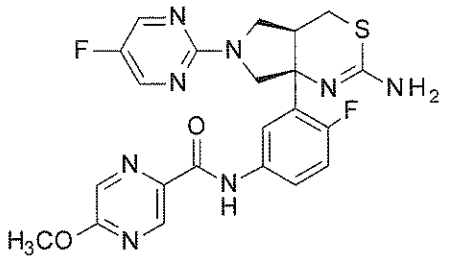
removal of pre-existing plaque deposits while at the same time reduce or prevent further deposition of Abeta by inhibiting the generation of Abeta.

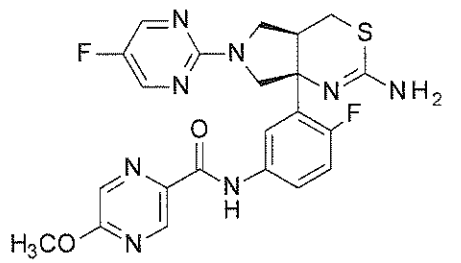
US 2009/0209755 discloses fused aminodihydrothiazine derivatives which possess BACE inhibitory activity and are further disclosed as useful therapeutic agents for a neurodegenerative disease caused by Aβ peptide, such as Alzheimer's type dementia. In addition, *J. Neuroscience*, 31(46), pages 16507-16516 (2011) discloses (S)-4-(2,4-difluoro-5-pyrimidin-5-yl-phenyl)-4-methyl-5,6-dihydro-4*H*-[1,3]thiazin-2-ylamine, an orally administered CNS-active BACE inhibitor. U.S. Patent No. 8,278,334 discloses a method of treating a cognitive or neurodegenerative disease comprising administering a substituted cyclic amine BACE-1 inhibitor with an anti-amyloid antibody. Further, *J. Neuroscience*, 34(35), pages 11621-11630 (2014) discloses that combined treatment with a BACE inhibitor and an anti-abeta antibody Gentenerumab enhances amyloid reduction in APP_{London} mice.

In one aspect of the present disclosure, there is provided a use of a compound of the formula:



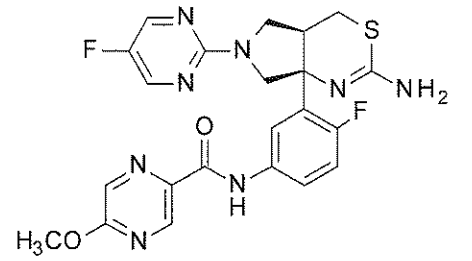
or a pharmaceutically acceptable salt thereof, in combination with an effective amount of an anti-N3pGlu Abeta monoclonal antibody in the manufacture of a medicament for treating Alzheimer's disease.

In another aspect of the present disclosure, there is provided a pharmaceutical composition, comprising a compound of the formula:



or a pharmaceutically acceptable salt thereof, with one or more pharmaceutically acceptable carriers, diluents, or excipients, in combination with a pharmaceutical composition of anti-N3pGlu Abeta monoclonal antibody, with one or more pharmaceutically acceptable carriers, diluents, or excipients.

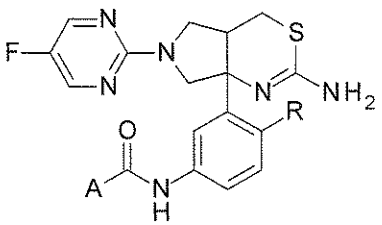
In a further aspect of the present disclosure, there is provided a compound of the formula:



or a pharmaceutically acceptable salt thereof, in combination with an anti-N3pGlu Abeta monoclonal antibody for use in the treatment of Alzheimer's disease.

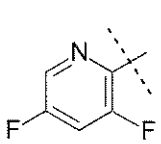
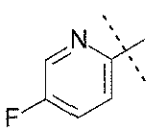
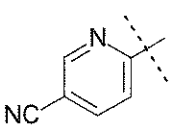
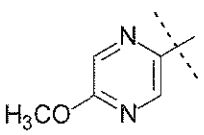
~~Accordingly, t~~The present ~~invention~~ disclosure also provides a method of treating a cognitive or neurodegenerative disease, comprising administering to a patient in need of such treatment an effective amount of a BACE inhibitor in combination with an effective amount of an anti-N3pGlu Abeta monoclonal antibody.

More specifically, the present disclosure ~~invention~~ provides a method of treating a cognitive or neurodegenerative disease, comprising administering to a patient in need of such treatment an effective amount of a compound of Formula I:

 Formula I

wherein R is H or F; and

A is:

 ,  ,  , or  ;

or a pharmaceutically acceptable salt thereof; in combination with an effective amount of an anti-N3pGlu Abeta monoclonal antibody.

The present disclosure ~~invention~~ also provides a method of treating a disease that is characterized by the formation and deposition of Abeta, comprising administering to a patient in need of such treatment an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, in combination with an effective amount of an anti-N3pGlu Abeta monoclonal antibody.

The present disclosure ~~invention~~ further provides a method of treating Alzheimer's disease, comprising administering to a patient in need of such treatment an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, in combination with an effective amount of an anti-N3pGlu Abeta monoclonal antibody.

The present disclosure ~~invention~~ also provides a method of treating mild Alzheimer's disease, comprising administering to a patient in need of such treatment an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, in combination with an effective amount of an anti-N3pGlu Abeta monoclonal antibody.

The present disclosure ~~invention~~ further provides a method of treating mild cognitive impairment, comprising administering to a patient in need of such treatment an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, in combination with an effective amount of an anti-N3pGlu Abeta monoclonal antibody.

The present disclosure ~~invention~~ further provides a method of treating prodromal Alzheimer's disease, comprising administering to a patient in need of such treatment an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, in combination with an effective amount of an anti-N3pGlu Abeta monoclonal antibody.

In addition, the present disclosure ~~invention~~ provides a method for the prevention of the progression of mild cognitive impairment to Alzheimer's disease, comprising administering to a patient in need of such treatment an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, in combination with an effective amount of an anti-N3pGlu Abeta monoclonal antibody.

The present disclosure ~~invention~~ further provides a method of treating cerebral amyloid angiopathy (CAA), comprising administering to a patient in need of such treatment an

effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, in combination with an effective amount of an anti-N3pGlu Abeta monoclonal antibody.

Furthermore, the present disclosure ~~invention~~ provides a compound of Formula I or a pharmaceutically acceptable salt thereof, in combination with an effective amount of an anti-N3pGlu Abeta monoclonal antibody, for use in therapy, in particular for the treatment of Alzheimer's disease, mild Alzheimer's disease, prodromal Alzheimer's disease or for the prevention of the progression of mild cognitive impairment to Alzheimer's disease.

The ~~invention~~ present disclosure further provides a pharmaceutical composition, comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, with one or more pharmaceutically acceptable carriers, diluents, or excipients, in combination with a pharmaceutical composition of an anti-N3pGlu Abeta monoclonal antibody, with one or more pharmaceutically acceptable carriers, diluents, or excipients.

In addition, the ~~invention~~ present disclosure provides a kit, comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, and an anti-N3pGlu Abeta monoclonal antibody. The ~~invention~~ present disclosure further provides a kit, comprising a pharmaceutical composition, comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, with one or more pharmaceutically acceptable carriers, diluents, or excipients, and a pharmaceutical composition, comprising an anti-N3pGlu Abeta monoclonal antibody with one or more pharmaceutically acceptable carriers, diluents, or excipients. As used herein, a "kit" includes separate containers of each component, wherein one component is a compound of Formula I, or a pharmaceutically acceptable salt thereof, and another component is an anti-N3pGlu Abeta monoclonal antibody, in a single package. A "kit" may also include separate containers of each component, wherein one component is a compound of Formula I, or a pharmaceutically acceptable salt thereof, and another component is an anti-N3pGlu Abeta monoclonal antibody, in separate packages with instructions to administer each component as a combination.

The ~~invention~~ present disclosure further provides the use of a combination of a compound of the Formula I, or a pharmaceutically acceptable salt thereof, and an effective amount of an anti-N3pGlu Abeta monoclonal antibody, for the manufacture of a medicament for the

treatment of Alzheimer's disease, mild Alzheimer's disease, prodromal Alzheimer's disease or for the prevention of the progression of mild cognitive impairment to Alzheimer's disease.

One of ordinary skill in the art will appreciate and recognize that "anti-N3pGlu Abeta monoclonal antibody", and the specific antibodies, "B12L" and "R17L" are identified and disclosed along with methods for making and using said antibodies by one of ordinary skill in the art, in U.S. Patent No. 8,679,498 B2, entitled "Anti-N3pGlu Amyloid Beta Peptide Antibodies and Uses Thereof", issued March 25, 2014 (USSN 13/810,895). See for example Table 1 of U.S. Patent No. 8,679,498 B2.

In addition, amino acid sequences for certain antibodies used in the present disclosure ~~invention~~ are provided below in Table A:

Table A-Antibody SEQ ID NOs

Antibody	Light Chain	Heavy Chain	LCVR	HCVR
B12L	12	13	9	10
R17L	12	14	9	11

A cognitive or neurodegenerative disease includes Alzheimer's disease, mild Alzheimer's disease, mild cognitive impairment, prodromal Alzheimer's disease, cerebral amyloid angiopathy (CAA), Down's syndrome, and the like.

As used herein, the terms "treating", "to treat", or "treatment", includes restraining, slowing, stopping, reducing, or reversing the progression or severity of an existing symptom, disorder, condition, or disease.

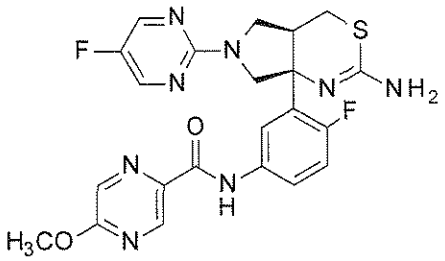
As used herein, the term "patient" refers to a human.

The term "inhibition of production of Abeta peptide" is taken to mean decreasing of *in vivo* levels of Abeta peptide in a patient.

As used herein, the term "effective amount" refers to the amount or dose of compound of Formula I, or a pharmaceutically acceptable salt thereof, and to the amount or dose of an anti-N3pGlu Abeta monoclonal antibody which, upon single or multiple dose administration to the patient, provides the desired effect in the patient under diagnosis or treatment. It is understood that the combination therapy of the present

WE CLAIM:

1. Use of ~~A method of treating Alzheimer's disease in a patient, comprising administering to a patient in need of such treatment an effective amount of~~ a compound of the formula:



,

or a pharmaceutically acceptable salt thereof, in combination with an effective amount of an anti-N3pGlu Abeta monoclonal antibody in the manufacture of a medicament for treating Alzheimer's disease.

2. The ~~method~~ use according to claim 1 wherein the anti-N3pGlu Abeta monoclonal antibody is B12L or R17L.

3. The use ~~method~~ according to either claim 1 or claim 2 wherein the anti-N3pGlu Abeta monoclonal antibody is B12L.

4. The use ~~method~~ according to any one of claims 1 to 3 wherein the compound is N-[3-[(4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4a,5,6,7-tetrahydropyrrolo[3,4-d][1,3]thiazin-7a(4H)-yl]-4-fluoro-phenyl]-5-methoxy-pyrazine-2-carboxamide.

5. The use ~~method~~ according to any one of claims 1 to 4 wherein the compound is crystalline Form 2 N-[3-[(4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4a,5,6,7-tetrahydropyrrolo[3,4-d][1,3]thiazin-7a(4H)-yl]-4-fluoro-phenyl]-5-methoxy-pyrazine-2-carboxamide.

6. The use ~~method~~ according to claim 5 wherein the crystalline Form 2 N-[3-[(4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4a,5,6,7-tetrahydropyrrolo[3,4-d][1,3]thiazin-7a(4H)-yl]-4-fluoro-phenyl]-5-methoxy-pyrazine-2-carboxamide is characterized by a substantial peak in the X-ray diffraction spectrum, at diffraction angle 2-theta of 11.8°, with one or more

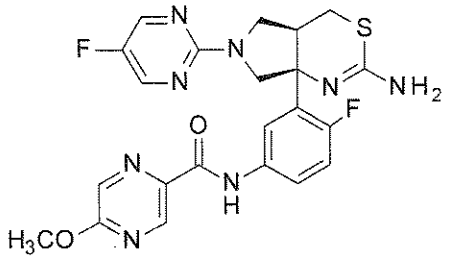
peaks selected from the group consisting of 18.6°, 19.3°, and 26.7°; with a tolerance for the diffraction angles of 0.2 degrees.

7. The use ~~method~~ according to any one of claims 1 to 6 wherein the compound and the anti-N3pGlu Abeta monoclonal antibody are to be administered simultaneously.

8. The use ~~method~~ according to according to any one of claims 1 to 6 wherein the compound is to be administered prior to the administration of the anti-N3pGlu Abeta monoclonal antibody.

9. The use ~~method~~ according to any one of claims 1 to 6 wherein the anti-N3pGlu Abeta monoclonal antibody is to be administered prior to the administration of the compound.

10. A pharmaceutical composition, comprising a compound of the formula:



,

or a pharmaceutically acceptable salt thereof, with one or more pharmaceutically acceptable carriers, diluents, or excipients, in combination with a pharmaceutical composition of anti-N3pGlu Abeta monoclonal antibody, with one or more pharmaceutically acceptable carriers, diluents, or excipients.

11. The pharmaceutical composition according to claim 10 wherein the anti-N3pGlu Abeta monoclonal antibody is B12L or R17L.

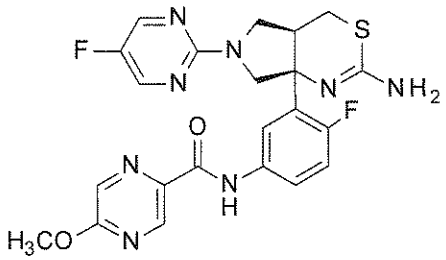
12. The pharmaceutical composition according to either claim 10 or claim 11 wherein the anti-N3pGlu Abeta monoclonal antibody is B12L.

13. The pharmaceutical composition according to any one of claims 10 to 12 wherein the compound is N-[3-[(4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4a,5,6,7-tetrahydropyrrolo[3,4-d][1,3]thiazin-7a(4H)-yl]-4-fluoro-phenyl]-5-methoxy-pyrazine-2-carboxamide.

14. The pharmaceutical composition according to any one of claims 10 to 13 wherein the compound is crystalline Form 2 N-[3-[(4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4a,5,6,7-tetrahydropyrrolo[3,4-d][1,3]thiazin-7a(4H)-yl]-4-fluoro-phenyl]-5-methoxy-pyrazine-2-carboxamide.

15. The pharmaceutical composition according to claim 14 wherein the crystalline Form 2 N-[3-[(4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4a,5,6,7-tetrahydropyrrolo[3,4-d][1,3]thiazin-7a(4H)-yl]-4-fluoro-phenyl]-5-methoxy-pyrazine-2-carboxamide is characterized by a substantial peak in the X-ray diffraction spectrum, at diffraction angle 2-theta of 11.8°, with one or more peaks selected from the group consisting of 18.6°, 19.3°, and 26.7°; with a tolerance for the diffraction angles of 0.2 degrees.

16. A compound of the formula:



or a pharmaceutically acceptable salt thereof, in combination with an anti-N3pGlu Abeta monoclonal antibody for use in the treatment of Alzheimer's disease.

17. The ~~use~~ compound according to claim 16 wherein the anti-N3pGlu Abeta monoclonal antibody is B12L or R17L.

18. The compound ~~use~~ according to either claim 16 or claim 17 wherein the anti-N3pGlu Abeta monoclonal antibody is B12L.

19. The compound ~~use~~ according any one of claims 16 to 18 wherein the compound is N-[3-[(4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4a,5,6,7-tetrahydropyrrolo[3,4-d][1,3]thiazin-7a(4H)-yl]-4-fluoro-phenyl]-5-methoxy-pyrazine-2-carboxamide.

20. The compound ~~use~~ according any one of claims 16 to 19 wherein the compound is crystalline Form 2 N-[3-[(4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-

4a,5,6,7-tetrahydropyrrolo[3,4-d][1,3]thiazin-7a(4H)-yl]-4-fluoro-phenyl]-5-methoxy-pyrazine-2-carboxamide.

21. The compound ~~use~~ according to claim 20 wherein the crystalline Form 2 N-[3-[(4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4a,5,6,7-tetrahydropyrrolo[3,4-d][1,3]thiazin-7a(4H)-yl]-4-fluoro-phenyl]-5-methoxy-pyrazine-2-carboxamide is characterized by a substantial peak in the X-ray diffraction spectrum, at diffraction angle 2-theta of 11.8°, with one or more peaks selected from the group consisting of 18.6°, 19.3°, and 26.7°; with a tolerance for the diffraction angles of 0.2 degrees.