

CLAIMS

1. ~~Use of a therapeutically effective amount of tramiprosate, a pharmaceutically acceptable salt of tramiprosate, a tramiprosate prodrug, a tramiprosate derivative, or an active tramiprosate metabolite in the manufacture of a medicament for~~ A method of selecting and treating an adult human subject comprising the steps of:

1. ~~a. selecting an adult human subject who is determined to:~~

- i. have at least one APOE4 allele,
- ii. be asymptomatic for Alzheimer's disease, and
- iii. have at least one of:
 - (1) a hippocampal volume below a threshold level; or
 - (2) cortical thickness below a threshold level; ~~and~~

~~b. administering to the selected subject a therapeutically effective amount of tramiprosate, a pharmaceutically acceptable salt of tramiprosate, a tramiprosate prodrug, a tramiprosate derivative, or an active tramiprosate metabolite.~~

2. The ~~method-use~~ of claim 1, wherein the subject is selected on the basis of having determined to have a hippocampal volume below a threshold level.

3. The ~~method-use~~ of claim 2, wherein the threshold level is based upon a baseline measure of hippocampal volume obtained from the same subject 6-36 months prior to selection.

4. The ~~method-use~~ of claim 2, wherein the threshold level is based upon the average age-adjusted hippocampal volume determined from a population of normal humans.

5. The ~~method-use~~ of claim 1, wherein the subject is selected on the basis of having determined to have a cortical thickness below a threshold level.

6. The ~~usemethod~~ of claim 4, wherein the threshold level is based upon a baseline measure of cortical thickness obtained from the same subject 12-36 months prior to selection.

7. The ~~use~~method of claim 4, wherein the threshold level is based upon is the average age-adjusted cortical thickness determined in a population of normal humans.
8. The ~~use~~method of any one of claims 1-7, wherein the subject is ~~selected on the basis of having determined to have~~ both a cortical thickness below a threshold level and a hippocampal volume below a threshold level.
9. The ~~use~~method of any one of claims 1-8, wherein the subject is ~~selected~~treated only if the subject is determined to have two APOE4 alleles.
10. The ~~use~~method of claim 9, wherein the subject is ~~selected~~treated if the hippocampal volume is at least 5% lower than the baseline hippocampal volume, and the baseline hippocampal volume is obtained within 12 months prior to selection.
11. The ~~use~~method of claim 9, wherein the subject is ~~selected~~treated if the hippocampal volume is at least 10% lower than the baseline hippocampal volume, and the baseline hippocampal volume is obtained less than 24 months prior to selection.
12. The ~~use~~method of claim 9, wherein the subject is ~~selected~~treated if the hippocampal volume is at least 10% below the average age-adjusted hippocampal volume determined in a population of normal humans.
13. The ~~use~~method of claim 12, wherein the subject is ~~selected~~treated if the hippocampal volume is less than 4.75 cm³.
14. The ~~use~~method of claim 9, wherein the subject is ~~selected~~treated if the cortical thickness is at least 3% less than the baseline cortical thickness, and the baseline cortical thickness is obtained within 12 months prior to selection.
15. The ~~use~~method of claim 9, wherein the subject is ~~selected~~treated if the cortical thickness is at least 6% less than the baseline cortical thickness, and the baseline cortical thickness is obtained within 24 months prior to selection.

16. The ~~use~~method of claim 9, wherein the subject is ~~selected~~treated if the hippocampal volume is at least 6% below less the average age-adjusted cortical thickness determined in a population of normal humans.
17. The ~~use~~method of claim 9, wherein the subject is ~~selected~~treated if the cortical thickness is less than 2.50 mm.
18. The ~~use~~method of any one of claims 1 to 17, wherein the subject is determined to have an APOE3/APOE4 genotype, and wherein the subject is ~~selected~~treated only if the subject is further determined to be positive for amyloid deposits in the brain.
19. The ~~use~~method of claim 18, wherein the subject is ~~selected~~treated if the hippocampal volume is at least 5% lower than the baseline hippocampal volume, and the baseline hippocampal volume is obtained within 12 months prior to the selection.
20. The ~~use~~method of claim 18, wherein the subject is ~~selected~~treated if the hippocampal volume is at least 10% lower than the baseline hippocampal volume, and the baseline hippocampal volume is obtained less than 24 months prior to the selection.
21. The ~~use~~method of claim 18, wherein the subject is ~~selected~~treated if the hippocampal volume is at least 10% below less the average age-adjusted hippocampal volume determined in a population of normal humans.
22. The ~~use~~method of claim 21, wherein the subject is ~~selected~~treated if the hippocampal volume is less than 5.10 cm³.
23. The ~~use~~method of claim 18, wherein the subject is ~~selected~~treated if the cortical thickness is at least 3% less than the baseline cortical thickness, and the baseline cortical thickness is obtained within 12 months prior to the selection.
24. The ~~use~~method of claim 18, wherein the subject is ~~selected~~treated if the cortical thickness is at least 6% less than the baseline cortical thickness, and the baseline cortical thickness is obtained within 24 months prior to the selection.

25. The ~~use~~method of claim 18, wherein the subject is ~~selected~~treated if the hippocampal volume is at least 6% below less the average age-adjusted cortical thickness determined in a population of normal humans.

26. The ~~use~~method of claim 18, wherein the subject is ~~selected~~treated if the cortical thickness is less than 2.50 mm.

27. The ~~use~~method of claim 1, wherein the subject is determined to have an APOE2/APOE4 genotype, and wherein the subject is ~~selected~~treated only if the subject is further determined to be positive for amyloid deposits in the brain.

28. The ~~use~~method of claim 27, wherein the subject is ~~selected~~treated if the hippocampal volume is at least 4% lower than the baseline hippocampal volume, and the baseline hippocampal volume is obtained within 12 months prior to the selection.

29. The ~~use~~method of claim 27, wherein the subject is ~~selected~~treated if the hippocampal volume is at least 7% lower than the baseline hippocampal volume, and the baseline hippocampal volume is obtained less than 36 months prior to the selection.

30. The ~~use~~method of claim 27, wherein the subject is ~~selected~~treated if the hippocampal volume is at least 7% below less the average age-adjusted hippocampal volume determined in a population of normal humans.

31. The ~~use~~method of claim 30, wherein the subject is ~~selected~~treated if the hippocampal volume is less than 6.10 cm³.

32. The ~~use~~method of claim 27, wherein the subject is ~~selected~~treated if the cortical thickness is at least 2% less than the baseline cortical thickness, and the baseline cortical thickness is obtained within 12 months prior to the selection.

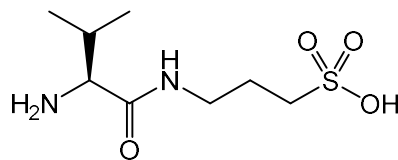
33. The ~~use~~method of claim 27, wherein the subject is ~~selected~~treated if the cortical thickness is at least 4% less than the baseline cortical thickness, and the baseline cortical thickness is obtained within 36 months prior to the selection.

34. The ~~use~~method of claim 27, wherein the subject is ~~selected~~treated if the hippocampal volume is at least 4% below less the average age-adjusted cortical thickness determined in a population of normal humans.

35. The ~~use~~method of claim 18, wherein the subject is ~~selected~~treated if the cortical thickness is less than 2.50 mm.

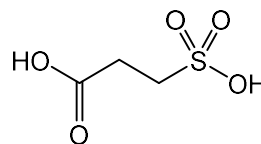
36. The ~~use~~method of any one of claims 1-35, wherein the subject is 50 years of age or greater at the time of the ~~selection~~treatment.

37. The ~~use~~method of any one of claims 1-36, wherein the ~~selected~~ human subject is to be



administered a tramiprosate prodrug of the formula: , or a pharmaceutically acceptable salt thereof.

38. The ~~use~~method of any one of claims 1-36, wherein the ~~selected~~ human subject is to be



administered a tramiprosate metabolite of the formula: , or a pharmaceutically acceptable salt thereof.

39. The ~~use~~method of any one of claims 1-38, wherein the subject is determined to be asymptomatic for Alzheimer's disease if the subject scores 28 or higher on a MMSE.

40. The ~~use~~method of any one of claims 1-39, wherein one or both of hippocampal volume and cortical thickness is measured by MRI.

41. The ~~use~~method of any one of claims 18-40, wherein amyloid deposits are detected by PET imaging or cerebral spinal fluid biomarkers.