

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

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

5 This invention was made with government support under U01 AG058608 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND

10 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-

15 4-yl]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).

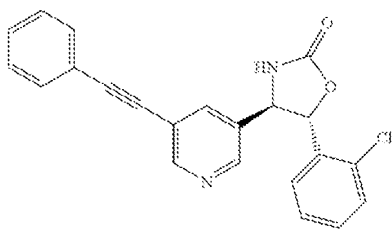
There remains a need for compounds and compositions that modulate mGluR5 to improve mental health and treat CNS disorders.

20

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 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):

25



, sufficient to produce:

- a) a C_{max} (maximum concentration) of about 10 ng/mL to about 1000 ng/mL;
 - b) a T_{max} (time at maximum concentration) of about 0.75 h to about 7 h;
 - c) an AUC_{0-24} (area under the plasma concentration time curve from time zero to 24 hours) of about 50 ng•h/mL to about 7400 ng•h/mL;
 - d) an AUC_{last} (area under the plasma concentration time curve to the last measurable plasma concentration) of about 48 ng•h/mL to about 9200 ng•h/mL;
- 30

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

f) an mGluR5 receptor occupancy (RO, e.g., at the time of C_{trough}) of about 2% to about 99%.

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 any 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).

10 In any embodiment where the therapeutically effective amount produces (a), alone or in combination with any 2, 3, 4, 5, or 6 of (b)-(f), the C_{max} is from about 20 ng/mL to about 500 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 22, about 126, about 190, about 290, about 456, or about 481 ng/mL. In any embodiment where the therapeutically effective amount produces (a), alone or in combination with
15 any 2, 3, 4, or 5 of (b)-(f), the C_{max} is from about 10 to about 30, about 60 to about 180, about 100 to about 270, about 150 to about 450, about 250 to about 700, or about 300 to about 600 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 22 to about 480, from about 30 to about 190, from about 40 to about 190, from about 50 to about 190, from about 60 to about 190, from about 70 to about 190, from
20 about 80 to about 190, from about 90 to about 190, from about 100 to about 190, from about 110 to about 190, from about 120 to about 190, from about 130 to about 190, from about 140 to about 190, from about 150 to about 190, from about 160 to about 190, from about 170 to about 190, from about 180 to about 190, from about 125 to about 480, from about 130 to about 475, from about 135 to about 470, from about 140 to about 465, from about 145 to about 460, from about 150 to about 455, from about 155 to about
25 450, from about 160 to about 445, from about 165 to about 440, from about 170 to about 435, from about 175 to about 430, from about 180 to about 425, from about 185 to about 420, from about 190 to about 415, from about 195 to about 410, from about 200 to about 405, from about 205 to about 400, from about 210 to about 395, from about 215 to about 390, from about 220 to about 385, from about 225 to about 380, from about 230 to about 375, from about 235 to about 370, from about 240 to about 365, from about
30 245 to about 360, from about 250 to about 355, from about 255 to about 350, from about 260 to about 345, from about 265 to about 340, from about 270 to about 335, from about 275 to about 330, from about 280 to about 325, from about 285 to about 320, from about 290 to about 315, from about 295 to about 310, from about 300 to about 305, from about 300 to about 480, from about 400 to about 480, or from about 450 to about 480 ng/mL.

35 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 1 h to 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 about 1.5, about 1.6, about 1.9, about 2.1, about 2.2, or about 3.4 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 1 to about 4.5, from about 1.3 to about 1.7, from about 1.5 to about 1.8, from about 1.7 to about 2.1, from about 1.9 to about 2.3, from about 2.0 to about 2.4, from about 2.5 to about 2.7, from about 2.7 to about 2.9, from about 2.9 to about 3.1, from about 3.1 to about 3.3, or from about 3.2 to about 3.6 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_{0-24} is from about 100 ng•h/mL to about 4000 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_{0-24} is about 100, about 930, about 960, about 1540, about 1720, about 3100, or about 3700 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_{0-24} is about 50 to about 150, about 600 to about 1300, about 300 to about 1600, about 750 to about 2200, about 1500 to about 4700, or about 2500 to about 5000 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_{0-24} is from about 100 to about 3700, from about 100 to about 250, from about 280 to about 400, from about 420 to about 530, from about 560 to about 610, from about 630 to about 700, from about 720 to about 810, from about 850 to about 920, from about 930 to about 960, from about 960 to about 1250, from about 1300 to about 1600, from about 1680 to about 2050, from about 2150 to about 2400, from about 2480 to about 2800, from about 2900 to about 3150, from about 3250 to about 3500, or from about 3600 to about 3700 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)-(f), the AUC_{last} is from about 50 ng•h/mL to about 5000 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)-(f), the AUC_{last} is about 97, about 1157, about 1404, about 1961, about 4161, or about 4552 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)-(f), the AUC_{last} is from about 50 to about 150, about 400 to about 2400, about 750 to about 1550, about 1000 to about 3000, about 2000 to about 6000, or about 3000 to about 6000 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)-(f), the AUC_{last} is from about 97 to about 4552, from about 97 to about 185, from about 220 to about 320, from about 360 to about 460, from about 505 to about 600, from about 640 to about 735, from about 775 to about 875, from about 910 to about 1010, from about 1050 to about 1157, from about 1157 to about 1404, from about 1680 to about 1961, from about 1780 to about 2280, from about 2350 to about 2900, from about 3030 to about 3550, from about 3650 to about 4180, or from about 4260 to about 4552 ng•h/mL.

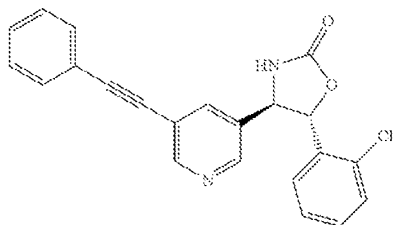
In any embodiment where the therapeutically effective amount produces (e), alone or in combination with any 2, 3, 4, or 5 of (a)-(d) and (f), the $T_{1/2}$ is from about 7 h to about 21 h. In any embodiment where the therapeutically effective amount produces (e), alone or in combination with any 2, 3, 4, or 5 of (a)-(d) and (f), the $T_{1/2}$ is about 7.4, about 14, about 14.4, about 15, about 18, about 19.4, or about 20.5 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 2 to about 13, about 9 to about 20, about 10 to about 18, about 13 to about 25, about 14 to about 22, or about 14 to 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), the $T_{1/2}$ is from about 7.4 to about 20.5, from about 7.4 to about 8.7, from about 9.2 to about 10.8, from about 11.3 to about 12.6, from about 13.2 to about 14.7, from about 15.1 to about 16.5, from about 17.0 to about 18.3, or from about 18.8 to about 20.5 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 mGluR5 receptor occupancy (RO), e.g., at the time of C_{trough} , is about 4%, about 7%, about 8%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 38%, about 39%, about 48%, about 50%, about 77%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, or about 90%.

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 mGluR5 receptor occupancy (RO), e.g., at the time of C_{trough} , is from about 3% to about 99%, from about 4% to about 99%, from about 5% to about 99%, from about 10% to about 99%, from about 15% to about 99%, from about 20% to about 99%, from about 25% to about 99%, from about 30% to about 99%, from about 35% to about 99%, from about 40% to about 99%, from about 45% to about 99%, from about 50% to about 99%, from about 55% to about 99%, from about 60% to about 99%, from about 65% to about 99%, from about 70% to about 99%, from about 75% to about 99%, from about 80% to about 99%, from about 85% to about 99%, from about 90% to about 99%, from about 95% to about 99%, from about 5% to about 10%, from about 5% to about 20%, from about 5% to about 30%, from about 5% to about 40%, from about 5% to about 50%, from about 5% to about 60%, from about 5% to about 70%, from about 5% to about 80%, from about 5% to about 90%, from about 5% to about 95%, from about 10% to about 95%, from about 10% to about 90%, from about 10% to about 80%, from about 20% to about 70%, from about 30% to about 60%, from about 40% to about 50%, from about 50% to about 90%, from about 60% to about 90%, from about 70% to about 90%, from about 80% to about 90%, from about 2% to about 25%, from about 2% to about 10%, from about 50% to about 85%, from about 50% to about 80%, from about 50% to about 75%, from about 40% to about 50%, from about 2% to about 25%, from about 25% to about 50%, from about 25% to about 75%, or from about 25% to about 90%. 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 mGluR5 receptor occupancy (RO), e.g., at the time of C_{trough} , is at least 75%, e.g., at least 80%, 85%, 90%, or 95%.

In any of the above embodiments, Compound 1 may be administered without food.

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 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):



, with food.

In some embodiments, the therapeutically effective amount is an amount sufficient to produce:

- a) a C_{max} (maximum concentration) of about 250 ng/mL to about 3000 ng/mL;
- b) a T_{max} (time at maximum concentration) of about 0.8 h to about 6.2 h;
- c) an AUC_{0-24} (area under the plasma concentration time curve from time zero to 24 hours) of about 1300 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 1200 ng·h/mL to about 120000 ng·h/mL; and/or
- e) a $T_{1/2}$ (half-life) of about 5.5 h to about 36 h.

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

In any embodiment where the therapeutically effective amount produces (a), alone or in combination with any 2, 3, or 4 of (b)-(e), the C_{max} is from about 400 ng/mL to about 2500 ng/mL, e.g., 400 ng/mL to about 900 ng/mL. In any embodiment where the therapeutically effective amount produces (a), alone or in combination with any 2, 3, or 4 of (b)-(e), the C_{max} is about 250 ng/mL, about 400 ng/mL, about 450 ng/mL, about 560 ng/mL, about 670 ng/mL, about 680 ng/mL, about 690 ng/mL, about 900 ng/mL, about 990 ng/mL, about 1600, about 2500 ng/mL, or about 3000 ng/mL. In any embodiment where the therapeutically effective amount produces (a), alone or in combination with any 2, 3, or 4 of (b)-(e), the C_{max} is from about 250 to about 350, from about 250 to about 1000, from about 350 to about 450, from about 450 to about 550, from about 550 to about 650, from about 650 to about 750, from about 750 to about 850, from about 850 to about 950, from about 950 to about 1000, from about 1000 to about 2000,

from about 700 to about 2500, from about 600 to about 3000 ng/mL, or from about 2000 to about 3000 ng/mL.

In any embodiment where the therapeutically effective amount produces (b), alone or in combination with any 2, 3, or 4 of (a) and (c)-(e), the T_{max} is from about 1.5 h to about 4.6 h. In any
5 embodiment where the therapeutically effective amount produces (b), alone or in combination with any 2, 3, or 4 of (a) and (c)-(e), the T_{max} is about 1 h, about 1.5 h, about 1.9 h, about 2 h, about 2.5 h, about 3 h, about 3.1 h, about 4.6 h, or about 6 h. In any embodiment where the therapeutically effective amount produces (b), alone or in combination with any 2, 3, or 4 of (a) and (c)-(e), the T_{max} is from about 0.8 to about 1.0, from about 1.0 to about 1.2, from about 1.2 to about 1.4, from about 1.4 to about 1.6, from
10 about 1.6 to about 1.8, from about 1.8 to about 2.0, from about 2.0 to about 2.2, from about 2.0 to about 3.0, from about 2.2 to about 2.4, from about 2.4 to about 2.6, from about 2.6 to about 2.8, from about 2.8 to about 3.0, from about 3.0 to about 3.2, from about 3.2 to about 3.4, from about 3.4 to about 3.6, from about 3.6 to about 3.8, from about 3.8 to about 4.0, from about 4.0 to about 4.2, from about 4.2 to about 4.4, from about 4.4 to about 4.6, from about 4.6 to about 4.8, from about 4.8 to about 5.0, from about 5.0
15 to about 5.2, from about 5.2 to about 5.4, from about 5.4 to about 5.6, from about 5.6 to about 5.8, from about 5.8 to about 6.0, or from about 6.0 to about 6.2 h.

In any embodiment where the therapeutically effective amount produces (c), alone or in combination with any 2, 3, or 4 of (a)-(b) and (d)-(e), the AUC_{0-24} is from about 2000 ng•h/mL to about 48000 ng•h/mL, e.g., about 5000 to about 60000 ng•h/mL or about 1200 to about 9000 ng•h/mL or about
20 8800 to about 48000 ng•h/mL. In any embodiment where the therapeutically effective amount produces (c), alone or in combination with any 2, 3, or 4 of (a)-(b) and (d)-(e), the AUC_{0-24} is about 1300 ng•h/mL, about 2370 ng•h/mL, about 4100 ng•h/mL, about 4600 ng•h/mL, about 5700 ng•h/mL, about 6900 ng•h/mL, about 8620 ng•h/mL, about 8900 ng•h/mL, about 28500 ng•h/mL, about 48000 ng•h/mL, or about 60000 ng•h/mL. In any embodiment where the therapeutically effective amount produces (c) alone
25 or in combination with any 2, 3, or 4 of (a)-(b) and (d)-(e), the AUC_{0-24} is from about 1300 to about 1800, from about 1800 to about 2300, from about 2300 to about 2800, from about 2800 to about 3300, from about 3300 to about 3800, from about 3800 to about 4300, from about 4300 to about 4800, from about 4800 to about 5300, from about 5300 to about 5800, from about 5800 to about 6300, from about 6300 to about 6800, from about 6800 to about 7300, from about 7300 to about 7800, from about 7800 to about
30 8300, from about 8300 to about 8800, from about 8800 to about 9000, from about 9000 to about 10000, from about 10000 to about 11000, from about 11000 to about 12000, from about 12000 to about 13000, from about 13000 to about 14000, from about 14000 to about 15000, from about 15000 to about 16000, from about 16000 to about 17000, from about 17000 to about 18000, from about 18000 to about 19000, from about 19000 to about 20000, from about 20000 to about 21000, from about 21000 to about 22000,
35 from about 22000 to about 23000, from about 23000 to about 24000, from about 24000 to about 25000, from about 25000 to about 26000, from about 26000 to about 27000, from about 27000 to about 28000, from about 28000 to about 29000, from about 29000 to about 30000, from about 30000 to about 31000,

from about 31000 to about 32000, from about 32000 to about 33000, from about 33000 to about 34000, from about 34000 to about 35000, from about 35000 to about 36000, from about 36000 to about 37000, from about 37000 to about 38000, from about 38000 to about 39000, from about 39000 to about 40000, from about 40000 to about 41000, from about 41000 to about 42000, from about 42000 to about 43000, from about 43000 to about 44000, from about 44000 to about 45000, from about 45000 to about 46000, from about 46000 to about 47000, from about 47000 to about 48000, from about 48000 to about 49000, from about 49000 to about 50000, from about 50000 to about 51000, from about 51000 to about 52000, from about 52000 to about 53000, from about 53000 to about 54000, from about 54000 to about 55000, from about 55000 to about 56000, from about 56000 to about 57000, from about 57000 to about 58000, from about 58000 to about 59000, or from about 59000 to about 60000 ng•h/mL.

In any embodiment where the therapeutically effective amount produces (d), alone or in combination with any 2, 3, or 4 of (a)-(c) and (e), the AUC_{last} is from about 1200 ng•h/mL to about 120000 ng•h/mL, e.g., about 1200 to about 22000 ng•h/mL or about 13500 to about 116000 ng•h/mL or about 5500 to about 120000 ng•h/mL. In any embodiment where the therapeutically effective amount produces (d), alone or in combination with any 2, 3, or 4 of (a)-(c) and (e), the AUC_{last} is about 1230 ng•h/mL, 1310 ng•h/mL, about 4600 ng•h/mL, about 4990 ng•h/mL, about 6660 ng•h/mL, about 12100 ng•h/mL, about 14000 ng•h/mL, about 21600 ng•h/mL, about 65000 ng•h/mL, about 116000 ng•h/mL, or about 120000 ng•h/mL. In any embodiment where the therapeutically effective amount produces (d), alone or in combination with any 2, 3, or 4 of (a)-(c) and (e), the AUC_{last} is from about 1200 to about 2200, from about 2200 to about 3200, from about 3200 to about 4200, from about 4200 to about 5200, from about 5200 to about 6200, from about 6200 to about 7200, from about 7200 to about 8200, from about 8200 to about 9200, from about 9200 to about 10200, from about 10200 to about 11200, from about 11200 to about 12200, from about 12200 to about 13200, from about 13200 to about 14200, from about 14200 to about 15200, from about 15200 to about 16200, from about 16200 to about 17200, from about 17200 to about 18200, from about 18200 to about 19200, from about 19200 to about 20200, from about 20200 to about 21200, from about 21200 to about 22000, from about 22000 to about 32000, from about 32000 to about 42000, from about 42000 to about 52000, from about 52000 to about 62000, from about 62000 to about 72000, from about 72000 to about 82000, from about 82000 to about 92000, from about 92000 to about 102000, from about 102000 to about 112000, or from about 112000 to about 120000 ng•h/mL.

In any embodiment where the therapeutically effective amount produces (e), alone or in combination with any 2, 3, or 4 of (a)-(d), the $T_{1/2}$ is from about 9 h to about 25 h or about 13 to about 30 h. In any embodiment where the therapeutically effective amount produces (e), alone or in combination with any 2, 3, or 4 of (a)-(d), the $T_{1/2}$ is about 5.9 h, about 9.2 h, about 13.2 h, about 13.8 h, about 15.9 h, about 16.9 h, about 20 h, about 24.7 h, about 27.2 h, about 28.8 h, or about 35.5 h. In any embodiment where the therapeutically effective amount produces (e), alone or in combination with any 2, 3, 4, 5, or 6 of (a)-(d), the $T_{1/2}$ is from about 5.5 to about 7.5, from about 7.5 to about 9.5, from about 9.5 to about 11.5, from about 11.5 to about 13.5, from about 13.5 to about 15.5, from about 15.5 to about 17.5, from

about 17.5 to about 19.5, from about 19.5 to about 21.5, from about 21.5 to about 23.5, from about 23.5 to about 25.5, from about 25.5 to about 27.5, from about 27.5 to about 29.5, from about 29.5 to about 31.5, from about 31.5 to about 33.5, from about 33.5 to about 35.5, from about 35.5 to about 36 h.

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 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).

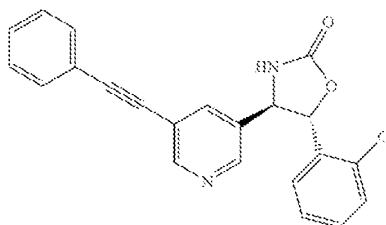
In any of the above embodiments, Compound 1 is in a pharmaceutical composition.

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, 40 mg, 70 mg, 100 mg, 150 mg, or 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 once, 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, 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_{0-24} , AUC_{last} , $T_{1/2}$, and/or mGluR5 RO resulting in effective treatment of diseases such as Alzheimer's disease.

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

Scan 1				Scan 2				AveragePos. [°2 θ]	Average d-spacing [Å]
Pos. [°2 θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]	Pos. [°2 θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]		
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
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

Scan 1				Scan 2				AveragePos. [°2 θ]	Average d-spacing [Å]
Pos. [°2 θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]	Pos. [°2 θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]		
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
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 2 θ , each ± 0.2 degrees 2 θ . 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 K α 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

Pos. [°2 θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]
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
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

Pos. [°2 θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]
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
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

Pos. [°2 θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]
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 2 θ , each ± 0.2 degrees 2 θ . 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 2 θ , each ± 0.2 degrees 2 θ . 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 2 θ , each ± 0.2 degrees 2 θ . 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 K α 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 [$\text{\AA}$]	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

Pos. [°2 θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]
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
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 2 θ , each ± 0.2 degrees 2 θ . 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 2 θ , each ± 0.2 degrees 2 θ . 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 2 θ , each ± 0.2 degrees 2 θ . 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 K α 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. [°2 θ]	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

Pos. [°2 θ]	Height [cts]	d-spacing [Å]	Rel. Int. [%]
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
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 2 θ , each ± 0.2 degrees 2 θ . Form C, prepared from vapor diffusion using isopropyl alcohol, may also be

5 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

10 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 2 θ , each ± 0.2 degrees 2 θ . 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)

15 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 2 θ , each ± 0.2 degrees 2 θ . In some embodiments, Form C, prepared from vapor diffusion using isopropyl alcohol, analyzed by differential scanning calorimetry (DSC) thermogram shows an

20 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).

25 **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

30 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

35 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, Adebayo 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 hydroxyanisole (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 gluconate, 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 behenate, 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, mint, 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.

10

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_{0-24} , (d) AUC_{last} , (e) $T_{1/2}$, and/or (f) mGluR5 RO 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 any combination of five of (a)-(f). In some embodiments, the therapeutically effective amount is sufficient to produce any combination of all six of (a)-(f). Values of C_{max} , T_{max} , AUC_{0-24} , AUC_{last} , $T_{1/2}$, and/or mGluR5 RO are provided herein.

The present disclosure also provides a method of treating one or more diseases or conditions by administering Compound 1 with food. Such methods may result in (a) C_{max} , (b) T_{max} , (c) AUC_{0-24} , (d) AUC_{last} , and/or (e) $T_{1/2}$ effective to treat one or more diseases or conditions. In some embodiments, the therapeutically effective amount is sufficient to produce any one of (a)-(e). In some embodiments, the therapeutically effective amount is sufficient to produce any combination of two of (a)-(e). In some embodiments, the therapeutically effective amount is sufficient to produce any combination of three of (a)-(e). In some embodiments, the therapeutically effective amount is sufficient to produce any combination of four of (a)-(e). In some embodiments, the therapeutically effective amount is sufficient to produce any combination of all five of (a)-(e). Values of C_{max} , T_{max} , AUC_{0-24} , AUC_{last} , and/or $T_{1/2}$ for Compound 1 administered with food are provided herein.

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 decreases, 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.

10 *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 $\text{A}\beta_0$ -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 $\text{A}\beta_0$ 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 amnesic 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.

15

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

25

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.

- 5 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

- 10 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
- 15 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
- 20 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
- 25 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
- 30 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
- 35 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.

5 **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.

10 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
15 Ed., John Wiley & Sons, Hoboken: 2013, the entire contents of which are hereby incorporated by reference.

As used herein, the term "about" means $\pm 10\%$ 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
20 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,
25 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.

30 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.

35 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 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_{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 “receptor occupancy” (abbreviated as RO), as used herein, refers to the percentage of a target receptor (e.g., mGluR5) that is bound with Compound 1. RO may be measured at any appropriate time, e.g., at the time of C_{trough} or at the time of C_{max} . Alternatively, RO may be measured as the average RO over a period of time, e.g., between doses or over a 24 h period.

5 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.

10 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.

15 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
20 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.

25 **EXAMPLES**

Example 1.

Overview of Study Design

30 This was an open-label, single ascending doses (SAD) study in healthy male and female participants 50 to 80 years of age (inclusive) with no history of cognitive impairment to evaluate the safety and PK of single oral doses of Compound 1. A substudy to evaluate mGluR5 occupancy by Compound 1 using PET of [^{18}F]FPEB as a mGluR5 specific PET ligand was concurrently conducted in consenting participants.

35 Six cohorts of 6 participants each received a single oral dose of Compound 1 in the fasted state at the following dose levels: 10, 40, 70, 100, 150, and 200 mg and then were followed for 7 days; the starting dose of 10 mg was <10% of the 140 mg human equivalent dose (HED) of the rat NOAEL in the GLP 28-day rat study of 15 mg/kg.

Study medication was capsules containing 5, 50, or 100 mg of nano-milled active pharmaceutical ingredient; doses for each cohort were achieved using combinations of these capsules. Doses were administered in an inpatient setting where all participants were closely monitored prior to discharge on Day 3, with follow-up in-person visits occurring on Days 4 and 7 and a phone call to inquire about general health occurring on Day 5.

Compound 1 administration was carefully monitored within and between cohorts to ensure patient safety and determination of whether to open the next dose cohort was made after all participants in a given cohort had completed the study and all available clinical, safety, and PK data were reviewed by the Investigator, Medical Monitor, DSMB, and IND Sponsor. Of note, dose escalation for the next cohort was based on PK results from the most recent cohort as follows:

- If plasma $AUC_{0-24h} < 24,000$ ng·h/mL (12.5% NOAEL), then dose increase according to schedule.
- If plasma AUC_{0-24h} 24,000-48,000 ng·h/mL (12.5%-25% NOAEL), then dose increase maximum of 2-fold.
- If plasma AUC_{0-24h} 48,001-96,000 ng·h/mL (25%-50% NOAEL), then dose increase maximum of 1.5-fold.
- If plasma AUC_{0-24h} 96,001-120,000 ng·h/mL (50%-67.5% NOAEL), then dose increase maximum of 1.3-fold.
- If plasma $AUC_{0-24h} > 120,000$ ng·h/mL (>67.5% NOAEL), then stop escalation.

Following study drug administration, vital signs were monitored every 1 hour for the first 8 hours and then every 3 hours until discharge on Day 3 and an ECG was performed at approximately 6, 24, and 48 hours after drug administration. In order to monitor for changes in consciousness, the Glasgow Coma Scale (GCS) was administered pre-dose and then every 2 hours for the first 8 hours and then every 3 hours until discharge on Day 3. In order to monitor for cognitive or psychiatric side effects, the MOCA, GDS, and NPIQ were administered prior to oral dose administration, again at approximately 6 hours post-dose (approximate peak concentration), and approximately 24 hours post-dose. Adverse events were monitored continuously. Blood was collected for safety laboratory studies prior to drug dose administration and on Days 2 and 3, and plasma for PK analysis was collected as shown in Table 8. In addition, 24-hour urine collections for analysis of urine drug and metabolite levels occurred starting at the time of study drug administration and from 24-48 hours after study drug administration.

Table 8. Phase 1 Schedule for Pharmacokinetic Sampling

	Day 1 (Dosing Day)	Day 2	Day 3	Day 4	Day 7
Plasma Samples	Pre-Dose, and post-dose at 30 min (± 10 min), 1 h (± 10 min),	24 h (± 1 h)	48 h (± 2 h)	72 h (± 6 h)	Day 7 $\pm$ 1 day

	Day 1 (Dosing Day)	Day 2	Day 3	Day 4	Day 7
	2 h ($\pm$ 10 min), 4 h ($\pm$ 10 min), 8h ($\pm$ 1 h), 12 h ($\pm$ 1 h)				
Urine Samples	24-hour collection starting immediately post-dose	Second 24- hour collection from 24 to 48 hours post-dose			

Participants who consented to the RO substudy underwent PET scans off drug (up to 60 days prior to baseline or more than 7 days post-dose), approximately 4 hours post-dose, and approximately 24 hours post-dose.

5

Participant Disposition, Demography and Baseline Characteristics

A total of 36 participants (6 per dose cohort) enrolled in and completed the trial. Across the cohorts, the mean age and body mass index (BMI) at baseline ranged from 68.3 to 72.8 years and from 24.8 to 27.8, respectively.

10

The majority of participants were white (97%) and female (58.3%), and mean scores on the cognitive and depression scales administered at baseline were not indicative of cognitive impairment or clinically meaningful signs of depression (Table 9).

Table 9. Participant Demography and Baseline Characteristics

Parameter	Cohort 1 (10 mg)	Cohort 2 (40 mg)	Cohort 3 (70 mg)	Cohort 4 (100 mg)	Cohort 5 (150 mg)	Cohort 6 (200 mg)
Age, Mean (SD)	70.9 (3.2)	71.3 (5.6)	70.3 (2.5)	68.3 (5.5)	72.8 (6.1)	68.1 (9.1)
Sex						
Male N (%)	2 (33.3 %)	2 (33.3 %)	2 (33.3 %)	2 (33.3%)	3 (50.0%)	4 (66.7%)
Female N (%)	4 (66.7%)	4 (66.7%)	4 (66.7%)	4 (66.7%)	3 (50.0%)	2 (33.3%)
Body weight (kg), Mean (SD)	77.6 (13.3)	77.7 (23.5)	69.0 (7.3)	71.3 (10.8)	70.6 (9.3)	72.4 (15.4)
BMI (kg/m ²), Mean (SD)	26.5 (4.6)	27.8 (6.2)	24.8 (3.3)	26.7 (3.5)	26.0 (2.2)	24.8 (3.5)

Parameter	Cohort 1 (10 mg)	Cohort 2 (40 mg)	Cohort 3 (70 mg)	Cohort 4 (100 mg)	Cohort 5 (150 mg)	Cohort 6 (200 mg)
CDR, Mean (SD) ¹	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Logical Memory II Subscale, Delayed, Mean (SD) ²	14.2 (3.1)	13.8 (2.4)	11.2 (4.0)	11.3 (3.6)	13.2 (3.4)	13.8 (4.4)
MMSE, Mean (SD) (scores >25 are normal) ³	29.3 (0.5)	28.8 (1.5)	29.5 (0.5)	29.0 (0.6)	29.5 (0.8)	29.5 (0.8)
GCS, Mean (SD) ⁴	15.0 (0.0)	15.0 (0.0)	15.0 (0.0)	15.0 (0.0)	15.0 (0.0)	15.0 (0.0)
GDS, Mean (SD) ⁵	0.0 (0.0)	0.3 (0.8)	1.5 (1.5)	0.8 (1.0)	1.2 (1.9)	1.0 (0.9)
MoCA, Mean (SD) ⁶	28.2 (2.1)	26.8 (2.3)	26.5 (3.4)	26.0 (2.9)	27.5 (1.4)	27.2 (1.6)

Abbreviations: BMI = body mass index; CDR = Clinical Dementia Rating scale; GCS = Glasgow Coma Scale; GDS = Geriatric Depression Scale; MMSE = mini mental state exam; MoCA = Montreal Cognitive Assessment; SD = standard deviation.

¹ Scores of above 0 indicate progressive decline due to a cognitive disorder.

5 ² Scores range from 1 to 19; with higher scores indicating better delayed verbal recall.

³ Scores range from 1 to 30; with higher scores indicating better cognitive performance

⁴ Scores range from 3 to 15; with lower scores indicating impaired consciousness.

⁵ Scores range from 0 to 15; with higher scores indicating a greater likelihood of depression.

⁶ Scores range from 0 to 30; with higher scores indicating better cognitive performance

10

Safety Results

Single oral doses of Compound 1 were well tolerated with no deaths, SAEs, or severe TEAEs observed in any participant. There was also no evidence in any participant of clinically significant changes in consciousness as measured by the GCS, or in cognitive or psychiatric side effects as measured by the
15 MOCA, the GDS, and the NPIQ. All TEAEs were mild or moderate in intensity and 8 TEAEs were considered possibly related to treatment; all others were assessed as unlikely related. These possibly related TEAEs consisted of 3 reports of brief oral sensations (abnormal taste, tongue tingling, mouth pain), 1 brief episode of dizziness, 2 reports of transient headache (one treated with a single dose of

acetaminophen 500 mg), 1 episode of transient hypertension, and 1 lab measurement of increase in triglycerides on Day 7 in a participant with a history of hypertriglyceridemia.

Pharmacokinetic Results

5 Pharmacokinetic parameters were obtained in all 36 participants across all 7 days of evaluation. Importantly, all dose escalations occurred as planned because no human plasma AUC_{0-24h} value exceeded the cutoff of 24,000 ng·h/mL (12.5% rat NOAEL), which would have required smaller dose increments.

10 Mean PK parameters of Compound 1 are presented in Table 10. Overall, dose-dependent linearity was observed across all doses, except the 100 mg dose group, which experienced a lower exposure than predicted. As the 100 mg group was the first to be administered a single 100-mg strength capsule, we hypothesized that lower bioavailability was due to a dissolution difference of the 100-mg strength capsule compared to the 5- or 50-mg strength capsules used to achieve previous dose strengths. The second possibility for variability was water volumes administered with the drug at time of
15 ingestion, with the 100-mg single capsule requiring smaller water volumes than the 5 total capsules used in the 70-mg doses group (one 50-mg capsule and four 5-mg capsules).

Table 10. Summary of Compound 1 Pharmacokinetic Parameters in Plasma Following Oral Administration

		Cohort 1 (10 mg) (N=6)	Cohort 2 (40 mg) (N=6)	Cohort 3 (70 mg) (N=6)	Cohort 4 (100 mg) (N=6)	Cohort 5 (150 mg) (N=6)	Cohort 6 (200 mg) (N=6)	Overall (N=36)
C_{max} (ng/mL)	Mean (SD)	21.86 (7.847)	189.15 (82.178)	294.22 (150.57)	125.85 (63.721)	480.83 (235.20)	455.65 (167.89)	261.26 (213.33)
	Median (Min;Max)	24.3 (11.5 ; 29.2)	202.6 (78.6 ; 290.7)	292.5 (101.5 ; 495.3)	152.0 (28.4 ; 183.5)	560.0 (154.3 ; 743.6)	520.8 (218.0 ; 621.5)	201.9 (11.5 ; 743.6)
	CV (%)	35.90	43.45	51.17	50.63	48.91	36.85	81.66
T_{max} (h)	Mean (SD)	1.49 (0.571)	1.60 (0.505)	2.18 (1.439)	2.17 (0.983)	1.93 (0.325)	3.40 (1.055)	2.13 (1.047)
	Median (Min;Max)	1.5 (0.9 ; 2.1)	1.8 (1.0 ; 2.1)	1.6 (1.0 ; 4.0)	2.0 (1.0 ; 4.0)	2.0 (1.3 ; 2.2)	4.0 (2.1 ; 4.3)	2.0 (0.9 ; 4.3)
	CV (%)	38.40	31.55	66.03	45.38	16.90	31.01	49.23
AUC_{last} (h·ng/mL)	Mean (SD)	97.34 (50.414)	1157.4 (409.12)	1961.1 (1102.7)	1403.9 (1053.0)	4161.0 (2189.4)	4551.9 (1576.0)	2222.1 (2016.3)
	Median (Min;Max)	93.3 (46.5 ; 172.7)	1239.0 (496.4 ; 1710.8)	2107.4 (683.3 ; 3394.0)	1084.3 (449.5 ; 3208.5)	4467.3 (683.1 ; 6909.9)	4803.0 (1907.0 ; 6397.3)	1581.3 (46.5 ; 6909.9)
	CV (%)	51.79	35.35	56.23	75.01	52.62	34.62	90.74
AUC₀₋₂₄ (h·ng/mL)	Mean (SD)	102.18 (48.264)	928.95 (340.65)	1542.9 (767.57)	959.09 (678.67)	3108.7 (1640.8)	3700.4 (1237.6)	1723.7 (1560.1)
	Median (Min;Max)	100.7 (54.3 ; 173.7)	965.5 (432.6 ; 1465.3)	1679.1 (655.2 ; 2518.1)	817.4 (259.8 ; 1980.6)	3458.3 (590.0 ; 5019.8)	4090.8 (1436.5 ; 4748.8)	1206.0 (54.3 ; 5019.8)
	CV (%)	47.23	36.67	49.75	70.76	52.78	33.45	90.51
T_{1/2} (h)	Mean (SD)	7.36 (5.282)	19.39 (6.646)	14.03 (4.203)	20.54 (6.778)	18.03 (4.620)	14.44 (5.040)	15.63 (6.783)

		Cohort 1 (10 mg) (N=6)	Cohort 2 (40 mg) (N=6)	Cohort 3 (70 mg) (N=6)	Cohort 4 (100 mg) (N=6)	Cohort 5 (150 mg) (N=6)	Cohort 6 (200 mg) (N=6)	Overall (N=36)
	Median (Min;Max)	4.7 (3.7 ; 17.2)	16.7 (13.9 ; 31.6)	13.7 (8.4 ; 19.5)	21.5 (12.3 ; 30.4)	18.6 (11.6 ; 25.3)	12.8 (10.0 ; 23.1)	15.1 (3.7 ; 31.6)
	CV (%)	71.82	34.28	29.95	33.01	25.63	34.89	43.40

Abbreviations: AUC₀₋₂₄ = area under the plasma concentration time curve over the last 24 h dosing interval; AUC_{last} = area under the plasma concentration time curve to the last measurable plasma concentration; T_{1/2} = half-life; C_{max} = maximum concentration; T_{max} = time at maximum concentration; CV = coefficient of variation; SD = standard deviation.

5

Importantly, a wide safety margin was observed relative to the rat NOAEL at all doses as shown below in Table 11, which presents the margin of human exposure relative to the rat as fold-below the rat NOAEL.

10

Table 11. Margin of Human Exposure to Rat NOAEL

Compound 1 Human Dose (mg)	Rat NOAEL C _{max} : Human C _{max} Ratio	Rat NOAEL AUC _(last) : Human AUC ₍₀₋₂₄₎ Ratio
10	489	1824
40	57	206
70	36	124
100	85	198
150	22	61
200	23	51

Abbreviations: AUC₀₋₂₄ = area under the plasma concentration-time curve over the last 24-h dosing interval; AUC_{last}=area under the plasma concentration-time curve to the last measurable plasma concentration; C_{max}=maximum concentration; GLP = Good Laboratory Practice; NOAEL=no observed adverse effect level.

15

Note: In the GLP 28-day rat study, mean C_{max} and AUC_{last} (final time point collected at 24 hours post last dose on Day 28) values at the NOAEL of 15 mg/kg/day were 10,700 ng/mL and 192,000 ng·h/mL, respectively (based on male/female combined).

20 *Receptor Occupancy Results*

To evaluate occupancy of mGluR5, [¹⁸F]FPEB PET scans were collected off study drug at Baseline and at 4 and 24 hours post dose in 2 participants each in the 10, 40, 70, and 100 mg cohorts. Receptor occupancy at 4 and 24 hours post dose, expressed as a percentage of total mGluR5 availability, and plasma concentrations of Compound 1 are presented by participant in Table 12.

25

Table 12. mGluR5 Receptor Occupancy and Compound 1 Plasma Concentration by Participant at 4- and 24-Hours Post Dose by Participant

(Compound 1 Dose) - hours Post	Receptor Occupancy (RO)	Compound 1 Plasma Concentration (ng/mL)
(10 mg) – 4 hours	7.0%	2.7
(10 mg) – 24 hours	-4.9%	0
(10 mg) – 4 hours	23.0%	5.3
(10 mg) – 24 hours	3.9%	0
(40 mg) – 4 hours	77.1%	81.2
(40 mg) – 24 hours	4.2%	9.0
(40 mg) – 4 hours	84.4%	107.1
(40 mg) – 24 hours	21.4%	13.6
(70 mg) – 4 hours	80.9%	98.9
(70 mg) – 24 hours	23.8%	18.3
(70 mg) – 4 hours	84.2%	93.8
(70 mg) – 24 hours	27.5%	4.6
(100 mg) – 4 hours	82.6%	111.0
(100 mg) – 24 hours	48.1%	36.8
(100 mg) – 4 hours	38.7%	27.3
(100 mg) – 24 hours	8.0%	5.7

- 5 The relationship between Compound 1 plasma concentration (CP) and RO was evaluated using the conventional sigmoidal maximum RO ($r_{\max}$) model where the half maximal inhibitory concentration (IC₅₀) is the CP required to produce 50% of the $r_{\max}$:

$$RO = \frac{r_{\max} \times C_p}{IC_{50} + C_p}$$

- 10 A nonlinear least squares analysis was used to estimate the parameters from all scans. The data supported a model with 1 parameter (IC₅₀, $r_{\max}$ = 100%). Based on this analysis, IC₅₀ (standard error [SE]) = 33.9 (4.0) ng/mL and 80% maximal inhibitory concentration (IC₈₀) (SE) = 135.7 (16.0) ng/mL.

- 15 There is a strong relationship between CP and RO. However, the IC₈₀ calculated from the model may be an overestimation of plasma concentrations required to achieve 80% RO as the model does not account for the potential impact of nonspecific binding. Moreover, from the tabulated data in Table 12, it appears that 77.1% RO was observed at a much lower concentration of 81.23 ng/mL. Importantly, when trough exposure concentrations (C_{trough}, ng/mL) were simulated in the population PK model with the high

dose of 225 mg BID, they exceeded the IC₈₀ level for the dosing interval in 95% of the target population with a median trough concentration of 205.30 ng/mL and median C_{avg} value predicted at 504.44 ng/mL.

Example 2.

5

This study was 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 PK.

Twelve cognitively healthy older adults were randomized 1:1 to receive a single 150-mg dose of Compound 1 in one of two treatment sequences: either fasting followed by fed or fed followed by fasting. There was a 10-day washout period between doses. Standardized meals were provided. For the fasting period, the study drug 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.

A follow-up phone call was completed 14 days after the last dose of study medication.

20

Disposition and Demography

Twelve participants were enrolled in and completed this study, and the study demography is summarized in Table 13. The mean age and BMI at baseline were 55.2 years and 26.57 kg/m², respectively. The majority of participants were white (66.7%) and one-half were female. Mean scores on the cognitive and depression scales administered at baseline were not indicative of cognitive impairment or clinically meaningful signs of depression.

Table 13. Demographic and baseline summary of subjects in food effect study

Parameter	Fed and Fasted, N=12
Age, Mean (SD)	55.2 (2.59)
Sex	
Male N (%)	6 (50.0)
Female N (%)	6 (50.0)
Race (%)	
African American	2 (16.7)
White N	8 (66.7)
Asian	1 (8.3)
Multiple	1 (8.3)
Body Weight (kg), Mean (SD)	74.35 (11.174)
BMI (kg/m ²), Mean (SD)	26.57 (2.707)
GDS ¹	≤5
MoCA ²	>25

Abbreviations: BMI = body mass index; GDS = Geriatric Depression Scale; MoCA = Montreal Cognitive Assessment; SD = standard deviation.

¹Scores range from 0 to 15; with higher scores indicating a greater likelihood of depression.

5 ²Scores range from 0 to 30; with higher scores indicating better cognitive performance

Safety Results

10 A total of 10 TEAEs were reported in 5 participants. There were no deaths, SAEs, severe TEAEs, or discontinuations due to TEAEs in any participant, nor were there any clinically significant changes in safety laboratory, ECG, physical/neurological examination, or vital sign results. All TEAEs (100%) were mild in intensity and most (8/10, 80%) were unrelated. The 2 possibly related TEAEs occurred in a single participant and included 1 report each of diarrhea and stomachache. All TEAEs recovered/resolved.

Pharmacokinetic Results

15 Pharmacokinetic parameters were obtained in all 12 participants for both the fed and fasted conditions, and the pharmacokinetic results are summarized in Table 14. 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.

Table 14. Summary of pharmacokinetic results from food effect study using a single dose of 150 mg of Compound 1

		Fasted (N=12)	Fed (N=12)
C_{max} (ng/mL)	Mean (SD)	468.44 (281.813)	670.83 (226.086)
	Median (Min;Max)	361.04 (80.31 ; 952.79)	684.14 (253.11 ; 984.38)
	CV (%)	60.2	33.7
T_{max} (h)	Mean (SD)	2.07 (0.981)	3.06 (1.496)
	Median (Min;Max)	2.01 (1.01 ; 4.00)	3.01 (1.00 ; 6.01)
	CV (%)	47.5	48.8
AUC_{last} (h•ng/mL)	Mean (SD)	4359.09 (4433.870)	6657.24 (5424.533)
	Median (Min;Max)	3218.15 (505.78 ; 17195.65)	4990.91 (1308.66 ; 21546.94)
	CV (%)	101.7	81.5
AUC₀₋₂₄ (h•ng/mL)	Mean (SD)	2920.81 (2139.906)	4594.69 (2218.529)
	Median (Min;Max)	2377.58 (424.60 ; 8224.00)	4095.30 (1308.64 ; 8615.86)
	CV (%)	73.3	48.3
T_{1/2} (h)	Mean (SD)	18.55 (6.541)	16.86 (7.750)
	Median (Min;Max)	18.90 (7.57 ; 34.20)	15.82 (5.90 ; 35.43)
	CV (%)	35.3	46

Abbreviations: AUC₀₋₂₄ = area under the plasma concentration time curve over the last 24 h dosing interval; AUC_{last} = area under the plasma concentration time curve to the last measurable plasma concentration; T_{1/2} = half-life; C_{max} = maximum concentration; T_{max} = time at maximum concentration; CV = coefficient of variation; SD = standard deviation.

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
5 “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,
10 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
15 (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
20 from the true scope and spirit of the disclosure in its broader aspects.

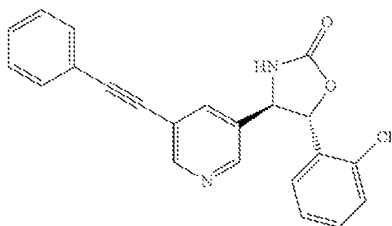
While the present disclosure has been described at some length and with some particularity with respect to the several described embodiments, it is not intended that it should be limited to any such particulars or embodiments or any particular embodiment, but it is to be construed with references to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

Other embodiments are in the claims.

What is claimed is:

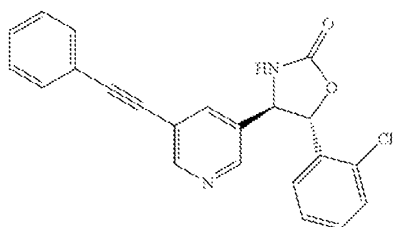
CLAIMS

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:



8. The method of any one of claims 1-7, wherein Form A of Compound 1 is administered.
9. The method of any one of claims 1-8, wherein the $C_{\max}$ is about 10 ng/mL to about 1000 ng/mL.
10. The method of any one of claims 1-9, wherein the $T_{\max}$ is about 0.75 h to about 7 h.
11. The method of any one of claims 1-10, wherein the AUC_{0-24} is about 50 ng•h/mL to about 7400 ng•h/mL.
12. The method of any one of claims 1-11, wherein the AUC_{last} is about 48 ng•h/mL to about 9200 ng•h/mL.
13. The method of any one of claims 1-12, wherein the $T_{1/2}$ is about 3 h to about 42 h.
14. The method of any one of claims 1-13, wherein the mGluR5 receptor occupancy is about 2% to about 99%.
15. The method of any one of claims 1-14, wherein the $C_{\max}$ is about 20 ng/mL to about 500 ng/mL.
16. The method of any one of claims 1-15, wherein the $T_{\max}$ is about 1 h to about 4 h.
17. The method of any one of claims 1-16, wherein the AUC_{0-24} is about 100 ng•h/mL to about 4000 ng•h/mL.
18. The method of any one of claims 1-17, wherein the AUC_{last} is about 50 ng•h/mL to about 5000 ng•h/mL.
19. The method of any one of claims 1-18, wherein the $T_{1/2}$ is about 7 h to about 21 h.
20. The method of any one of claims 1-19, wherein the mGluR5 receptor occupancy is about 4% to about 90%.
21. The method of any one of claims 1-20, wherein the $C_{\max}$ is about 22 ng/mL, about 126 ng/mL, about 190 ng/mL, about 290 ng/mL, about 456 ng/mL, or about 481 ng/mL.

22. The method of any one of claims 1-21, wherein the $T_{\max}$ is about 1.5 h, about 1.6 h, about 1.9 h, about 2.1, about 2.2 h, or about 3.4 h.
23. The method of any one of claims 1-22, wherein the AUC_{0-24} is about 100 ng•h/mL, about 930 ng•h/mL, about 960 ng•h/mL, about 1540 ng•h/mL, about 1720 ng•h/mL, about 3100 ng•h/mL, or about 3700 ng•h/mL.
24. The method of any one of claims 1-23, wherein the AUC_{last} is about 97 ng•h/mL, about 1157 ng•h/mL, about 1404 ng•h/mL, about 1961 ng•h/mL, about 4161 ng•h/mL, or about 4552 ng•h/mL.
25. The method of any one of claims 1-24, wherein the $T_{1/2}$ is about 7.4 h, about 14 h, about 14.4 h, about 15 h, about 18 h, about 19.4 h, or about 20.5 h.
26. The method of any one of claims 1-25, wherein the mGluR5 receptor occupancy is about 4%, about 7%, about 8%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 38%, about 39%, about 48%, about 50%, about 77%, about 80%, about 81%, about 82%, about 83%, about 84%, or about 85%.
27. 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:



, with food.

28. The method of claim 27, wherein the therapeutically effective amount is an amount sufficient to produce:
- a) a $C_{\max}$ (maximum concentration) of about 250 ng/mL to about 3000 ng/mL;
 - b) a $T_{\max}$ (time at maximum concentration) of about 0.8 h to about 6.2 h;
 - c) an AUC_{0-24} (area under the plasma concentration time curve from time zero to 24 hours) of about 1300 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 1200 ng•h/mL to about 120000 ng•h/mL; and/or
 - e) a $T_{1/2}$ (half-life) of about 5.5 h to about 36 h.

29. The method of claim 27 or 28, wherein Compound 1 is in a pharmaceutical composition.
30. The method of any one of claims 27-29, wherein the pharmaceutical composition further comprises a pharmaceutically acceptable plasticizer, binder, bulking agent, carrier, excipient, lubricant, disintegrant, and/or surfactant.
31. The method of any one of claims 27-30, wherein about 10 mg, 40 mg, 70 mg, 100 mg, 150 mg, or 200 mg of Compound 1 is administered.
32. The method of any one of claims 27-31, wherein Compound 1 is administered orally.
33. The method of any one of claims 27-32, wherein Compound 1 is administered once, twice, three, or four times a day.
34. The method of any one of claims 27-33, wherein Compound 1 is administered once a day.
35. The method of any one of claims 27-34, wherein Form A of Compound 1 is administered.
36. The method of any one of claims 28-35, wherein the $C_{\max}$ is about 250 ng/mL to about 3000 ng/mL.
37. The method of any one of claims 28-36, wherein the $T_{\max}$ is about 0.8 h to about 6.2 h.
38. The method of any one of claims 28-37, wherein the AUC_{0-24} is about 1300 ng•h/mL to about 60000 ng•h/mL.
39. The method of any one of claims 28-38, wherein the AUC_{last} is about 1200 ng•h/mL to about 120000 ng•h/mL.
40. The method of any one of claims 28-39, wherein the $T_{1/2}$ is about 5.5 h to about 36 h.
41. The method of any one of claims 28-40, wherein the $C_{\max}$ is about 400 ng/mL to about 2500 ng/mL or .
42. The method of any one of claims 28-41, wherein the $T_{\max}$ is about 1.5 h to about 4.6 h.

43. The method of any one of claims 28-42, wherein the AUC_{0-24} is about 2000 ng•h/mL to about 48000 ng•h/mL.
44. The method of any one of claims 28-43, wherein the AUC_{last} is about 1200 ng•h/mL to about 120000 ng•h/mL.
45. The method of any one of claims 28-44, wherein the $T_{1/2}$ is about 9 h to about 30 h.
46. The method of any one of claims 28-40 and 42-45, wherein the C_{max} is about 250 ng/mL, about 400 ng/mL, about 450 ng/mL, about 560 ng/mL, about 670 ng/mL, about 680 ng/mL, about 690 ng/mL, about 900 ng/mL, about 990 ng/mL, about 1600 ng/mL, about 2500 ng/mL, or about 3000 ng/mL.
47. The method of any one of claims 28-41 and 43-46, wherein the T_{max} is about 1 h, about 1.5 h, about 1.9 h, about 2 h, about 2.5 h, about 3 h, about 3.1 h, about 4.6 h, or about 6 h.
48. The method of any one of claims 28-42 and 44-47, wherein the AUC_{0-24} is about 1300 ng•h/mL, about 2370 ng•h/mL, about 4100 ng•h/mL, about 4600 ng•h/mL, about 5700 ng•h/mL, about 6900 ng•h/mL, about 8620 ng•h/mL, about 8900 ng•h/mL, about 28500 ng•h/mL, about 48000 ng•h/mL, or about 60000 ng•h/mL.
49. The method of any one of claims 28-43 and 45-48, wherein the AUC_{last} is about 1230 ng•h/mL, 1310 ng•h/mL, about 4600 ng•h/mL, about 4990 ng•h/mL, about 6660 ng•h/mL, about 12100 ng•h/mL, about 14000 ng•h/mL, about 21600 ng•h/mL, about 65000 ng•h/mL, about 116000 ng•h/mL, or about 120000 ng•h/mL.
50. The method of any one of claims 28-44 and 46-49, wherein the $T_{1/2}$ is about 5.9 h, about 9.2 h, about 13.2 h, about 13.8 h, about 15.9 h, about 16.9 h, about 20 h, about 24.7 h, about 27.2 h, about 28.8 h, or about 35.5 h.
51. The method of any one of claims 28-40, 42-46, and 48-50, wherein the C_{max} is 400 ng/mL to about 900 ng/mL.
52. The method of any one of claims 28-40, 42-46, and 48-50, wherein the C_{max} is from about 250 to about 350, from about 250 to about 1000, from about 350 to about 450, from about 450 to about 550, from about 550 to about 650, from about 650 to about 750, from about 750 to about 850, from about 850 to about 950, from about 950 to about 1000, from about 1000 to about 2000, from about 700 to about 2500, from about 600 to about 3000 ng/mL, or from about 2000 to about 3000 ng/mL.

53. The method of any one of claims 28-41, 43-46, and 48-52, wherein the $T_{\max}$ is from about 0.8 to about 1.0, from about 1.0 to about 1.2, from about 1.2 to about 1.4, from about 1.4 to about 1.6, from about 1.6 to about 1.8, from about 1.8 to about 2.0, from about 2.0 to about 2.2, from about 2.2 to about 2.4, from about 2.4 to about 2.6, from about 2.6 to about 2.8, from about 2.8 to about 3.0, from about 3.0 to about 3.2, from about 3.2 to about 3.4, from about 3.4 to about 3.6, from about 3.6 to about 3.8, from about 3.8 to about 4.0, from about 4.0 to about 4.2, from about 4.2 to about 4.4, from about 4.4 to about 4.6, from about 4.6 to about 4.8, from about 4.8 to about 5.0, from about 5.0 to about 5.2, from about 5.2 to about 5.4, from about 5.4 to about 5.6, from about 5.6 to about 5.8, from about 5.8 to about 6.0, or from about 6.0 to about 6.2 h.

54. The method of any one of claims 28-42, 44-47, and 49-53, wherein the AUC_{0-24} is from about 5000 to about 60000 ng•h/mL or about 1200 to about 9000 ng•h/mL or about 8800 to about 48000 ng•h/mL.

55. The method of any one of 28-42, 44-47, and 49-53, wherein the AUC_{0-24} is from about 1300 to about 1800, from about 1800 to about 2300, from about 2300 to about 2800, from about 2800 to about 3300, from about 3300 to about 3800, from about 3800 to about 4300, from about 4300 to about 4800, from about 4800 to about 5300, from about 5300 to about 5800, from about 5800 to about 6300, from about 6300 to about 6800, from about 6800 to about 7300, from about 7300 to about 7800, from about 7800 to about 8300, from about 8300 to about 8800, from about 8800 to about 9000, from about 9000 to about 10000, from about 10000 to about 11000, from about 11000 to about 12000, from about 12000 to about 13000, from about 13000 to about 14000, from about 14000 to about 15000, from about 15000 to about 16000, from about 16000 to about 17000, from about 17000 to about 18000, from about 18000 to about 19000, from about 19000 to about 20000, from about 20000 to about 21000, from about 21000 to about 22000, from about 22000 to about 23000, from about 23000 to about 24000, from about 24000 to about 25000, from about 25000 to about 26000, from about 26000 to about 27000, from about 27000 to about 28000, from about 28000 to about 29000, from about 29000 to about 30000, from about 30000 to about 31000, from about 31000 to about 32000, from about 32000 to about 33000, from about 33000 to about 34000, from about 34000 to about 35000, from about 35000 to about 36000, from about 36000 to about 37000, from about 37000 to about 38000, from about 38000 to about 39000, from about 39000 to about 40000, from about 40000 to about 41000, from about 41000 to about 42000, from about 42000 to about 43000, from about 43000 to about 44000, from about 44000 to about 45000, from about 45000 to about 46000, from about 46000 to about 47000, from about 47000 to about 48000, from about 48000 to about 49000, from about 49000 to about 50000, from about 50000 to about 51000, from about 51000 to about 52000, from about 52000 to about 53000, from about 53000 to about 54000, from about 54000 to

about 55000, from about 55000 to about 56000, from about 56000 to about 57000, from about 57000 to about 58000, from about 58000 to about 59000, or from about 59000 to about 60000 ng•h/mL.

56. The method of any one of claims 28-43, 45-48, and 50-55, wherein the AUC_{last} is from about 1200 to about 22000 ng•h/mL or about 13500 to about 116000 ng•h/mL or about 5500 to about 120000 ng•h/mL.

57. The method of any one of claims 28-43, 45-48, and 50-55, wherein the AUC_{last} is from about 1200 to about 2200, from about 2200 to about 3200, from about 3200 to about 4200, from about 4200 to about 5200, from about 5200 to about 6200, from about 6200 to about 7200, from about 7200 to about 8200, from about 8200 to about 9200, from about 9200 to about 10200, from about 10200 to about 11200, from about 11200 to about 12200, from about 12200 to about 13200, from about 13200 to about 14200, from about 14200 to about 15200, from about 15200 to about 16200, from about 16200 to about 17200, from about 17200 to about 18200, from about 18200 to about 19200, from about 19200 to about 20200, from about 20200 to about 21200, from about 21200 to about 22000, from about 22000 to about 32000, from about 32000 to about 42000, from about 42000 to about 52000, from about 52000 to about 62000, from about 62000 to about 72000, from about 72000 to about 82000, from about 82000 to about 92000, from about 92000 to about 102000, from about 102000 to about 112000, or from about 112000 to about 120000 ng•h/mL.

58. The method of any one of claims 28-44, 46-49, and 51-57, wherein the $T_{1/2}$ is from about 5.5 to about 7.5, from about 7.5 to about 9.5, from about 9.5 to about 11.5, from about 11.5 to about 13.5, from about 13.5 to about 15.5, from about 15.5 to about 17.5, from about 17.5 to about 19.5, from about 19.5 to about 21.5, from about 21.5 to about 23.5, from about 23.5 to about 25.5, from about 25.5 to about 27.5, from about 27.5 to about 29.5, from about 29.5 to about 31.5, from about 31.5 to about 33.5, from about 33.5 to about 35.5, from about 35.5 to about 36 h.

59. The method of any one of claims 1-26, wherein the C_{max} is from about 10 to about 30, about 60 to about 180, about 100 to about 270, about 150 to about 450, about 250 to about 700, or about 300 to about 600 ng/mL.

60. The method of any one of claims 1-26, wherein the C_{max} is from about 22 to about 480, from about 30 to about 190, from about 40 to about 190, from about 50 to about 190, from about 60 to about 190, from about 70 to about 190, from about 80 to about 190, from about 90 to about 190, from about 100 to about 190, from about 110 to about 190, from about 120 to about 190, from about 130 to about 190, from about 140 to about 190, from about 150 to about 190, from about 160 to about 190, from about 170 to about 190, from about 180 to about 190, from about 125 to about 480, from about 130 to about 475,

from about 135 to about 470, from about 140 to about 465, from about 145 to about 460, from about 150 to about 455, from about 155 to about 450, from about 160 to about 445, from about 165 to about 440, from about 170 to about 435, from about 175 to about 430, from about 180 to about 425, from about 185 to about 420, from about 190 to about 415, from about 195 to about 410, from about 200 to about 405, from about 205 to about 400, from about 210 to about 395, from about 215 to about 390, from about 220 to about 385, from about 225 to about 380, from about 230 to about 375, from about 235 to about 370, from about 240 to about 365, from about 245 to about 360, from about 250 to about 355, from about 255 to about 350, from about 260 to about 345, from about 265 to about 340, from about 270 to about 335, from about 275 to about 330, from about 280 to about 325, from about 285 to about 320, from about 290 to about 315, from about 295 to about 310, from about 300 to about 305, from about 300 to about 480, from about 400 to about 480, or from about 450 to about 480 ng/mL.

61. The method of any one of claims 1-26 and 59-60, wherein the $T_{\max}$ is from about 1 to about 4.5, from about 1.3 to about 1.7, from about 1.5 to about 1.8, from about 1.7 to about 2.1, from about 1.9 to about 2.3, from about 2.0 to about 2.4, from about 2.5 to about 2.7, from about 2.7 to about 2.9, from about 2.9 to about 3.1, from about 3.1 to about 3.3, or from about 3.2 to about 3.6 h.

62. The method of any one of claims 1-26 and 59-61, wherein the AUC_{0-24} is about 50 to about 150, about 600 to about 1300, about 300 to about 1600, about 750 to about 2200, about 1500 to about 4700, or about 2500 to about 5000 ng•h/mL.

63. The method of any one of claims 1-26 and 59-61, wherein the AUC_{0-24} is from about 100 to about 3700, from about 100 to about 250, from about 280 to about 400, from about 420 to about 530, from about 560 to about 610, from about 630 to about 700, from about 720 to about 810, from about 850 to about 920, from about 930 to about 960, from about 960 to about 1250, from about 1300 to about 1600, from about 1680 to about 2050, from about 2150 to about 2400, from about 2480 to about 2800, from about 2900 to about 3150, from about 3250 to about 3500, or from about 3600 to about 3700 ng•h/mL.

64. The method of any one of claims 1-26 and 59-63, wherein the AUC_{last} is from about 50 to about 150, about 400 to about 2400, about 750 to about 1550, about 1000 to about 3000, about 2000 to about 6000, or about 3000 to about 6000 ng•h/mL.

65. The method of any one of claims 1-26 and 59-63, wherein the AUC_{last} is from about 97 to about 4552, from about 97 to about 185, from about 220 to about 320, from about 360 to about 460, from about 505 to about 600, from about 640 to about 735, from about 775 to about 875, from about 910 to about 1010, from about 1050 to about 1157, from about 1157 to about 1404, from about 1680 to about 1961,

from about 1780 to about 2280, from about 2350 to about 2900, from about 3030 to about 3550, from about 3650 to about 4180, or from about 4260 to about 4552 ng•h/mL.

66. The method of any one of claims 1-26 and 59-65, wherein the $T_{1/2}$ is from about 2 to about 13, about 9 to about 20, about 10 to about 18, about 13 to about 25, about 14 to about 22, or about 14 to about 27 h.

67. The method of any one of claims 1-26 and 59-65, wherein the $T_{1/2}$ is from about 7.4 to about 20.5, from about 7.4 to about 8.7, from about 9.2 to about 10.8, from about 11.3 to about 12.6, from about 13.2 to about 14.7, from about 15.1 to about 16.5, from about 17.0 to about 18.3, or from about 18.8 to about 20.5 h.

68. The method of any one of claims 1-26 and 59-67, wherein the mGluR5 receptor occupancy (RO) is from about 3% to about 99%, from about 4% to about 99%, from about 5% to about 99%, from about 10% to about 99%, from about 15% to about 99%, from about 20% to about 99%, from about 25% to about 99%, from about 30% to about 99%, from about 35% to about 99%, from about 40% to about 99%, from about 45% to about 99%, from about 50% to about 99%, from about 55% to about 99%, from about 60% to about 99%, from about 65% to about 99%, from about 70% to about 99%, from about 75% to about 99%, from about 80% to about 99%, from about 85% to about 99%, from about 90% to about 99%, from about 95% to about 99%, from about 5% to about 10%, from about 5% to about 20%, from about 5% to about 30%, from about 5% to about 40%, from about 5% to about 50%, from about 5% to about 60%, from about 5% to about 70%, from about 5% to about 80%, from about 5% to about 90%, from about 5% to about 95%, from about 10% to about 95%, from about 10% to about 90%, from about 10% to about 80%, from about 20% to about 70%, from about 30% to about 60%, from about 40% to about 50%, from about 50% to about 90%, from about 60% to about 90%, from about 70% to about 90%, from about 80% to about 90%, from about 2% to about 25%, from about 2% to about 10%, from about 50% to about 85%, from about 50% to about 80%, from about, 50% to about 75%, from about 40% to about 50%, from about 2% to about 25%, from about 25% to about 50%, from about 25% to about 75%, or from about 25% to about 90%.

69. The method of any one of claims 1-26 and 59-67, wherein the mGluR5 receptor occupancy (RO) is at least 75%, e.g., at least 80%, 85%, 90%, or 95%.