

Having described our invention, we claim:

1. Use of aA composition comprising low dose pioglitazone in the manufacture of a medicament for use in treating cognitive impairment of the Alzheimer's type, wherein the composition comprises from 0.5 to 9 milligrams of pioglitazone.
2. ~~The composition-use~~ of claim 1, wherein said treating comprises delaying the onset of cognitive impairment of the Alzheimer's type.
3. ~~The composition-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 composition-use~~ of claim 1, claim 2 or claim 3, wherein said low dose pioglitazone is to be administered in unit dosage form.
5. ~~The composition-use~~ of claim 4, wherein said unit dosage form comprises from 0.5 to 12 6 milligrams of pioglitazone.
6. ~~The composition-use~~ of claim 4, wherein said unit dosage form comprises from 0.5 to 40 1.5 milligrams of pioglitazone.
7. ~~The composition of claim 4, wherein said unit dosage form comprises from 1.5 to 12 milligrams of pioglitazone.~~
8. ~~The composition of claim 4, wherein said unit dosage form comprises from 1.5 to 10 milligrams of pioglitazone.~~
9. ~~The composition of claim 4, wherein said unit dosage form comprises from 0.5 to 8 milligrams of pioglitazone.~~

~~10. The composition of claim 4, wherein said unit dosage form comprises from 1.5 to 6 milligrams of pioglitazone.~~

~~417. 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 0.5 to 9 milligrams of pioglitazone.~~

~~428. The use of claim 417, wherein said pharmaceutical formulation is a tablet.~~

~~439. The use of claim 417, wherein said pharmaceutical formulation is a capsule.~~

~~4410. The use of claim 417, wherein said pharmaceutical formulation is a caplet.~~

~~4511. The use of claim 417, wherein said pharmaceutical formulation is a liquid.~~

~~4612. The use of claim 417, wherein said pharmaceutical formulation is a semi-solid.~~

~~4713. The use of claim 417, wherein said pharmaceutical formulation is a solid.~~

~~4814. The use of any one of claims 417-4713, 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 $\mu\text{g}\cdot\text{h/mL}$.~~

~~4915. A Use of a composition comprising low dose pioglitazone in the manufacture of a medicament for use in the treatment of cognitive decline, wherein the composition comprises from 0.5 to 9 milligrams of pioglitazone.~~

~~2016. A method of 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, comprising administering to said subject a low dose pioglitazone wherein the composition comprises from 0.5 to 9 milligrams of pioglitazone.~~

~~2417. The method of use according to claim 2016, wherein said treating comprises delaying the onset of cognitive impairment of the Alzheimer's type.~~

2218. The ~~method of~~use according to claim 2016 or claim 2417, wherein said subject is at increased risk in 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.

2319. The ~~method of~~use according to claim 2016 or claim 2417, wherein said subject is at increased risk in developing cognitive impairment of the Alzheimer's type within the next 5-7 years, said risk based upon the subject's age.

2420. The ~~method of~~use according to any of claims 2016-2319, wherein said subject is at least 50 years old.

2521. The ~~method of~~use according to any of claims 2016-2319, wherein said subject is at least 55 years old.

2622. The ~~method of~~use according to any of claims 2016-2319, wherein said subject is at least 60 years old.

2723. The ~~method of~~use according to any of claims 2016-2319, wherein said subject is at least 62 years old.

2824. The ~~method of~~use according to any of claims 2016-2319, wherein said subject is at least 68 years old.

2925. The ~~method of~~use according to any of claims 2016-2319, wherein said subject is at least 70 years old.

3026. The ~~method of~~use according to any of claims 2016-2925, wherein said subject is a Caucasian subject.

3127. The ~~method of~~use according to any of claims 2016-2925, wherein said subject is a non-Caucasian subject.

3228. ~~The method of use according to~~ any of claims 2016-2925, wherein said subject does not have one or two APOE2 alleles.

3329. ~~The method of use according to~~ any of claims 2016-3228, wherein said administering is low dose pioglitazone is to be administered once daily.

3430. ~~The method of use according to~~ any of claims 2417-3329, wherein said delaying comprises delaying the onset of impairment in episodic memory.

3531. ~~A method of Use of low dose pioglitazone in the manufacture of a medicament for treating cognitive decline in a human subject in need thereof, comprising administering to said subject low dose pioglitazone wherein the low dose pioglitazone comprises from 0.5 to 9 milligrams of pioglitazone.~~

3632. 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.

3733. The method of claim 3632, wherein said determining further comprises detecting from a biological sample of said subject the APOE genotype of said subject, wherein the presence of an APOE2 allele in said genotype indicates the subject is not at increased risk.

3834. 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 0.5 to 9 milligrams of pioglitazone.

3935. The method of claim 3834, wherein said determining further comprises detecting from a biological sample of said subject the APOE genotype of said subject, wherein the presence of an APOE2 allele in said genotype does not indicate treatment.

4036. The method of claim 3834 or claim 3935, wherein said subject has normal cognition.

~~4137. A method of~~ 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:

a- determining the presence of at least one genetic variant of the TOMM40 gene, wherein said genetic variant is an rs10524523 allele, ~~and~~ 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 0.5 to 9 milligrams of pioglitazone.

~~b. administering an effective amount of low dose pioglitazone or a salt thereof to said subject thereby delaying the onset of Alzheimer's disease in said subject.~~

4238. A method of 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:

a. determining the presence of at least one genetic variant of the TOMM40 gene, wherein said genetic variant is an rs10524523 allele, ~~and 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 0.5 to 9 milligrams of pioglitazone.

~~b. administering an effective amount of low dose pioglitazone or a salt thereof to said subject thereby delaying the onset of mild cognitive impairment in said subject.~~

4339. Use of low dose pioglitazone in the manufacture of a medicament forA method of delaying the onset of amnestic mild cognitive impairment in a subject at risk of developing Alzheimer's disease comprising:

a. determining the presence of at least one genetic variant of the TOMM40 gene, wherein said genetic variant is an rs10524523 allele, ~~and 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 0.5 to 9 milligrams of pioglitazone.

~~b. administering an effective amount of low dose pioglitazone or a salt thereof to said subject thereby delaying the onset of amnestic mild cognitive impairment in said subject.~~

4440. Use of low dose pioglitazone in the manufacture of a medicament forA method of delaying the onset of preclinical Alzheimer's disease in a subject at risk of developing Alzheimer's disease comprising:

a. determining the presence of at least one genetic variant of the TOMM40 gene, wherein said genetic variant is an rs10524523 allele, ~~and 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 0.5 to 9 milligrams of pioglitazone.

~~b. administering an effective amount of low dose pioglitazone or a salt thereof to said subject thereby delaying the onset of preclinical Alzheimer's disease in said subject.~~

4541. Use of low dose pioglitazone in the manufacture of a medicament for~~A method of~~ delaying the onset of prodromal Alzheimer's disease in a subject at risk of developing Alzheimer's disease comprising:

a. determining the presence of at least one genetic variant of the TOMM40 gene, wherein said genetic variant is an rs10524523 allele, and 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 0.5 to 9 milligrams of pioglitazone.

~~b. administering an effective amount of low dose pioglitazone or a salt thereof to said subject thereby delaying the onset of prodromal Alzheimer's disease in said subject.~~

4642. Use of low dose pioglitazone in the manufacture of a medicament for~~A method of~~ delaying the onset of physiological changes associated with Alzheimer's disease in a subject at risk of developing Alzheimer's disease comprising:

a. determining the presence of at least one genetic variant of the TOMM40 gene, wherein said genetic variant is an rs10524523 allele, and 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 0.5 to 9 milligrams of pioglitazone. ~~b. administering an effective amount of low dose pioglitazone or a salt thereof to said subject thereby delaying the onset of physiological changes associated with Alzheimer's disease in said subject.~~

4743. ~~The method of~~use according to any one of claims 4137-46-42 wherein the pioglitazone is to be administered at a dosage of 0.5 mg to 9 mg per day.

4844. ~~The method of~~use according to any one of claims 4137-4642, 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 $\mu\text{g}\cdot\text{h/mL}$.

4945. The ~~method-use~~ according to any one of claims 37-4241-46, wherein ~~said administration step comprises administering the pioglitazone or a salt thereof~~ is to be administered to said subject in accordance with a daily treatment regimen.

5046. The ~~method-use~~ according to claim 4945, wherein ~~said administration step comprises administering the pioglitazone or a salt thereof~~ is to be administered to said subject as a pharmaceutical formulation.

5147. The ~~method-use~~ according to claim 5046, wherein said pharmaceutical formulation is a tablet.

5248. The ~~method-use~~ according to claim 5046, wherein said pharmaceutical formulation is a capsule.

5349. The ~~method-use~~ according to claim 5046, wherein said pharmaceutical formulation is a caplet.

5450. The ~~method-use~~ according to claim 5046, wherein said pharmaceutical formulation is a liquid.

5551. The ~~method-use~~ according to claim 5046, wherein said pharmaceutical formulation is a semi-solid.

5652. The ~~method-use~~ according to claim 5046, wherein said pharmaceutical formulation is a solid.

5753. The ~~method-of-use~~ according to claim 5147, wherein said tablet is an orally disintegrating tablet.

5854. The ~~method-of-use~~ according to claim 5551, wherein said semi-solid pharmaceutical formulation is selected from a group of semi-solid pharmaceutical formulations consisting of a gel, cream, lotion, ointment, salve and balm.

~~5955. The method of~~use according to claim 5450, wherein ~~said administration step comprises orally administering the liquid pioglitazone pharmaceutical formulation~~ is to be administered orally into the subject.

~~6056.~~ The ~~method of~~use according to claim ~~5450~~, wherein ~~said administration step comprises injecting the liquid pioglitazone pharmaceutical formulation~~ is to be administered by injection into said subject.

~~6157.~~ The ~~method of~~use according to claim ~~5450~~, wherein ~~said administration step comprises intra-nasally administering the liquid pioglitazone pharmaceutical formulation~~ is to be administered intra-nasally to said subject.

~~6258.~~ The ~~method of~~use according to claim ~~5551~~, wherein ~~said administration step comprises: intra-nasally administering the semi-solid pioglitazone pharmaceutical formulation~~ is to be administered intra-nasally to said subject.

~~6359.~~ The ~~method of~~use according to claim ~~5551~~, wherein ~~said administration step comprises topically administering said semi-solid pioglitazone pharmaceutical formulation~~ is to be administered topically to said subject.

~~6460.~~ The ~~method of~~use according to claim ~~5652~~, wherein said pharmaceutical formulation is a powder.

~~6561.~~ The ~~method of~~use according to claim ~~5652~~, wherein ~~said administration step comprises topically administering said solid pioglitazone pharmaceutical formulation~~ is to be administered topically to said subject.

~~6662.~~ The ~~method of~~use according to any one of claims ~~4137-4642~~, wherein said subject has normal cognition.

~~6763.~~ The ~~method of~~use according to any one of claims ~~4137-4642~~, wherein said ~~administration occurs~~low dose pioglitazone is to be administered when said subject is younger than 60.

~~6864.~~ The ~~method of~~use according to any one of claims ~~4137-4642~~, wherein said ~~administration occurs~~low dose pioglitazone is to be administered when said subject is between the ages of 60 and 70.

6965. The ~~method of~~use according to any one of claims 4137-4642, wherein said subject has one copy of the long TOMM40 rs10524523 allele.

7066. The ~~method of~~use according to any one of claims 4137-4642, wherein said subject has two copies of the long TOMM40 rs10524523 allele.

~~7167.~~ The ~~method of~~use according to any one of claims ~~4137-4642~~, wherein said subject has an increased risk of developing Alzheimer's disease as compared to a control subject.

~~7268.~~ The ~~method of~~use according to claim ~~7167~~, wherein said control subject carries at least one copy of the TOMM40 rs10524523 allele comprising a poly-T repeat that is less than 19 nucleotides in length.

~~7369.~~ The ~~method of~~use according to claim ~~7167~~, wherein said control subject does not have a copy of the TOMM40 rs10524523 allele comprising a poly-T repeat that is ~~greater than 19 or~~ greater nucleotides in length.

~~7470.~~ The ~~method of~~use according to claims ~~5046-6561~~, wherein the pharmaceutical formulation is a bioequivalent formulation.

~~7571.~~ The ~~method of~~use according to claims ~~5046-6561~~, wherein the pharmaceutical formulation is a pharmaceutically equivalent formulation.

~~7672.~~ The ~~method of~~use according to claims ~~5046-6561~~, wherein the pharmaceutical formulation is a therapeutically equivalent formulation.

~~77.~~ The ~~method of~~ claims ~~20, 35 and 38~~, wherein said unit dosage comprises from 0.5 to 12 mg of pioglitazone.

~~78.~~ The ~~method of~~ claims ~~20, 35 and 38~~, wherein said unit dosage comprises from 0.5 to 10 mg of pioglitazone.

~~7973.~~ The ~~method of~~use according to ~~claims 2016, and 35-31 and the method of claim 3438~~, wherein said unit dosage comprises from 0.5 to ~~8-6~~ mg of pioglitazone.

~~8074.~~ The ~~method of~~use according to claims ~~2016, and 35-31 and the method of claim 3834~~, wherein said unit dosage comprises from ~~1.50.5~~ to ~~6-1.5~~ mg of pioglitazone.

~~81.~~ Low dose pioglitazone for use in the treatment of cognitive impairment of the Alzheimer's type.

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 genotype of said subject, wherein the presence of an APOE2 allele in said genotype indicates the subject is not at increased risk.