and clinically tolerable pharmacological effects, for use in the treatment of PD, AD, and other dopaminergic CNS disorders.

Summary

In one aspect of the present disclosure, there is provided a use of LY3154207, or a pharmaceutical composition thereof, in the manufacture of a medicament for the treatment of a dopaminergic central nervous system disorder in a patient, wherein one or more doses of LY3154207, or pharmaceutical compositions thereof, of about 0.5 mg to about 75 mg are to be administered per day, up to a maximum total dose of 75 mg per day.

Description

The present invention provides clinical therapeutic dosing regimens and methods of using LY3154207, and/or pharmaceutical compositions thereof, for use in the treatment of dopaminergic central nervous system disorders. A dopaminergic central nervous system disorder, as defined herein, is one selected from the group consisting of Lewy body dementia (LBD), Parkinson's Disease, Alzheimer's' Disease, Vascular Dementia, Schizophrenia, ADHD, Depression, Autism, chronic musculoskeletal pain, fibromyalgia, cognitive impairment disorders, sleep disorders, excessive daytime sleepiness, narcolepsy, shift work disorder, traumatic brain injury, chronic traumatic encephalopathy, obesity and appetite regulation, mood disorders, lethargy, apathy, and addiction disorders. In the dosing regimens of the present invention, and as used herein, LY3154207 is 2-(2,6-dichlorophenyl)-1-[(1S,3R)-3-(hydroxymethyl)-5-(3-hydroxy-3-methylbutyl)-1-methyl-3,4-dihydroisoquinolin-2(1H)-yl]ethanone in any form, and includes crystalline and co-crystalline forms thereof, in particular the benzoic acid co-crystalline form, and/or pharmaceutical compositions comprising these agents. The present invention provides a method for use of LY3154207 in the treatment of a dopaminergic central nervous system disorder in a patient, comprising administering to said patient a dose of about 0.5 mg to about 75 mg, up to a maximum total dose of 75 mg per day, of LY3154207, or pharmaceutical composition thereof. The present invention further provides a method for use of LY3154207 in the treatment of a dopaminergic central nervous system disorder in a patient, comprising administering to said patient a dose of about 0.5 mg to about

15 mg, up to a maximum total dose of 15 mg per day, of LY3154207, or pharmaceutical composition thereof.

LY3154207, and a related D1 PAM compound referred to herein as DPTQ, have been studied in primates and/or human phase I studies of healthy volunteers and PD patients, and LY3154207 has entered a phase II clinical study for Parkinson's Disease Dementia (referred to as PRESENCE, NCT03305809). Studies including those described in Example 1 (Phase I Clinical Studies of LY3154207) and Example 2 (Spatial Working Memory in the Adult Rhesus Monkey) have resulted in the concept that LY3154207, when used according to the dosing regimens of the present invention, may induce a surprisingly marked improvement in signs and symptoms of dopaminergic CNS disorders, such as treatment of PD or AD

We claim:

1. Use of LY3154207, or a pharmaceutical composition thereof, in the manufacture of a medicament for the treatment of a dopaminergic central nervous system disorder in a patient, wherein one or more doses of LY3154207, or pharmaceutical compositions thereof, of about 0.5 mg to about 75 mg are to be administered per day, up to a maximum total dose of 75 mg per day.
2. The use according to claim 1, wherein one or more doses of LY3154207, or pharmaceutical compositions thereof, of about 0.5 mg to about 15 mg are to be administered per day, up to a maximum total dose of 15 mg per day.
3. The use according to claim 1, wherein a dose selected from the group consisting of 0.5 mg, 1 mg, 2 mg, 3 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 50 mg, and 75 mg of LY3154207, or pharmaceutical composition thereof is to be administered per day.
4. The use according to claim 1, wherein one or more doses of LY3154207, or pharmaceutical compositions thereof, of about 0.5 mg to about 75 mg are to be administered per day, up to a maximum total dose of 75 mg per day, wherein the patient is to be treated for at least 21 consecutive days.
5. The use according to claim 4, wherein one or more doses of about 0.5 mg to about 15 mg of LY3154207, or pharmaceutical compositions thereof, are to be chronically administered per day, up to a maximum total dose of 15 mg per day.
6. The use according to claim 4, wherein a dose selected from the group consisting of 0.5 mg, 1 mg, 2 mg, 3 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 50 mg, and 75 mg of LY3154207, or pharmaceutical composition thereof, is to be chronically administered per day.
7. The use according to any one of claims 1-6, wherein said dopaminergic central nervous system disorder is selected from the group consisting of Lewy body dementia (LBD), Parkinson’s Disease, Alzheimer’s Disease, Vascular Dementia, Schizophrenia, ADHD, Depression, Autism, chronic musculoskeletal pain, fibromyalgia, cognitive impairment disorders, excessive daytime sleepiness, narcolepsy, shift work disorder, traumatic brain injury, chronic traumatic encephalopathy, obesity and appetite regulation, mood disorders, lethargy, apathy, and addiction disorders.
8. The use according to claim 3, wherein a dose of 0.5 mg of LY3154207, or pharmaceutical compositions thereof, is to be administered per day.

9. The use according to claim 3, wherein a dose of 1 mg of LY3154207, or pharmaceutical compositions thereof, is to be administered per day.
10. The use according to claim 3, wherein a dose of 2 mg of LY3154207, or pharmaceutical compositions thereof, is to be administered per day.
11. The use according to claim 3, wherein a dose of 3 mg of LY3154207, or pharmaceutical compositions thereof, is to be administered per day.
12. The use according to claim 3, wherein a dose of 5 mg of LY3154207, or pharmaceutical compositions thereof, is to be administered per day.
13. The use according to claim 3, wherein a dose of 10 mg of LY3154207, or pharmaceutical compositions thereof, is to be administered per day.
14. The use according to claim 3, wherein a dose of 15 mg of LY3154207, or pharmaceutical compositions thereof, is to be administered per day.
15. The use according to claim 3, wherein a dose of 20 mg of LY3154207, or pharmaceutical compositions thereof, is to be administered per day.
16. The use according to claim 3, wherein a dose of 30 mg of LY3154207, or pharmaceutical compositions thereof, is to be administered per day.
17. The use according to claim 3, wherein a dose of 50 mg of LY3154207, or pharmaceutical compositions thereof, is to be administered per day.
18. The use according to claim 3, wherein a dose of 75 mg of LY3154207, or pharmaceutical compositions thereof, is to be administered per day.
19. The use according to claim 7, wherein said dopaminergic central nervous system disorder is Parkinson's Disease.
20. The use according to claim 19, wherein the patient meets the revised MDS criteria for PD and mild-to-moderate dementia as defined by a decline in cognitive function with an MoCA score between 10 and 23.
21. The use according to claim 7, wherein said dopaminergic central nervous system disorder is Alzheimer's Disease.
22. The use according to claim 7, wherein said dopaminergic central nervous system disorder is obesity.