control disorders have also been reported in a significant percentage of RLS patients using these drugs for long term.

Thus, there is a need for more effective treatment of RLS and its symptoms without the undesirable side effects associated with existing drug therapy.

The present disclosure addresses this need and describes leucine and acetyl-leucine for treating RLS.

In an aspect, there is provided the use of leucine, acetyl-leucine, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating restless legs syndrome (RLS) or one or more symptoms associated with RLS in a subject in need thereof, wherein the RLS is primary RLS.

In another aspect, there is provided the use of a therapeutically effective amount of leucine, acetyl-leucine, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for diminishing, inhibiting, or eliminating one or more symptoms of restless legs syndrome (RLS) in a subject in need thereof, wherein the RLS is primary RLS.

Acetyl-leucine in racemate form (acetyl-DL-leucine) and salts of the same have been used in the treatment of vertigo of various origins, notably Meniere's vertigo and vertigo of inflammatory (vestibular neuritis) or toxic origin. For example, acetyl-leucine is marketed by Pierre Fabre Medicament in racemate form as an anti-vertigo medicament under the name Tanganil®. Clinical results of Tanganil® reported by various authors demonstrate an improvement in vertigo symptomology in more than 95% of cases, including the disappearance of vertigo attacks.

Acetyl-DL-leucine has been used in France to treat acute vertigo since 1957. A FDG-µPET study in a rat model of an acute unilateral labyrinthectomy (Zwergal *et al.* (2016) *Brain Struct Funct*; 221(1): 159-70) showed a significant effect of an L-enantiomer, N-acetyl-L-leucine, on postural compensation by activation of the vestibulo-cerebellum and a deactivation of the posterolateral thalamus (Gunther *et al.* (2015) *PLoS One*; 10(3): e0120891). The symptomatic improvement of cerebellar ataxia using acetyl-DL-leucine was shown in a case series with cerebellar patients (Strupp *et al.* (2013) *J*

Neurol; 260(10): 2556-61). Another case series did not find benefit (Pelz *et al.* (2015) *J Neurol*; 262(5): 1373-5). Quantitative gait analysis showed that acetyl-DL-leucine improved temporal gait variability in patients with cerebellar ataxia (Schniepp *et al.* (2015) *Cerebellum*; 3:8). In a one-month study involving 12 patients with Niemann-Pick Type C (NPC), symptomatic improvement of ataxia was shown (Bremova *et al.* (2015) *Neurology*; 85(16): 1368-75). Further, a PET study in patients with ataxia given acetyl-DL-leucine demonstrated an increased metabolism in the midbrain and lower brainstem in responders (Becker-Bense *et al.* (2015) *Abstract EAN*).

Acetyl-leucine, however, is not known to treat RLS. As evidenced by the examples described herein, it has been found in accordance with the present disclosure that leucine, acetyl-leucine, or a pharmaceutically acceptable salt thereof can be used in a

Claims:

1. Use of leucine, acetyl-leucine, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating restless legs syndrome (RLS) or one or more symptoms associated with RLS in a subject in need thereof, wherein the RLS is primary RLS.

2. Use according to claim 1, wherein the a therapeutically effective amount of the leucine, acetyl-leucine, or pharmaceutically acceptable salt thereof is to be administered to the subject.

3. Use according to claim 2, wherein the adminstration occurs over time and the subject's International Restless Leg Syndrome Rating Scale (IRLS) is reduced by at least 10% after the adminstration compared to a baseline.

4. Use according to claim 3, wherein the subject's International Restless Leg Syndrome Rating Scale (IRLS) is reduced by at least 50% after the adminstration compared to the baseline.

5. Use according to any of claims 1-4, wherein the leucine is DL-leucine or the acetyl-leucine is acetyl-DL-leucine.

6. Use according to any of claims 1-4, wherein the leucine or acetyl-leucine has an enantiomeric excess of the L-enantiomer or the D-enantiomer.

7. Use according to any of claims 1-6, wherein the acetyl-leucine is to be administered to the subject in need thereof at a therapeutically effective amount of from 1 g to 15 g per day, from 1 g to 10 g per day, from 1.5 g to 7 g per day, from 4 g to 6 g per day, or from 4 g to 5 g per day.

8. Use of a therapeutically effective amount of leucine, acetyl-leucine, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for diminishing, inhibiting, or eliminating one or more symptoms of restless legs syndrome (RLS) in a subject in need thereof, wherein the RLS is primary RLS.

9. The use of claim 8, wherein the one or more symptoms are chosen from lower leg sensations, periodic leg movements of sleep, unpleasant leg sensations, urge to move, restlessness, daytime sleepiness, and sleep disturbances.

10. The use according to claim 8 or 9, wherein the leucine is DL-leucine or the acetyl-leucine is acetyl-DL-leucine.

11. The use according to claim 8 or 9, wherein the leucine or acetyl-leucine has an enantiomeric excess of the L-enantiomer or the D-enantiomer.

12. The use according to any of claims 8-11, wherein the therapeutically effective amount of from 1 g to 15 g per day, from 1 g to 10 g per day, from 1.5 g to 7 g per day, from 4 g to 6 g per day, or from 4 g to 5 g per day.