

CLAIMS

1. A method of selecting and treating an adult human subject comprising the steps of:
 - 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 of claim 1, wherein the subject is selected on the basis of having a hippocampal volume below a threshold level.
3. The method 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 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 of claim 1, wherein the subject is selected on the basis of having a cortical thickness below a threshold level.
6. The method 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 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 method of any one of claims 1-7, wherein the subject is selected on the basis of having both a cortical thickness below a threshold level and a hippocampal volume below a

threshold level.

9. The method of any one of claims 1-8, wherein the subject is selected only if the subject is determined to have two APOE4 alleles.
10. The method of claim 9, wherein the subject is selected 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 method of claim 9, wherein the subject is selected 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 method of claim 9, wherein the subject is selected if the hippocampal volume is at least 10% below the average age-adjusted hippocampal volume determined in a population of normal humans.
13. The method of claim 12, wherein the subject is selected if the hippocampal volume is less than 4.75 cm³.
14. The method of claim 9, wherein the subject is selected 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 method of claim 9, wherein the subject is selected 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 method of claim 9, wherein the subject is selected if the hippocampal volume is at least 6% below less the average age-adjusted cortical thickness determined in a population of normal humans.

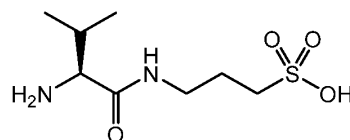
17. The method of claim 9, wherein the subject is selected if the cortical thickness is less than 2.50 mm.
18. The method of any one of claims 1 to 17, wherein the subject is determined to have an APOE3/APOE4 genotype, and wherein the subject is selected only if the subject is further determined to be positive for amyloid deposits in the brain.
19. The method of claim 18, wherein the subject is selected 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 method of claim 18, wherein the subject is selected 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 method of claim 18, wherein the subject is selected 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 method of claim 21, wherein the subject is selected if the hippocampal volume is less than 5.10 cm³.
23. The method of claim 18, wherein the subject is selected 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 method of claim 18, wherein the subject is selected 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 method of claim 18, wherein the subject is selected 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 method of claim 18, wherein the subject is selected if the cortical thickness is less than 2.50 mm.
27. The method of claim 1, wherein the subject is determined to have an APOE2/APOE4 genotype, and wherein the subject is selected only if the subject is further determined to be positive for amyloid deposits in the brain.
28. The method of claim 27, wherein the subject is selected 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 method of claim 27, wherein the subject is selected 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 method of claim 27, wherein the subject is selected 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 method of claim 30, wherein the subject is selected if the hippocampal volume is less than 6.10 cm³.
32. The method of claim 27, wherein the subject is selected 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 method of claim 27, wherein the subject is selected 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 method of claim 27, wherein the subject is selected 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 method of claim 18, wherein the subject is selected if the cortical thickness is less than 2.50 mm.

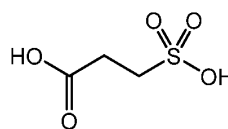
36. The method of any one of claims 1-35, wherein the subject is 50 years of age or greater at the time of the selection.

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



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

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



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

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

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