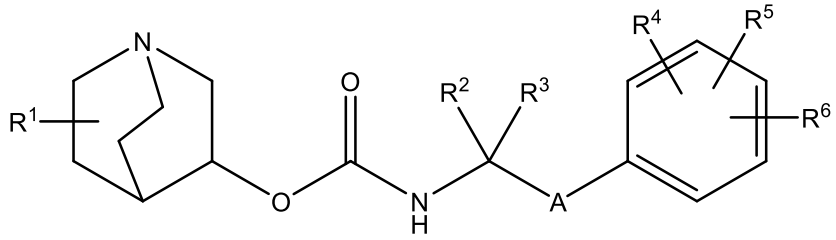
CLAIMS

1. Use of a compound in the manufacture of a medicament for use in a method for enhancing neuronal connectivity within the brain of a human subject, wherein the subject has been diagnosed with, or at risk of developing, a lysosomal storage disease, and wherein the compound is a compound of formula (I),



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from hydrogen, halogen (e.g., fluorine), cyano, nitro, hydroxy, thio, amino, C_{1-6}-alkyl (e.g., methyl or ethyl), C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-alkyloxy, C_{2-6}-alkenyloxy, and C_{2-6}-alkynyloxy, wherein said alkyl, alkenyl, alkynyl, alkyloxy, alkenyloxy, or alkynyloxy is optionally substituted with one or more (e.g., 1, 2, or 3) groups selected from halogen, cyano, nitro, hydroxy, thio, and amino;

R^2 and R^3 are independently selected from C_{1-3}-alkyl, optionally substituted by one or more (e.g., 1, 2, or 3) halogens, or R^2 and R^3 together form a cyclopropyl or cyclobutyl group, optionally substituted by one or more (e.g., 1 or 2) halogens;

R^4, R^5, and R^6 are each independently selected from hydrogen, halogen, nitro, hydroxy, thio, amino, C_{1-6}-alkyl, and C_{1-6}-alkyloxy, wherein said alkyl or alkyloxy is optionally substituted by one or more (e.g., 1, 2 or 3) groups selected from halogen, hydroxy, cyano, and C_{1-6}-alkyloxy; and

A is a 5- or 6-membered aryl or heteroaryl group (e.g., phenyl or thiazolyl), optionally substituted with 1, 2, or 3 groups independently selected from halogen, hydroxy, thio, amino, nitro, C_{1-6}-alkoxy, and C_{1-6}-alkyl.

2. The use of claim 1, wherein said compound is selected from: quinuclidin-3-yl (2-(4'-fluoro-[1,1'-biphenyl]-3-yl)propan-2-yl)carbamate; (*S*)-quinuclidin-3-yl (2-(2-(4-fluorophenyl)thiazol-4-yl)propan-2-yl)carbamate; and (*S*)-quinuclidin-3-yl (2-(4'-(2-methoxyethoxy)-[1,1'-biphenyl]-4-yl)propan-2-yl)carbamate; and the pharmaceutically

acceptable salts thereof, optionally wherein said compound is (*S*)-quinuclidin-3-yl (2-(2-(4-fluorophenyl)thiazol-4-yl)propan-2-yl)carbamate in malate salt form.

3. The use of claim 1 or claim 2, wherein the subject has Gaucher disease Type 3.

4. The use of any one of claims 1-3, wherein:

(a) said medicament is for systemic administration, *e.g.* via a non-parenteral route, optionally wherein said medicament is for oral administration;

(b) the subject undergoes concurrent treatment with enzyme replacement therapy (ERT), e.g., using a glucocerebrosidase (e.g., imiglucerase, velaglucerase, or taliglucerase);

(c) the subject is to be administered a daily dose of 1 mg to 50 mg of the compound, e.g., from 5 to 50 mg, or from 10 to 40 mg, or from 10 to 30 mg, or from 10 to 20 mg, or from 20 to 30 mg, or from 30 to 40 mg, or from 40 to 50 mg, or from 5 to 25 mg, or from 20 to 50 mg, or from 5 to 15 mg, or from 15 to 30 mg, or 15 mg;

(d) the subject is to be administered a single daily dose of 15 mg (measured as the quantity of free base) of (*S*)-quinuclidin-3-yl (2-(2-(4-fluorophenyl)thiazol-4-yl)propan-2-yl)carbamate in malate salt form; and/or

(e) the compound is not to be administered concurrently with a strong or moderate inducer of CYP3A, e.g., rifampin, phenobarbital, or efavirenz.

5. The use of any one of claims 1-4, wherein the subject is an adult or pediatric patient ≥12 years of age with Gaucher disease Type 3 who is stabilized with enzyme replacement therapy (ERT) using imiglucerase for systemic conditions, and wherein the subject is to be administered a single daily dose of 15 mg (measured as the quantity of free base) of (*S*)-quinuclidin-3-yl (2-(2-(4-fluorophenyl)thiazol-4-yl)propan-2-yl)carbamate in malate salt form.

6. The use of any one of claims 1-5, wherein the method is effective to improve cognitive ability or reduce cognitive deficits, e.g., as measured by a reduction in the time taken to complete the trail-making test (TMT), TMT-A and/or TMT-B, a reduction in the difference between TMT-A time and TMT-B time (TMT-A – TMT-B), for example, a

reduction of at least 10%, or at least 20%, or at least 30%, or at least 40%, or at least 50% (e.g., wherein TMT-A decreases by 5-20%, and/or TMT-B decreases by 25-30%, and/or [TMT-A – TMT-B] decreases by 25-30%).

7. The use of any one of claims 1-6, wherein the method results in:

(a) increased blood flow in the brain (e.g., in one or more of the frontal, occipital, parietal, or temporal lobes), for example, as shown by fMRI imaging;

(b) increased nodal connectivity in the brain (e.g., between posterior and anterior aspects of the brain, and/or between occipital-parietal structures and frontal, temporal and/or limbic structures, for example, as shown by fMRI imaging);

(c) enhanced connectivity in brain regions associated with executive function;

(d) resting-state functional networks with improved connectivity between default mode and medial and frontal networks; and/or

(e) enhanced connectivity between RSNs 1, 2 and 3 (perception-vision, cognition-language-orthography, cognition space) and RSNs 6, 7 and 8 (sensorimotor, auditory and executive control).

8. Use of a compound in the manufacture of a medicament for use in a method for increasing brain tissue volume, or preventing or delaying loss of brain tissue volume, in a human subject, wherein the subject has been diagnosed with, or at risk of developing a lysosomal storage disease and wherein the compound is a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in claim 1 or claim 2.

9. The use of claim 8, wherein the method results in:

(a) an increase in brain tissue volume, or prevention or delay in loss of brain tissue volume, in one or more brain regions selected from: right accumbens, left putamen, left entorhinal cortex, right putamen, right postcentral lobe, left pericalcarine, right amygdala, left cuneus and left lingual;

(b) increased brain volume in one or more brain regions associated with executive function;

(c) the increase in brain volume in the one or more brain regions accompanied by an enhancement in neuronal connectivity within the one or more brain regions, e.g., as shown using functional magnetic resonance imaging (fMRI); and/or

(d) an increase in the whole brain tissue volume.

10. The use of claim 8 or claim 9, wherein the subject and/or administration of the compound of formula (I), or a pharmaceutically acceptable salt thereof, is as defined in any one of claims 3-5.

11. Use of a compound in the manufacture of a medicament for use in treating a neurological disorder associated with a lysosome storage disease in a human subject, wherein said compound is a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in claim 1 or claim 2, said treatment comprising measuring brain tissue volume of the subject over a time period during the course of the treatment, e.g. using volumetric magnetic resonance imaging (vMRI), and assessing the extent of any change in brain tissue volume over said time period, optionally wherein said time period is from 3 months to 24 months, e.g. 3 months to 12 months, 3 months to 6 months, 6 months to 24 months, 6 months to 18 months, 6 months to 12 months, 12 months to 24 months, or 12 to 18 months.

12. The use of claim 10, wherein, if there is a decrease or absence of an increase in whole brain volume and/or in volumes in three or more of the following brain regions: right accumbens area, left putamen, left entorhinal cortex, right putamen, right postcentral lobe, left pericalcarine, right amygdala, left cuneus and left lingual, observed over said time period, the treatment further comprises increasing the dosage of the compound of formula (I), or a pharmaceutically acceptable salt thereof, to be administered to the subject and reassessing the extent of any change in brain tissue volume after a further time period over the course of the modified treatment with the increased dosage.

13. The use of claim 11 or claim 12, wherein the subject and/or administration of the compound of formula (I), or a pharmaceutically acceptable salt thereof, is as defined in any one of claims 3-5.

14. Use of a compound in the manufacture of a medicament for use in a method for treating a neurological disorder associated with a lysosomal storage disease in a human subject, wherein said compound is a compound of formula (I), or a pharmaceutically

acceptable salt thereof, as defined in claim 1 or claim 2, wherein said treatment commences after identifying the onset of said neurological disorder by:

a) measuring the brain tissue volume of the subject (e.g., using vMRI) and comparing against a reference standard to assess whether brain tissue volume is lower than the reference standard; and

b) where the brain tissue volume identified in step (a) is lower than the reference standard, identifying the onset of said neurological disorder.

15. The use of claim 14, wherein:

(a) the subject undergoes concurrent treatment with imiglucerase;

(b) the subject has been administered enzyme replacement therapy (e.g., imiglucerase, velaglucerase, and/or taliglucerase) prior to the initiation of treatment with the compound;

(c) the subject has been administered imiglucerase therapy for at least 6 months (optionally at a stable dose) prior to beginning therapy with the compound; and/or

(d) the method further comprises the step of transitioning the subject from ERT therapy (e.g., imiglucerase, velaglucerase, or taliglucerase) to the treatment with the compound.

16. The use of claim 14 or claim 15, wherein the subject has a hemoglobin level of at least 11 g/dL for females and at least 12 g/dL for males; a platelet count of at least 100,000/cubic millimeter; a splenic volume of less than 10 multiples of normal (MN); and/or a hepatic volume of less than 1.5 MN.

17. The use of any one of claims 14-16, wherein measuring of brain tissue volume of the subject is by brain positron emission tomography (PET) or by volumetric magnetic resonance imaging (vMRI).

18. The use of any one of claims 14-17, wherein:

(a) the subject is found to have brain tissue volume lower than the reference standard;

(b) comparison against the reference standard indicates that the subject has a lower brain tissue volume in one or more brain regions selected from: right accumbens, left putamen, left entorhinal cortex, right putamen, right postcentral lobe, left pericalcarine, right amygdala, left cuneus, and left lingual;

(c) comparison against the reference standard indicates that the subject has a lower brain tissue volume in one or more brain regions associated with executive function;

(d) comparison against the reference standard indicates that the subject has a lower brain tissue volume in one or more brain regions where loss of neuronal connectivity is assessed to be present, e.g. as shown using functional magnetic resonance imaging (fMRI); and/or

(e) comparison against the reference standard indicates that the subject has a lower whole brain tissue volume.

19. The use of any one of claims 14-18, wherein brain tissue volume of the subject is measured a plurality of times, intermittently or routinely, e.g., weekly, monthly, every 2, 3, 4, 6, 9, 12 months, etc., after the treatment with the compound is commenced to assess a change in brain tissue volume.

20. The use of any one of claims 14-19, wherein the subject and/or administration of the compound of formula (I), or a pharmaceutically acceptable salt thereof, is as defined in any one of claims 3-5.