CLAIMS

1. Use of a therapeutically effective amount of 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione in the manufacture of a medicament for treating a disease or disorder in a patient, wherein:

(a) an amount of 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione, or a pharmaceutically acceptable salt thereof, is to be administered to the patient per day;

(b) a plasma sample from the patient is to be obtained after at least four days of administering according to (a);

(c) the plasma concentration of 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione in the plasma sample obtained in (b) is determined; and

(d) a recalculated amount of 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione, or a pharmaceutically acceptable salt thereof, in milligrams, is to be administered to the patient per day as determined according to the Equation **1**:

$$\text{recalculated amount in mg} = \text{SD} \times \left(\frac{\text{CMT}}{\text{PC}} \right) \qquad \text{Equation } \mathbf{1},$$

wherein:

SD is the amount of 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione, or a pharmaceutically acceptable salt thereof, to be administered to the patient in (a) in mg;

CMT is the $C_{min\ target}$ in ng/mL;

$C_{min\ target}$ = (target AUC in ng·h/mL x 0.0341 ± 20%) - 1104 ± 20%; and

PC is the plasma concentration in ng/mL of 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione determined in (c),

wherein the target AUC is 100 μg.h/mL to 300 μg.h/mL.

2. The use of claims 1, wherein the plasma sample is to be obtained from the patient after at least 7 days of administering according to (a).

3. The use of claim 2, wherein a plasma sample is to be obtained from the patient after at least 10 days of administering according to (a).

4. The use of claim 3, wherein a plasma sample is to be obtained from the patient after at least 14 days of administering according to (a).

5. The use of any one of claims 1-4, wherein the 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione, or a pharmaceutically acceptable salt thereof, is to be administered orally to the patient in (a) and (d).

6. The use of any one of claims 1-5, wherein 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione hydrochloride is to be administered to the patient per day in (a) and (d).

7. The use of any one of claims 1-6, wherein the target AUC is 50 µg·h/mL to 100 µg·h/mL.

8. The use of claim 1, wherein 180 mg of 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione hydrochloride is to be administered to the patient per day in (a) and the target AUC is 200 ng.h/mL.

9. The use of any one of claims 6-8, wherein a recalculated amount of 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione hydrochloride is to be administered to the patient per day in (d).

10. The use of any one of claims 5-9, wherein the 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione hydrochloride is to be administered to the patient in (a) and (d) as a suspension comprising 15 mg of 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione hydrochloride per mL.

11. Use of a therapeutically effective amount of 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione in the manufacture of a medicament for treating a disease or disorder in a patient, wherein:

(a) 5 to 20 milliliters of an oral suspension of 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione hydrochloride is to be administered to the patient per day, wherein the oral suspension comprises 15 mg of 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione hydrochloride per mL;

(b) a plasma sample from the patient is to be obtained following 5 days or more of administering according to (a);

(c) the $C_{min\ ss}$ of 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione in the plasma sample obtained in (b) is determined; and

(d) a recalculated amount, in milliliters, of the oral suspension is to be administered to the patient per day as determined according to the Equation **4**:

$$Dose_{V1} = Dose_{pre-V1} \text{ x } \frac{C_{min_{TAR}}}{C_{min_{V1}}} \qquad \text{Equation } \mathbf{4},$$

wherein:

$Dose_{V1}$ is the recalculated amount, in milliliters, of the oral suspension to be administered to the patient per day in (d);

$Dose_{pre-V1}$ is the amount, in milliliters, of the oral suspension to be administered to the patient in (a);

$C_{min_{V1}}$ is the $C_{min\ ss}$, in ng/mL, of 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione determined in (c) taken 22 hours to 26 hours after the last administration; and

$C_{min_{TAR}}$ is the targeted concentration in ng/mL of 5 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione, wherein:

(A) $C_{min_{TAR}}$ is calculated according to Equation **5A**:

$$C_{min_{TAR}} = 7700 - (88.5 \text{ x } Dose_{pre-V1}) \qquad \text{Equation } \mathbf{5A}$$

if the plasma sample in (b) was obtained 18 hours to 19.9 hours after the last administration of the oral suspension in (a);

(B) $C_{min_{TAR}}$ is calculated according to Equation **5B**:

$$C_{min_{TAR}} = 7440 - (103.4 \text{ x } Dose_{pre-V1}) \quad \text{Equation } \mathbf{5B}$$

if the plasma sample in (b) was obtained 20 hours to 21.9 hours after the last administration of the oral suspension in (a);

(C) $C_{min_{TAR}}$ is 5716 if the plasma sample in (b) was obtained 22 hours to 25.9 hours after the last administration of the oral suspension in (a);

(D) $C_{min_{TAR}}$ is calculated according to Equation **5D**:

$$C_{min_{TAR}} = 6740 - (138.6 \text{ x } Dose_{pre-V1}) \quad \text{Equation } \mathbf{5D}$$

if the plasma sample in (b) was obtained 26 hours to 27.9 hours after the last administration of the oral suspension in (a); or

(E) $C_{min_{TAR}}$ is calculated according to Equation **5E**:

$$C_{min_{TAR}} = 6520 - (148.0 \text{ x } Dose_{pre-V1}) \quad \text{Equation } \mathbf{5E}$$

if the plasma sample in (b) was obtained 28 hours to 30 hours after the last administration of the oral suspension in (a).

12. The use of claim 11, wherein:

(i) a plasma sample from the patient is to be obtained following 5 days or more of administering the recalculated amount, in milliliters, of the oral suspension of 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione hydrochloride to the patient per day in (d);

(ii) the $C_{min_{calcd}}$, in ng/mL, of 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione in the plasma sample obtained in (i) is determined according to Equation **6**:

$$C_{min_{calcd}} = \frac{Dose_{V1} \text{ x } C_{min_{V2}}}{Dose_{last\ taken}} \quad \text{Equation } \mathbf{6};$$

(iii) the AUC_{Calcd}, in µg·h/mL, of 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione based on the $C_{min_{calcd}}$ determined in (ii) is determined, wherein:

(A) the AUC_{Calcd} is calculated according to Equation **7A**:

$$AUC_{Calcd} = \frac{C_{min_{calcd}} + (88.5 \text{ x } Dose_{last\ taken})}{38.5} \quad \text{Equation } \mathbf{7A},$$

if the plasma sample in (i) was obtained between 18 hours to 19.9 hours after the last administration of the oral suspension;

(B) the AUC_{Calcd} is calculated according to Equation **7B**:

$$AUC_{Calcd} = \frac{C_{min_{calcd}} + (103.4 \text{ x } Dose_{last\ taken})}{37.2}$$

Equation **7B**,

if the plasma sample in (i) was obtained 20 hours to 21.9 hours after the last administration of the oral suspension;

(C) the AUC_{Calcd} is calculated according to Equation **7C**:

$$AUC_{Calcd} = \frac{C_{min_{calcd}} + 1104.1}{34.1}$$ Equation **7C**,

if the plasma sample in (i) was obtained 22 hours to 25.9 hours after the last administration of the oral suspension;

(D) the AUC_{Calcd} is calculated according to Equation **7D**:

$$AUC_{Calcd} = \frac{C_{min_{calcd}} + (138.6 \text{ x } Dose_{last\ taken})}{33.7}$$ Equation **7D**,

if the plasma sample in (i) was obtained 26 hours to 27.9 hours after the last administration of the oral suspension; or

(E) the AUC_{Calcd} is calculated according to Equation **7E**:

$$AUC_{Calcd} = \frac{C_{min_{calcd}} + (148 \text{ x } Dose_{last\ taken})}{32.6}$$ Equation **7E**,

if the plasma sample in (i) was obtained 28 hours to 30 hours after the last administration of the oral suspension; and

(iv) the same recalculated amount, in milliliters, of the oral suspension is to be administered to the patient per day as in (i) for 5 days or more if the AUC_{Calcd} is 150 to 240 µg·h/mL and, optionally, repeating (i)-(iii); or

(v) a new amount, in milliliters, of the oral suspension is to be administered to the patient per day in (i) if the AUC_{Calcd} is less than 150 or more than 240 µg·h/mL.

13. Use of a therapeutically effective amount of 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione in the manufacture of a medicament for treating a disease or disorder in a patient, wherein an initial dose of 5 to 20 milliliters of an oral suspension comprising 15 mg of 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-

yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione hydrochloride per ml is to be administered to the patient once per day for 5 days or more; and

(a) a higher dose of the oral suspension is to be administered to the patient once per day if the plasma concentration of 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione in the patient is less than 149 µg·h/mL;

(b) a lower dose of the oral suspension is to be administered to the patient once per day if the plasma concentration of 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione in the patient is more than 241 µg·h/mL; or

(c) an unchanged dose of the oral suspension is to be administered to the patient once per day if the plasma concentration of 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione in the patient is between 150 µg·h/mL and 240 µg·h/mL.

14. Use of a therapeutically effective amount of 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione in the manufacture of a medicament for treating a disease or disorder in a patient, wherein:

(a) an initial dose of 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione hydrochloride is to be administered to the patient once per day for 5 or more days; and

(b) a recalculated dose of 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione hydrochloride is to be administered to the patient according to:

(i) Equation **8a**:

$$D_{recal} = D_{initial}*(AUC_{Tar} / AUC_0t) \qquad \text{Equation } \mathbf{8a}$$

wherein:

D_{recal} is recalculated dose of the 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione hydrochloride to be administered to the patient in milligrams;

$D_{initial}$ is the initial dose of the 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione hydrochloride to be administered to the patient in milligrams;

AUC_{Tar} is the targeted exposure of Compound (**1)** in the patient 24 hours after the last administration in (a) in ng·h/ml; and

AUC_0t is the calculated exposure of Compound (**1)** in the patient 24 hours after the last administration in (a) in ng·h/ml; and

(ii) Equation **8b**:

$AUC_0t = (28.31+0.472*\Delta T)*C+(34410+2234*\Delta T)*D_{initial}/150$ Equation **8b**

wherein:

AUC_0t is the calculated exposure of Compound (**1)** in the patient 24 hours after the last administration in (a) in ng·h/ml;

$D_{initial}$ is the initial dose of the 5-[[4-[2-[5-(1-hydroxyethyl)pyridin-2-yl]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione hydrochloride to be administered to the patient in milligrams;

C is the plasma concentration of Compound (**1**) in the patient in ng/ml, wherein the plasma sample is to be taken from the patient 24 ± 6 hours after the last administration in (a); and

ΔT is the difference between the time the plasma sample is taken from the patient and 24 hours after the last administration in (a) in hours;

wherein the targeted exposure is 50,000 ng·h/mL to 250,000 ng·h/mL.

15. The use of claim 14, wherein the targeted exposure is 100,000 ng.h/mL to 200,000 ng.h/mL.

16. The use of claim 14, wherein the targeted exposure is 50,000 ng.h/mL to 100,000 ng.h/mL.

17. The use of any one of claims 1-16, wherein the disease or disorder is selected from the group consisting of central nervous system disease or disorder, mitochondrial disease, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), chronic granulomatous disorder, a polycystic ovary syndrome, a thyroid carcinoma, a thyroid autoimmune

disorder, a pituitary adenoma, atherosclerosis, hypertension, a skin disease, an inflammation and autoimmune disease, and an inflammatory respiratory disease.

18. The use of claim 17, wherein the disease or disorder is a central nervous system disease or disorder.

19. The use of claim 18, wherein the central nervous system disease or disorder is selected from the group consisting of neurodegenerative disease, cerebrovascular disease, seizure, epilepsy, viral disease, neuroinflammatory disease, brain tumor, organic acidemias, fatty acid disorder, and genetic mitochondrial disorder.

20. The use of claim 19, wherein the central nervous system disease or disorder is a neurodegenerative disease.

21. The use of claim 20, wherein the neurodegenerative disease is selected from the group consisting of Alzheimer's disease, Huntington's chorea, Parkinson's disease, multiple sclerosis, neuromyelitis optica, leukodystrophy, ALS, degenerative ataxia, multiple system atrophy, NBIA (neurodegeneration and brain iron accumulation disorders), neuromyopathy, and a motor neuron disease.

22. The use of claim 21, wherein the leukodystrophy is X-linked adrenoleukodystrophy.

23. The use of claim 21, wherein the degenerative ataxia is Friedreich's ataxia.

24. The use of claim 21, wherein the motor neuron disease is selected from the group consisting of progressive bulbar palsy, pseudobulbar palsy, primary lateral sclerosis (PLS), progressive muscular atrophy, spinal muscular atrophy (SMA), post-polio syndrome (PPS)-Marie-Tooth disease, Guillan-Barré syndrome, and adrenomyeloneuropathy (AMN).

25. The use of claim 19, wherein the central nervous system disorder is a cerebrovascular disease selected from the group consisting of global or local ischemia, intracerebral haemorrhage, stroke, and vascular dementia.

26. The use of claim 19, the central nervous system disorder is a viral disease selected from the group consisting of meningitis, encephalitis, rabies, measles, mumps, poliomyelitis, herpes simplex, and varicella zoster.

27. The use of claim 19, wherein the rare metabolic disease is selected from the group consisting of organic acidemias, fatty acid disorders and genetic mitochondrial disorders.

28. The use of claim 17, wherein the disease or disorder is a mitochondrial disease.

29. The use of claim 28, wherein the mitochondrial disease is a primary mitochondrial disorder selected from the group consisting of Rett syndrome, Alper's disease; Leber's hereditary optic neuropathy (LHON); Kearns-Sayre syndrome (KSS); Leigh's syndrome; Leigh-like syndrome; maternally inherited Leigh syndrome (MILS); mitochondrial depletion syndrome (MDS); mitochondrial DNA depletion syndrome (MDDS); mitochondrial encephalomyopathy; mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS); myoclonic epilepsy with ragged red fibers (MERRF); mitochondrial neurogastrointestinal encephalopathy syndrome (MNGIE); neuropathy, ataxia, and retinitis pigmentosa (NARP); Pearson syndrome; chronic progressive external opthalmoplegia (CPEO); dominant optic atrophy (DOA); autosomal dominant optic atrophy (ADOA); mitochondrial myopathy; cardiomyopathy; mitochondrial encephalopathy; myoclonic epilepsy; maternally inherited diabetes and deafness (MIDD); ataxia neuropathy spectrum; 3-methylglutaconic aciduria; sensoneural deafness; neuroradiological findings of Leigh-like syndrome (MEGDEL); SURF1 (COX definient Leigh syndrome due to complex IV surfeit protein deficiency); oxidative phosphorylation disorders; Berth syndrome; lethal infantile cardiomyopathy (LIC); pyruvate carboxylase deficiency; pyruvate dehydrogenase deficiency; POLG mutation; isolated or combined OXPHOS deficiencies with so far unsolved genetic defect including disturbed pyruvate oxidation and ATP plus PCr production rates; POLG2 mutation; carnitine-acyl-cartinine deficiency; carnitine deficiency; creatinine deficiency syndromes; Co-Enzyme Q10 deficiency; Complex I deficiency; Complex II deficiency;

Complex III deficiency; Complex IV deficiency; Complex V deficiency; lactic acidosis; leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation (LBSL); Luft disease; carnitine palmitoyltransferase (CPT I or CPT II) deficiency; short-chain acyl-CoA dehydrogenase deficiency (SCAD); short-chain 3-hydroxyacetyl-CoA dehydrogenase deficiency (SCHAD); medium-chain acyl-CoA dehydrogenase deficiency (MCAD); multiple acyl-CoA dehydrogenase deficiency (MADD); long-chain acyl-CoA dehydrogenase deficiency (LCAD); very long-chain acyl-CoA dehydrogenase deficiency (VLCAD); trifunctional protein (TFP) deficiency; and glutaric aciduria Type II.

30. The use of claim 28, wherein the mitochondrial disease is selected from the group consisting of Rett syndrome; dominant optic atrophy (DOA); autosomal dominant optic atrophy (ADOA); Complex I deficiency; Leber hereditary optic neuropathy (LHON); Kearns-Sayre syndrome (KSS); Leigh's syndrome; mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS); myoclonic epilepsy with ragged red fibers (MERRF); mitochondrial neurogastrointestinal encephalopathy syndrome (MNGIE); neuropathy, ataxia, and retinitis pigmentosa (NARP); Pearson syndrome; and chronic progressive external opthalmoplegia (CPEO).

31. The use of claim 28, wherein the mitochondrial disease is a secondary mitochondrial disorder selected from the group consisting of Duchenne muscular dystrophy (DMD); Becker muscular dystrophy (BMD); myotonic dystrophy (BMD); congenital myopathies; glycogen storage disorders; spinal-bulbar muscular atrophy (SBMA); argininosuccinic aciduria; autism spectrum disorder (ASD); autoimmune diseases of the skin (such as pemphigus vulgaris and lupus); methylmalonic and propionic acidurias; disorders or purine and/or pyrimidine synthesis; facioscapulohumeral muscular dystrophy (FSHD); congenital muscular dystrophies; collagen VI muscular dystrophies (e.g., Ullrich congenital muscular dystrophy, Bethlem myopathy, oculopharyngeal distal and Emery-Dreifuss); DiGeorge syndrome; and neuromuscular disorders (such as limb-girdle muscular dystrophy, inflammatory myopathies, Charcot Marie Tooth (CMT) neuropathy, and drug-induced peripheral neuropathies).

32. The use of claim 17, wherein the disease or disorder is nonalcoholic steatohepatitis (NASH).