In one aspect, there is disclosed the use of acetyl-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for treating one or more symptoms associated with a lysosomal storage disorder (LSD) in a subject in need thereof, wherein the LSD is not Niemann-Pick Type C.

In another aspect, there is disclosed the use of acetyl-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for delaying progression of a LSD over time as compared to typical disease progression in a subject in need thereof, wherein the subject is asymptomatic.

In another aspect, there is disclosed the use of acetyl-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for delaying onset of one or more symptoms of a LSD that would otherwise be expected to manifest according to typical disease progression.

In another aspect, there is disclosed the use of acetyl-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for treating one or more symptoms associated with a LSD in a subject in need thereof, wherein the LSD is not Niemann-Pick Type C, and a therapeutically effective amount of the acetyl-leucine is to be administered to the subject in need thereof for a duration chosen from at least about 3 months, at least about 6 months, at least about 1 year, at least about 2 years, and at least about 5 years.

In a further aspect, there is disclosed the use of acetyl-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for delaying progression of one or more symptoms associated with a LSD over time as compared to typical disease progression, wherein the LSD is not Niemann-Pick Type C, and a therapeutically effective amount of the acetyl-leucine is to be administered to the subject in need thereof for a duration chosen from at least about 3 months, at least about 6 months, at least about 1 year, at least about 2 years, and at least about 5 years.

In another aspect, there is disclosed the use of acetyl-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for reversing progression of one or more symptoms associated with a LSD over time, wherein the LSD is not Niemann-Pick Type C, and a therapeutically effective amount of the acetyl-leucine is to be administered to the subject in need thereof for a duration chosen from

at least about 3 months, at least about 6 months, at least about 1 year, at least about 2 years, and at least about 5 years.

In another aspect, there is disclosed the use of acetyl-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for reducing lysosomal volume in a subject having increased lysosomal volume as a biochemical marker of LSD, and wherein the LSD is not Niemann-Pick Type C, and a therapeutically effective amount of the acetyl-leucine is to be administered to the subject for a duration chosen from at least about 3 months, at least about 6 months, at least about 1 year, at least about 2 years, and at least about 5 years.

In another aspect, there is disclosed the use of acetyl-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for reducing the severity of or eliminating one or more existing symptoms associated with a LSD in a subject in need thereof, wherein the LSD is not Niemann-Pick Type C.

In another aspect, there is disclosed the use of acetyl-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for providing neuroprotection in a subject having, suspected of having, or at risk of having a LSD, wherein a therapeutically effective amount of the acetyl-leucine is to be administered to the subject for a duration chosen from at least about 3 months, at least about 6 months, at least about 1 year, at least about 2 years, and at least about 5 years.

In one example, there is disclosed acetyl-leucine, or a pharmaceutically acceptable salt thereof, for use in a method of treating a LSD or one or more symptoms associated with a LSD in a subject in need thereof, wherein the LSD is not Niemann-Pick Type C.

In one example of the present disclosure, acetyl-leucine, or a pharmaceutically acceptable salt thereof, is disclosed for use in a method of treating a LSD in a subject in need thereof, wherein the subject is asymptomatic.

In another example, there is disclosed acetyl-leucine, or a pharmaceutically acceptable salt thereof, for use in a method of delaying onset of a LSD or one or more symptoms of a LSD that would otherwise be expected to manifest according to typical disease progression.

In a further example, the present disclosure includes acetyl-leucine, or a pharmaceutically acceptable salt thereof, for use in a method of treating a LSD or one or more symptoms associated with a LSD in a subject in need thereof, wherein the method comprises administering a therapeutically effective amount of the acetyl-leucine to the subject in need thereof for a duration chosen from at least about 3 months, at least about 6 months, at least about 1 year, at least about 2 years, and at least about 5 years.

In one example, the present disclosure describes acetyl-leucine, or a pharmaceutically acceptable salt thereof, for use in a method of delaying progression of a LSD or one or more symptoms associated with a LSD over time as compared to typical disease progression, wherein the method comprises administering a therapeutically effective amount of the acetyl-leucine to the subject in need thereof for a duration chosen from at least about 3 months, at least about 6 months, at least about 1 year, at least about 2 years, and at least about 5 years.

In a further example, acetyl-leucine, or a pharmaceutically acceptable salt thereof, is disclosed for use in a method of reversing progression of a LSD or one or more symptoms associated with a LSD over time, wherein the method comprises administering a therapeutically effective amount of the acetyl-leucine to the subject in need thereof for a duration chosen from at least about 3 months, at least about 6 months, at least about 1 year, at least about 2 years, and at least about 5 years.

In another example, acetyl-leucine, or a pharmaceutically acceptable salt thereof, is disclosed for use in a method of improving in a subject in need thereof a biochemical

marker of a LSD over time, wherein the method comprises administering a therapeutically effective amount of the acetyl-leucine to the subject in need thereof for a duration chosen from at least about 3 months, at least about 6 months, at least about 1 year, at least about 2 years, and at least about 5 years.

In another example, the present disclosure includes acetyl-leucine, or a pharmaceutically acceptable salt thereof, for use in a method of reducing the severity of a LSD or reducing the severity of or eliminating one or more existing symptoms associated with a LSD in a subject in need thereof, wherein the LSD is not Niemann-Pick Type C.

In a further example, the present disclosure includes acetyl-leucine, or a pharmaceutically acceptable salt thereof, for use in a method of providing neuroprotection in a subject having, suspected of having, or at risk of having a LSD, wherein the method comprises administering a therapeutically effective amount of the acetyl-leucine to the subject for a duration chosen from at least about 3 months, at least about 6 months, at least about 1 year, at least about 2 years, and at least about 5 years.

Additional examples of the present disclosure include, acetyl-leucine, or a pharmaceutically acceptable salt thereof, for use in a method of delaying progression of a lysosomal storage disorder (LSD) in a subject. Acetyl-leucine, or a pharmaceutically acceptable salt thereof, for use in a method of providing neuroprotection in a subject having a LSD. The acetyl-leucine is in racemate form, in an enantiomeric excess of the L-enantiomer or in an enantiomeric excess of the D-enantiomer. The methods further comprise administering the acetyl-leucine in a dose of between 1.5 g and 10 g per day. Further, the methods comprise administering the acetyl-leucine for a treatment duration of two weeks or more. The methods may also comprise administering the acetyl-leucine, or a pharmaceutically acceptable salt thereof, before the onset of a symptom of a LSD. The methods may further comprise administering another therapy or agent intended to prevent or treat the LSD. A further example of the present disclosure is a kit for delaying progression of a LSD in a subject, the kit comprising a means for diagnosing or prognosing a LSD, and acetyl-leucine or a pharmaceutically acceptable salt thereof. The kit comprises a means for diagnosing or prognosing a LSD, and acetyl-leucine or a pharmaceutically acceptable salt thereof. Still yet another example of the present disclosure is use of acetyl-leucine, or a pharmaceutically acceptable salt thereof, as a neuroprotective agent in a subject having a LSD. In a further example of the method, the kit, or the use, the LSD is Niemann-Pick Type C

(NPC1 and/or NPC2 defect), Smith-Lemli-Opitz Syndrome (SLOS), an inborn error of cholesterol synthesis, Tangier disease, Pelizaeus-Merzbacher disease, a neuronal ceroid lipofuscinosis, a primary glycosphingolipidosis, Farber disease or multiple sulphatase deficiency. Additionally, in another example of the method, the kit, or the use, the primary glycosphingolipidosis is Gaucher disease, Fabry disease, GM1 gangliosidosis, GM2 gangliosidosis, Krabbe disease or metachromatic leukodystrophy (MLD). A further example of the method, the kit, or the use, the LSD is NPC, Tay-Sachs disease, Sandhoff disease, GM1 gangliosidosis, Fabry disease, a neurodegenerative mucopolysaccharidosis, MPS I, MPS IH, MPS IS, MPS II, MPS III, MPS IIIA, MPS IIIB, MPS IIIC, MPS HID, MPS, IV, MPS IV A, MPS IV B, MPS VI, MPS VII, MPS IX, a disease with secondary lysosomal involvement, SLOS, or Tangier disease. Another example of the method, the kit, or the use, the LSD is Niemann Pick disease, Niemann Pick type C, Niemann Pick type A, Sandhoff's disease, Tay-Sachs disease or mucolipidosis type II.

These and other examples and features of the present disclosure will be apparent from the following description and the claims.

Brief Description of the Figures

Figure 1 shows photographs of treated (Figure 1A) and untreated (Figure 1B) *Npc1*$^{-/-}$ mice at nine weeks of age.

Figures 2A and 2B show weight data for *Npc1*$^{-/-}$ mice compared to wild-type (*Npc1*$^{+/+}$) mice, with and without acetyl-DL-leucine treatment from weaning.

Figures 3A - 3G show gait analysis data for *Npc1*$^{-/-}$ mice compared to wild-type (*Npc1*$^{+/+}$) mice, with and without acetyl-DL-leucine treatment from weaning. For example, diagonal support, cadence and step sequence data are shown in Figures 3A - 3C, respectively. Figures 3D and 3E show front paw (FP) data (stand mean and step cycle in panel D; duty cycle in panel E). Figures 3F and 3G show hind paw (HP) data (stand mean and step cycle in panel F; duty cycle in panel G).

Figures 4A - 4H show motor function analysis data for *Npc1*$^{-/-}$ mice compared to wild-type (*Npc1*$^{+/+}$) mice, with and without acetyl-DL-leucine treatment from weaning. Centre rearing, activity, rearing and front to back (FR) count are shown in Figures 4A - 4D, respectively. Active time, mobile time, rearing time and total manual rearing count are shown in Figures 4E - 4H, respectively.

Claims:

1. Use of acetyl-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for treating one or more symptoms associated with a lysosomal storage disorder (LSD) in a subject in need thereof, wherein the LSD is not Niemann-Pick Type C.

2. The use according to claim 1, wherein the LSD is chosen from glycogen storage disease, mucopolysaccaridoses, mucolipidoses, oligosaccharidoses, lipidoses, sphingolipidoses, and lysosomal transport diseases.

3. The use according to claim 1, wherein the LSD is chosen from a primary lysosomal hydrolase defect, a post-translational processing defect of lysosomal enzymes, a trafficking defect for lysosomal enzymes, a defect in lysosomal enzyme protection, a defect in soluble non-enzymatic lysosomal proteins, a transmembrane (non-enzyme) protein defect, and an unclassified defect.

4. The use according to claim 1, wherein the LSD is chosen from Tay-Sachs disease, the AB variant of Tay-Sachs disease, Sandhoff disease, Niemann-Pick type A disease, Niemann-Pick type B disease, Fabry disease, neuronal ceroid lipofuscinoses, Krabbe disease, Farber disease, Gaucher disease, metachromatic leukodystrophy, multiple sulphatase deficiency, mucolipidosis II, mucolipidosis III, MPS III, MPS VII, GM1 gangliosidosis, and aspartylglucosaminuria.

5. The use according to claim 1, wherein the LSD is chosen from Tay-Sachs disease, the AB variant of Tay-Sachs disease, Sandhoff disease, Niemann Pick type A disease, mucolipidosis II, mucolipidosis III, MPS III, MPS VII, GM1 gangliosidosis, and aspartylglucosaminuria.

6. Use of acetyl-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for delaying progression of a LSD over time as compared to typical disease progression in a subject in need thereof, wherein the subject is asymptomatic.

7. The use according to claim 6, wherein the subject has been found to have a genetic and/or biochemical marker of the LSD.

8. Use of acetyl-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for delaying onset of one or more symptoms of a LSD that would otherwise be expected to manifest according to typical disease progression.

9. Use of acetyl-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for treating one or more symptoms associated with a LSD in a subject in need thereof, wherein the LSD is not Niemann-Pick Type C, and a therapeutically effective amount of the acetyl-leucine is to be administered to the subject in need thereof for a duration chosen from at least about 3 months, at least about 6 months, at least about 1 year, at least about 2 years, and at least about 5 years.

10. Use of acetyl-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for delaying progression of one or more symptoms associated with a LSD over time as compared to typical disease progression, wherein the LSD is not Niemann-Pick Type C, and a therapeutically effective amount of the acetyl-leucine is to be administered to the subject in need thereof for a duration chosen from at least about 3 months, at least about 6 months, at least about 1 year, at least about 2 years, and at least about 5 years.

11. Use of acetyl-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for reversing progression of one or more symptoms associated with a LSD over time, wherein the LSD is not Niemann-Pick Type C, and a therapeutically effective amount of the acetyl-leucine is to be administered to the subject in need thereof for a duration chosen from at least about 3 months, at least about 6 months, at least about 1 year, at least about 2 years, and at least about 5 years.

12. Use of acetyl-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for reducing lysosomal volume in a subject having increased lysosomal volume as a biochemical marker of LSD, and wherein the LSD is not Niemann-Pick Type C, and a therapeutically effective amount of the acetyl-leucine is to be administered to the subject for a duration chosen from at least about 3 months, at least about 6 months, at least about 1 year, at least about 2 years, and at least about 5 years.

13. The use according to any of claims 1-12, wherein a therapeutically effective amount of acetyl-leucine is to be administered to the subject in need thereof when the subject is asymptomatic.

14. The use according to claim 13, wherein the therapeutically effective amount of acetyl-leucine is to be administered after the subject has been found to have a genetic and/or biochemical marker of the LSD.

15. The use according to any of claims 1-8, wherein a therapeutically effective amount of the acetyl-leucine is to be administered to the subject in need thereof for a duration chosen from at least about 3 months, at least about 6 months, at least about 1 year, at least about 2 years, and at least about 5 years.

16. The use according to any of claims 1-15, wherein the acetyl-leucine is acetyl-DL-leucine.

17. The use according to any of claims 1-15, wherein the acetyl-leucine has an enantiomeric excess of the L-enantiomer or the D-enantiomer.

18. The use according to any of claims 1-15, wherein the acetyl-leucine is in a single enantiomeric form of either the L-enantiomer or the D-enantiomer.

19. The use according claim 18, wherein the single enantiomeric form is the L-enantiomer.

20. The use according to any of claims 1-8, wherein the acetyl-leucine is to be administered to the subject in need thereof at a therapeutically effect amount chosen from 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.

21. The use according to any of claims 9-15, wherein the therapeutically effective amount of acetyl-leucine is chosen 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.

22. The use according to any of claims 6-12, wherein the LSD is chosen from glycogen storage disease, mucopolysaccaridoses, mucolipidoses, oligosaccharidoses, lipidoses, sphingolipidoses, and lysosomal transport diseases.

23. The use according to any of claims 6-12, wherein the LSD is chosen from a primary lysosomal hydrolase defect, a post-translational processing defect of lysosomal enzymes, a trafficking defect for lysosomal enzymes, a defect in lysosomal enzyme protection, a defect in soluble non-enzymatic lysosomal proteins, a transmembrane (non-enzyme) protein defect, and an unclassified defect.

24. The use according to any of claims 6-12, wherein the LSD is chosen from Tay-Sachs disease, the AB variant of Tay-Sachs disease, Sandhoff disease, Niemann-Pick type A disease, Niemann-Pick type B disease, Fabry disease, neuronal ceroid lipofuscinoses, Krabbe disease, Farber disease, Gaucher disease, metachromatic leukodystrophy, multiple sulphatase deficiency, mucolipidosis II, mucolipidosis III, MPS III, MPS VII, GM1 gangliosidosis, and aspartylglucosaminuria

25. The use according to any of claim 6-12, wherein the LSD is chosen from Tay-Sachs disease, the AB variant of Tay-Sachs disease, Sandhoff disease, Niemann Pick type A disease, mucolipidosis II, mucolipidosis III, MPS III, MPS VII, GM1 gangliosidosis, and aspartylglucosaminuria

26. Use of acetyl-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for reducing the severity of or eliminating one or more existing symptoms associated with a LSD in a subject in need thereof, wherein the LSD is not Niemann-Pick Type C.

27. Use of acetyl-leucine, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for providing neuroprotection in a subject having, suspected of having, or at risk of having a LSD, wherein a therapeutically effective amount of the acetyl-leucine is to be administered to the subject for a duration chosen from at least about 3 months, at least about 6 months, at least about 1 year, at least about 2 years, and at least about 5 years.