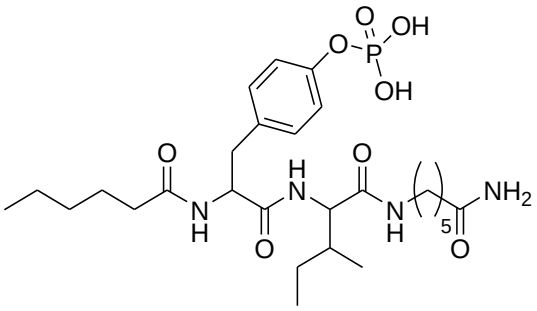
strategies are largely hindered by challenges related to gene delivery and transduction with limited brain exposure, uncontrollable dose over long-term treatment, and potential immune complications (Piguet, 2017).

[0005] Therefore, a small molecule approach capable of passing the blood brain barrier and entering all regions of the brain, presents a superior therapeutic strategy for targeting neurotrophic factors to treat neurodegenerative disorders.

SUMMARY

[0006] The present disclosure provides, methods of treating mild to moderate Alzheimer's disease.

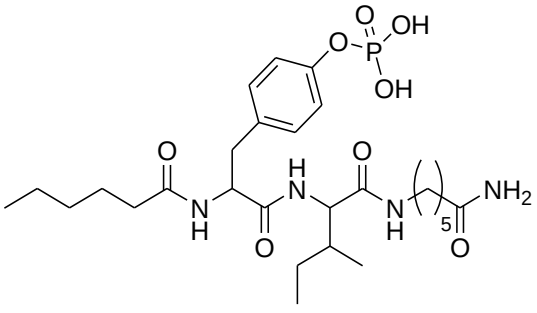
Example 1. A method of treating mild to moderate Alzheimer's disease (AD), comprising administering to a patient in need thereof 2-90 mg per day of a compound of formula A19



A19

or a pharmaceutically acceptable salt thereof.

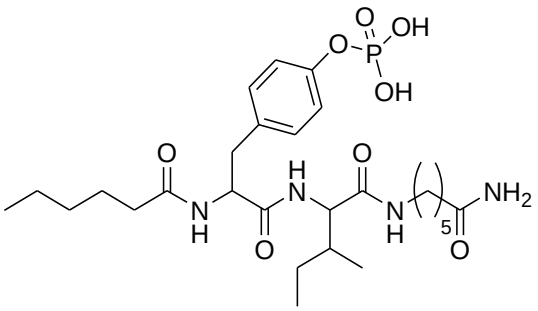
Example 2. A method of treating mild AD, comprising administering to a patient in need thereof 2-90 mg per day of a compound of formula A19



A19

or a pharmaceutically acceptable salt thereof.

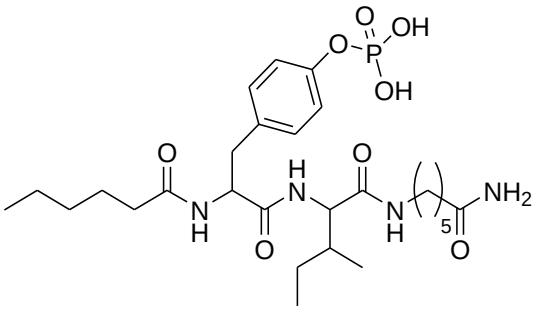
Example 3. A method of treating moderate AD, comprising administering to a patient in need thereof 2-90 mg per day of a compound of formula A19



A19

or a pharmaceutically acceptable salt thereof.

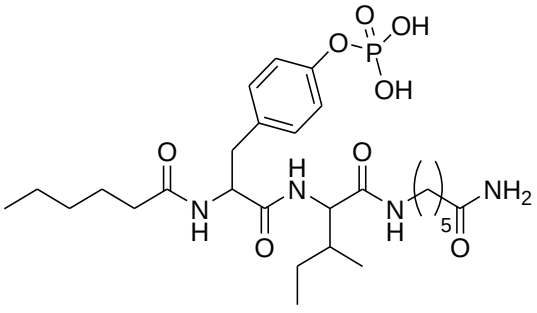
Example 4. A method of slowing the decline in cognition or improving cognition in a patient, comprising administering to a patient in need thereof 2-90 mg per day of a compound of formula A19



A19

or a pharmaceutically acceptable salt thereof.

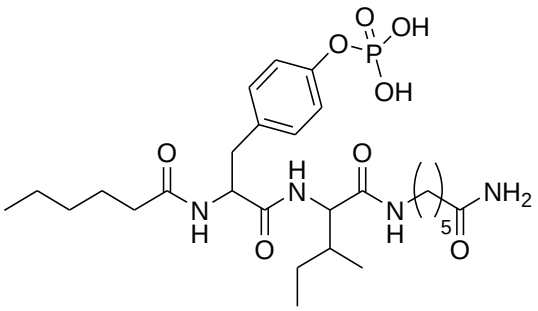
Example 5. A method of slowing the decline in the ability to perform activities of daily living and verbal fluency or improving the ability to perform activities of daily living and verbal fluency in a patient diagnosed with mild to moderate AD, comprising administering to the patient 2-90 mg per day of a compound of formula A19



A19

or a pharmaceutically acceptable salt thereof.

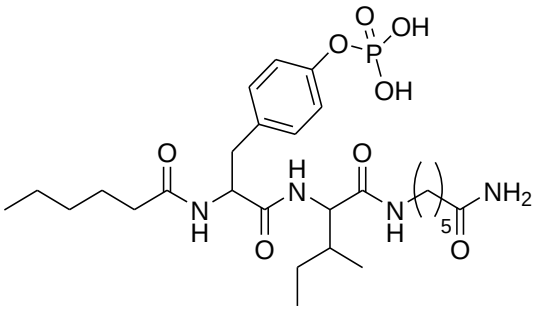
Example 6. A method of slowing the decline in functional or cognitive capacity in a patient diagnosed with mild to moderate AD, comprising administering to the patient 2-90 mg per day of a compound of formula A19



A19

or a pharmaceutically acceptable salt thereof.

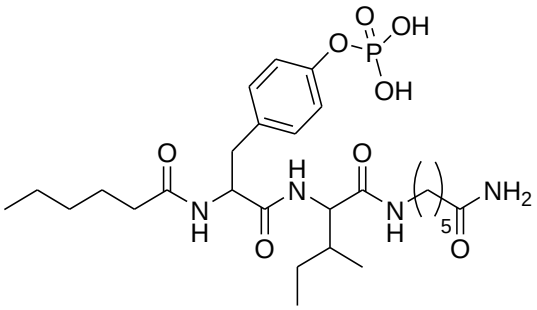
Example 7. A method of slowing clinical decline in a patient diagnosed with mild to moderate AD, comprising administering to a patient diagnosed with mild to moderate AD 2-90 mg per day of a compound of formula A19



A19

or a pharmaceutically acceptable salt thereof.

Example 8. A method of improving executive memory function in a patient diagnosed with mild to moderate AD, comprising administering to a patient diagnosed with mild to moderate AD 2-90 mg per day of a compound of formula A19



A19

or a pharmaceutically acceptable salt thereof.

Example 9. The method of any one of the preceding examples, wherein the patient has a Mini-Mental State Examination (MMSE) score of at least 14, between 14 and 24, between 15 and 24, between 16 and 24, between 17 and 24, between 18 and 24, between

19 and 24, between 20 and 24, between 21 and 24, between 22 and 24, between 23 and 24 prior to the start of treatment with the compound of formula A19.

Example 10. The method of any one of the preceding examples, wherein the patient has been diagnosed with mild AD.

Example 11. The method of any one of the preceding examples, wherein the patient has an MMSE score between 20 and 24 prior to the start of treatment with the compound of formula A19.

Example 12. The method of any one of the preceding examples, wherein the patient has been diagnosed with moderate AD.

Example 13. The method of any one of the preceding examples, wherein the patient has an MMSE score between 14 and 19 prior to the start of treatment with the compound of formula A19.

Example 14. The method of any one of the preceding examples, wherein the patient has a Clinical Dementia Rating (CDR) Scale global score of 1 or 2 prior to the start of treatment with the compound of formula A19.

Example 15. The method of any one of the preceding examples, wherein the patient is acetylcholinesterase inhibitor (AChEI) naïve or received an AChEI in the past, or received AChEI in the past and discontinued at least 4 weeks prior to administration of the compound.

Example 16. The method of any one of the preceding examples, wherein the patient is between age 55 and 85.

Example 17. The method of any one of the preceding examples, wherein the compound of formula A19 or the pharmaceutically acceptable salt thereof is administered by subcutaneous injection.

Example 18. The method of any one of the preceding examples, comprising administering the compound of formula A19 or the pharmaceutically acceptable salt thereof at a dose of 2 mg, 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, or 90 mg.

Example 19. The method of any one of the preceding examples, comprising administering the compound of formula A19 or the pharmaceutically acceptable salt thereof at a dose of 40 mg or 70 mg.

Example 20. The method of any one of the preceding examples, comprising administering the compound of formula A19 or the pharmaceutically acceptable salt thereof at a dose of 40 mg.

Example 21. The method of any one of the preceding examples, comprising administering the compound of formula A19 or the pharmaceutically acceptable salt thereof at a dose of 70 mg.

Example 22. The method of any one of the preceding examples, comprising administering the compound of formula A19 or the pharmaceutically acceptable salt thereof for 26 weeks or more.

Example 23. The method of any one of the preceding examples, which slows the decline in functional or cognitive capacity in the patient.

Example 24. The method of any one of the preceding examples, which slows the decline in cognition in the patient.

Example 25. The method of any one of the preceding examples, which improves cognition in the patient.

Example 26. The method of any one of the preceding examples, which slows the decline in the ability to perform activities of daily living and verbal fluency in the patient.

Example 27. The method of any one of the preceding examples, which improves the ability to perform activities of daily living and verbal fluency in the patient.

Example 28. The method of any one of examples 23-27, wherein the slowing of the decline or the improvement is determined after administering the treatment for at least 2 weeks, at least 4 weeks, at least 6 weeks, at least 8 weeks, at least 10 weeks, at least 12 weeks, at least 16 weeks, at least 18 weeks, at least 20 weeks, at least 22 weeks, at least 24 weeks, or at least 26 weeks.

Example 29. The method of any one of the preceding examples, wherein cognitive capacity is assessed by determining the patient's score before and after administration of the compound of formula A19 or the pharmaceutically acceptable salt thereof using an 11-item Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-Cog11).

Example 30. The method of example 23, wherein cognitive capacity is assessed prior to the start of treatment and at least 2 weeks, at least 4 weeks, at least 6 weeks, at least 8 weeks, at least 10 weeks, at least 12 weeks, at least 16 weeks, at least 18 weeks, at least 20 weeks, at least 22 weeks, at least 24 weeks, or at least 26 weeks after the start of treatment.

Example 31. The method of any one of the preceding examples, which reduces the rate of decline, stabilizes, or improves ADAS-Cog11.

Example 32. The method of any one of the preceding examples, which reduces the rate of decline, stabilizes, or improves Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC).

Example 33. The method of example 31 or example 32, wherein reducing the rate of decline, stabilizing, or improving is assessed by determining the patient's score prior to the start of treatment and at least 2 weeks, at least 4 weeks, at least 6 weeks, at least 8 weeks, at least 10 weeks, at least 12 weeks, at least 16 weeks, at least 18 weeks, at least 20 weeks, at least 22 weeks, at least 24 weeks, or at least 26 weeks after the start of treatment.

Example 34. The method of any one of examples 29-33, wherein the onset of the effect on ADAS-Cog11 and/or ADCS-CGIC begins by 6 weeks, or by 8 weeks, or by 10 weeks, or by 12 weeks, or by 14 weeks, or by 16 weeks, or by 18 weeks, or by 20 weeks, or by 22 weeks, or by 24 weeks, or by 26 weeks after the start of treatment.

Example 35. The method of any one of examples 29-34, wherein the effect on ADAS-Cog11 and/or ADCS-CGIC is maintained for at least 2 weeks or at least 4 weeks after the end of treatment.

Example 36. The method of any one of the preceding examples, which reduces the rate of decline, stabilizes, or improves at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten subdomains of a Neuropsychiatric inventory (NPI).

Example 37. The method of any one of the preceding examples, which reduces the rate of decline, stabilizes, or improves a NPI score, Alzheimer's disease cooperative study-activities of daily living, 23-item version (ADCS-ADL23) score and/or Controlled Oral Word Association Test (COWAT) score.

Example 38. The method of example 37, wherein the reduction in the rate of decline, stabilization, or improvement occurs by at least 2 weeks, at least 4 weeks, at least 6 weeks, at least 8 weeks, at least 10 weeks, at least 12 weeks, at least 16 weeks, at least 18 weeks, at least 20 weeks, at least 22 weeks, at least 24 weeks, or at least 26 weeks after the start of treatment.

Example 39. The method of any one of example 36-38, wherein reducing the rate of decline, stabilizing, or improving is assessed by determining the patient's score prior to the start of treatment and at least 2 weeks, at least 4 weeks, at least 6 weeks, at least 8 weeks, at least 10 weeks, at least 12 weeks, at least 16 weeks, at least 18 weeks, at least 20 weeks, at least 22 weeks, at least 24 weeks, or at least 26 weeks after the start of treatment.

Example 40. The method of any one of the preceding examples, which reduces the rate of decline, stabilizes, or improves a Resource utilization in dementia lite version (RUD-lite) scale, a EQ-5D-5L score, and/or Zarit burden interview (ZBI) score.

Example 41. The method of example 40, wherein the reduction in the rate of decline, stabilization, or improvement occurs by at least 2 weeks, at least 4 weeks, at least 6 weeks, at least 8 weeks, at least 10 weeks, at least 12 weeks, at least 16 weeks, at least 18 weeks, at least 20 weeks, at least 22 weeks, at least 24 weeks, or at least 26 weeks after the start of treatment.

Example 42. The method of example 40 or example 41, wherein reducing the rate of decline, stabilizing, or improving is assessed by determining the patient's score prior to the start of treatment and at least 2 weeks, at least 4 weeks, at least 6 weeks, at least 8 weeks, at least 10 weeks, at least 12 weeks, at least 16 weeks, at least 18 weeks, at least 20 weeks, at least 22 weeks, at least 24 weeks, or at least 26 weeks after the start of treatment.

Example 43. The method of any one of the preceding examples, which provides fast improvement or normalization of P300 values.

Example 44. The method of any one of the preceding examples, which provides fast improvement or normalization of EPR P300 latency values.

Example 45. The method of any one of the preceding examples, which provides fast improvement or normalization of ERP P300 latency values with some maintenance of effect at 4 weeks after discontinuation of treatment.

Example 46. The method of any one of the preceding examples, which provides fast improvement or normalization of ERP P300 latency values, which is maintained at 4 weeks after discontinuation of treatment.

Example 47. The method of any one of the preceding examples, which improves event-related potential (ERP) P300 latency.

Example 48. The method of any one of examples 43-47, wherein the improvement or normalization occurs by at least 2 weeks, at least 4 weeks, at least 6 weeks, at least 8 weeks, at least 10 weeks, at least 12 weeks, at least 16 weeks, at least 18 weeks, at least 20 weeks, at least 22 weeks, at least 24 weeks, or at least 26 weeks after the start of treatment.

Example 49. The method of any one of the preceding examples, which improves quantitative EEG (qEEG).

Example 50. The method of any one of the preceding examples, which improves qEEG at least 2 weeks, at least 4 weeks, at least 6 weeks, at least 8 weeks, at least 10 weeks, at least 12 weeks, at least 16 weeks, at least 18 weeks, at least 20 weeks, at least 22 weeks, at least 24 weeks, or at least 26 weeks after the start of treatment.

Example 51. The method of any one of the preceding examples, which improves serum NFL and/or neurogranin levels.

Example 52. The method of any one of the preceding examples, which improves serum NFL and/or neurogranin levels, and at least one of phospho-tau, ABeta 1-42, and/or YLK41 levels.

Example 53. The method of any one of the preceding examples, which has an acceptable safety and tolerability profile.

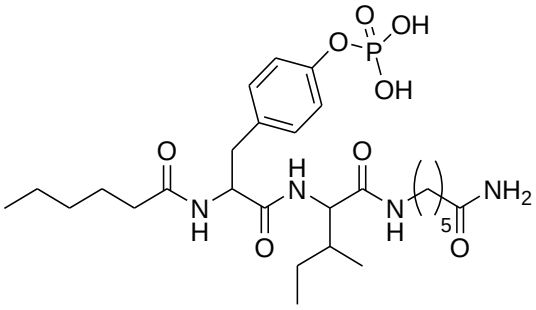
Example 54. The method of any one of the preceding examples, which is generally safe and well tolerated.

Example 55. The method of any one of the preceding examples, comprising administering a sodium salt of the compound of formula A19.

Example 56. The method of any one of the preceding examples, comprising administering a monosodium salt of the compound of formula A19.

Example 57. The method of any one of the preceding examples, comprising administering ATH-1017.

[0006a] In one aspect, the present disclosure provides use of a compound of formula A19



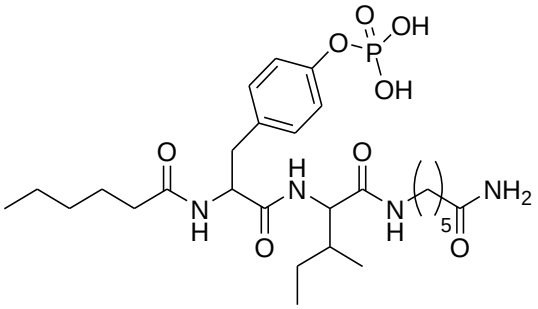
A19

or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for slowing the decline in cognition or improving cognition in a patient, wherein 40 mg per day of the compound is to be administered to a patient in need thereof, and wherein:

the patient is acetylcholinesterase inhibitor (AChEI) naïve; or

the patient received an AChEI in the past and preferably discontinued AChEI therapy at least 4 weeks prior to administration of the compound.

[0006b] In another aspect, the present disclosure provides use of a compound of formula A19



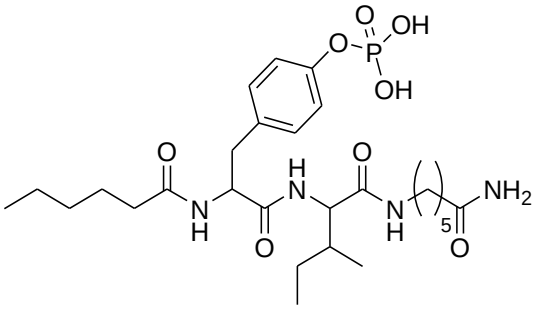
A19

or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for slowing the decline in the ability to perform activities of daily living and verbal fluency or improving the ability to perform activities of daily living and verbal fluency in a patient diagnosed with mild to moderate Alzheimer's disease (AD), wherein 40 mg per day of the compound is to be administered to a patient in need thereof, and wherein:

the patient is acetylcholinesterase inhibitor (AChEI) naïve; or

the patient received an AChEI in the past and preferably discontinued AChEI therapy at least 4 weeks prior to administration of the compound.

[0006c] In another aspect, the present disclosure provides use of a compound of formula A19



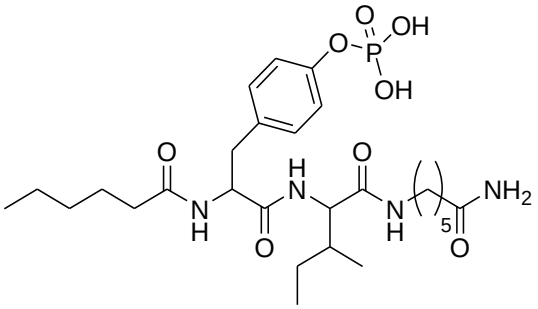
A19

or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for slowing the decline in functional or cognitive capacity in a patient diagnosed with mild to moderate AD, wherein 40 mg per day of the compound is to be administered to a patient in need thereof, and wherein:

the patient is acetylcholinesterase inhibitor (AChEI) naïve; or

the patient received an AChEI in the past and preferably discontinued AChEI therapy at least 4 weeks prior to administration of the compound.

[0006d] In another aspect, the present disclosure provides use of a compound of formula A19



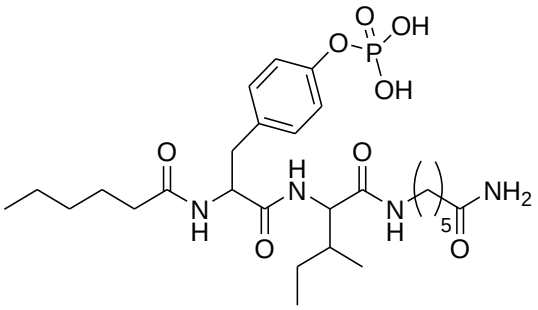
A19

or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for slowing clinical decline in a patient diagnosed with mild to moderate AD, wherein 40 mg per day of the compound is to be administered to a patient in need thereof, and wherein:

the patient is acetylcholinesterase inhibitor (AChEI) naïve; or

the patient received an AChEI in the past and preferably discontinued AChEI therapy at least 4 weeks prior to administration of the compound.

[0006e] In another aspect, the present disclosure provides use of a compound of formula A19



A19

or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for improving executive memory function in a patient diagnosed with mild to moderate AD, wherein 40 mg per day of the compound is to be administered to a patient in need thereof, and wherein:

the patient is acetylcholinesterase inhibitor (AChEI) naïve; or

the patient received an AChEI in the past and preferably discontinued AChEI therapy at least 4 weeks prior to administration of the compound.

BRIEF DESCRIPTION OF THE FIGURES

[0007] FIG. 1A shows P300 latency change from baseline in the study population, grouped by patients receiving placebo with and without AChEI therapy and patients receiving fosgonimeton (ATH-1017) with and without AChEI therapy.

[0008] FIG. 1B shows P300 latency change from baseline in a portion of the study population, grouped by patients receiving placebo with AChEI therapy and patients receiving fosgonimeton (ATH-1017) with AChEI therapy.

[0009] FIG. 1C shows P300 latency change from baseline in a portion of the study population, grouped by patients receiving placebo without AChEI therapy and patients receiving fosgonimeton (ATH-1017) without AChEI therapy.

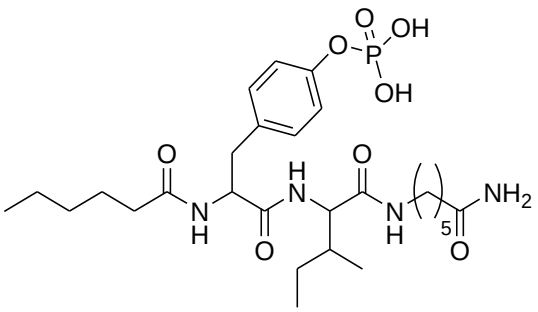
[00010] FIG. 2A shows ADAS-Cog score change from baseline in the study population, grouped by patients receiving placebo with and without AChEI therapy, and patients receiving fosgonimeton (ATH-1017) with and without AChEI therapy.

[00011] FIG. 2B shows ADAS-Cog score change from baseline in a portion of the study population, grouped by patients receiving placebo with AChEI therapy, and patients receiving fosgonimeton (ATH-1017) with AChEI therapy.

[00012] FIG. 2C shows ADAS-Cog score change from baseline in a portion of the study population, grouped by patients receiving placebo without AChEI therapy, and patients receiving fosgonimeton (ATH-1017) without AChEI therapy.

What is claimed is:

1. Use of a compound of formula A19



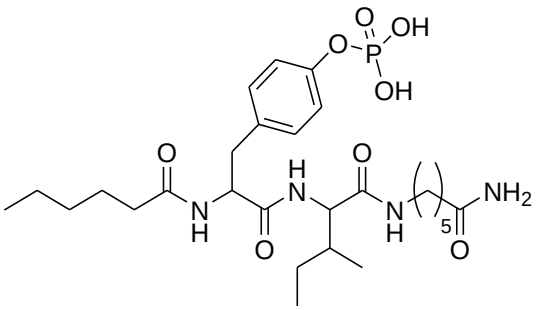
A19

or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for slowing the decline in cognition or improving cognition in a patient, wherein 40 mg per day of the compound is to be administered to a patient in need thereof, and wherein:

the patient is acetylcholinesterase inhibitor (AChEI) naïve; or

the patient received an AChEI in the past and preferably discontinued AChEI therapy at least 4 weeks prior to administration of the compound.

2. Use of a compound of formula A19



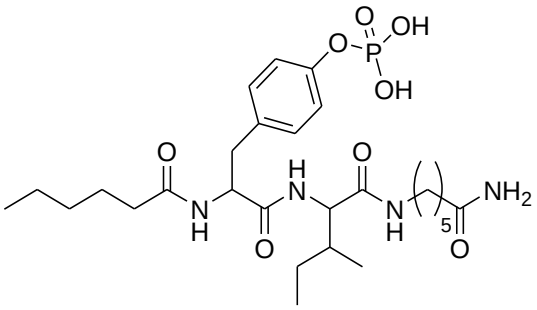
A19

or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for slowing the decline in the ability to perform activities of daily living and verbal fluency or improving the ability to perform activities of daily living and verbal fluency in a patient diagnosed with mild to moderate Alzheimer's disease (AD), wherein 40 mg per day of the compound is to be administered to a patient in need thereof, and wherein:

the patient is acetylcholinesterase inhibitor (AChEI) naïve; or

the patient received an AChEI in the past and preferably discontinued AChEI therapy at least 4 weeks prior to administration of the compound.

3. Use of a compound of formula A19



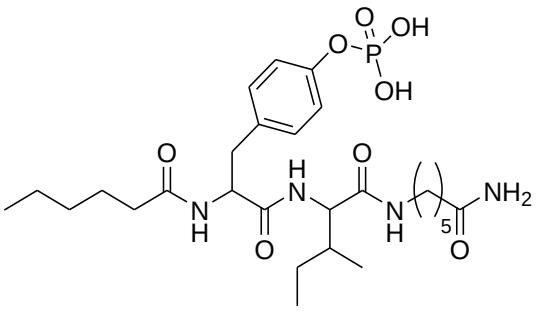
A19

or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for slowing the decline in functional or cognitive capacity in a patient diagnosed with mild to moderate AD, wherein 40 mg per day of the compound is to be administered to a patient in need thereof, and wherein:

the patient is acetylcholinesterase inhibitor (AChEI) naïve; or

the patient received an AChEI in the past and preferably discontinued AChEI therapy at least 4 weeks prior to administration of the compound.

4. Use of a compound of formula A19



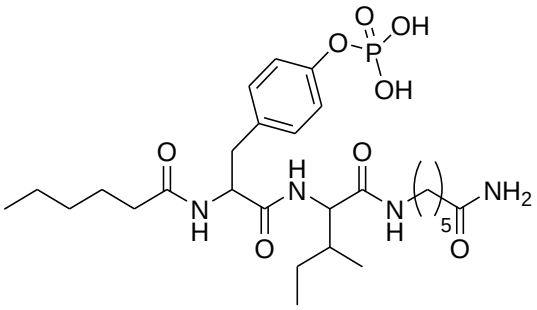
A19

or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for slowing clinical decline in a patient diagnosed with mild to moderate AD, wherein 40 mg per day of the compound is to be administered to a patient in need thereof, and wherein:

the patient is acetylcholinesterase inhibitor (AChEI) naïve; or

the patient received an AChEI in the past and preferably discontinued AChEI therapy at least 4 weeks prior to administration of the compound.

5. Use of a compound of formula A19



A19

or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for improving executive memory function in a patient diagnosed with mild to moderate AD, wherein 40 mg per day of the compound is to be administered to a patient in need thereof, and wherein:

the patient is acetylcholinesterase inhibitor (AChEI) naïve; or

the patient received an AChEI in the past and preferably discontinued AChEI therapy at least 4 weeks prior to administration of the compound.

6. The use of any one of claims 1 to 5, wherein the patient is acetylcholinesterase inhibitor (AChEI) naïve.
7. The use of any one of claims 1 to 5, wherein the patient received an AChEI in the past and preferably discontinued AChEI therapy at least 4 weeks prior to administration of the compound.
8. The use of any one of claims 1 to 7, which reduces the rate of decline, stabilizes, or improves ADAS-Cog11, for example, by 26 weeks after the start of treatment.
9. The use of any one of claims 1 to 8, wherein the patient has a Mini-Mental State Examination (MMSE) score of at least 14, between 14 and 24, between 15 and 24, between 16 and 24, between 17 and 24, between 18 and 24, between 19 and 24, between 20 and 24, between 21 and 24, between 22 and 24, between 23 and 24 prior to the start of treatment with the compound of formula A19.
10. The use of any one of claims 1 to 9, wherein the patient has been diagnosed with mild AD or moderate AD.
11. The use of any one of claims 1 to 10, wherein the patient has a Clinical Dementia Rating (CDR) Scale global score of 1 or 2 prior to the start of treatment with the compound of formula A19.
12. The use of any one of claims 1 to 11, wherein the patient is between age 55 and 85.
13. The use of any one of claims 1 to 12, wherein the compound of formula A19 or the pharmaceutically acceptable salt thereof is to be administered by subcutaneous injection.

14. The use of any one of claims 1 to 13, wherein the compound of formula A19 or the pharmaceutically acceptable salt thereof is to be administered for 26 weeks or more.
15. The use of any one of claims 1 to 14, wherein:
    i) the decline in functional or cognitive capacity in the patient is to be slowed;
    ii) the decline in cognition in the patient is to be slowed;
    iii) cognition in the patient is to be improved;
    iv) the decline in the ability to perform activities of daily living and verbal fluency in the patient is to be slowed; or
    v) the ability to perform activities of daily living and verbal fluency in the patient is to be improved.
16. The use of claim 15, wherein the slowing of the decline or the improvement is to be determined after the treatment is to be administered for at least 2 weeks, at least 4 weeks, at least 6 weeks, at least 8 weeks, at least 10 weeks, at least 12 weeks, at least 16 weeks, at least 18 weeks, at least 20 weeks, at least 22 weeks, at least 24 weeks, or at least 26 weeks.
17. The use of any one of claims 1 to 16, wherein cognitive capacity is to be assessed by determining the patient's score before and after administration of the compound of formula A19 or the pharmaceutically acceptable salt thereof using an 11-item Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-Cog11).
18. The use of any one of claims 15 to 17, wherein cognitive capacity is to be assessed prior to the start of treatment and at least 2 weeks, at least 4 weeks, at least 6 weeks, at least 8 weeks, at least 10 weeks, at least 12 weeks, at least 16 weeks, at least 18 weeks, at least 20 weeks, at least 22 weeks, at least 24 weeks, or at least 26 weeks after the start of treatment, preferably, at least 26 weeks after the start of treatment.
19. The use of any one of claims 1 to 18, which reduces the rate of decline, stabilizes, or improves Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC).
20. The use of any one of claims 17 to 19, wherein the onset of the effect on ADAS-Cog11 and/or ADCS-CGIC begins by 6 weeks, or by 8 weeks, or by 10 weeks, or by 12 weeks, or by 14 weeks, or by 16 weeks, or by 18 weeks, or by 20 weeks, or by 22 weeks, or by 24 weeks, or by 26 weeks after the start of treatment.
21. The use of any one of claims 1 to 20, which reduces the rate of decline, stabilizes, or improves at least one, at least two, at least three, at least four, at least five, at least six, at

least seven, at least eight, at least nine, or at least ten subdomains of a Neuropsychiatric inventory (NPI).

22. The use of any one of claims 1 to 21, which reduces the rate of decline, stabilizes, or improves a NPI score, Alzheimer's disease cooperative study-activities of daily living, 23-item version (ADCS-ADL23) score and/or Controlled Oral Word Association Test (COWAT) score.
23. The use of any one of claims 1 to 22, which reduces the rate of decline, stabilizes, or improves a Resource utilization in dementia lite version (RUD-lite) scale, a EQ-5D-5L score, and/or Zarit burden interview (ZBI) score.
24. The use of any one of claims 21, 22, or 23, wherein the reduction in the rate of decline, stabilization, or improvement occurs by at least 2 weeks, at least 4 weeks, at least 6 weeks, at least 8 weeks, at least 10 weeks, at least 12 weeks, at least 16 weeks, at least 18 weeks, at least 20 weeks, at least 22 weeks, at least 24 weeks, or at least 26 weeks after the start of treatment; optionally, wherein reducing the rate of decline, stabilizing, or improving is to be assessed by determining the patient's score prior to the start of treatment and at least 2 weeks, at least 4 weeks, at least 6 weeks, at least 8 weeks, at least 10 weeks, at least 12 weeks, at least 16 weeks, at least 18 weeks, at least 20 weeks, at least 22 weeks, at least 24 weeks, or at least 26 weeks after the start of treatment.
25. The use of any one of claims 1 to 24, which improves serum NFL and/or neurogranin levels, for example, which improves serum NFL and/or neurogranin levels, and at least one of phospho-tau, ABeta 1-42, and/or YLK-41 levels.
26. The use of any one of claims 1 to 25, wherein ATH-1017 is to be administered.