METHODS OF USE OF (4R,5R)-5-(2-CHLOROPHENYL)-4-(5-(PHENYLETHYNYL)PYRIDIN-3-YL)OXAZOLIDIN-2-ONE

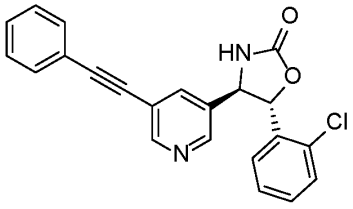
BACKGROUND

Glutamate is the primary excitatory neurotransmitter in the brain and is involved in various psychiatric and medical conditions. Glutamate regulates central nervous system functions through the actions of ionotropic and metabotropic receptors. The three groups of metabotropic (mGlu) receptors modify neuronal activity through G-protein coupled signaling. In particular, the Group I receptor, mGluR5 receptor, plays an important role in mental health and various central nervous system (CNS) disorders. Several mGluR5 antagonists have been designed, such as 3-[2-methyl-1,3-thiazol-4yl]ethynyl]pyridine (MTEP), acamprostate, memantine, AFQ056, and Fenobam. Allosteric modulators of mGluR5 can be sorted into positive allosteric modulators (PAMs), negative allosteric modulators (NAMs), and silent allosteric modulators (SAMs).

There remains a need for compounds and compositions that modulate mGluR5 to improve mental health and treat CNS disorders.

SUMMARY OF THE DISCLOSURE

In an aspect, the invention features a method of treating Alzheimer's Disease, seizures, synapse loss, or Tau accumulation of a subject in need thereof, comprising administering to the subject a therapeutically effective amount of Compound 1:



, e.g., with food, sufficient to produce:

a) a C_{max} (maximum concentration) of about 200 ng/mL to about 850 ng/mL;

b) a T_{max} (time at maximum concentration) of about 3 h to about 5 h;

c) an AUC_{tau} (area under the plasma concentration time curve over a dosage interval of tau, wherein tau is from 0 h to 12 h) of about 1000 ng•h/mL to about 10000 ng•h/mL;

d) an AUC_{last} (area under the plasma concentration time curve to the last measurable plasma concentration) of about 1200 ng•h/mL to about 21000 ng•h/mL;

e) a $T_{1/2}$ (half-life) of about 8 h to about 31 h; and/or

f) a C_{trough} (plasma concentration of Compound 1 immediately before administration of next dosage of Compound 1) of about 10 to 600 ng/mL.

In some embodiments, the therapeutically effective amount is sufficient to produce any one of (a)-(f). In some embodiments, the therapeutically effective amount is sufficient to produce any combination of

two of (a)-(f). In some embodiments, the therapeutically effective amount is sufficient to produce any combination of three of (a)-(f). In some embodiments, the therapeutically effective amount is sufficient to produce any combination of four of (a)-(f). In some embodiments, the therapeutically effective amount is sufficient to produce the combination of five of (a)-(f). In some embodiments, the therapeutically effective amount is sufficient to produce the combination of all six of (a)-(f).

In any embodiment where the therapeutically effective amount produces (a), alone or in combination with any 2, 3, 4, or 5 of (b)-(f), the C_{max} is from about 400 ng/mL to about 750 ng/mL. In any embodiment where the therapeutically effective amount produces (a), alone or in combination with any 2, 3, 4,or 5 of (b)-(f), the C_{max} is about 450 ng/mL, about 500 ng/mL, about 550 ng/mL, about 600 ng/mL, about 650 ng/mL, or about 700 ng/mL. In any embodiment where the therapeutically effective amount produces (a), alone or in combination with any 2, 3, 4, or 5 of (b)-(f), the C_{max} is from about 250 to about 350, about 300 to about 400, about 350 to about 450, about 400 to about 500, from about 450 to about 550, from about 500 to about 600, from about 550 to about 650, from about 500 to about 700, from about 450 to about 750, from about 600 to about 700, or from about 650 to about 750 ng/mL.

In any embodiment where the therapeutically effective amount produces (b), alone or in combination with any 2, 3, 4, or 5 of (a) and (c)-(f), the T_{max} is about 4 or from about 3.2 h to about 4.8 h. In any embodiment where the therapeutically effective amount produces (b), alone or in combination with any 2, 3, 4, or 5 of (a) and (c)-(f), the T_{max} is about 3.5 h, about 3.6 h, about 3.7 h, about 3.8 h, or about 4 h . In any embodiment where the therapeutically effective amount produces (b), alone or in combination with any 2, 3, 4, or 5 of (a) and (c)-(f), the T_{max} is from about 3 to about 3.5 h, from about 3.5 to about 4, from about 3.5 to about 4.5, from about 3.8 to about 4.2, from about 4 to about 5, from about 4.5 to about 5, from about 4.2 to about 5, from about 4.8 to about 5, from about 5 to about 5.5, or from about 5.2 to about 5.5 h.

In any embodiment where the therapeutically effective amount produces (c), alone or in combination with any 2, 3, 4, or 5 of (a)-(b) and (d)-(f), the AUC_{tau} is from about 2000 ng•h/mL to about 8000 ng•h/mL. In any embodiment where the therapeutically effective amount produces (c), alone or in combination with any 2, 3, 4, or 5 of (a)-(b) and (d)-(f), the AUC_{tau} is about 1200 ng•h/mL, about 1500 ng•h/mL, about 2000 ng•h/mL, about 2500 ng•h/mL, about 3000 ng•h/mL, about 3500 ng•h/mL, about 4000 ng•h/mL, about 4500 ng•h/mL, about 5000 ng•h/mL, about 6000 ng•h/mL, about 7000 ng•h/mL, or about 7500 ng•h/mL. In any embodiment where the therapeutically effective amount produces (c) alone or in combination with any 2, 3, 4, or 5 of (a)-(b) and (d)-(f), the AUC_{tau} is from about 2000 to about 5000, from about 2000 to about 3000, from about 2500 to about 4500, from about 3000 to about 4000, from about 4000 to about 6000, from about 3000 to about 5000, from about 5000 to about 7000, from about 5500 to about 7500, from about 6000 to about 8000, from about 5000 to about 6000, from about 7000 to about 8000, or from about 6500 to about 8000 ng•h/mL.

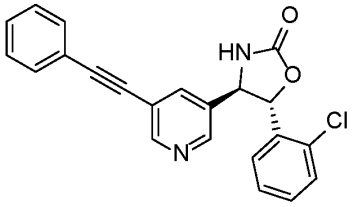
In any embodiment where the therapeutically effective amount produces (d), alone or in combination with any 2, 3, 4, 5 of (a)-(c) and (f), the AUC_{last} is from about 5000 ng•h/mL to about 16000

ng•h/mL or from about 10000 ng•h/mL to about 20000 ng•h/mL. In any embodiment where the therapeutically effective amount produces (d), alone or in combination with any 2, 3, 4, or 5 of (a)-(c) and (e), the AUC_{last} is about 5500 ng•h/mL, about 6000 ng•h/mL, about 6500 ng•h/mL, about 7000 ng•h/mL, about 7500 ng•h/mL, about 8000 ng•h/mL, about 8500 ng•h/mL, about 9000 ng•h/mL, about 9500 ng•h/mL, about 10000 ng•h/mL, about 10500 ng•h/mL, about 11000 ng•h/mL, about 12000 ng•h/mL, about 13000 ng•h/mL, about 14000 ng•h/mL, or about 15000 ng•h/mL. In any embodiment where the therapeutically effective amount produces (d), alone or in combination with any 2, 3, 4, or 5 of (a)-(c) and (e), the AUC_{last} is from about 7000 to about 10000, about 10000 to about 13000, from about 11000 to about 13000, from about 12000 to about 14000, from about 13000 to about 16000, from about 12500 to about 13500, from about 14000 to about 15000, from about 14500 to about 15500, or from about 15000 to about 16000 ng•h/mL.

In any embodiment where the therapeutically effective amount produces (e), alone or in combination with any 2, 3, 4, or 5 of (a)-(d) and (f), the $T_{1/2}$ is from about 12 h to about 22 h or about 20 h to about 30 h. In any embodiment where the therapeutically effective amount produces (e), alone or in combination with any 2, 3, 4, or 5 of (a)-(d) and (f), the $T_{1/2}$ is about 14 h, about 15 h, about 16 h, about 17 h, about 18 h, about 19 h, about 20 h, about 21 h, about 22 h, about 23 h, about 24 h, about 25 h, about 26 h, or about 27 h. In any embodiment where the therapeutically effective amount produces (e), alone or in combination with any 2, 3, 4, or 5 of (a)-(d) and (f), the $T_{1/2}$ is from about 12 to about 16, from about 13 to about 17, from about 14 to about 18, from about 15 to about 20, from about 13 to about 17, from about 12 to about 18, from about 16 to about 20, from about 17 to about 21, from about 18 to about 20, from about 19 to about 21, from about 18 to about 23, from about 20 to about 24, or from about 20 to about 22 h.

In any embodiment where the therapeutically effective amount produces (f), alone or in combination with any 2, 3, 4, or 5 of (a)-(e), the C_{trough} is from about 100 ng/mL to about 400 ng/mL. In any embodiment where the therapeutically effective amount produces (f), alone or in combination with any 2, 3, 4, or 5 of (a)-(e), the C_{trough} is about 120 ng/mL, about 150 ng/mL, about 200 ng/mL, about 225 ng/mL, about 250 ng/mL, about 300 ng/mL, or about 350 ng/mL. In any embodiment where the therapeutically effective amount produces (f), alone or in combination with any 2, 3, 4, or 5 of (a)-(e), the C_{trough} is from about 100 to about 150, from about 100 to about 200, from about 150 to about 250, from about 200 to about 250, from about 200 to about 300, or from about 300 to about 400 ng/mL.

In an aspect, the invention features a method of treating Alzheimer's Disease, seizures, synapse loss, or Tau accumulation of a subject in need thereof, comprising administering to the subject a therapeutically effective amount of Compound 1:



, e.g., with food, sufficient to produce:

a) a C_{max} (maximum concentration) of about 500 ng/mL to about 3000 ng/mL;

b) a T_{max} (time at maximum concentration) of about 1 h to about 4 h;

c) an AUC_{tau} (area under the plasma concentration time curve over a dosage interval of tau, wherein tau is from 0 h to 12 h) of about 2000 ng•h/mL to about 30000 ng•h/mL;

d) an AUC_{last} (area under the plasma concentration time curve to the last measurable plasma concentration) of about 4500 ng•h/mL to about 120000 ng•h/mL;

e) a $T_{1/2}$ (half-life) of about 13 h to about 29 h; and/or

f) a C_{trough} (plasma concentration of Compound 1 immediately before administration of next dosage of Compound 1) of about 50 to 2500 ng/mL.

In some embodiments, the therapeutically effective amount is sufficient to produce any one of (a)-(f). In some embodiments, the therapeutically effective amount is sufficient to produce any combination of two of (a)-(f). In some embodiments, the therapeutically effective amount is sufficient to produce any combination of three of (a)-(f). In some embodiments, the therapeutically effective amount is sufficient to produce any combination of four of (a)-(f). In some embodiments, the therapeutically effective amount is sufficient to produce the combination of five of (a)-(f). In some embodiments, the therapeutically effective amount is sufficient to produce the combination of all six of (a)-(f).

In any embodiment where the therapeutically effective amount produces (a), alone or in combination with any 2, 3, 4, or 5 of (b)-(f), the C_{max} is from about 1250 ng/mL to about 1750 ng/mL or about 1500 ng/mL to about 2000 ng/mL. In any embodiment where the therapeutically effective amount produces (a), alone or in combination with any 2, 3, 4, or 5 of (b)-(f), the C_{max} is about 1500 ng/mL, about 1550 ng/mL, about 1600 ng/mL, about 1650 ng/mL, about 1700 ng/mL, about 1750 ng/mL, about 1800 ng/mL, or about 1850 ng/mL. In any embodiment where the therapeutically effective amount produces (a), alone or in combination with any 2, 3, 4, or 5 of (b)-(f), the C_{max} is from about 1450 to about 1550, from about 1500 to about 1600, from about 1550 to about 1650, from about 1600 to about 1700, from about 1700 to about 1900, from about 1650 to about 1850, from about 1700 to about 1800, from about 1800 to about 1900, or from about 1900 to about 2000 ng/mL.

In any embodiment where the therapeutically effective amount produces (b), alone or in combination with any 2, 3, 4, or 5 of (a) and (c)-(f), the T_{max} is from about 2 h to about 3 h. In any embodiment where the therapeutically effective amount produces (b), alone or in combination with any 2, 3, 4, or 5 of (a) and (c)-(f), the T_{max} is about 2.2 h, about 2.4 h, about 2.5, about 2.6 h, or about 2.8 h. In any embodiment where the therapeutically effective amount produces (b), alone or in combination with

any 2, 3, 4, or 5 of (a) and (c)-(f), the T_{max} is from about 2 to about 2.5, from about 2.6 to about 2.7, from about 2.7 to about 2.8, from about 2.8 to about 2.9, from about 2.4 to about 3.0, from about 2.5 to about 3, from about 2.6 to about 3, from about 2.7 to about 3, from about 2.8 to about 3, or from about 2.9 to about 3 h.

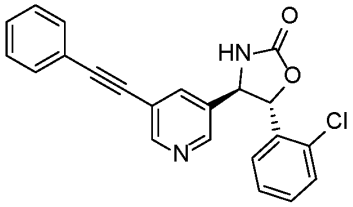
In any embodiment where the therapeutically effective amount produces (c), alone or in combination with any 2, 3, 4, or 5 of (a)-(b) and (d)-(f), the AUC_{tau} is from about 5000 ng•h/mL to about 25000 ng•h/mL. In any embodiment where the therapeutically effective amount produces (c), alone or in combination with any 2, 3, 4, or 5 of (a)-(b) and (d)-(f), the AUC_{tau} about 12000 ng•h/mL, about 13000 ng•h/mL, about 14000 ng•h/mL, about 15000 ng•h/mL, about 16000 ng•h/mL, about 17000 ng•h/mL, about 19000 ng•h/mL, about 20000 ng•h/mL, or about 22000 ng•h/mL . In any embodiment where the therapeutically effective amount produces (c) alone or in combination with any 2, 3, 4, or 5 of (a)-(b) and (d)-(f), the AUC_{tau} is from about 5000 to about 10000, from about 6000 to about 12000, from about 7000 to about 10000, from about 10000 to about 14000, from about 11000 to about 15000, from about 11500 to about 14500, from about 12000 to about 15000, from about 13000 to about 16000, from about 14000 to about 15000, from about 15000 to about 20000, from about 18000 to about 23000, or from about 20000 to about 25000 ng•h/mL.

In any embodiment where the therapeutically effective amount produces (d), alone or in combination with any 2, 3, 4, 5 of (a)-(c) and (f), the AUC_{last} is from about 20000 ng•h/mL to about 90000 ng•h/mL. In any embodiment where the therapeutically effective amount produces (d), alone or in combination with any 2, 3, 4, 5 of (a)-(c) and (f), the AUC_{last} is about 30000 ng•h/mL, about 40000 ng•h/mL, about 50000 ng•h/mL, about 60000 ng•h/mL, about 70000 ng•h/mL, or about 80000 ng•h/mL. In any embodiment where the therapeutically effective amount produces (d), alone or in combination with any 2, 3, 4, 5 of (a)-(c) and (f), the AUC_{last} is from about 20000 to about 30000, from about 25000 to about 35000, from about 27000 to about 40000, from about 30000 to about 45000, from about 45000 to about 55000, from about 50000 to about 60000, from about 55000 to about 65000, from about 60000 to about 70000, from about 65000 to about 75000, from about 70000 to about 80000 ng•h/mL, from about 75000 to about 85000, or from about 80000 to about 90000 ng•h/mL.

In any embodiment where the therapeutically effective amount produces (e), alone or in combination with any 2, 3, 4, or 5 of (a)-(d) and (f), the $T_{1/2}$ is from about 16 h to about 22 h. In any embodiment where the therapeutically effective amount produces (e), alone or in combination with any 2, 3, 4, or 5 of (a)-(d) and (f), the $T_{1/2}$ is about 17 h, about 17.5 h, about 18 h, about 18.5 h, about 19 h, about 19.5 h, about 20 h, about 20.5 h, or about 21 h. In any embodiment where the therapeutically effective amount produces (e), alone or in combination with any 2, 3, 4, or 5 of (a)-(d) and (f), the $T_{1/2}$ is from about 16 to about 17, from about 16.5 to about 17.5, from about 16 to about 18, from about 17 to about 18, from about 16 to about 18.5, from about 16 to about 19, from about 16 to about 20, from about 17 to about 21, from about 18 to about 20, from about 19 to about 21, or from about 20 to about 22 h.

In any embodiment where the therapeutically effective amount produces (f), alone or in combination with any 2, 3, 4, or 5 of (a)-(e), the C_{trough} is from about 200 ng/mL to about 1500 ng/mL. In any embodiment where the therapeutically effective amount produces (f), alone or in combination with any 2, 3, 4, or 5 of (a)-(e), the C_{trough} is about 400 ng/mL, about 600 ng/mL, about 800 ng/mL, about 900 ng/mL, about 1000 ng/mL, about 1200 ng/mL, or about 1500 ng/mL. In any embodiment where the therapeutically effective amount produces (f), alone or in combination with any 2, 3, 4, or 5 of (a)-(e), the C_{trough} is from about 200 to about 500, from about 300 to about 500, from about 450 to about 600, from about 600 to about 800, from about 650 to about 850, from about 700 to about 900, from about 750 to about 950, from about 800 to about 1000, from about 900 to about 1200, or from about 1000 to about 1500 ng/mL.

In an aspect, the invention features a method of treating Alzheimer's Disease, seizures, synapse loss, or Tau accumulation of a subject in need thereof, including treating the subject with a therapeutically effective amount of (4R,5R)-5-(2-chlorophenyl)-4-(5-(phenylethynyl)pyridin-3-yl)oxazolidin-2-one (Compound 1):



, e.g., with food, sufficient to produce:

a) a C_{max} (maximum concentration) of about 1500 ng/mL to about 7000 ng/mL, e.g., about 2000 ng/mL to about 6500 ng/mL;

b) a T_{max} (time at maximum concentration) of about 1.5 h to about 4.5 h, e.g., about 2 h to about 4 h;

c) an AUC_{tau} (area under the plasma concentration time curve over a dosage interval of tau, wherein tau is from 0 h to 12 h) of about 18000 ng•h/mL to about 70000 ng•h/mL, e.g., about 20000 ng•h/mL to about 60000 ng•h/mL;

d) an AUC_{last} (area under the plasma concentration time curve to the last measurable plasma concentration) of about 45000 ng•h/mL to about 560000 ng•h/mL, e.g., about 47000 ng•h/mL to about 557000 ng•h/mL;

e) a $T_{1/2}$ (half-life) of about 3 h to about 42 h; and/or

f) a C_{trough} (plasma concentration of Compound 1 immediately before administration of next dosage of Compound 1) of about 1000 to 5000 ng/mL.

In some embodiments, the therapeutically effective amount is sufficient to produce any one of (a)-(f). In some embodiments, the therapeutically effective amount is sufficient to produce any combination of two of (a)-(f). In some embodiments, the therapeutically effective amount is sufficient to produce any combination of three of (a)-(f). In some embodiments, the therapeutically effective amount is sufficient to

produce any combination of four of (a)-(f). In some embodiments, the therapeutically effective amount is sufficient to produce the combination of five of (a)-(f). In some embodiments, the therapeutically effective amount is sufficient to produce the combination of all six of (a)-(f).

In any embodiment where the therapeutically effective amount produces (a), alone or in combination with any 2, 3, 4, or 5 of (b)-(f), the C_{max} is from about 3000 ng/mL to about 5000 ng/mL. In any embodiment where the therapeutically effective amount produces (a), alone or in combination with any 2, 3, 4, or 5 of (b)-(f), the C_{max} is about 3250 ng/mL, about 3500 ng/mL, about 3750 ng/mL, about 4000 ng/mL, about 4250 ng/mL, or about 4500 ng/mL. In any embodiment where the therapeutically effective amount produces (a), alone or in combination with any 2, 3, 4, or 5 of (b)-(f), the C_{max} is from about 3000 to about 3500, from about 3200 to about 4000, from about 3500 to about 4000, from about 3800 to about 4500, from about 4000 to about 4500, from about 4200 to about 5000, from about 4500 to about 4000, or from about 4800 to about 5000 ng/mL.

In any embodiment where the therapeutically effective amount produces (b), alone or in combination with any 2, 3, 4, or 5 of (a) and (c)-(f), the T_{max} is from about 2.5 h to about 3.5 h. In any embodiment where the therapeutically effective amount produces (b), alone or in combination with any 2, 3, 4, or 5 of (a) and (c)-(f), the T_{max} is about 2.7 h, about 2.9 h, about 3.0, about 3.2 h, or about 3.3 h. In any embodiment where the therapeutically effective amount produces (b), alone or in combination with any 2, 3, 4, or 5 of (a) and (c)-(f), the T_{max} is from about 2.5 to about 2.6, from about 2.6 to about 2.7, from about 2.7 to about 2.8, from about 2.8 to about 2.9, from about 2.9 to about 3.0, from about 3.0 to about 3.1, from about 3.1 to about 3.2, from about 3.2 to about 3.3, from about 3.3 to about 3.4, or from about 3.4 to about 3.5 h.

In any embodiment where the therapeutically effective amount produces (c), alone or in combination with any 2, 3, 4, or 5 of (a)-(b) and (d)-(f), the AUC_{tau} is from about 30000 ng•h/mL to about 50000 ng•h/mL. In any embodiment where the therapeutically effective amount produces (c), alone or in combination with any 2, 3, 4, or 5 of (a)-(b) and (d)-(f), the AUC_{tau} is about 20000 ng•h/mL, about 25000 ng•h/mL, about 30000 ng•h/mL, about 33000 ng•h/mL, about 34000 ng•h/mL, about 35000 ng•h/mL, about 36000 ng•h/mL, about 37000 ng•h/mL, about 38000 ng•h/mL, about 40000 ng•h/mL, about 42000 ng•h/mL, or about 45000 ng•h/mL. In any embodiment where the therapeutically effective amount produces (c) alone or in combination with any 2, 3, 4, or 5 of (a)-(b) and (d)-(f), the AUC_{tau} is from about 30000 to about 35000, from about 30000 to about 40000, from about 35000 to about 40000, from about 35000 to about 45000, from about 40000 to about 45000, from about 40000 to about 50000, from about 45000 to about 50000, from about 35000 to about 50000, from about 38000 to about 42000, from about 39000 to about 43000, from about 42000 to about 45000, or from about 46000 to about 50000 ng•h/mL.

In any embodiment where the therapeutically effective amount produces (d), alone or in combination with any 2, 3, 4, 5 of (a)-(c) and (f), the AUC_{last} is from about 50000 ng•h/mL to about 410000 ng•h/mL. In any embodiment where the therapeutically effective amount produces (d), alone or in combination with any 2, 3, 4, 5 of (a)-(c) and (f), the AUC_{last} is about 100000 ng•h/mL, about 150000

ng•h/mL, about 200000 ng•h/mL, about 250000 ng•h/mL, about 300000 ng•h/mL, or about 350000 ng•h/mL In any embodiment where the therapeutically effective amount produces (d), alone or in combination with any 2, 3, 4, 5 of (a)-(c) and (f), the AUC_{last} is from about 50000 to about 100000, from about 100000 to about 150000, from about 150000 to about 200000, from about 200000 to about 250000, from about 250000 to about 300000, from about 300000 to about 350000, from about 350000 to about 400000, or from about 400000 to about 410000 ng•h/mL.

In any embodiment where the therapeutically effective amount produces (e), alone or in combination with any 2, 3, 4, or 5 of (a)-(d) and (f), the $T_{1/2}$ is from about 15 h to about 70 h. In any embodiment where the therapeutically effective amount produces (e), alone or in combination with any 2, 3, 4, or 5 of (a)-(d) and (f), the $T_{1/2}$ is about 20 h, about 26 h, about 32 h, about 38 h, about 44 h, about 50 h, or about 60 h.= In any embodiment where the therapeutically effective amount produces (e), alone or in combination with any 2, 3, 4, or 5 of (a)-(d) and (f), the $T_{1/2}$ is from about 15 to about 20, from about 20 to about 25, from about 25 to about 30, from about 30 to about 35, from about 35 to about 40, from about 40 to about 45, from about 45 to about 50, from about 50 to about 55, from about 55 to about 60, from about 60 to about 65, or from about 65 to about 70 h.

In any embodiment where the therapeutically effective amount produces (f), alone or in combination with any 2, 3, 4, or 5 of (a)-(e), the C_{trough} is from about 2000 ng/mL to about 4000 ng/mL. In any embodiment where the therapeutically effective amount produces (f), alone or in combination with any 2, 3, 4, or 5 of (a)-(e), the C_{trough} is about 1500 ng/mL, about 2000 ng/mL, about 2200 ng/mL, about 2500 ng/mL, about 2700 ng/mL, about 3000 ng/mL, about 3300 ng/mL, or about 3500 ng/mL. In any embodiment where the therapeutically effective amount produces (f), alone or in combination with any 2, 3, 4, or 5 of (a)-(e), the C_{trough} is from about 2000 to about 3000, from about 2000 to about 2500, from about 2000 to about 3500, from about 2500 to about 3500, from about 3000 to about 3500, or from about 3000 to about 4000 ng/mL.

In some embodiments of any of the foregoing aspects, administration to the subject occurs without food.

In some embodiments of any of the foregoing aspects, administration to the subject occurs with food. In some embodiments, administration to the subject occurs less than 30 minutes prior to consuming food or after consuming food, e.g., immediately prior to the consumption of food up to 1 hour after consumption. In some embodiments, the administration to the subject is substantially at the same time as food. In some embodiments, the administration to the subject is about 30 minutes after consumption of food. In some embodiments of any of the foregoing methods, the food is a high protein food. In some embodiments of any of the foregoing methods, the food is a high fat food (e.g., at least 25, 30, 40, or 50% of the calories are from fat). In some embodiments of any of the foregoing methods, the food is a high protein and high fat food. In some embodiments, the food is high calorie food (e.g., the food includes at least 100 calories, e.g., at least 200 calories, at least 300 calories, at least 400 calories, at least 500

calories, e.g., 500-1500 or 800-1000 calories). In some embodiments of any of the foregoing methods, the food is a meal, e.g., breakfast, lunch, or dinner.

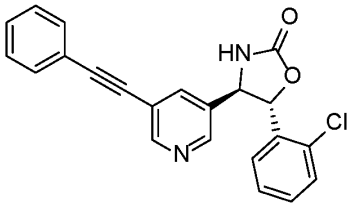
In some embodiments of any of the foregoing aspects, the consumption of food occurs prior to the administration of Compound 1 (e.g., the consumption of food occurs between 1 hour up to immediately prior to the administration of sepiapterin). In some embodiments, the consumption of food occurs after the administration of Compound 1 (e.g., the consumption of food occurs between immediately after administration up to 30 minutes after administration).

In any of the above embodiments, Compound 1 is in a pharmaceutical composition.

In any of the above embodiments, the pharmaceutical composition further comprises a pharmaceutically acceptable plasticizer, binder, bulking agent, carrier, excipient, lubricant, disintegrant, and/or surfactant.

In any of the above embodiments, about 10 mg, about 40 mg, about 50 mg, about 70 mg, about 100 mg, about 150 mg, or about 200 mg of Compound 1 is administered. In any of the above embodiments, Compound 1 is administered orally. In any of the above embodiments, Compound 1 is administered every 12 hours. In any of the above embodiments, Compound 1 is administered twice, three, or four times a day. In any of the above embodiments, Compound 1 is administered once a day. In any of the above embodiments, Compound 1 is administered for at least 10 days, 20 days, 30 days, 90 days, or 180 days. In any of the above embodiments, Form A of Compound 1 is administered, e.g., orally.

DETAILED DESCRIPTION

The present disclosure provides methods of using (4R,5R)-5-(2-chlorophenyl)-4-(5-(phenylethynyl)pyridin-3-yl)oxazolidin-2-one 

(Compound 1). The mGluR5 receptor is expressed broadly throughout the CNS with predominant post-synaptic localization, although pre-synaptic expression is also present. It is a Gαq-coupled receptor activating phospholipase C and elevating intracellular calcium levels, leading to activation of downstream signaling molecules. Many studies have demonstrated a role for the receptor in regulating N-methyl-D-aspartate (NMDA) receptor activity as well as synaptic plasticity, suggesting this receptor plays a key role in glutamatergic signal transduction.

Compound 1 binds to mGluR5 and is an allosteric modulator of mGluR5, e.g., a silent allosteric modulator. Thus, Compound 1 can be administered to modulate mGluR5 and to treat individual subjects having a disease, disorder and/or condition related to mGluR5, such as, but not limited to, CNS disorders. The present disclosure provides methods that result in advantageous pharmacokinetic outcomes in

patients. In particular, the methods result in advantageous in vivo C_{max}, T_{max}, AUC_{tau}, AUC_{last}, $T_{1/2}$, and/or C_{trough}, resulting in effective treatment of diseases such as Alzheimer's disease. The methods may provide a C_{trough} at or above IC_{80} for mGluR5.

Compound 1 is described in U.S. Patent No. 8,691,821, hereby incorporated by reference. Compound 1 may be prepared using any convenient methodology known to a person of the art, such as the methods disclosed in U.S. Patent No. 8,691,821.

Solid forms of Compound 1, including compositions and methods thereof, are described in WO 2023/183656, which is incorporated by reference. An anhydrous (AH) form (Form A), two solvated forms (Solvates S1 and S2, interchangeably referred to as Form B and Form C, respectively), and multiple amorphous forms of Compound 1 have been discovered. The amorphous forms resulted in a gel after evaporation in various solvent systems. The anhydrous Form A is the most stable form, e.g., as determined by DSC and TGA analyses.

Form A can be identified with single crystal X-ray Powder Diffraction (XRPD) by irradiation with Cu Kα X-rays. The main peaks of Form A were identified and their relative intensities are listed in Table 1. As will be understood by a person skilled in the art, the relative intensities of the peaks within Table 1 may vary due to various factors such as the purity of the material being analyzed, orientation effects of crystals in the X-ray beam, the degree of crystallinity of the sample, and so on. The peak positions may also shift for variations of sample height, but the peak positions will remain substantially as defined in Table 1. A person skilled in the art will also understand that measurements using a different wavelength will result in different shifts according to the Bragg equation ($n\lambda=2d \sin\theta$). Such further XRPD patterns generated by use of alternative wavelengths are alternative representations of the XRPD patterns of the crystalline materials.

Table 1. XRPD peak listing for Form A

Scan 1				Scan 2				AveragePos. [°2θ]	Average d-spacing [Å]
Pos. [°2θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]	Pos. [°2θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]		
6.74	2780.79	13.11	37.19	6.77	965.33	13.05	36.02	6.75	13.08
6.87	1591.51	12.86	21.28	6.89	427.17	12.82	15.94	6.88	12.84
9.01	2852.25	9.81	38.15	9.03	903.15	9.79	33.70	9.02	9.80
11.65	2579.35	7.59	34.50	11.66	1026.93	7.58	38.32	11.65	7.59
11.85	2702.90	7.46	36.15	11.87	863.80	7.45	32.24	11.86	7.46
12.14	1407.87	7.29	18.83	12.16	550.33	7.27	20.54	12.15	7.28
13.53	3336.83	6.54	44.63	13.56	1311.85	6.53	48.96	13.55	6.53
14.98	80.72	5.91	1.08	15.00	30.92	5.90	1.15	14.99	5.90

Scan 1				Scan 2				AveragePos. [°2θ]	Average d-spacing [Å]
Pos. [°2θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]	Pos. [°2θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]		
15.58	405.33	5.68	5.42	15.61	150.97	5.67	5.63	15.59	5.68
17.84	5285.83	4.97	70.69	17.25	40.08	5.14	1.50	17.55	5.05
18.07	563.88	4.91	7.54	17.86	2378.92	4.96	88.78	17.97	4.93
18.82	1346.22	4.71	18.00	18.08	215.72	4.90	8.05	18.45	4.81
19.01	1481.62	4.66	19.81	18.84	557.62	4.71	20.81	18.93	4.69
19.90	6593.53	4.46	88.18	19.02	587.76	4.66	21.93	19.46	4.56
20.77	7477.32	4.27	100.00	19.92	2679.63	4.45	100.00	20.34	4.36
21.40	874.05	4.15	11.69	20.78	2567.51	4.27	95.82	21.09	4.21
21.56	413.19	4.12	5.53	21.41	337.05	4.15	12.58	21.49	4.13
22.20	2651.80	4.00	35.46	21.56	184.99	4.12	6.90	21.88	4.06
22.37	606.52	3.97	8.11	22.20	1161.04	4.00	43.33	22.29	3.99
23.15	5660.54	3.84	75.70	22.35	416.94	3.97	15.56	22.75	3.91
24.03	2770.47	3.70	37.05	23.16	2206.67	3.84	82.35	23.59	3.77
24.43	1652.16	3.64	22.10	24.05	1055.99	3.70	39.41	24.24	3.67
24.63	120.01	3.61	1.60	24.44	653.73	3.64	24.40	24.54	3.63
25.54	356.43	3.48	4.77	24.63	334.35	3.61	12.48	25.08	3.55
25.72	213.92	3.46	2.86	25.53	191.14	3.49	7.13	25.63	3.47
26.14	2867.60	3.41	38.35	26.14	902.51	3.41	33.68	26.14	3.41
26.64	675.40	3.34	9.03	26.23	623.52	3.39	23.27	26.44	3.37
26.96	656.82	3.31	8.78	26.67	294.78	3.34	11.00	26.81	3.32
27.27	544.99	3.27	7.29	26.98	265.85	3.30	9.92	27.12	3.29
27.76	452.52	3.21	6.05	27.29	252.78	3.27	9.43	27.53	3.24
28.16	1939.19	3.17	25.93	27.78	210.61	3.21	7.86	27.97	3.19
28.66	638.67	3.11	8.54	28.17	819.35	3.17	30.58	28.41	3.14
29.28	608.80	3.05	8.14	28.69	252.58	3.11	9.43	28.99	3.08
29.60	151.87	3.02	2.03	29.30	253.45	3.05	9.46	29.45	3.03
30.06	327.79	2.97	4.38	29.60	68.53	3.02	2.56	29.83	2.99
30.47	1132.52	2.93	15.15	30.09	103.24	2.97	3.85	30.28	2.95
30.76	419.02	2.90	5.60	30.48	457.90	2.93	17.09	30.62	2.92
30.94	965.50	2.89	12.91	30.80	185.44	2.90	6.92	30.87	2.89
31.36	307.89	2.85	4.12	30.95	444.54	2.89	16.59	31.15	2.87
31.93	246.24	2.80	3.29	31.38	150.99	2.85	5.63	31.65	2.82

Scan 1				Scan 2				AveragePos. [°2θ]	Average d-spacing [Å]
Pos. [°2θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]	Pos. [°2θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]		
32.58	84.71	2.75	1.13	31.93	118.39	2.80	4.42	32.25	2.77
33.04	260.30	2.71	3.48	32.61	56.84	2.74	2.12	32.82	2.73
33.24	463.75	2.69	6.20	33.02	114.28	2.71	4.26	33.13	2.70
33.31	262.78	2.69	3.51	33.28	259.31	2.69	9.68	33.29	2.69
34.24	233.43	2.62	3.12	34.22	96.21	2.62	3.59	34.23	2.62
34.91	261.55	2.57	3.50	34.94	124.15	2.57	4.63	34.93	2.57
35.76	468.82	2.51	6.27	35.77	220.59	2.51	8.23	35.76	2.51
36.66	405.30	2.45	5.42	36.65	191.58	2.45	7.15	36.66	2.45
37.85	88.21	2.37	1.18	37.86	36.47	2.37	1.36	37.86	2.37
38.65	211.71	2.33	2.83	38.62	89.21	2.33	3.33	38.64	2.33
39.01	146.75	2.31	1.96	39.03	52.43	2.31	1.96	39.02	2.31
40.40	293.92	2.23	3.93	40.45	108.07	2.23	4.03	40.43	2.23
40.98	253.43	2.20	3.39	40.99	94.52	2.20	3.53	40.99	2.20
41.67	190.55	2.17	2.55	41.69	89.05	2.16	3.32	41.68	2.17
42.31	225.89	2.13	3.02	42.33	83.60	2.13	3.12	42.32	2.13
44.01	136.98	2.06	1.83	44.06	100.21	2.05	3.74	44.03	2.05

Form A may be characterized by any of its peaks in Table 1. For example, Form A may be characterized by any of the following peaks, among others: 6.75, 6.88, 9.02, 11.65, 11.86, 12.15, 13.55, 14.99, 15.59, 17.55, 17.97, 18.45, 18.93, 19.46, 20.34, 21.09, 21.49, 21.88, 22.29, 22.75, 23.59, 24.24, 24.54, 25.08, 25.63, 26.14, 26.44, 26.81, 27.12, 27.53, 27.97, 28.41, 28.99, 29.45, 29.83, 30.28, 30.62, 30.87, 31.15, 31.65, 32.25, 32.82, 33.13, 33.29, 34.23, 34.93, 35.76, 36.66, 37.86, 38.64, 39.02, 40.43, 40.99, 41.68, 42.32, or 44.03 degrees 2θ, each ±0.2 degrees 2θ. Form A may also be characterized by any of the following d-spacing, among others: 13.08, 12.84, 9.80, 7.59, 7.46, 7.28, 6.53, 5.90, 5.68, 5.05, 4.93, 4.81, 4.69, 4.56, 4.36, 4.21, 4.13, 4.06, 3.99, 3.91, 3.77, 3.67, 3.63, 3.55, 3.47, 3.41, 3.37, 3.32, 3.29, 3.24, 3.19, 3.14, 3.08, 3.03, 2.99, 2.95, 2.92, 2.89, 2.87, 2.82, 2.77, 2.73, 2.70, 2.69, 2.62, 2.57, 2.51, 2.45, 2.37, 2.33, 2.31, 2.23, 2.20, 2.17, 2.13, 2.05 Å, each ±0.2 Å. In some embodiments, the anhydrous crystalline form of Compound 1 is Form A and has an X-ray powder diffraction (XRPD) pattern including one or more peaks of any of 6.75, 6.88, 9.02, 11.65, 11.86, 12.15, 13.55, 14.99, 15.59, 17.55, 17.97, 18.45, 18.93, 19.46, 20.34, 21.09, 21.49, 21.88, 22.29, 22.75, 23.59, 24.24, 24.54, 25.08, 25.63, 26.14, 26.44, 26.81, 27.12, 27.53, 27.97, 28.41, 28.99, 29.45, 29.83, 30.28, 30.62, 30.87, 31.15, 31.65, 32.25, 32.82, 33.13, 33.29, 34.23, 34.93, 35.76, 36.66, 37.86, 38.64, 39.02, 40.43, 40.99, 41.68, 42.32, or

44.03 degrees 2θ, each ±0.2 degrees 2θ. In some embodiments, the anhydrous crystalline form of Compound 1 is Form A and has an X-ray powder diffraction (XRPD) pattern including all the peaks of 6.75, 6.88, 9.02, 11.65, 11.86, 12.15, 13.55, 14.99, 15.59, 17.55, 17.97, 18.45, 18.93, 19.46, 20.34, 21.09, 21.49, 21.88, 22.29, 22.75, 23.59, 24.24, 24.54, 25.08, 25.63, 26.14, 26.44, 26.81, 27.12, 27.53, 27.97, 28.41, 28.99, 29.45, 29.83, 30.28, 30.62, 30.87, 31.15, 31.65, 32.25, 32.82, 33.13, 33.29, 34.23, 34.93, 35.76, 36.66, 37.86, 38.64, 39.02, 40.43, 40.99, 41.68, 42.32, and 44.03 degrees 2θ, each ±0.2 degrees 2θ. In some embodiments, Form A analyzed by differential scanning calorimetry (DSC) thermogram shows a melting endothermic peak at about 134 °C-138 °C. In some embodiments, Form A analyzed by thermogravimetric analysis (TGA) exhibits a dehydration from ambient to about 250 °C with a weight loss of about 0.02% (w/w).

Form B can be identified with single crystal X-ray Powder Diffraction (XRPD) by irradiation with Cu Kα X-rays. The main peaks of Form B were identified and their relative intensities are listed in Table 2. As will be understood by a person skilled in the art, the relative intensities of the peaks within Table 2 may vary due to various factors such as the purity of the material being analyzed, orientation effects of crystals in the X-ray beam, the degree of crystallinity of the sample, and so on. The peak positions may also shift for variations of sample height, but the peak positions will remain substantially as defined in Table 2. A person skilled in the art will also understand that measurements using a different wavelength will result in different shifts according to the Bragg equation ($n\lambda=2d \sin\theta$). Such further XRPD patterns generated by use of alternative wavelengths are alternative representations of the XRPD patterns of the crystalline materials.

Table 2. XRPD peak listing for Form B

Pos. [°2θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]
3.36	61.60	26.31	1.75
6.75	1416.59	13.09	40.26
6.85	509.62	12.90	14.48
8.19	369.60	10.79	10.5
10.14	11.35	8.72	0.32
10.84	253.71	8.15	7.21
13.18	122.51	6.71	3.48
13.40	117.88	6.60	3.35
13.54	282.19	6.54	8.02
13.70	1567.79	6.46	44.56
15.65	50.32	5.66	1.43
16.07	429.49	5.51	12.21
16.27	3518.31	5.45	100

Pos. [°2θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]
16.58	1033.66	5.34	29.38
16.77	122.09	5.28	3.47
17.15	87.86	5.17	2.5
17.74	126.15	4.99	3.59
18.63	659.62	4.76	18.75
18.73	310.84	4.73	8.83
19.16	573.48	4.63	16.3
19.44	1293.36	4.56	36.76
19.63	857.16	4.52	24.36
19.95	432.1	4.45	12.28
20.21	349.07	4.39	9.92
20.36	354.79	4.36	10.08
20.60	175.19	4.31	4.98
21.56	1694.51	4.12	48.16
21.78	1489.37	4.08	42.33
22.42	648.49	3.96	18.43
22.88	924.23	3.88	26.27
23.06	506.07	3.85	14.38
23.22	1210.94	3.83	34.42
23.43	249.07	3.79	7.08
23.75	627.13	3.74	17.82
23.99	2134.33	3.71	60.66
24.53	910.49	3.63	25.88
24.88	426.02	3.58	12.11
25.23	249.95	3.53	7.1
25.43	559.47	3.50	15.9
26.03	482.33	3.42	13.71
26.63	511.02	3.34	14.52
26.89	560.15	3.31	15.92
27.27	38.44	3.27	1.09
27.70	28.66	3.22	0.81
28.22	681.80	3.16	19.38
29.44	97.09	3.03	2.76
29.95	56.56	2.98	1.61

Pos. [°2θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]
30.24	37.57	2.95	1.07
30.51	82.92	2.93	2.36
30.71	66.32	2.91	1.89
31.14	283.87	2.87	8.07
31.72	164.07	2.82	4.66
32.01	98.64	2.79	2.8
32.27	242.08	2.77	6.88
32.47	448.45	2.75	12.75
32.85	170.23	2.72	4.84
33.48	65.35	2.67	1.86
33.62	129.03	2.66	3.67
34.15	204.29	2.62	5.81
34.63	278.19	2.59	7.91
35.23	48.56	2.55	1.38
35.91	65.65	2.50	1.87
36.16	89.48	2.48	2.54
36.71	81.75	2.45	2.32
37.31	75.67	2.41	2.15
37.79	61.02	2.38	1.73
38.20	119.43	2.35	3.39
38.83	38.49	2.32	1.09
39.92	44.75	2.26	1.27
40.26	95	2.24	2.7
40.58	74.17	2.22	2.11
41.37	31.17	2.18	0.89
42.56	74.2	2.12	2.11
43.38	50.74	2.08	1.44
44.67	26.4	2.03	0.75

Form B may be characterized by any of its peaks in Table 2. For example, Form B may be characterized by any of the following peaks, among others: 3.36, 6.75, 6.85, 8.19, 10.14, 10.84, 13.18, 13.4, 13.54, 13.7, 15.65, 16.07, 16.27, 16.58, 16.77, 17.15, 17.74, 18.63, 18.73, 19.16, 19.44, 19.63, 19.95, 20.21, 20.36, 20.6, 21.56, 21.78, 22.42, 22.88, 23.06, 23.22, 23.43, 23.75, 23.99, 24.53, 24.88, 25.23, 25.43, 26.03, 26.63, 26.89, 27.27, 27.7, 28.22, 29.44, 29.95, 30.24, 30.51, 30.71, 31.14, 31.72, 32.01, 32.27, 32.47, 32.85, 33.48, 33.62, 34.15, 34.63, 35.23, 35.91, 36.16, 36.71, 37.31, 37.79, 38.2,

38.83, 39.92, 40.26, 40.58, 41.37, 42.56, 43.38, or 44.67 degrees 2θ, each ±0.2 degrees 2θ. Form B may also be characterized by any of the following d-spacing, among others: 26.31, 13.09, 12.9, 10.79, 8.72, 8.15, 6.71, 6.6, 6.54, 6.46, 5.66, 5.51, 5.45, 5.34, 5.28, 5.17, 4.99, 4.76, 4.73, 4.63, 4.56, 4.52, 4.45, 4.39, 4.36, 4.31, 4.12, 4.08, 3.96, 3.88, 3.85, 3.83, 3.79, 3.74, 3.71, 3.63, 3.58, 3.53, 3.5, 3.42, 3.34, 3.31, 3.27, 3.22, 3.16, 3.03, 2.98, 2.95, 2.93, 2.91, 2.87, 2.82, 2.79, 2.77, 2.75, 2.72, 2.67, 2.66, 2.62, 2.59, 2.55, 2.5, 2.48, 2.45, 2.41, 2.38, 2.35, 2.32, 2.26, 2.24, 2.22, 2.18, 2.12, 2.08, or 2.03, each ±0.2 Å. In some embodiments, the solvate form of Compound 1 is Form B and has an X-ray powder diffraction (XRPD) pattern including one or more peaks of any of 3.36, 6.75, 6.85, 8.19, 10.14, 10.84, 13.18, 13.4, 13.54, 13.7, 15.65, 16.07, 16.27, 16.58, 16.77, 17.15, 17.74, 18.63, 18.73, 19.16, 19.44, 19.63, 19.95, 20.21, 20.36, 20.6, 21.56, 21.78, 22.42, 22.88, 23.06, 23.22, 23.43, 23.75, 23.99, 24.53, 24.88, 25.23, 25.43, 26.03, 26.63, 26.89, 27.27, 27.7, 28.22, 29.44, 29.95, 30.24, 30.51, 30.71, 31.14, 31.72, 32.01, 32.27, 32.47, 32.85, 33.48, 33.62, 34.15, 34.63, 35.23, 35.91, 36.16, 36.71, 37.31, 37.79, 38.2, 38.83, 39.92, 40.26, 40.58, 41.37, 42.56, 43.38, or 44.67 degrees 2θ, each ±0.2 degrees 2θ. In some embodiments, the solvate form of Compound 1 is Form B and has an X-ray powder diffraction (XRPD) pattern including all the peaks of 3.36, 6.75, 6.85, 8.19, 10.14, 10.84, 13.18, 13.4, 13.54, 13.7, 15.65, 16.07, 16.27, 16.58, 16.77, 17.15, 17.74, 18.63, 18.73, 19.16, 19.44, 19.63, 19.95, 20.21, 20.36, 20.6, 21.56, 21.78, 22.42, 22.88, 23.06, 23.22, 23.43, 23.75, 23.99, 24.53, 24.88, 25.23, 25.43, 26.03, 26.63, 26.89, 27.27, 27.7, 28.22, 29.44, 29.95, 30.24, 30.51, 30.71, 31.14, 31.72, 32.01, 32.27, 32.47, 32.85, 33.48, 33.62, 34.15, 34.63, 35.23, 35.91, 36.16, 36.71, 37.31, 37.79, 38.2, 38.83, 39.92, 40.26, 40.58, 41.37, 42.56, 43.38, and 44.67 degrees 2θ, each ±0.2 degrees 2θ. In some embodiments, Form B analyzed by differential scanning calorimetry (DSC) thermogram shows a melting endothermic peak at about 134-138 °C. In some embodiments, Form B analyzed by thermogravimetric analysis (TGA) exhibits a desolvation from ambient to about 200 °C with a weight loss of about 6.7% (w/w)

Form C, prepared from a long-term slurry using isopropyl alcohol, can be identified with single crystal XRPD by irradiation with Cu Kα X-rays. The main peaks of Form C were identified and their relative intensities are listed in Table 3. As will be understood by a person skilled in the art, the relative intensities of the peaks within Tables 3 may vary due to various factors such as the purity of the material being analyzed, orientation effects of crystals in the X-ray beam, the degree of crystallinity of the sample, and so on. The peak positions may also shift for variations of sample height, but the peak positions will remain substantially as defined in Table 3. A person skilled in the art will also understand that measurements using a different wavelength will result in different shifts according to the Bragg equation ($n\lambda=2d \sin \theta$). Such further XRPD patterns generated by use of alternative wavelengths are alternative representations of the XRPD patterns of the crystalline materials.

Table 3. XRPD peak listing for Form C prepared from a long-term slurry using isopropyl alcohol

Pos. [°2θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]
3.40	114.39	25.93	5.51
6.83	2075.69	12.92	100.00
8.33	330.50	10.61	15.92
10.94	95.09	8.08	4.58
13.32	143.33	6.64	6.90
13.82	597.53	6.40	28.79
16.32	1503.18	5.43	72.42
16.66	591.16	5.32	28.48
16.95	121.30	5.23	5.84
17.24	69.38	5.14	3.34
18.76	448.85	4.73	21.62
19.27	208.51	4.60	10.05
19.60	660.49	4.53	31.82
20.13	453.96	4.41	21.87
20.31	282.83	4.37	13.63
20.81	195.56	4.26	9.42
21.86	764.5	4.06	36.83
22.72	172.54	3.91	8.31
23.15	728.32	3.84	35.09
23.38	78.88	3.80	3.80
23.57	327.26	3.77	15.77
23.86	405.15	3.73	19.52
24.30	328.60	3.66	15.83
24.89	330.49	3.57	15.92
25.61	299.01	3.48	14.41
26.24	128.37	3.39	6.18
26.92	139.98	3.31	6.74
27.28	132.49	3.27	6.38
28.53	172.30	3.13	8.30
29.51	107.49	3.02	5.18
30.63	56.99	2.92	2.75
31.64	50.31	2.83	2.42

Pos. [°2θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]
32.22	41.39	2.78	1.99
32.59	207.50	2.75	10.00
32.96	105.52	2.72	5.08
33.72	107.37	2.66	5.17
34.34	74.88	2.61	3.61
34.80	162.69	2.58	7.84
35.36	34.06	2.54	1.64
36.25	52.56	2.48	2.53
36.91	66.84	2.43	3.22
38.24	37.92	2.35	1.83
42.75	37.28	2.11	1.80
43.52	17.75	2.08	0.85
44.99	11.58	2.01	0.56

Form C, prepared from a long-term slurry using isopropyl alcohol, may be characterized by any of its peaks in Table 3. For example, Form C may be characterized by any of the following peaks, among others: 3.40, 6.83, 8.33, 10.94, 13.32, 13.82, 16.32, 16.66, 16.95, 17.24, 18.76, 19.27, 19.6, 20.13, 20.31, 20.81, 21.86, 22.72, 23.15, 23.38, 23.57, 23.86, 24.30, 24.89, 25.61, 26.24, 26.92, 27.28, 28.53, 29.51, 30.63, 31.64, 32.22, 32.59, 32.96, 33.72, 34.34, 34.8, 35.36, 36.25, 36.91, 38.24, 42.75, 43.52, or 44.99 degrees 2θ, each ±0.2 degrees 2θ. Form C, prepared from a long-term slurry from isopropyl alcohol, may also be characterized by any of the following d-spacing, among others: 25.93, 12.92, 10.61, 8.08, 6.64, 6.4, 5.43, 5.32, 5.23, 5.14, 4.73, 4.6, 4.53, 4.41, 4.37, 4.26, 4.06, 3.91, 3.84, 3.8, 3.77, 3.73, 3.66, 3.57, 3.48, 3.39, 3.31, 3.27, 3.13, 3.02, 2.92, 2.83, 2.78, 2.75, 2.72, 2.66, 2.61, 2.58, 2.54, 2.48, 2.43, 2.35, 2.11, 2.08, or 2.01, each ±0.2 Å. In some embodiments, the solvate form of Compound 1 is Form C, prepared from a long-term slurry using isopropyl alcohol, and has an X-ray powder diffraction (XRPD) pattern including one or more peaks of any of 3.40, 6.83, 8.33, 10.94, 13.32, 13.82, 16.32, 16.66, 16.95, 17.24, 18.76, 19.27, 19.6, 20.13, 20.31, 20.81, 21.86, 22.72, 23.15, 23.38, 23.57, 23.86, 24.30, 24.89, 25.61, 26.24, 26.92, 27.28, 28.53, 29.51, 30.63, 31.64, 32.22, 32.59, 32.96, 33.72, 34.34, 34.8, 35.36, 36.25, 36.91, 38.24, 42.75, 43.52, or 44.99 degrees 2θ, each ±0.2 degrees 2θ. In some embodiments, the solvate form of Compound 1 is Form C, prepared from a long-term slurry using isopropyl alcohol, and has an X-ray powder diffraction (XRPD) pattern including all the peaks of 3.40, 6.83, 8.33, 10.94, 13.32, 13.82, 16.32, 16.66, 16.95, 17.24, 18.76, 19.27, 19.6, 20.13, 20.31, 20.81, 21.86, 22.72, 23.15, 23.38, 23.57, 23.86, 24.30, 24.89, 25.61, 26.24, 26.92, 27.28, 28.53, 29.51, 30.63, 31.64, 32.22, 32.59, 32.96, 33.72, 34.34, 34.8, 35.36, 36.25, 36.91, 38.24, 42.75, 43.52, and 44.99 degrees 2θ, each ±0.2 degrees

2θ. In some embodiments, Form C, prepared from a long-term slurry using isopropyl alcohol, analyzed by differential scanning calorimetry (DSC) thermogram shows a melting endothermic peak at about 129-133 °C. In some embodiments, Form C, prepared from a long-term slurry using isopropyl alcohol, analyzed by thermogravimetric analysis (TGA) exhibits a dehydration from ambient to about 200 °C with a weight loss of about 3.4% (w/w).

Form C, prepared from vapor diffusion using isopropyl alcohol, can be identified with single crystal XRPD by irradiation with Cu Kα X-rays. The main peaks of Form C were identified and their relative intensities are listed in Table 4. As will be understood by a person skilled in the art, the relative intensities of the peaks within Table 4 may vary due to various factors such as the purity of the material being analyzed, orientation effects of crystals in the X-ray beam, the degree of crystallinity of the sample, and so on. The peak positions may also shift for variations of sample height, but the peak positions will remain substantially as defined in Table 4. A person skilled in the art will also understand that measurements using a different wavelength will result in different shifts according to the Bragg equation ($n\lambda=2d \sin\theta$). Such further XRPD patterns generated by use of alternative wavelengths are alternative representations of the XRPD patterns of the crystalline materials.

Table 4. XRPD peak listing for Form C prepared from vapor diffusion using isopropyl alcohol

Pos. [°2θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]
3.38	28.72	26.12	2.76
6.85	1041.25	12.90	100.00
8.35	136.82	10.58	13.14
10.95	26.05	8.07	2.50
13.31	71.42	6.65	6.86
13.84	224.21	6.39	21.53
16.31	638.67	5.43	61.34
16.65	260.45	5.32	25.01
16.99	66.38	5.21	6.38
17.23	45.42	5.14	4.36
18.76	176.23	4.73	16.93
19.33	105.99	4.59	10.18
19.60	227.91	4.53	21.89
20.13	258.97	4.41	24.87
20.30	135.22	4.37	12.99
20.80	75.82	4.27	7.28
21.05	30.05	4.22	2.89

Pos. [°2θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]
21.86	307.79	4.06	29.56
22.68	86.26	3.92	8.28
23.13	237.36	3.84	22.80
23.60	131.05	3.77	12.59
23.88	158.79	3.72	15.25
24.30	158.25	3.66	15.20
24.90	134.33	3.57	12.90
25.64	150.40	3.47	14.44
26.24	59.59	3.39	5.72
26.88	54.13	3.31	5.20
27.26	59.17	3.27	5.68
28.00	31.11	3.18	2.99
28.53	79.40	3.13	7.63
29.53	68.23	3.02	6.55
30.66	29.9	2.91	2.87
31.64	23.45	2.83	2.25
32.59	64.00	2.75	6.15
32.95	33.61	2.72	3.23
33.74	37.32	2.65	3.58
34.78	59.85	2.58	5.75
36.21	28.95	2.48	2.78
36.94	54.09	2.43	5.19
38.24	14.02	2.35	1.35
40.17	13.28	2.24	1.28
40.80	12.38	2.21	1.19
43.55	26.21	2.08	2.52

Form C, prepared from vapor diffusion using isopropyl alcohol, may be characterized by any of its peaks in Table 4. For example, Form C may be characterized by any of the following peaks, among others: 3.38, 6.85, 8.35, 10.95, 13.31, 13.84, 16.31, 16.65, 16.99, 17.23, 18.76, 19.33, 19.6, 20.13, 20.30, 20.80, 21.05, 21.86, 22.68, 23.13, 23.6, 23.88, 24.3, 24.9, 25.64, 26.24, 26.88, 27.26, 28, 28.53, 29.53, 30.66, 31.64, 32.59, 32.95, 33.74, 34.78, 36.21, 36.94, 38.24, 40.17, 40.80, or 43.55 degrees 2θ, each ±0.2 degrees 2θ. Form C, prepared from vapor diffusion using isopropyl alcohol, may also be characterized by any of the following d-spacing, among others: 26.12, 12.9, 10.58, 8.07, 6.65, 6.39, 5.43,

5.32, 5.21, 5.14, 4.73, 4.59, 4.53, 4.41, 4.37, 4.27, 4.22, 4.06, 3.92, 3.84, 3.77, 3.72, 3.66, 3.57, 3.47, 3.39, 3.31, 3.27, 3.18, 3.13, 3.02, 2.91, 2.83, 2.75, 2.72, 2.65, 2.58, 2.48, 2.43, 2.35, 2.24, 2.21, or 2.08, each ±0.2 Å. In some embodiments, the solvate form of Compound 1 is Form C, prepared from vapor diffusion using isopropyl alcohol, and has an X-ray powder diffraction (XRPD) pattern including one or more peaks of any of 3.38, 6.85, 8.35, 10.95, 13.31, 13.84, 16.31, 16.65, 16.99, 17.23, 18.76, 19.33, 19.6, 20.13, 20.30, 20.80, 21.05, 21.86, 22.68, 23.13, 23.6, 23.88, 24.3, 24.9, 25.64, 26.24, 26.88, 27.26, 28, 28.53, 29.53, 30.66, 31.64, 32.59, 32.95, 33.74, 34.78, 36.21, 36.94, 38.24, 40.17, 40.80, or 43.55 degrees 2θ, each ±0.2 degrees 2θ. In some embodiments, the solvate form of Compound 1 is Form C, prepared from vapor diffusion using isopropyl alcohol, and has an X-ray powder diffraction (XRPD) pattern including all the peaks of 3.38, 6.85, 8.35, 10.95, 13.31, 13.84, 16.31, 16.65, 16.99, 17.23, 18.76, 19.33, 19.6, 20.13, 20.30, 20.80, 21.05, 21.86, 22.68, 23.13, 23.6, 23.88, 24.3, 24.9, 25.64, 26.24, 26.88, 27.26, 28, 28.53, 29.53, 30.66, 31.64, 32.59, 32.95, 33.74, 34.78, 36.21, 36.94, 38.24, 40.17, 40.80, and 43.55 degrees 2θ, each ±0.2 degrees 2θ. In some embodiments, Form C, prepared from vapor diffusion using isopropyl alcohol, analyzed by differential scanning calorimetry (DSC) thermogram shows an endothermic peak at about 89.4 °C and a smaller endothermic peak at about 134.2 °C. In some embodiments, Form C, prepared from vapor diffusion using isopropyl alcohol, analyzed by thermogravimetric analysis (TGA) exhibits a dehydration at ambient to about 200 °C with a weight loss of about 3.2% (w/w).

Pharmaceutical Compositions

In some embodiments, Compound 1 is administered to humans, human patients, or subjects. For the purposes of the present disclosure, the phrase “active ingredient” generally refers to the compounds as described herein.

Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to any other animal, e.g., to non-human animals, e.g., non-human mammals. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with merely ordinary, if any, experimentation. Subjects to which administration of the pharmaceutical compositions is contemplated include, but are not limited to, humans and/or other primates; mammals, including commercially relevant mammals such as cattle, pigs, horses, sheep, cats, dogs, mice, and/or rats; and/or birds, including commercially relevant birds such as poultry, chickens, ducks, geese, and/or turkeys.

Formulations of the pharmaceutical compositions described herein may be prepared by any method known or hereafter developed in the art of pharmacology. In general, such preparatory methods include the step of bringing the active ingredient into association with an excipient and/or one or more

other accessory ingredients, and then, if necessary and/or desirable, dividing, shaping and/or packaging the product into a desired single- or multi-dose unit.

A pharmaceutical composition in accordance with the disclosure may be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" is discrete amount of the pharmaceutical composition including a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition in accordance with the disclosure will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may include between 0.1% and 100%, e.g., between 0.5 and 50%, between 1-30%, between 5-80%, at least 80% (w/w) active ingredient.

Compound 1 can be formulated using one or more excipients to: (1) increase stability; (2) permit the sustained or delayed release; (3) alter the biodistribution; (4) alter the release profile of the compounds in vivo. Non-limiting examples of the excipients include any and all solvents, dispersion media, diluents, or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, and preservatives. Accordingly, the formulations of the disclosure may include one or more excipients, each in an amount that together increases the stability of the compounds.

Excipients

Pharmaceutical formulations may include a pharmaceutically acceptable excipient, which, as used herein, includes any and all solvents, dispersion media, diluents, or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington: The Science and Practice of Pharmacy, 23rd Edition, Adeboye Adejare (2020; incorporated herein by reference in its entirety)) discloses various excipients used in formulating pharmaceutical compositions and known techniques for the preparation thereof. Except insofar as any conventional excipient medium is incompatible with a substance or its derivatives, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition, its use is contemplated to be within the scope of this disclosure.

In some embodiments, a pharmaceutically acceptable excipient is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% pure. In some embodiments, an excipient is approved for use in humans and for veterinary use. In some embodiments, an excipient is approved by United States Food and Drug Administration. In some embodiments, an excipient is pharmaceutical grade. In some

embodiments, an excipient meets the standards of the United States Pharmacopoeia (USP), the European Pharmacopoeia (EP), the British Pharmacopoeia, and/or the International Pharmacopoeia.

Pharmaceutically acceptable excipients used in the manufacture of pharmaceutical compositions include, but are not limited to, inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Such excipients may optionally be included in pharmaceutical compositions.

Exemplary diluents include, but are not limited to, calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, and/or combinations thereof.

Exemplary granulating and/or dispersing agents include, but are not limited to, potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose and wood products, natural sponge, cation-exchange resins, calcium carbonate, silicates, sodium carbonate, cross-linked poly(vinyl-pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross-linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (VEEGUM®), sodium lauryl sulfate, quaternary ammonium compounds, and/or combinations thereof.

Exemplary surface active agents and/or emulsifiers include, but are not limited to, natural emulsifiers (e.g. acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (e.g. bentonite [aluminum silicate] and VEEGUM® [magnesium aluminum silicate]), long chain amino acid derivatives, high molecular weight alcohols (e.g. stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (e.g. carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (e.g. carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (e.g. polyoxyethylene sorbitan monolaurate [TWEEN®20], polyoxyethylene sorbitan [TWEEN®60], polyoxyethylene sorbitan monooleate [TWEEN®80], sorbitan monopalmitate [SPAN®40], sorbitan monostearate [SPAN®60], sorbitan tristearate [SPAN®65], glyceryl monooleate, sorbitan monooleate [SPAN®80]), polyoxyethylene esters (e.g. polyoxyethylene monostearate [MYRJ®45], polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and Kolliphor® (SOLUTOL®)), sucrose fatty acid esters, polyethylene glycol fatty acid esters (e.g. CREMOPHOR®), polyoxyethylene ethers, (e.g. polyoxyethylene lauryl ether [BRIJ®30]), poly(vinyl-pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, PLURONIC®F 68, POLOXAMER®188,

cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, Kolliphor SLS, and/or combinations thereof.

Exemplary binding agents include, but are not limited to, starch (e.g. cornstarch and starch paste); gelatin; sugars (e.g. sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol,); natural and synthetic gums (e.g. acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl-pyrrolidone), magnesium aluminum silicate (Veegum®), and larch arabogalactan); alginates; polyethylene oxide; polyethylene glycol; inorganic calcium salts; silicic acid; polymethacrylates; waxes; water; alcohol; and combinations thereof.

Exemplary preservatives may include, but are not limited to, antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and/or other preservatives. Exemplary antioxidants include, but are not limited to, alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and/or sodium sulfite. Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA), citric acid monohydrate, disodium edetate, dipotassium edetate, edetic acid, fumaric acid, malic acid, phosphoric acid, sodium edetate, tartaric acid, and/or trisodium edetate. Exemplary antimicrobial preservatives include, but are not limited to, benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and/or thimerosal. Exemplary antifungal preservatives include, but are not limited to, butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and/or sorbic acid. Exemplary alcohol preservatives include, but are not limited to, ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and/or phenylethyl alcohol. Exemplary acidic preservatives include, but are not limited to, vitamin A, vitamin C, vitamin E, beta-carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and/or phytic acid. Other preservatives include, but are not limited to, tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluene (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, GLYDANT PLUS®, PHENONIP®, methylparaben, GERMALL®115, GERMABEN®II, NEOLONE™, KATHON™, and/or EUXYL®.

Exemplary buffering agents include, but are not limited to, citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium glubionate, calcium gluceptate, calcium gluconate, D-gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium

phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl alcohol, and/or combinations thereof.

Exemplary lubricating agents include, but are not limited to, magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behanate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, and combinations thereof.

Exemplary oils include, but are not limited to, almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, chamomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and/or combinations thereof.

Excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and/or perfuming agents can be present in the composition, according to the judgment of the formulator.

The compound of the present disclosure may be included in a pharmaceutical composition as disclosed in U.S. Patent No. 8,691,821 and WO 2023/183656, which are incorporated by reference.

In some embodiments, the compositions of the present disclosure include Compound 1, such as the AH crystalline form of Compound 1 (e.g., Form A), a solvate form of Compound 1 (e.g., Form B and Form C), or a mixture thereof, optionally at least one carrier (such as but not limited to lactose monohydrate), optionally at least one disintegrant (such as but not limited to croscarmellose sodium), and/or optionally at least one lubricant (such as but not limited to magnesium stearate). In some embodiments, the composition including Compound 1 is a nanomilled suspension or a spray dried nanosuspension. The composition optionally includes hypromellose (HPMC; such as HPMC 63), sodium lauryl sulfate (SLS; such as Kolliphor SLS), lactose monohydrate, croscarmellose, magnesium stearate, or a mixture thereof. The amount of Compound 1 in these compositions is between about 5% (w/w) to about 30% (w/w), such as about 5% (w/w), about 10% (w/w), about 15% (w/w), about 20% (w/w), about

25% (w/w), or about 30% (w/w). Non-limiting examples of the nano-suspension and active granules compositions are shown in Table 5 below. Non-limiting examples of active capsule compositions are shown in Table 6 below. DL = drug loading.

Table 5. Nano-suspension and active granules composition

	Input nanosuspension	**25% DL granules**		**5% DL granules**	
	% (w/w)	**g/ batch**	**% (w/w)**	**g/ batch**	**% (w/w)**
Compound 1	10.00	250.00	25.06	70.00	5.05
Hypromellose (HPMC 603)	2.00	50.00	5.01	14.00	1.01
Sodium lauryl sulfate (Kolliphor SLS fine) SLS	0.50	12.50	1.25	3.50	0.25
Water	87.50	Removed during spraying			
Lactose monohydrate (11SD)		685.00	68.67	1300.00	93.69
TOTAL	100.00	997.50	100.00	1387.50	100.00

Table 6. Active capsules composition

	5 mg strength		**50 mg strength**		**100 mg strength**	
	%(w/w)	**mg/cps**	**%(w/w)**	**mg/cps**	**%(w/w)**	**mg/cps**
Compound 1	4.79	5.00	23.81	50.00	23.81	100.00
Hypromellose (HPMC 603)	0.96	1.00	4.76	10.00	4.76	20.00
Sodium lauryl sulfate (Kolliphor SLS fine) SLS	0.24	0.25	1.19	2.50	1.19	5.00
Lactose monohydrate (11SD)	89.01	92.86	65.24	137.00	65.24	274.00
Croscarmellose (Ac-di-Sol)	4.00	4.17	4.00	8.40	4.00	16.80
Magnesium stearate (Ligamed MF-2-V)	1.00	1.04	1.00	2.10	1.00	4.20
TOTAL	100.00	104.32	100.00	210.00	100.00	420.00

Some embodiments of the present application provide a pharmaceutical composition including an effective amount of Compound 1, such as the AH crystalline form of Compound 1 (e.g., Form A), a solvate form of Compound 1 (e.g., Form B and Form C), or a mixture thereof. In some embodiments, between about 5% (w/w) to about 30% (w/w) of Compound 1 (such as Form A, Form B, or Form C) may be in the pharmaceutical composition. In some embodiments, about 5% (w/w), 10% (w/w), 24% (w/w) or

about 25% (w/w) of Compound 1 (such as Form A, Form B, or Form C) may be in the pharmaceutical composition. The pharmaceutical composition may further include at least one of hypromellose (such as HPMC 603), sodium lauryl sulfate (such as Kolliphor SLS), or lactose monohydrate (such as 11SD), and optionally at least one of croscarmellose (such as Ac-di-Sol) or magnesium stearate (such as Ligamed MF-2-V). Examples of weight percentages of the components are shown in Table 7. In some embodiments, the pharmaceutical composition may be in the form of capsules, such as capsules including 5 mg, 50 mg or 100 mg of Compound 1 (e.g., Form A, Form B, or Form C).

Table 7. Weight percentages of the components

Components	Weight percentages
Compound 1 (such as Form A, Form B, or Form C)	5%-30% (such as between about 5% to about 10%, between 10% to about 20%, between about 20% to about 30%; such as about 5%, about 10%, about 24%, about 25%)
Binder, e.g., hypromellose	0-10% (such as between about 1% to about 2%, between about 2% to about 3%, between about 3% to about 4%, between about 4% to about 5%; such as about 1%, about 2%, about 5%)
Surfactant, e.g., sodium lauryl sulfate	0-5% (such as between about 0.1% to about 0.5%, between about 0.5% to about 1%, between about 1% to about 1.5%; such as about 0.2%, 0.25%, about 0.5%, about 1.2%, about 1.25%)
Carrier, e.g., lactose monohydrate	0-95% (such as between about 50% to about 60%, between about 60% to about 70%, between about 70% to about 80%, between about 80% to about 90%, between about 90% to about 95%; such as about 65%, about 68%, about 90%, about 93%)
Disintegrant, e.g., croscarmellose	0-10% (such as between about 1% to about 5%, between about 5% to about 10%; such as about 4%)
Lubricant, e.g., magnesium stearate	0-5% (such as between about 0.5% to about 1.5%; such as about 1%)

Methods of Use

The present disclosure provides methods of administering Compound 1 resulting in (a) C_{max}, (b) T_{max}, (c) AUC_{tau}, (d) AUC_{last}, (e) $T_{1/2}$, and/or (f) C_{trough}, effective to treat one or more diseases or conditions. In some embodiments, the therapeutically effective amount is sufficient to produce any one of (a)-(f). In some embodiments, the therapeutically effective amount is sufficient to produce any combination of two of (a)-(f). In some embodiments, the therapeutically effective amount is sufficient to produce any combination of three of (a)-(f). In some embodiments, the therapeutically effective amount is sufficient to produce any combination of four of (a)-(f). In some embodiments, the therapeutically effective amount is sufficient to produce the combination of five of (a)-(f). In some embodiments, the therapeutically effective

amount is sufficient to produce the combination of all six of (a)-(f). Values of C_{max}, T_{max}, AUC_{tau}, AUC_{last}, and/or $T_{1/2}$ are provided herein. Administration may continue indefinitely. Administration may continue at least until steady state of Compound 1 is achieved in plasma. For example, administration may continue at least 10-16 days.

Compound 1 has therapeutic utility in CNS and peripheral disease states including, but not limited to, schizophrenia, cognitive impairment, Alzheimer's disease, Parkinson's disease, Parkinson's disease levodopa-induced dyskinesia, addiction, anxiety, depression, psychosis, epilepsy, Fragile X, gastroesophageal reflux disease, migraine, pain, infectious or genetically acquired prion disease (such as but limited to Creutzfeldt-Jakob disease (CJD), Gerstmann-Straussler-Scheinker syndrome (GSS) and fatal familial insomnia), tauopathies (such as but not limited to frontotemporal dementia, corticobasal syndrome, Richardson syndrome, parkinsonism, pure akinesia with gait freezing and, rarely, motor neuron symptoms or cerebellar ataxia), rare neurodegenerative diseases similar to Parkinson's disease, and others.

In some embodiments, a therapeutically effective amount of Compound 1 of the present disclosure can be used for the treatment of CNS disorders and neurological or psychiatric disorders, such as but not limited to, schizophrenia, cognitive impairment, Alzheimer's disease, Parkinson's disease, Parkinson's disease levodopa-induced dyskinesia, addiction, anxiety, depression, psychosis, epilepsy, Fragile X, gastroesophageal reflux disease, migraine, pain, borderline personality disorder, bipolar disorder, or other neurological and/or psychiatric disorder associated with glutamate dysfunction.

In one embodiment, a method for the treatment of Alzheimer's disease is provided, including administering to a patient in need thereof a therapeutically effective amount of Compound 1. In some embodiments, a therapeutically effective amount of a compound or composition of the present disclosure is used to reverse synapse density decreases or synapse loss, such as cortical and hippocampal synapse density deceases, of a subject in need thereof. In some embodiments, a therapeutically effective amount of Compound 1 is used to reduce Tau accumulation of a subject in need thereof.

In some embodiments, a method of preventing seizure is provided, including administering to a patient in need thereof a therapeutically effective amount of Compound 1.

Alzheimer's disease

Allosteric mGluR5 modulators have been subdivided as positive (PAMs), negative (NAMs) and silent (SAMs). PAMs enhance and NAMs suppress glutamate-induced G-protein-mediated Ca^{2+} mobilization and/or shift glutamate efficacy. Multiple NAMs reduce both physiological glutamate signaling and Aßo-PrP^C-dependent synaptic deficits. As a dose-limiting side-effect, blockade of glutamate at mGluR5 with a NAM impairs learning and memory independently of AD. Compound 1 does not alter basal or glutamate signaling but does inhibit the PrP^C-mGluR5 interaction to prevent pathological Aβo signaling. Compound 1 greatly expands the potential therapeutic window for mGluR5 as a disease-modifying AD target.

In some embodiments, Compound 1 is used to regulate the expression of neuronal and glial genes, regulate neuro-immune interaction in AD synapse loss, restore synaptic density, and prevent synaptic localization of C1q without altering total C1q levels or overall gliosis.

In some embodiments, Compound 1 is used to increase synaptic density, slow down the loss of synaptic density, reduce the loss of synaptic density, increase pre- and post-synaptic marker levels (SV2A and PSD-95), recover the loss of synaptic markers (SV2A and PSD-95), prevent seizure, inhibit the human transporters P-glycoprotein (P-gp), organic ion transporting polypeptide (OATP)1B1 and OATP1B3. In some embodiments, Compound 1, is used to regulate cerebrospinal fluid (CSF) or plasma biomarkers, such as but not limited to total Tau protein levels, phospho-tau protein levels, SNAP-24, neurofilament light chain, GAP-43, synaptotagmin-1, alpha-synuclein (including phosphorylated versions), and neurogranin. In some embodiments, Compound 1 is used to regulate complement activation biomarkers.

In some embodiments, patients who receive Compound 1 have changes in fluorodeoxyglucose (FDG)-positron emission tomography (PET) imaging, synaptic vesicle glycoprotein 2A (SV2A)-PET imaging, metabotropic glutamate receptor subtype 5 (mGluR5)-PET imaging, Tau PET imaging, amyloid beta PET imaging, electroencephalography (EEG) activities, functional magnetic resonance imaging and/or volumetric magnetic resonance imaging.

In some embodiments, the patient is diagnosed with either amnestic mild cognitive impairment (aMCI) or mild dementia due to AD, e.g., based on the following:

Mild dementia due to AD	**aMCI due to AD**
(i) National Institute on Aging (NIA)-Alzheimer's Association core clinical criteria for dementia due to probable AD (ii) Mini Mental Status Exam (MMSE) score between 18 and 26 (inclusive) (iii) Clinical Dementia Rating Scale (CDR) global score of 0.5 or 1	(i) Subjective memory complaint preferably corroborated by an informant (ii) aMCI as evidenced by abnormal memory function documented by scoring 1.5 standard deviations (SD) below the education adjusted cutoff on the Logical Memory II subscale (Delayed Paragraph Recall) from the Wechsler Memory Scale – Revised (maximum score is 25): ≤8 for 16 or more years of education; ≤4 for 8-15 years of education; ≤2 for 0-7 years of education (iii) Normal activities of daily living (iv) CDR global score of 0.5.

Combination Therapies

In some embodiments, the present invention provides a method of treating a disease or disorder described herein, including administering a compound or composition of the present disclosure in combination with one or more additional active agents or therapies. Suitable pharmaceutical agents or therapies that may be used in combination with the compound of the present disclosure include but not

limited to anti-amyloid immunotherapies, anti-tau immunotherapies, active agents aimed at reducing amyloid beta levels in any form, active agents that those specifically aimed at blocking amyloid-beta oligomer toxicity, microglial inflammation targeted therapies, acetylcholinesterase inhibitors, and NMDA receptor antagonists (such as but not limited to donepezil and memantine).

The compound or composition of the present disclosure and the additional active agent(s) may be administered simultaneously, sequentially, or at any order. The compound or composition of the present disclosure and the additional active agent(s) may be administered at different dosages, with different dosing frequencies, or via different routes, whichever is suitable.

Dosing and Administration

The present disclosure encompasses the delivery of Compound 1 by any appropriate route taking into consideration likely advances in the sciences of drug delivery. These include, but are not limited to oral, intravenous (into a vein), intrathecal (into the spinal canal or into the subarachnoid space to reach the CSF), intraparenchymal (into the brain parenchyma), in ear drops, nasal aerosol or inhalation. In specific embodiments, Compound 1 may be administered in a way which allows it to cross the blood-brain barrier, vascular barrier, or other epithelial barrier.

In some embodiments, Compound 1 may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, and aqueous suspensions and solutions. In the case of tablets for oral use, carriers that are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are administered orally, the active ingredient may be combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

In some embodiments, Compound 1 of the present disclosure may be formulated to be administered to the CNS by routes known in the art such as, but not limited to, direct intraparenchymal administration, intrathecal delivery and intracerebroventricular infusion.

Dosage Forms

A pharmaceutical composition described herein can be formulated into a dosage form described herein, such as a capsule, tablet, aqueous suspension or solution, topical, intranasal, intratracheal, or injectable (e.g., intravenous, intraocular, intravitreal, intramuscular, intracardiac, intraperitoneal, subcutaneous). It will be understood that the total daily usage of a composition of the present disclosure may be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective, prophylactically effective, or appropriate imaging dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration,

and rate of excretion of Compound 1; the duration of the treatment; drugs used in combination or coincidental with Compound 1; and like factors well known in the medical arts.

In some embodiments, a composition in accordance with the present disclosure may be administered at dosage levels sufficient to deliver from about 0.0001 mg/kg to about 100 mg/kg, from about 0.001 mg/kg to about 0.05 mg/kg, from about 0.005 mg/kg to about 0.05 mg/kg, from about 0.001 mg/kg to about 0.005 mg/kg, from about 0.05 mg/kg to about 0.5 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, from about 0.1 mg/kg to about 40 mg/kg, from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, or from about 1 mg/kg to about 25 mg/kg, from about 25 mg/kg to about 50 mg/kg, from about 50 mg/kg to about 100 mg/kg, from about 100 mg/kg to about 125 mg/kg, from about 125 mg/kg to about 150 mg/kg, from about 150 mg/ to about 175 mg/kg, from about 175 mg/kg to about 200 mg/kg, from about 200 mg/kg to about 250 mg/kg of subject body weight per day, one or more times a day, to obtain the desired therapeutic, diagnostic, prophylactic, or imaging effect. The desired dosage may be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In some embodiments, the desired dosage may be delivered using multiple administrations (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations). When multiple administrations are employed, split dosing regimens such as those described herein may be used. In some embodiments, Compound 1 is administered by continuous infusion.

As used herein, a “split dose” is the division of single unit dose or total daily dose into two or more doses, e.g., two or more administrations of the single unit dose. As used herein, a “single unit dose” is a dose of any therapeutic administered in one dose/at one time/single route/single point of contact, i.e., single administration event. As used herein, a “total daily dose” is an amount given or prescribed in 24 hr period. It may be administered as a single unit dose.

The administration of Compound 1 disclosure can be used as a chronic or acute therapy. The amount of drug that may be combined with the carrier to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w).

Upon improvement of a patient's condition, a maintenance dose of Compound 1, composition, or combination of the present disclosure may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level, treatment should cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

As the skilled artisan will appreciate, lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of Compound 1, the age, body weight, general health status, gender, diet,

time of administration, rate of excretion, drug combination, the severity and course of disease, the patient's disposition to disease and the judgment of the treating physician.

In some embodiments, the subjects are treated with about 10 mg, about 40 mg, about 70 mg, about 100 mg, about 150 mg, or about 200 mg of Compound 1. In some embodiments, the subjects are treated once, twice, three, or four times a day a day. In a non-limiting example, the subjects are treated with between about 75 mg to about 125 mg of Compound 1 twice a day. In another non-limiting example, the subjects are treated with at least 200 mg of Compound 1 once a day.

In some embodiments, Compound 1 administered in capsules via oral routes. In some embodiments, the capsules contain about 5 mg, about 25 mg, about 50 mg, about 75 mg, or about 100 mg of the compound. In some embodiments, the capsules further include lactose monohydrate, croscarmellose sodium, and/or magnesium stearate. The lactose monohydrate may be spray dried. The croscarmellose sodium and magnesium stearate are in extra-granular form. In some embodiments, the concentration of the compound in the capsules is between about 1% (w/w) to about 50% (w/w), such as between about 1% (w/w) to about 5% (w/w), between about 6% (w/w) to about 10% (w/w), between about 11% (w/w) to about 20% (w/w), between about 21% (w/w) to about 30% (w/w), between about 31% (w/w) to about 40% (w/w), or between about 41% (w/w) to about 50% (w/w). In one embodiment, the capsule has about 5mg Compound 1, and Compound 1 has a concentration of about 5% (w/w) in the capsule. In another embodiment, the capsule has about 50mg or 100 mg of Compound 1, and Compound 1 has a concentration of about 25% (w/w) in the capsule.

In some embodiments, the capsules are stored at 25 °C/60% relative humidity (RH). The compound in the capsules is stable for at least 30 months, and the capsules are stable for at least 1 month, under accelerated and long-term stability conditions.

Definitions

For convenience, the meaning of certain terms and phrases used in the specification, examples, and appended claims, are provided below. If there is an apparent discrepancy between the usage of a term in other parts of this specification and its definition provided in this section, the definition in this section shall prevail.

The abbreviations used herein have their conventional meaning within the scientific arts. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in M. Loudon, Organic Chemistry, 5th Ed., Roberts and Company, Greenwood Village, Colo.: 2009; and M. B. Smith, March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure, 7th Ed., John Wiley & Sons, Hoboken: 2013, the entire contents of which are hereby incorporated by reference.

As used herein, the term “about” means ± 10% of the recited value.

The terms "subject" or "patient", as used herein, refer to any organism to which the particles may be administered, e.g., for experimental, therapeutic, diagnostic, and/or prophylactic purposes. Typical subjects include animals (e.g., mammals such as mice, rats, rabbits, guinea pigs, cattle, pigs, sheep, horses, dogs, cats, hamsters, lamas, non-human primates, and humans).

The terms "treating" or "preventing", as used herein, can include preventing a disease, disorder or condition from occurring in an animal that may be predisposed to the disease, disorder and/or condition but has not yet been diagnosed as having the disease, disorder or condition; inhibiting the disease, disorder or condition, e.g., impeding its progress; and relieving the disease, disorder, or condition, e.g., causing regression of the disease, disorder and/or condition. Treating the disease, disorder, or condition can include ameliorating at least one symptom of the particular disease, disorder, or condition, even if the underlying pathophysiology is not affected, such as treating the pain of a subject by administration of an analgesic agent even though such agent does not treat the cause of the pain.

The term "therapeutic effect" is art-recognized and refers to a local or systemic effect in animals, particularly mammals, and more particularly humans caused by a pharmacologically active substance. The term thus means any substance intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease, disorder or condition in the enhancement of desirable physical or mental development and conditions in an animal, e.g., a human.

The terms "sufficient" and "effective", as used interchangeably herein, refer to an amount (e.g., mass, volume, dosage, concentration, and/or time period) needed to achieve one or more desired result(s). A "therapeutically effective amount" is at least the minimum concentration required to affect a measurable improvement or prevention of at least one symptom or a particular condition or disorder, to affect a measurable enhancement of life expectancy, or to generally improve patient quality of life. The therapeutically effective amount is thus dependent upon the specific biologically active molecule and the specific condition or disorder to be treated. Therapeutically effective amounts of many active agents, such as antibodies, are known in the art. The therapeutically effective amounts of compounds and compositions described herein, e.g., for treating specific disorders may be determined by techniques that are well within the craft of a skilled artisan, such as a physician.

The term "active agent" includes, without limitation, physiologically or pharmacologically active substances that act locally or systemically in the body. A bioactive agent is a substance used for the treatment (e.g., therapeutic agent), prevention (e.g., prophylactic agent), diagnosis (e.g., diagnostic agent), cure or mitigation of disease or illness, a substance which affects the structure or function of the body, or pro-drugs, which become biologically active or more active after they have been placed in a predetermined physiological environment.

The term "pharmaceutically acceptable", as used herein, refers to compounds, materials, compositions, and/or dosage forms that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problems or complications commensurate with a reasonable benefit/risk ratio, in

accordance with the guidelines of agencies such as the U.S. Food and Drug Administration. A "pharmaceutically acceptable carrier", as used herein, refers to all components of a pharmaceutical formulation that facilitate the delivery of the composition *in vivo*. Pharmaceutically acceptable carriers include, but are not limited to, diluents, preservatives, binders, lubricants, disintegrators, swelling agents, fillers, stabilizers, and combinations thereof.

The term "C_{max}," as used herein, refers to the maximum plasma concentration of Compound 1.

The term "C_{min}," as used herein, refers to the minimum plasma concentration of Compound 1.

The term "C_{trough}," as used herein, refers to the plasma concentration of Compound 1 immediately before the next dosage is administered. The time of C_{trough} is the time of the next dosage, e.g., about 24, about 12, about, about 6, or about 4 h for once, twice, thrice, four times, and six times daily dosing.

The term "C_{avg}," as used herein, refers to the average plasma concentration of Compound 1 during a dosing interval.

The term "T_{max}," as used herein, refers to the amount of time to reach maximum plasma concentration of Compound 1 following its administration.

The term "AUC_{0-24}," as used herein, refers to the area under the plasma concentration time curve from time zero to 24 hours after the administration of a dosage of Compound 1.

The term "AUC_{tau}," as used herein, refers to the area under the plasma concentration time curve during a dosage interval after the administration of a dosage of Compound 1. As used herein, tau (i.e., the dosage interval) is from 0 h to 12 h after the administration of a dosage of Compound 1.

The term "AUC_{last}," as used herein, refers to the area under the plasma concentration time curve to the last measurable plasma concentration of Compound 1.

The terms "$T_{1/2}$" and "half-life," as used herein, refer to the amount of time for the plasma concentration of Compound 1 to be reduced by one-half.

The term "food," as used herein, refers to solid food or a nutritional liquid beverage with sufficient bulk and fat content that it is not rapidly dissolved and absorbed in the stomach. For example, a meal, such as breakfast, lunch, or dinner.

The term "with food," as used herein refers to administration of a composition between about 30 minutes prior to about two hours after eating, e.g., eating a meal.

The terms "without food," "fasted," or "an empty stomach" refer to the condition of not having consumed solid food or nutritional liquid beverage for at least about 2 hours until about 30 minutes prior to consuming further solid food. In some embodiments, solid food or nutritional liquid beverage is not consumed for at least 30 minutes after administration, e.g., at least 1 hour.

The details of one or more embodiments of the disclosures are set forth in the accompanying description below. Although any materials and methods similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, the preferred materials and methods are now described. Other features, objects and advantages of the disclosure will be apparent from the description. In the description, the singular forms also include the plural unless the context clearly dictates

otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. In the case of conflict, the present description will control.

The present disclosure is further illustrated by the following non-limiting examples.

EXAMPLES

Example 1. Compound 1 food effect pharmacokinetics in human subjects

The study is a randomized, open-label, 2-period, crossover study of Compound 1 in healthy older adults to assess the effect of food on its safety and pharmacokinetics.

Twelve cognitively healthy older adults (N = 12) were randomized 1:1 to receive a single 150 mg dose of Compound 1 in one of two treatment sequences: (1) fasting followed by fed; or (2) fed followed by fasting. There was a 10 day washout period between doses. Standardized meals were provided. For the fasting period, Compound 1 was administered after a minimum 10 hour overnight fast, and participants remained in a semi-recumbent position for at least 1 hour post dose. Participants continued to fast from food and liquids other than water for at least 4 hours post dose.

For the fed period, study participants underwent a 10-hour overnight fast, then began eating a high-fat breakfast 30 minutes prior to administration of study medication. The meal was consumed in 30 minutes or less. Thirty minutes after starting the meal, participants were administered study medication and remained in a semi-recumbent position for at least 1 hour post dose. Participants fasted from food and liquids other than water for at least 4 hours post dose.

Pharmacokinetic parameters were obtained in all 12 participants for both the fed and fasted conditions (Table 8). There was a modest increase in exposures in the fed group compared to the fasted group, allowing for the removal of the pre- and post-dose fasting requirement from future studies. In this study, the geometric means for the AUC_{last} and C_{max} in fed condition were, respectively, 175% and 164.7 % greater than the geometric means in the fasted condition. Thus, improved pharmacokinetics was observed in the fed state in human subjects.

Table 8. Compound 1 Pharmacokinetics in Plasma Following Oral Administration in the Fed and Fasted States

Parameter	Statistic	Compound 1 Food Effect Single Dose	
		Fasted State 150 mg Compound 1	Fed State 150 mg Compound 1
N		12	12
C_{max} (ng/mL)	Mean (SD)	468.44 (281.81)	670.83 (226.09)
	Median	361	684.1
	Min, Max	80.3 , 952.8	253.1 , 984.4
	CV %	60.16	33.7
T_{max} (h)	Mean (SD)	2.04 (0.988)	3.04 (1.484)
	Median	2	3
	Min, Max	1.0 ; 4.0	1.0 ; 6.0
	CV %	48.37	48.79
AUC_{last} (ng·h/mL)	Mean (SD)	4362.2 (4435.9)	6659.9 (5417.7)
	Median	3215.5	5008.1
	Min, Max	506.5 , 17208	1309.2 , 21522
	CV %	101.69	81.35
AUC_{0-24} (ng·h/mL)	Mean (SD)	2923.7 (2139.6)	4600.2 (2220.4)
	Median	2337.2	4113.2
	Min, Max	425.3, 8227.6	1309.2, 8620.2
	CV %	73.18	48.27
AUC_{0-12} (ng·h/mL)	Mean (SD)	2236.7 (1515.4)	3491.6 (1351.9)
	Median	1809.7	3277.6
	Min, Max	348.5, 5644.4	1175.1, 5575.0
	CV %	67.75	38.72
$T_{1/2}$ (h)	Mean (SD)	18.56 (6.560)	16.84 (7.709)
	Median	18.9	15.8
	Min, Max	7.6 , 34.3	5.9 , 35.2
	CV %	35.35	45.77

Abbreviations: AUC_{0-24} = area under the plasma concentration-time curve over the last 24-h dosing interval; AUC_{0-12}= area under the plasma concentration-time curve over the last 12-h dosing interval; AUC_{last}= area under the plasma concentration-time curve to the last measurable plasma concentration; C_{max} = maximum concentration; CV = coefficient of variation; Max=maximum value; Min=minimum value; PK=pharmacokinetic; SD = standard deviation; T_{max} = time at maximum concentration; $T_{1/2}$ = half-life

Example 2. Phase 1b Clinical Trial

The study is a 2 stage, multiple ascending dose, randomized, placebo-controlled, double-blind Phase 1b trial.

In Stage 1, a total of 32 cognitively healthy older adults was recruited in four sequential cohorts. Each cohort of eight consisted of six participants randomized to receive Compound 1, and two participants received placebo. The doses of Compound 1 for Stage 1 were 50, 100, or 150 mg administered twice daily. Cohort 1 received the lowest dose and the dose was escalated for each cohort based on a predetermined escalation scheme after an end of cohort review of safety and pharmacokinetic (PK) data. Participants in Cohorts 1 and 2 were treated for 10 days with an initial three night inpatient period for safety monitoring. Participants in succeeding cohorts were treated for either 10 or 20 days depending on the PK results from the preceding cohort. If cohort(s) were treated for 20 days, participants were inpatient on Days 1-7 and Days 20-26. Each sequential cohort completed the study before the next cohort entered the treatment phase. Participants in Stage 1 participated in the study for approximately 60 days, which included up to 30 days of screening, up to 20 days on treatment, and up to 10 days of follow-up.

In Stage 2, a total of 18 participants with early AD is randomized to receive one of two doses of Compound 1 or placebo in a 1:1:1 ratio. The doses of Compound 1 are the top two doses from Stage 1 (100 and 150 mg). Participants in Stage 2 participate in the study for approximately 14 weeks, which includes up to 60 days in screening, 28 days of treatment, and 7 days of follow-up.

The drug products were Compound 1 capsules each containing either 5, 50, or 100 mg of Compound 1 and spray-dried lactose monohydrate and extra-granular croscarmellose sodium and magnesium stearate. Prior to granulation with lactose, Compound 1 was prepared as a nano milled suspension in water with hypromellose and sodium lauryl sulfate. The placebo was filled with lactose monohydrate and magnesium stearate.

Participants were dosed with a meal while in the clinic and instructed to take their dose with a meal when at home. Participants were instructed to begin the meal 30 minutes prior to their dose, and the meal must be completed in full prior to dose administration. Participants were instructed to drink at least 8 oz of water with the study drug. Drug dosing in both Stage 1 and Stage 2 are twice daily, as close to 12 hours apart as possible.

Stage 1 Pharmacokinetic Results

Pharmacokinetic parameters were obtained in all participants across all days of evaluation. Mean pharmacokinetic parameters from Cohort 1 (50 mg of Compound 1 BID, 10 days) and Cohort 2 (100 mg of Compound 1 BID, 10 days) are presented in Table 9, while mean pharmacokinetic parameters from Cohort 3 (100 mg of Compound 1 BID, 20 days) and Cohort 4 (150 mg of Compound 1 BID, 20 days) are presented in Table 10. Overall, Compound 1 achieved high plasma exposures, was well tolerated in

subjects, and exhibited a wide safety window. No SAEs were observed, and all 19 AEs were mild and resolved.

Table 9. Summary of 50 and 100 mg BID dosing of Compound 1 Pharmacokinetic Parameters in Plasma Following Oral Administration in Stage 1 Cohorts at Day 10 (N = 6 per cohort)

50 mg BID Compound 1	C_{max} (ng/mL)	Mean (SD)	483.59 (228.228)
		Median (Min;Max)	468.25 (220.84, 847.57)
		CV (%)	47.2
	T_{max} (h)	Mean (SD)	4.00 (0)
		Median (Min;Max)	4.00 (4.00, 4.00)
		CV (%)	0
	AUC_{last} (h•ng/mL)	Mean (SD)	8605.307 (7361.974)
		Median (Min;Max)	7640.15 (1659.38, 20599.33)
		CV (%)	85.6
	AUC_{tau} (h•ng/mL)*	Mean (SD)	3775.270 (2541.060)
		Median (Min;Max)	3615.25 (1255.62, 7865.69)
		CV (%)	67.3
	$T_{1/2}$ (h)	Mean (SD)	21.480 (8.868)
		Median (Min;Max)	21.10 (8.68, 30.65)
		CV (%)	41.3
	C_{trough} (ng/mL)	Mean (SD)	223.284 (206.978)
		Median (Min;Max)	189.67 (36.12 ; 563.66)
		CV (%)	92.7
100 mg BID Compound 1	C_{max} (ng/mL)	Mean (SD)	2080.04 (353.639)
		Median (Min;Max)	2084.08 (1678.47, 2610.30)
		CV (%)	17
	T_{max} (h)	Mean (SD)	2.83 (1.329)
		Median (Min;Max)	3.00 (1.00, 4.00)
		CV (%)	46.9
	AUC_{last} (h•ng/mL)	Mean (SD)	42881.44 (20,556.144)
		Median (Min;Max)	39007.44 (21887.29, 73089.28)
		CV (%)	47.9
	AUC_{tau} (h•ng/mL)*	Mean (SD)	17210.54 (5369.897)
		Median (Min;Max)	1761.60 (11336.79, 25621.72)
		CV (%)	31.2
	$T_{1/2}$ (h)	Mean (SD)	31.21 (17.542)
		Median (Min;Max)	25.25 (15.46, 55.11)
		CV (%)	56.2
	C_{trough} (ng/mL)	Mean (SD)	1062.39 (545.930)
		Median (Min;Max)	1060.71 (488.42 ; 1838.72)
		CV (%)	51.4

*The dosage interval tau in the AUC_{tau} value is from 0 h to 12 h.

Table 10. Summary of 100 and 150 mg BID dosing of Compound 1 Pharmacokinetic Parameters in Plasma Following Oral Administration in Stage 1 Cohorts at Day 20 (N = 6 per cohort)

100 mg BID Compound 1	C_{max} (ng/mL)	Mean (SD)	1558.31 (879.803)
		Median (Min;Max)	1533.53 (559.62; 2916.91)
		CV (%)	56.5
	T_{max} (h)	Mean (SD)	2.50 (0.548)
		Median (Min;Max)	2.50 (2.00; 3.00)
		CV (%)	21.9
	AUC_{last} (h•ng/mL)	Mean (SD)	64535.01 (50770.535)
		Median (Min;Max)	68215.49 (4510.61; 119423.24)
		CV (%)	78.7
	AUC_{tau} (h•ng/mL)*	Mean (SD)	14141.81 (9715.478)
		Median (Min;Max)	14188.18 (2808.48, 28899.06)
		CV (%)	68.7
	$T_{1/2}$ (h)	Mean (SD)	20.46 (6.705)
		Median (Min;Max)	19.15 (13.21; 28.74)
		CV (%)	32.8
	C_{trough} (ng/mL)	Mean (SD)	881.55 (683.348)
		Median (Min;Max)	897.62 (83.53 ; 1898.43)
		CV (%)	77.5
150 mg BID Compound 1	C_{max} (ng/mL)	Mean (SD)	4064.83 (1824.582)
		Median (Min;Max)	3919.76 (2005.98 ; 6315.61)
		CV (%)	44.9
	T_{max} (h)	Mean (SD)	3.00 (0.632)
		Median (Min;Max)	3.00 (2.00 ; 4.00)
		CV (%)	21.1
	AUC_{last} (h•ng/mL)	Mean (SD)	226922.71 (179195.185)
		Median (Min;Max)	188197.35 (49558.17 ; 556579.74)
		CV (%)	79
	AUC_{tau} (h•ng/mL)*	Mean (SD)	39989.59 (19995.886)
		Median (Min;Max)	37425.35 (18465.61, 68811.30)
		CV (%)	50
	$T_{1/2}$ (h)	Mean (SD)	31.48 (35.544)
		Median (Min;Max)	18.60 (10.30 ; 103.57)
		CV (%)	112.9
	C_{trough} (ng/mL)	Mean (SD)	2723.09 (1324.769)
		Median (Min;Max)	2782.06 (1116.81 ; 4210.95)
		CV (%)	48.6

*The dosage interval tau in the AUC_{tau} value is from 0 h to 12 h.

The terminal half-life of Compound 1 ranged between 16 and 32 hours, and it was generally independent of dose. Half-lives of 24 hours or less were typically noted in most individuals. Mean steady-state C_{max} values were 483.6 ng/mL, 1558 ng/mL, and 4065 ng/mL for BID doses of 50 mg, 100 mg, and 150 mg, respectively. Mean steady-state AUC_{tau} values were 3775.4 ng•hr/mL, 14141.8 ng•hr/mL, and 39989.6 ng•hr/mL for BID doses of 50 mg, 100 mg, and 150 mg, respectively. Following oral administration, Compound 1 was rapidly absorbed, generally achieving C_{max} within 4 hours, followed by a relatively slow monoexponential terminal phase.

Importantly, Compound 1 successfully maintained safety margin to NOAEL at doses of 50, 100, and 150 mg, as shown in Table 9, which presents the margin of human exposure relative to the rat as fold-below the rat NOAEL.

Table 9. Margin of Human Exposure to Rat NOAEL

Dose (mg)	Rat NOAEL C_{max}: Human C_{max} Ratio	Rat NOAEL $AUC_{(0-24)}$: Human $AUC_{(0-24),ss}$ Ratio
50	22	25
100	5.1	5.6
100	6.9	6.8
150	2.5	2.4

Stage 2

Participants in Stage 2 are randomized to placebo or one of two doses of Compound 1 in a 1:1:1 ratio. The study drug doses for Stage 2 consist of the two highest Stage 1 doses that are determined to be safe based on safety, tolerability, and PK in Stage 1.

At Screening and/or Baseline before dosing, each participant undergoes baseline cognitive, functional, and behavioral assessments. The rationale for this is to ensure that Compound 1 does not have any significant short-term adverse effects on these measures and to evaluate any rapid "symptomatic" improvement in participants with AD. These assessments include the Alzheimer's Disease Assessment Scale-cognitive subscale 14 (ADAS cog), MOCA, Functional Assessment Questionnaire (FAQ), CDR, NPI Q, and GDS. The MOCA and C SSRS are also performed weekly as a more frequent safety assessment. The Logical Memory subscale – delayed recall will be administered only at screening. In Stage 2, participants also undergo a brain MRI scan as part of the screening evaluation and another at the end of the study (Visit 6 Day 28). The MRI ensures that participants do not meet exclusion criteria by showing evidence of infection, infarction, or other focal brain lesions. In addition, eligible participants have [^{18}F]SynVesT-1 PET brain scans performed to measure synaptic density before drug dosing after approximately 28 days of treatment.

Equivalents and Scope

Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments in accordance with the disclosure described herein. The scope of the present disclosure is not intended to be limited to the above Description, but rather is as set forth in the appended claims.

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 disclosure 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 disclosure includes embodiments in which more than one, or the entire group members are present in, employed in, or otherwise relevant to a given product or process.

It is also noted that the term "comprising" is intended to be open and permits but does not require the inclusion of additional elements or steps. When the term "comprising" is used herein, the term "consisting of" is thus also encompassed and disclosed.

Where ranges are given, endpoints are included. Furthermore, it is to be understood that 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 subrange within the stated ranges in different embodiments of the disclosure, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

In addition, it is to be understood that any particular embodiment of the present disclosure that falls within the prior art may be explicitly excluded from any one or more of the claims. Since 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 compositions of the disclosure (e.g., any antibiotic, therapeutic or active ingredient; any method of production; any method of use; etc.) can be excluded from any one or more claims, for any reason, whether or not related to the existence of prior art.

It is to be understood that the words which have been used are words of description rather than limitation, and that changes may be made within the purview of the appended claims without departing from the true scope and spirit of the disclosure in its broader aspects.

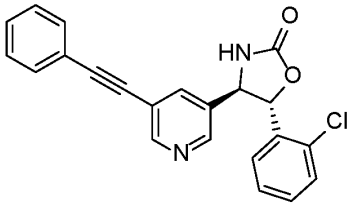
While the present disclosure has been described at some length and with some particularity with respect to the several described embodiments, it is not intended that it should be limited to any such particulars or embodiments or any particular embodiment, but it is to be construed with references to the appended claims so as to provide the broadest possible interpretation of such claims in view of the prior art and, therefore, to effectively encompass the intended scope of the disclosure.

Other embodiments are in the claims.

What is claimed is:

CLAIMS

1. A method of treating Alzheimer's Disease, seizures, synapse loss, or Tau accumulation of a subject in need thereof, comprising administering to the subject a therapeutically effective amount of Compound 1:



, sufficient to produce:

a) a C_{max} (maximum concentration) of about 200 ng/mL to about 850 ng/mL;

b) a T_{max} (time at maximum concentration) of about 3 h to about 5 h;

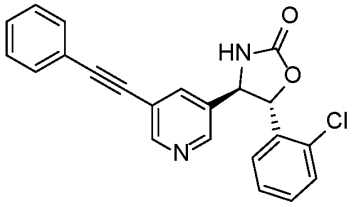
c) an AUC_{tau} (area under the plasma concentration time curve over a dosage interval of tau, wherein tau is from 0 h to 12 h) of about 1000 ng•h/mL to about 10000 ng•h/mL;

d) an AUC_{last} (area under the plasma concentration time curve to the last measurable plasma concentration) of about 1200 ng•h/mL to about 21000 ng•h/mL;

e) a $T_{1/2}$ (half-life) of about 8 h to about 31 h; and/or

f) a C_{trough} (plasma concentration of Compound 1 immediately before administration of next dosage of Compound 1) of about 10 to 600 ng/mL.

2. A method of treating Alzheimer's Disease, seizures, synapse loss, or Tau accumulation of a subject in need thereof, comprising administering to the subject a therapeutically effective amount of Compound 1:



, sufficient to produce:

a) a C_{max} (maximum concentration) of about 500 ng/mL to about 3000 ng/mL;

b) a T_{max} (time at maximum concentration) of about 1 h to about 4 h;

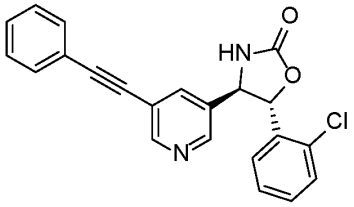
c) an AUC_{tau} (area under the plasma concentration time curve over a dosage interval of tau, wherein tau is from 0 h to 12 h) of about 2000 ng•h/mL to about 30000 ng•h/mL;

d) an AUC_{last} (area under the plasma concentration time curve to the last measurable plasma concentration) of about 4500 ng•h/mL to about 120000 ng•h/mL;

e) a $T_{1/2}$ (half-life) of about 13 h to about 29 h; and/or

f) a C_{trough} (plasma concentration of Compound 1 immediately before administration of next dosage of Compound 1) of about 50 to 2500 ng/mL.

3. A method of treating Alzheimer's Disease, seizures, synapse loss, or Tau accumulation of a subject in need thereof, comprising administering to the subject a therapeutically effective amount of Compound 1:



, sufficient to produce:

a) a C_{max} (maximum concentration) of about 1500 ng/mL to about 7000 ng/mL;

b) a T_{max} (time at maximum concentration) of about 1.5 h to about 4.5 h;

c) an AUC_{tau} (area under the plasma concentration time curve over a dosage interval of tau, wherein tau is from 0 h to 12 h) of about 18000 ng•h/mL to about 70000 ng•h/mL;

d) an AUC_{last} (area under the plasma concentration time curve to the last measurable plasma concentration) of about 45000 ng•h/mL to about 560000 ng•h/mL;

e) a $T_{1/2}$ (half-life) of about 7.5 h to about 110 h; and/or

f) a C_{trough} (plasma concentration of Compound 1 immediately before administration of next dosage of Compound 1) of about 1000 to 5000 ng/mL.

4. The method of any one of claims 1 to 3, wherein Compound 1 is in a pharmaceutical composition.

5. The method of any one of claims 1 to 4, wherein the pharmaceutical composition further comprises a pharmaceutically acceptable plasticizer, binder, bulking agent, carrier, excipient, lubricant, disintegrant, and/or surfactant.

6. The method of any one of claims 1-5, wherein about 50 mg, about 100 mg, or about 150 mg of Compound 1 is administered.

7. The method of any one of claims 1-6, wherein Compound 1is administered orally.

8. The method of any one of claims 1-7, wherein Compound 1 is administered twice, three, or four times a day.

9. The method of any one of claims 1-8, wherein Compound 1 is administered twice a day.

10. The method of any one of claims 1-9, wherein Form A of Compound 1 is administered.

11. The method of any one of claims 1 and 4-10, wherein the C_{max} is about 300 ng/mL to about 800 ng/mL.

12. The method of any one of claims 1 and 4-11, wherein the T_{max} is about 3.2 h to about 4.8 h.

13. The method of any one of claims 1 and 4-12, wherein the AUC_{tau} is about 2000 ng•h/mL to about 9000 ng•h/mL.

14. The method of any one of claims 1 and 4-13, wherein the AUC_{last} is about 5000 ng•h/mL to about 18000 ng•h/mL.

15. The method of any one of claims 1 and 4-14, wherein the $T_{1/2}$ is about 10 h to about 25 h.

16. The method of any one of claims 1 and 4-15, wherein the C_{trough} is about 50 ng/mL to about 500 ng/mL.

17. The method of any one of claims 1 and 4-16, wherein the C_{max} is about 400 ng/mL to about 750 ng/mL.

18. The method of any one of claims 1 and 4-17, wherein the T_{max} is about 3.3 h to about 4.5 h.

19. The method of any one of claims 1 and 4-18, wherein the AUC_{tau} is about 3000 ng•h/mL to about 8000 ng•h/mL.

20. The method of any one of claims 1 and 4-19, wherein the AUC_{last} is about 10000 ng•h/mL to about 16000 ng•h/mL.

21. The method of any one of claims 1 and 4-20, wherein the $T_{1/2}$ is about 12 h to about 22 h.

22. The method of any one of claims 1 and 4-21, wherein the C_{trough} is about 100 ng/mL to about 400 ng/mL.

23. The method of any one of claims 1 and 4-22, wherein the C_{max} is about 450 ng/mL, about 500 ng/mL, about 550 ng/mL, about 600 ng/mL, about 650 ng/mL, or about 700 ng/mL.

24. The method of any one of claims 1 and 4-23, wherein the T_{max} is about 3.5 h, about 3.6 h, about 3.7 h, about 3.8 h, or about 4 h.

25. The method of any one of claims 1 and 4-24, wherein the AUC_{tau} is about 3500 ng•h/mL, about 4000 ng•h/mL, about 4500 ng•h/mL, about 5000 ng•h/mL, about 6000 ng•h/mL, about 7000 ng•h/mL, or about 7500 ng•h/mL.

26. The method of any one of claims 1 and 4-25, wherein the AUC_{last} is about 10500 ng•h/mL, about 11000 ng•h/mL, about 12000 ng•h/mL, about 13000 ng•h/mL, about 14000 ng•h/mL, or about 15000 ng•h/mL.

27. The method of any one of claims 1 and 4-26, wherein the $T_{1/2}$ is about 14 h, about 15 h, about 16 h, about 17 h, about 18 h, about 19 h, or about 20 h.

28. The method of any one of claims 1 and 4-27, wherein the C_{trough} is about 120 ng/mL, about 150 ng/mL, about 200 ng/mL, about 225 ng/mL, about 250 ng/mL, about 300 ng/mL, or about 350 ng/mL.

29. The method of any one of claims 2 and 4-10, wherein the C_{max} is about 1000 ng/mL to about 2800 ng/mL.

30. The method of any one of claims 2, 4-10, and 29, wherein the T_{max} is about 1.5 h to about 3.5 h.

31. The method of any one of claims 2, 4-10, 29, and 30, wherein the AUC_{tau} is about 5000 ng•h/mL to about 25000 ng•h/mL.

32. The method of any one of claims 2, 4-10, and 29-31, wherein the AUC_{last} is about 10000 ng•h/mL to about 100000 ng•h/mL.

33. The method of any one of claims 2, 4-10, and 29-32, wherein the $T_{1/2}$ is about 15 h to about 25 h.

34. The method of any one of claims 2, 4-10, and 29-33, wherein the C_{trough} is about 80 ng/mL to about 2000 ng/mL.

35. The method of any one of claims 2, 4-10, and 29-34, wherein the C_{max} is about 1500 ng/mL to about 2000 ng/mL.

36. The method of any one of claims 2, 4-10, and 29-35, wherein the T_{max} is about 2 h to about 3 h.

37. The method of any one of claims 2, 4-10, and 29-36, wherein the AUC_{tau} is about 10000 ng•h/mL to about 20000 ng•h/mL.

38. The method of any one of claims 2, 4-10, and 29-37, wherein the AUC_{last} is about 20000 ng•h/mL to about 90000 ng•h/mL.

39. The method of any one of claims 2, 4-10, and 29-38, wherein the $T_{1/2}$ is about 16 h to about 22 h.

40. The method of any one of claims 2, 4-10, and 29-39, wherein the C_{trough} is about 200 ng/mL to about 1500 ng/mL.

41. The method of any one of claims 2, 4-10, and 29-40, wherein the C_{max} is about 1600 ng/mL, about 1650 ng/mL, about 1700 ng/mL, about 1750 ng/mL, about 1800 ng/mL, or about 1850 ng/mL.

42. The method of any one of claims 2, 4-10, and 29-41, wherein the T_{max} is about 2.2 h, about 2.4 h, about 2.5, about 2.6 h, or about 2.8 h.

43. The method of any one of claims 2, 4-10, and 29-42, wherein the AUC_{tau} is about 12000 ng•h/mL, about 13000 ng•h/mL, about 14000 ng•h/mL, about 15000 ng•h/mL, about 16000 ng•h/mL, about 17000 ng•h/mL, or about 19000 ng•h/mL.

44. The method of any one of claims 2, 4-10, and 29-43, wherein the AUC_{last} is about 30000 ng•h/mL, about 40000 ng•h/mL, about 50000 ng•h/mL, about 6000 ng•h/mL, about 70000 ng•h/mL, or about 80000 ng•h/mL.

45. The method of any one of claims 2, 4-10, and 29-44, wherein the $T_{1/2}$ is about 17 h, about 17.5 h, about 18 h, about 18.5 h, about 19 h, about 19.5 h, or about 20 h.

46. The method of any one of claims 2, 4-10, and 29-45, wherein the C_{trough} is about 400 ng/mL, about 600 ng/mL, about 800 ng/mL, about 900 ng/mL, about 1000 ng/mL, or about 1200 ng/mL.

47. The method of any one of claims 3-10, wherein the C_{max} is about 2000 ng/mL to about 6500 ng/mL.

48. The method of any one of claims 3-10 and 47, wherein the T_{max} is about 2 h to about 4 h.

49. The method of any one of claims 3-10, 47, and 48, wherein the AUC_{tau} is about 25000 ng•h/mL to about 60000 ng•h/mL.

50. The method of any one of claims 3-10 and 47-49, wherein the AUC_{last} is about 47000 ng•h/mL to about 557000 ng•h/mL.

51. The method of any one of claims 3-10 and 47-50, wherein the $T_{1/2}$ is about 10 h to about 105 h.

52. The method of any one of claims 3-10 and 47-51, wherein the C_{trough} is about 1500 ng/mL to about 4500 ng/mL.

53. The method of any one of claims 3-10 and 47-52, wherein the C_{max} is about 3000 ng/mL to about 5000 ng/mL.

54. The method of any one of claims 3-10 and 47-53, wherein the T_{max} is about 2.5 h to about 3.5 h.

55. The method of any one of claims 3-10 and 47-54, wherein the AUC_{tau} is about 30000 ng•h/mL to about 50000 ng•h/mL.

56. The method of any one of claims 3-10 and 47-55, wherein the AUC_{last} is about 50000 ng•h/mL to about 410000 ng•h/mL.

57. The method of any one of claims 3-10 and 47-56, wherein the $T_{1/2}$ is about 15 h to about 70 h.

58. The method of any one of claims 3-10 and 47-57, wherein the C_{trough} is about 2000 ng/mL to about 4000 ng/mL.

59. The method of any one of claims 3-10 and 47-58, wherein the C_{max} is about 3250 ng/mL, about 3500 ng/mL, about 3750 ng/mL, about 4000 ng/mL, about 4250 ng/mL, or about 4500 ng/mL.

60. The method of any one of claims 3-10 and 47-59, wherein the T_{max} is about 2.7 h, about 2.9 h, about 3.0, about 3.2 h, or about 3.3 h.

61. The method of any one of claims 3-10 and 47-60, wherein the AUC_{tau} is about 35000 ng•h/mL, about 36000 ng•h/mL, about 37000 ng•h/mL, about 38000 ng•h/mL, about 40000 ng•h/mL, about 42000 ng•h/mL, or about 45000 ng•h/mL.

62. The method of any one of claims 3-10 and 47-61, wherein the AUC_{last} is about 100000 ng•h/mL, about 150000 ng•h/mL, about 200000 ng•h/mL, about 250000 ng•h/mL, about 300000 ng•h/mL, or about 350000 ng•h/mL.

63. The method of any one of claims 3-10 and 47-62, wherein the $T_{1/2}$ is about 20 h, about 26 h, about 32 h, about 38 h, about 44 h, about 50 h, or about 60 h.

64. The method of any one of claims 3-10 and 47-63, wherein the C_{trough} is about 2200 ng/mL, about 2500 ng/mL, about 2700 ng/mL, about 3000 ng/mL, about 3300 ng/mL, or about 3500 ng/mL.

65. The method of any one of claims 1-64, wherein Compound 1 is administered for at least 10 days.

66. The method of any one of claims 1-65, wherein Compound 1 is administered every 12 hours.

67. The method of any one of claims 1-66, wherein Compound 1 is administered with food.

68. The method of any one of claims 1-66, wherein Compound 1 is administered without food.