CLAIMS

We claim:

1. A combination comprising a GLP1R agonist in combination with metformin for treating type 2 diabetes, for lowering blood-glucose in a subject, for increasing the therapeutic effectiveness of metformin, for increasing the therapeutic effectiveness of a glucagon-like peptide 1 receptor agonist ("GLP1R agonist"), for increasing the oral bioavailability of a GLP1R agonist, for use in treating a condition selected from the group consisting of metabolic syndrome, glucose intolerance, hyperglycemia, dyslipidemia, hypertriglyceridemia, syndrome X, insulin resistance, impaired glucose tolerance (IGT), obesity, diabetic dyslipidemia, hyperlipidemia, arteriosclerosis, atherosclerosis, other cardiovascular diseases, hypertension, metabolic disorders where agonism of GLP1R is beneficial, or complications resulting from or associated with diabetes, for treating type 1 diabetes, for treating obesity, for slowing gastric emptying, for lowering an HbA1c levels, for increasing glucose-dependent insulin secretion, for suppressing glucagon secretion, for treating an eating disorder, or for modulating a human GLP1R receptor, wherein the GLP1R agonist is to be administered orally and is (S)-3-(4'-cyano-biphenyl-4-yl)-2-{[(3R,7S)-3-[4-(3,4-dichloro-benzyloxy)-phenyl]-1-methyl-2-oxo-6-((S)-1-phenyl-propyl)-2,3,5,6,7,8-hexahydro-1*H*-4-oxa-1,6-diaza-anthracene-7-carbonyl]-amino}-propionic acid or a pharmaceutically acceptable salt thereof, or (S)-2-{[(3S,8S)-3-[4-(3,4-dichloro-benzyloxy)-phenyl]-7-((S)-1-phenyl-propyl)-2,3,6,7,8,9-hexahydro-[1,4]dioxino[2,3-g]isoquinoline-8-carbonyl]-amino}-3-[4-(2,3-dimethyl-pyridin-4-yl)-phenyl]-propionic acid or a pharmaceutically acceptable salt thereof.

2. The combination for the use of claim 1, wherein the metformin is metformin hydrochloride or 1,1-dimethylbiguanide.

3. The combination for the use of any of the previous claims, wherein the GLP1R agonist has an absolute bioavailability after oral administration to a subject of at least 1%.

4. The combination for the use of any of the previous claims, wherein the GLP1R agonist is (S)-3-(4'-cyano-biphenyl-4-yl)-2-{[(3R,7S)-3-[4-(3,4-dichloro-benzyloxy)-phenyl]-1-methyl-2-oxo-6-((S)-1-phenyl-propyl)-2,3,5,6,7,8-hexahydro-1*H*-4-oxa-1,6-diaza-anthracene-7-carbonyl]-amino}-propionic acid or a pharmaceutically acceptable salt thereof.

5. The combination for the use of any one of claims 1 to 3, wherein the GLP1R agonist is (S)-2-{[(3S,8S)-3-[4-(3,4-dichloro-benzyloxy)-phenyl]-7-((S)-1-phenyl-propyl)-2,3,6,7,8,9-hexahydro-[1,4]dioxino[2,3-g]isoquinoline-8-carbonyl]-amino}-3-[4-(2,3-dimethyl-pyridin-4-yl)-phenyl]-propionic acid or a pharmaceutically acceptable salt thereof.

6. The combination for the use of any of the previous claims, wherein the GLP1R agonist and the metformin are to be administered to the subject simultaneously, or wherein the GLP1R agonist and the metformin are to be administered, such that one is to be administered subsequent to the other.

7. The combination for the use of any of the previous claims, wherein the GLP1R agonist and the metformin are both to be administered orally in the same dosage form.

8. The combination for the use of any of the previous claims, wherein the subject is a human.

9. The combination for the use of any of the previous claims, wherein the amount of GLP1R agonist is between 1 mg/day and 1000 mg/day, and wherein the amount of metformin is between 250 mg/day and 2500 mg/day.

10. The combination for the use of any one of claims 1 to 8, wherein the GLP1R agonist is to be administered in a suboptimal amount, or wherein the metformin is to be administered in a suboptimal amount, or wherein the GLP1R agonist and the metformin are both to be administered in suboptimal amounts.

11. A pharmaceutical composition comprising a glucagon-like peptide 1 receptor ("GLP1R agonist") agonist, metformin, and at least one pharmaceutically acceptable carrier, wherein the GLP1R agonist is (S)-3-(4'-cyano-biphenyl-4-yl)-2-{[(3R,7S)-3-[4-(3,4-dichloro-benzyloxy)-phenyl]-1-methyl-2-oxo-6-((S)-1-phenyl-propyl)-2,3,5,6,7,8-hexahydro-1*H*-4-oxa-1,6-diaza-anthracene-7-carbonyl]-amino}-propionic acid or a pharmaceutically acceptable salt thereof, or (S)-2-{[(3S,8S)-3-[4-(3,4-dichloro-benzyloxy)-phenyl]-7-((S)-1-phenyl-propyl)-2,3,6,7,8,9-hexahydro-[1,4]dioxino[2,3-g]isoquinoline-8-carbonyl]-amino}-3-[4-(2,3-dimethyl-pyridin-4-yl)-phenyl]-propionic acid or a pharmaceutically acceptable salt thereof.

12. The pharmaceutical composition of claim 11, wherein the GLP1R agonist is (S)-3-(4'-cyano-biphenyl-4-yl)-2-{[(3R,7S)-3-[4-(3,4-dichloro-benzyloxy)-phenyl]-1-methyl-2-oxo-6-((S)-1-phenyl-propyl)-2,3,5,6,7,8-hexahydro-1*H*-4-oxa-1,6-diaza-anthracene-7-carbonyl]-amino}-propionic acid or a pharmaceutically acceptable salt thereof.

13. The pharmaceutical composition of claim 11, wherein the GLP1R agonist is (S)-2-{[(3S,8S)-3-[4-(3,4-dichloro-benzyloxy)-phenyl]-7-((S)-1-phenyl-propyl)-2,3,6,7,8,9-hexahydro-[1,4]dioxino[2,3-g]isoquinoline-8-carbonyl]-amino}-3-[4-(2,3-dimethyl-pyridin-4-yl)-phenyl]-propionic acid or a pharmaceutically acceptable salt thereof.

14. The pharmaceutical composition of any one of claims 11 to 13, wherein the metformin is metformin hydrochloride or 1,1-dimethylbiguanide.

15. The pharmaceutical composition of any one of claims 11 or 13, wherein the GLP1R agonist has an absolute oral bioavailability of greater than 1%.

16. The pharmaceutical composition of claim 11, wherein the GLP1R agonist is (S)-3-(4'-cyano-biphenyl-4-yl)-2-{[(3R,7S)-3-[4-(3,4-dichloro-benzyloxy)-phenyl]-1-methyl-2-oxo-6-((S)-1-phenyl-propyl)-2,3,5,6,7,8-

hexahydro-1*H*-4-oxa-1,6-diaza-anthracene-7-carbonyl]-amino}-propionic acid or a pharmaceutically acceptable salt thereof;

wherein the amount of the GLP1R agonist is less than 250 mg;

wherein the amount of metformin is between 100 mg and 1000 mg;

wherein the weight to weight ratio of the GLP1 agonist to metformin is between 1:2 and 1:100,

optionally wherein the GLP1R agonist is (S)-3-(4'-cyano-biphenyl-4-yl)-2-{[(3R,7S)-3-[4-(3,4-dichloro-benzyloxy)-phenyl]-1-methyl-2-oxo-6-((S)-1-phenyl-propyl)-2,3,5,6,7,8-hexahydro-1*H*-4-oxa-1,6-diaza-anthracene-7-carbonyl]-amino}-propionic acid hydrochloride salt, and

optionally wherein the metformin is metformin hydrochloride or 1,1-dimethylbiguanide, and

optionally wherein the weight to weight ratio of the GLP1 agonist to metformin is between 1:2 and 1:20.