CLAIMS

1. Use of a therapeutically effective amount of ulotaront or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating a neuropsychiatric disorder in a human subject in need thereof without significant physical dependency upon the cessation of treatment, wherein the ulotaront is to be selected, and is to be administered to the subject for an effective period until ceasing administration, whereupon the subject does not develop physical dependency that is significantly greater than that caused by placebo, optionally wherein the subject is at risk of developing, or has previously experienced, physical dependency.
2. Use of ulotaront or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating a neuropsychiatric disorder in a human subject in need thereof, wherein:
    a. a therapeutically effective amount of ulotaront or a pharmaceutically acceptable salt thereof is to be administered to the subject for an effective period, and
    b. ulotaront administration is to be ceased after the effective period, wherein the subject does not develop significant physical dependency upon the cessation of treatment,

    optionally wherein the subject is at risk of developing, or has previously experienced, physical dependency.
3. Use of ulotaront or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating a neuropsychiatric disorder in a human subject in need thereof, wherein:
    a. a therapeutically effective amount of ulotaront or a pharmaceutically acceptable salt thereof is to be administered to the subject for an effective period, and
    b. ulotaront administration is to be ceased after the effective period;

    wherein the use occurs without emergence of one or more withdrawal-related adverse event(s), optionally wherein the subject does not develop significant physical dependency upon the cessation of treatment, optionally wherein the subject is at risk of developing, or the subject has previously experienced, physical dependency.
4. The use according to claim 2 or 3, wherein, upon the cessation of treatment, the subject does not develop physical dependency that is significantly greater than that caused by placebo.
5. The use of any one of claims 1 to 3, wherein significant physical dependency is defined as the occurrence of a withdrawal-related adverse event comprising a clinically significant increase in the total score of the 20 item Physician Withdrawal Checklist (PWC-20); or wherein significant physical dependency is defined as the occurrence of a withdrawal-related adverse event comprising an increase in the total score of the 20 item Physician Withdrawal Checklist

(PWC-20) of more than 4.71; or wherein significant physical dependency is defined as the occurrence of a withdrawal-related adverse event defined by Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query: Drug withdrawal; or wherein significant physical dependency is defined as the occurrence of a withdrawal-related adverse event comprising one or more symptom(s) of neuropsychiatric medication withdrawal selected from somatic symptoms, mood symptoms, cognitive symptoms, fatigue symptoms, and gastrointestinal symptoms; or wherein significant physical dependency is defined as the occurrence of a withdrawal-related adverse event selected from cholinergic withdrawal symptoms, dopaminergic withdrawal symptoms (nigrostriatal), serotonin withdrawal symptoms, histaminergic withdrawal symptoms, dopaminergic withdrawal symptoms (mesolimbic or striatal), and adrenergic withdrawal symptoms.

6. The use of any one of claims 1-3, wherein the effective period is a term ≥ 2 weeks, ≥ 4 weeks, ≥ 8 weeks, ≥ 12 weeks, ≥ 26 weeks, ≥ one year, or ≥ two years; or wherein the effective period is sufficient for a clinically significant improvement from the neuropsychiatric disorder; or wherein the effective period is sufficient for full recovery from the neuropsychiatric disorder; or wherein the effective period is sufficient for full recovery from the neuropsychiatric disorder, as evidenced by a lack of diagnosis of the neuropsychiatric disorder under criteria set forth in DSM-5; or wherein the effective period is sufficient for full recovery from the neuropsychiatric disorder for a term ≥ 3 months, ≥ 6 months, ≥ 1 year, ≥ 18 months, or ≥ 2 years; or wherein the effective period is sufficient to judge the ineffectiveness of ulotaront against the subject's neuropsychiatric disorder; or wherein the effective period is sufficient to judge the ineffectiveness of ulotaront against the subject's neuropsychiatric disorder, as evidenced by the failure of a clinically significant improvement from the neuropsychiatric disorder; or wherein the effective period is sufficient to judge the ineffectiveness of ulotaront against the subject's neuropsychiatric disorder, as evidenced by a continued diagnosis of the neuropsychiatric disorder under criteria set forth in DSM-5.

7. The use of any one of claims 1-3, wherein the effective period is sufficient to judge the ineffectiveness of ulotaront against the subject's neuropsychiatric disorder, as evidenced by one or more of:

   a. inadequate clinical response for acute symptoms despite dose optimization and adequate duration of treatment trial;

   b. poor control of chronic symptoms and persistence of functional disabilities during maintenance therapy;

   c. relapse despite adequate prophylactic or maintenance treatment of the neuropsychiatric disorder; and

d. persistence of certain symptoms of the neuropsychiatric despite adequate doses of ulotaront.

8. The use of any one of claims 1-3, wherein the ceasing is abrupt.

9. The use of claim 1-3, wherein the ceasing is tapered.

10. The use of any one of claims 1-3, wherein the subject is at risk of one or more symptom(s) or syndrome(s) of neuropsychiatric medication withdrawal.

11. The use of any one of claims 1-3, wherein the subject has previously experienced one or more symptom(s) or syndrome(s) of neuropsychiatric medication withdrawal.

12. The use of any one of claims 1-3, wherein the use occurs without emergence of one or more symptom(s) or syndrome(s) of neuropsychiatric medication withdrawal.

13. The use of any one of claims 1-3, wherein the subject is at risk of, or the subject has previously experienced, or the use occurs without emergence of, a withdrawal-related adverse event comprising a clinically significant increase in the total score of the 20 item Physician Withdrawal Checklist (PWC-20); or a withdrawal-related adverse event comprising an increase in the total score of the 20 item Physician Withdrawal Checklist (PWC-20) of more than 4.71; or a withdrawal-related adverse event defined by Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query: Drug withdrawal.

14. The use of any one of claims 1-3, wherein the subject is at risk of, or the subject has previously experienced, or the use occurs without emergence of, a withdrawal-related adverse event comprising one or more symptom(s) of neuropsychiatric medication withdrawal selected from somatic symptoms, mood symptoms, cognitive symptoms, fatigue symptoms, and gastrointestinal symptoms.

15. The use of any one of claims 1-3, wherein the subject is at risk of, or the subject has previously experienced, or the use occurs without emergence of, a withdrawal-related adverse event comprising one or more somatic symptom(s) of neuropsychiatric medication withdrawal selected from (i) insomnia, (ii) diaphoresis, (iii) tremor–tremulousness, (iv) headaches, and (v) muscle aches or stiffness; or a withdrawal-related adverse event comprising one or more mood symptom(s) of neuropsychiatric medication withdrawal selected from (i) anxiety–nervousness, (ii) irritability, (iii) dysphoric mood–depression, (iv) restlessness–agitation, and (v) difficulty concentrating, remembering; or a withdrawal-related adverse event comprising one or more cognitive symptom(s) of neuropsychiatric medication withdrawal selected from (i) poor coordination, (ii) dizziness-lightheadedness, (iii) increased acuity for sound, smell, touch, and (iv) depersonalization–derealization; or a withdrawal-related adverse event comprising one or more fatigue symptom(s) of neuropsychiatric medication withdrawal selected from (i) fatigue–lethargy–lack of energy, (ii) weakness, and (iii) paresthesias; or a withdrawal-related adverse

event comprising one or more gastrointestinal symptom(s) of neuropsychiatric medication withdrawal selected from (i) loss of appetite, (ii) nausea-vomiting, and (iii) diarrhea.

16. The use of any one of claims 1-3, wherein the subject is at risk of, or the subject has previously experienced, or the use occurs without emergence of, a withdrawal-related adverse event comprising one or more withdrawal symptom(s) of mild, moderate, or severe magnitude.

17. The use of any one of claims 1-3, wherein the subject is at risk of, or the subject has previously experienced, or the use occurs without emergence of, a withdrawal-related adverse event comprising one or more syndrome(s) of neuropsychiatric medication withdrawal selected from:

    a. cholinergic syndrome evidenced by one or more of nausea, vomiting, headache, restlessness, anxiety, insomnia, fatigue, malaise, myalgia, diaphoresis, rhinitis, paresthesia, and loose bowels;

    b. dopaminergic syndrome evidenced by one or more of withdrawal dyskinesia, akathisia, dystonia, tardive dyskinesia; and

    c. rebound psychosis evidenced by one or more of psychosis above pre-treatment levels, illusions, hallucinations, and catatonia.

18. The use of any one of claims 1-3, wherein the subject is at risk of, or the subject has previously experienced, or the use occurs without emergence of, a withdrawal-related adverse event selected from cholinergic withdrawal symptoms, dopaminergic withdrawal symptoms (nigrostriatal), serotonin withdrawal symptoms, histaminergic withdrawal symptoms, dopaminergic withdrawal symptoms (mesolimbic or striatal), and adrenergic withdrawal symptoms.

19. The use of any one of claims 1-3, wherein the subject is at risk of, or the subject has previously experienced, or the use occurs without emergence of, a withdrawal-related adverse event comprising cholinergic withdrawal symptoms selected from agitation, insomnia, anxiety or depression, dizziness, light-headedness, tachycardia, nausea, vomiting, salivation, diarrhea, abdominal cramp, tremor, parkinsonism, restlessness, myalgia, rigidity, paresthesia, fear, hallucinations, confusion or disorientation, hypothermia, and sweating; or a withdrawal-related adverse event comprising dopaminergic withdrawal symptoms (nigrostriatal) selected from withdrawal dyskinesia, parkinsonism, neuroleptic malignant syndrome, and akathisia; or a withdrawal-related adverse event comprising serotonin withdrawal symptoms selected from flu-like symptoms, sweating or chills, dizziness, light-headedness or tachycardia, paresthesia, electric chock sensations, anxiety, agitation, low mood, insomnia, nightmares, nausea, vomiting, diarrhea, confusion, and decreased concentration; or a withdrawal-related adverse event comprising histaminergic withdrawal symptoms selected from irritability, insomnia, agitation, depressed affect, loss of appetite or nausea, tremulousness, incoordination, and lethargy or amnesia; or a withdrawal-related adverse event comprising dopaminergic

withdrawal symptoms (mesolimbic or striatal) selected from auditory hallucinations, persecutory delusions, and other psychotic symptoms; or a withdrawal-related adverse event comprising adrenergic withdrawal symptoms selected from headache, anxiety or agitation, hypertension, tachycardia, angina, palpitations, risk of myocardial infarction, pre-syncope, tremulousness, and sweating.

20. The use of any one of claims 1-3, wherein the subject is at risk of one or more withdrawal related adverse events.

21. The use of any one of claims 1-3, wherein the subject has previously experienced one or more withdrawal related adverse events.

22. The use of any one of claims 1-3, wherein the use occurs without emergence of one or more withdrawal related adverse events.

23. The use of any one of claims 1-3 wherein, after the effective period, ulotaront administration is to be ceased for the neuropsychiatric disorder, for a period ≥ 3 months, ≥ 6 months, ≥ 1 year, ≥ 18 months, or ≥ 2 years.

24. The use of any one of claims 1-3, wherein the therapeutically effective amount is an oral dose of 25-150 mg/day or 25-100 mg/day or 50-125 mg/day or 50-100 mg/day; or wherein the therapeutically effective amount is an oral dose of 25 mg/day, 50 mg/day, 75 mg/day, 100 mg/day, 125 mg/day, or 150 mg/day.

25. The use of any one of claims 1-3, wherein the therapeutically effective amount is to be administered once daily in the fed or fasted state.

26. The use of any one of claims 1-3, wherein the ulotaront is to be administered as the hydrochloride salt.

27. The use of any one of claims 1-3, wherein the neuropsychiatric disorder is selected from schizophrenia, schizophrenia spectrum disorder, acute schizophrenia, chronic schizophrenia, NOS schizophrenia, schizoid personality disorder, schizotypal personality disorder, delusional disorder, psychosis, psychotic disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to a general medical condition, drug-induced psychosis (e.g., cocaine, alcohol, amphetamine), psychoaffective disorder, aggression, delirium, Parkinson's psychosis, excitative psychosis, Tourette's syndrome, organic or NOS psychosis, seizure, agitation, post-traumatic stress disorder, behavior disorder, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, dyskinesias, Huntington's disease, dementia, mood disorder, anxiety, affective disorders (e.g., depression, e.g., major depressive disorder and dysthymia; bipolar disorder, e.g., bipolar depressive disorder; manic disorder; seasonal affective disorder; and attention deficit disorder (ADD) and attention deficit hyperactivity disorder (ADHD)), obsessive-compulsive disorder, vertigo, epilepsy, pain (e.g., neuropathic pain, sensitization accompanying neuropathic pain, and inflammatory pain), fibromyalgia, migraine, cognitive

impairment, movement disorder, restless leg syndrome (RLS), multiple sclerosis, sleep disorder, sleep apnea, narcolepsy, excessive daytime sleepiness, jet lag, drowsy side effect of medications, insomnia, substance abuse or dependency (e.g., nicotine, cocaine), addiction, eating disorder, sexual dysfunction, hypertension, emesis, Lesche-Nyhane disease, Wilson's disease, autism, Huntington's chorea, and premenstrual dysphoria.

28. The use of any one of claims 1-3, wherein the neuropsychiatric disorder is selected from schizophrenia, depression, and anxiety.

29. The use of any one of claims 1-3, wherein the neuropsychiatric disorder is schizophrenia.

30. The use of any one of claims 1-3, wherein the neuropsychiatric disorder is selected from bipolar depression and major depression.

31. The use of any one of claims 1-3, wherein the neuropsychiatric disorder is anxiety.