

Having described our invention, we claim:

1. Use of a composition comprising low dose pioglitazone in the manufacture of a medicament for treating cognitive impairment of the Alzheimer's type, wherein the composition comprises from about 0.5 to about 9 milligrams of pioglitazone.
2. The use of claim 1, wherein said treating comprises delaying the onset of cognitive impairment of the Alzheimer's type.
3. The use of claim 1, wherein said treating comprises delaying the onset of cognitive impairment of the Alzheimer's type in a human subject at increased risk of developing cognitive impairment of the Alzheimer's type within the next 5-7 years, said risk based upon the subject's age and rs10524523 genotype.
4. The use of claim 1, claim 2 or claim 3, wherein said low dose pioglitazone is to be administered in unit dosage form.
5. The use of claim 4, wherein said unit dosage form comprises from 0.5 to 6 milligrams of pioglitazone.
6. The use of claim 4, wherein said unit dosage form comprises from 0.5 to 1.5 milligrams of pioglitazone.

7. Use of low dose pioglitazone in the manufacture of a pharmaceutical formulation for the treatment of cognitive impairment of the Alzheimer's type, wherein the low dose pioglitazone comprises from about 0.5 to about 9 milligrams of pioglitazone.
8. The use of claim 7, wherein said pharmaceutical formulation is a tablet.
9. The use of claim 7, wherein said pharmaceutical formulation is a capsule.
10. The use of claim 7, wherein said pharmaceutical formulation is a caplet.
11. The use of claim 7, wherein said pharmaceutical formulation is a liquid.
12. The use of claim 7, wherein said pharmaceutical formulation is a semi-solid.
13. The use of claim 7, wherein said pharmaceutical formulation is a solid.
14. The use of any one of claims 7-13, wherein said pioglitazone is to be administered at a dosage that provides an AUC of from about 0.15 $\mu\text{g}\cdot\text{h/mL}$ to about 3.6 $\mu\text{g}\cdot\text{h/mL}$.
15. Use of a composition comprising low dose pioglitazone in the manufacture of a medicament for the treatment of cognitive decline, wherein the composition comprises from about 0.5 to about 9 milligrams of pioglitazone.
16. Use of low dose pioglitazone in the manufacture of a medicament for treating cognitive impairment of the Alzheimer's type in a human subject in need thereof, wherein the composition comprises from about 0.5 to about 9 milligrams of pioglitazone.
17. The use according to claim 16, wherein said treating comprises delaying the onset of cognitive impairment of the Alzheimer's type.

28. The use according to any of claims 16-25, wherein said subject does not have an ApoE genotype of $\epsilon 2/\epsilon 2$ or $\epsilon 2/\epsilon 3$ ~~one or two APOE2 alleles.~~

29. The use according to any of claims 16-28, wherein said low dose pioglitazone is to be administered once daily.

30. The use according to any of claims 17-29, wherein said delaying comprises delaying the onset of impairment in episodic memory.

31. Use of low dose pioglitazone in the manufacture of a medicament for treating cognitive decline in a human subject in need thereof, wherein the low dose pioglitazone comprises from about 0.5 to about 9 milligrams of pioglitazone.

32. A method of determining increased risk in developing cognitive impairment of the Alzheimer's type in a human subject at a predetermined age or age range, comprising:
detecting from a biological sample of said subject the rs10524523 genotype of said subject, wherein each allele of the rs10524523 genotype is assigned as:

- (a) short (S, less than 19 T residues);
- (b) long (L, 19-29 residues); or
- (c) very long (VL, 30 or more residues); and

determining from said rs10524523 genotype whether said subject is at increased risk in developing cognitive impairment of the Alzheimer's type at said predetermined age or age range, wherein:

- (1) age greater than about 62 and L,L or L,VL indicates increased risk;
- (2) age greater than about 62 and VL,VL does not indicate increased risk;
- (3) age greater than about 74 and S,L indicates increased risk;
- (4) age greater than about 77 and S,S indicates increased risk; and
- (5) age greater than about 76 and S,VL indicates increased risk.

33. The method of claim 32, wherein said determining further comprises detecting from a biological sample of said subject the ApoEAPOE genotype of said subject, wherein the presence of an ApoE genotype of $\epsilon 2/\epsilon 2$ or $\epsilon 2/\epsilon 3$ ~~APOE2 allele in said genotype~~ indicates the subject is not at increased risk.

34. A method of determining whether to administer low dose pioglitazone to a human subject for treatment of cognitive impairment of the Alzheimer's type, comprising:

detecting from a biological sample of said subject the rs10524523 genotype of the subject, wherein each allele is assigned as:

(a) short (S, less than 19 T residues);

(b) long (L, 19-29 residues); or

(c) very long (VL, 30 or more residues); and

determining from said rs10524523 genotype and from the age of said human subject whether to administer low dose pioglitazone to said subject for treatment of cognitive impairment of the Alzheimer's type, wherein:

(1) age greater than about 62 and L,L or L,VL indicates treatment;

(2) age greater than about 62 and VL,VL does not indicate treatment;

(3) age greater than about 74 and S,L indicates treatment;

(4) age greater than about 77 and S,S indicates treatment; and

(5) age greater than about 76 and S,VL indicates treatment

wherein the low dose pioglitazone comprises from about 0.5 to about 9 milligrams of pioglitazone.

35. The method of claim 34, wherein said determining further comprises detecting from a biological sample of said subject the ApoE genotype of said subject, wherein the presence of an ApoE genotype of $\epsilon 2/\epsilon 2$ or $\epsilon 2/\epsilon 3$ ~~APOE2 allele in said genotype~~ does not indicate treatment.

36. The method of claim 34 or claim 35, wherein said subject has normal cognition.

37. Use of low dose pioglitazone in the manufacture of a medicament for delaying the onset of Alzheimer's disease in a subject at risk of developing Alzheimer's disease comprising:

determining the presence of at least one genetic variant of the TOMM40 gene, wherein said genetic variant is an rs10524523 allele, wherein the presence of said at least one genetic variant indicates a risk of developing Alzheimer's disease; and wherein the low dose pioglitazone comprises from about 0.5 to about 9 milligrams of pioglitazone.

38. Use of low dose pioglitazone in the manufacture of a medicament for delaying the onset of mild cognitive impairment in a subject at risk of developing Alzheimer's disease comprising:

determining the presence of at least one genetic variant of the TOMM40 gene, wherein said genetic variant is an rs10524523 allele, wherein the presence of said at least one genetic variant indicates a risk of developing Alzheimer's disease; and wherein the low dose pioglitazone comprises from about 0.5 to about 9 milligrams of pioglitazone.

39. Use of low dose pioglitazone in the manufacture of a medicament for of delaying the onset of amnesic mild cognitive impairment in a subject at risk of developing Alzheimer's disease comprising:

determining the presence of at least one genetic variant of the TOMM40 gene, wherein said genetic variant is an rs10524523 allele, wherein the presence of said at least one genetic variant indicates a risk of developing Alzheimer's disease; and wherein the low dose pioglitazone comprises from about 0.5 to about 9 milligrams of pioglitazone.

40. Use of low dose pioglitazone in the manufacture of a medicament for delaying the onset of preclinical Alzheimer's disease in a subject at risk of developing Alzheimer's disease comprising:

determining the presence of at least one genetic variant of the TOMM40 gene, wherein said genetic variant is an rs10524523 allele, wherein the presence of said at least one genetic variant indicates a risk of developing Alzheimer's disease; and wherein the low dose pioglitazone comprises from about 0.5 to about 9 milligrams of pioglitazone.

41. Use of low dose pioglitazone in the manufacture of a medicament for delaying the onset of prodromal Alzheimer's disease in a subject at risk of developing Alzheimer's disease comprising:

determining the presence of at least one genetic variant of the TOMM40 gene, wherein said genetic variant is an rs10524523 allele, wherein the presence of said at least one genetic variant indicates a risk of developing Alzheimer's disease; and wherein the low dose pioglitazone comprises from about 0.5 to about 9 milligrams of pioglitazone.

42. Use of low dose pioglitazone in the manufacture of a medicament for delaying the onset of physiological changes associated with Alzheimer's disease in a subject at risk of developing Alzheimer's disease comprising:

determining the presence of at least one genetic variant of the TOMM40 gene, wherein said genetic variant is an rs10524523 allele, wherein the presence of said at least one genetic variant indicates a risk of developing Alzheimer's disease; and wherein the low dose pioglitazone comprises from about 0.5 to about 9 milligrams of pioglitazone.

43. The use according to any one of claims 37-42 wherein the pioglitazone is to be administered at a dosage of 0.5 mg to 9 mg per day.

44. The use according to any one of claims 37-42, wherein the pioglitazone is to be administered at a dosage that provides an AUC of from about 0.15 $\mu\text{g}\cdot\text{h/mL}$ to about 3.6 $\mu\text{g}\cdot\text{h/mL}$.

75. The use of claim 16, wherein the subject has mild cognitive impairment.
76. The use of claim 16, wherein the subject has mild Alzheimer's disease.
77. The use of claim 3, wherein determination of said risk based upon the subject's age and rs10524523 genotype comprises detecting from a biological sample of said subject the rs10524523 genotype of said subject, wherein each allele of the rs10524523 genotype is assigned as:
- (a) short (S, less than 19 T residues);
 - (b) long (L, 19-29 residues); or
 - (c) very long (VL, 30 or more residues); and
- determining from said rs10524523 genotype whether said subject is at increased risk in developing cognitive impairment of the Alzheimer's type at said predetermined age or age range, wherein:
- (1) age greater than about 62 and L,L or L,VL indicates increased risk;
 - (2) age greater than about 62 and VL,VL does not indicate increased risk;
 - (3) age greater than about 74 and S,L indicates increased risk;
 - (4) age greater than about 77 and S,S indicates increased risk; and
 - (5) age greater than about 76 and S,VL indicates increased risk.
78. The use of claim 77, wherein said determining further comprises detecting from a biological sample of said subject the ApoE/APOE genotype of said subject, wherein the presence of an ApoE genotype of $\epsilon 2/\epsilon 2$ or $\epsilon 2/\epsilon 3$ ~~APOE2 allele in said genotype~~ indicates the subject is not at increased risk.
79. The use according to claims 1-31 or 37-78, wherein the pioglitazone comprises a pharmaceutically acceptable salt of pioglitazone.
80. The use of claim 79, wherein the pioglitazone comprises pioglitazone hydrochloride.
81. The method according to claims 34-36, wherein the pioglitazone comprises a pharmaceutically acceptable salt of pioglitazone.
82. The method according to claim 81, wherein the pioglitazone comprises pioglitazone hydrochloride.