim 20~~any one of claims 88-90~~, wherein the crystalline form has a X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern depicted in FIG. 1.

~~92. The crystalline form of any one of claims 88-91, wherein the powder X-ray diffraction pattern was obtained using Cu Kα radiation.~~

~~93~~22. The crystalline form of claim 20 or 21 ~~any one of claims 88-92~~, wherein the crystalline form has a melting point onset as determined by differential scanning calorimetry at about 226.6 °C.

~~94~~23. A crystalline form of the compound of formula (II), wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ):

(i) 21.9±0.2, 18.5±0.2, and 17.8±0.2~~.~~; or

~~95. The crystalline form of claim 94, wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ):~~ (ii) 21.9±0.2, 18.5±0.2, 17.8±0.2, 10.2±0.2, and 20.5±0.2~~.~~; or

~~96. The crystalline form of claim 94 or 95, wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ):~~ (iii) 21.9±0.2, 18.5±0.2, 17.8±0.2, 10.2±0.2, 20.5±0.2, 25.2±0.2, 16.9±0.2, 24.2±0.2, 28.6±0.2, and 21.2±0.2.

~~97~~24. The crystalline form of claim 23~~any one of claims 94-96~~, wherein the crystalline form has a X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern depicted in FIG. 7.

~~98. The crystalline form of any one of claims 94-97, wherein the powder X-ray diffraction pattern was obtained using Cu Kα radiation.~~

~~99~~25. The crystalline form of claim 23 or 24~~any one of claims 94-98~~, wherein the crystalline form has a melting point onset as determined by differential scanning calorimetry at about 97.9, 131.6, 223.7, 83.8, 128.9, 168.9, or 224.4 °C.

~~100~~26. Use of the oral dosage form of any one of claims 1, and 3-19, or the crystalline form of any one of claims 23-25, in the manufacture of a medicament for ~~A method of~~ treating a neurological disorder in a subject in need thereof~~, wherein the method comprises administering to the subject the oral dosage form of any one of claims 1-45, the composition of any one of claims 46-87, or the crystalline form of any one of claims 88-99~~.

~~101~~27. The ~~method~~ use of claim ~~100~~26, wherein the neurological disorder is selected from the group consisting of epilepsy, seizure, pain, tremor, ataxia, tinnitus, and a disorder of wakefulness.

~~102. The method of claim 101, wherein the epilepsy is juvenile epilepsy.~~

~~103. The method of claim 101, wherein the epilepsy is genetic epilepsy (e.g., CACNA1G related genetic generalized epilepsy).~~

~~104. The method of claim 100, wherein the neurological disorder is absence seizure.~~

~~105. The method of claim 100, wherein the neurological disorder is absence epilepsy (e.g., CACNA1H related absence epilepsy).~~

~~106. The method of claim 100, wherein the neurological disorder is epilepsy related to CACNA1G, H or I.~~

~~107. The method of claim 101, wherein the epilepsy is childhood absence epilepsy (CAE).~~

~~108. The method of claim 101, wherein the epilepsy is juvenile absence epilepsy (JAE).~~

~~109. The method of claim 101, wherein the epilepsy is Lenox-Gastaut Syndrome.~~

~~110. The method of claim 100, wherein the neurological disorder is pain (e.g., acute pain, chronic pain, neuropathic pain, inflammatory pain, nociceptive pain, central pain; e.g., thalamic pain; or migraine)~~

~~111~~28. The ~~method~~ use of claim 26~~100~~, wherein the ~~neurological disorder is~~ tremor is an ~~(e.g.,~~ essential tremor, Parkinson's tremor, or cerebellar tremor, or a CACNA1G related tremor~~)~~.

~~112. The method of claim 100, wherein the neurological disorder is ataxia (e.g., spinocerebellar ataxia, or spinocerebellar ataxia with CACNA1G mutations).~~

~~113. The method of claim 100, wherein the neurological disorder is tinnitus.~~

~~114. The method of claim 100, wherein the neurological disorder is a disorder of wakefulness.~~

~~115~~29. Use of the oral dosage form of any one of claims 1, 3-19, or the crystalline form of any one of claims 23-25, in the manufacture of a medicament for ~~A method of~~ treating a psychiatric disorder in a subject in need thereof~~, wherein the method comprises administering to the subject the oral dosage form of any one of claims 1-45, the composition of any one of claims 46-87, or the crystalline form of any one of claims 88-99~~.

~~116~~30. The ~~method~~ use of claim ~~115~~29, wherein the psychiatric disorder is a mood disorder.

~~117. The method of claim 116, wherein the mood disorder is major depressive disorder.~~

~~118. The method of any one of claims 115-117, wherein the dosage form is administered to the subject once a day.~~

~~119. The method of any one of claims 115-118, wherein the dosage form is administered to the subject twice a day.~~

~~120. The method of any one of claims 115-119, wherein the dosage form is administered to the subject every other day.~~

~~121. The method of any one of claims 100-120, wherein about 15 mg to 25 mg (e.g., about 20 mg) of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) is administered to the subject daily.~~

~~122. The method of any one of claims 100-120, wherein about 30 mg to 50 mg (e.g., about 40 mg) of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) is administered to the subject daily.~~

~~123. The method of any one of claims 100-122, wherein the dosage form, upon administration to the subject, has a reduced C_{max} value than a reference oral dosage form (e.g., a dosage form with any intended release rate profile e.g., modified release rate profile, a dosage form that does not have a modified release rate profile, a dosage form that does not have a modified release polymer, e.g., an HPMC polymer).~~

~~124. The method of any one of claims 100-123, wherein the dosage form, upon administration to the subject, has a greater t_{max} value than a reference oral dosage form (e.g., a dosage form with any intended release rate profile e.g., modified release rate profile, a dosage form that does not have a modified release rate profile, a dosage form that does not have a modified release polymer, e.g., an HPMC polymer).~~

~~125. A method of treating a generalized epileptic syndrome with absence seizures in a patient in need thereof, comprising administering to the patient a sufficient amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) (e.g., the oral dosage form of any one of claims 1-45, the composition of any one of claims 46-87, or the crystalline form of any one of claims 88-99) that results in reduction of the number of seizures.~~

~~126. A method of treating a generalized epileptic syndrome with absence seizures in a patient in need thereof, comprising administering to the patient a sufficient amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) (e.g., the oral dosage form of any one of claims 1-45, the composition of any one of claims 46-87, or the crystalline form of any one of claims 88-99) that results in reduction of the seizure density as measured by Electroencephalogram (EEG).~~

~~127. A method of treating a generalized epileptic syndrome with absence seizures in a patient in need thereof, comprising administering to the patient a sufficient amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) (e.g., the oral dosage form of any one of claims 1-45, the composition of any one of claims 46-87, or the crystalline form of any one of claims 88-99) that results in reduction of the mean seizure duration as measured by EEG.~~

~~128. A method of treating a generalized epileptic syndrome with absence seizures in a patient in need thereof, comprising administering to the patient a sufficient amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II) (e.g., the oral dosage form of any one of claims 1-45, the composition of any one of claims 46-87, or the crystalline form of any one of claims 88-99) that results in reduction of the cumulative seizure duration as measured by EEG.~~

~~129. A method of treating a generalized epileptic syndrome with absence seizures in a patient in need thereof, comprising administering to the patient a sufficient amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) (e.g., the oral dosage form of any one of claims 1-45, the composition of any one of claims 46-87, or the crystalline form of any one of claims 88-99) that results in reduction of the total time with 2.5-4Hz spike wave discharges after hyperventilation and photic stimulation challenges as measured by EEG.~~

~~130. A method of treating a generalized epileptic syndrome with absence seizures in a patient in need thereof, comprising administering to the patient a sufficient amount of the compound of~~

~~formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) (e.g., the oral dosage form of any one of claims 1-45, the composition of any one of claims 46-87, or the crystalline form of any one of claims 88-99) that results in reduction of global severity as measured by Clinical Global Impression-Severity (CGI-S) or Clinical Global Impression-Improvement (CGI-I) scores.~~

~~131~~31. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, or the oral dosage form of any one of claims 1, 3-19, or the crystalline form of any one of claims 23-25, in the manufacture of a medicament~~A method of treating an essential tremor in a patient in need thereof, comprising administering to the patient a sufficient amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) (e.g., the oral dosage form of any one of claims 1-45, the composition of any one of claims 46-87, or the crystalline form of any one of claims 88-99)~~ that results in reduction of the essential tremor as assessed by The Essential Tremor Rating Assessment Scale (TETRAS) score; or as assessed by accelerometer-based upper limb score; or that results in reduction of sigma frequency band.

~~132~~32. The ~~method~~ use of claim 131, wherein the reduction of the essential tremor is assessed by The Essential Tremor Rating Assessment Scale (TETRAS) upper limb score; or TETRAS-ADL (activities of daily living); or TETRAS performance subscale score or TETRAS performance individual items.

~~133. The method of claim 131, wherein the reduction of the essential tremor is assessed by TETRAS-ADL (activities of daily living).~~

~~134. The method of claim 131 or 132, wherein the reduction of the essential tremor is assessed by TETRAS performance subscale score or TETRAS performance individual items.~~

~~135. A method of treating an essential tremor in a patient in need thereof, comprising administering to the patient a sufficient amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) (e.g., the oral dosage form of any one of claims 1-45, the composition of any one of claims 46-87, or the crystalline form of any one of claims 88-99) that results in reduction of the essential tremor as assessed by accelerometer-based upper limb score.~~

~~136. A method of treating an essential tremor in a patient in need thereof, comprising administering to the patient a sufficient amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) (e.g., the oral~~

~~dosage form of any one of claims 1-45, the composition of any one of claims 46-87, or the crystalline form of any one of claims 88-99) that results in reduction of sigma frequency band.~~

~~137~~33. The ~~method~~ use of claim 31 or 32~~any one of claims 131-136~~, wherein the essential tremor is upper limb tremor.

34. A compound of formula (I) or a pharmaceutically acceptable salt thereof, or the oral dosage form of any one of claims 1, 3-19, or the crystalline form of any one of claims 23-25, for use in therapy.