rate of decline of beta-cell function with time, they are associated with the side effects of weight gain and oedema.

It is known that DPIV inhibitors may be useful for the treatment of impaired glucose tolerance and diabetes mellitus, see International Patent Application No. W097/40832. Clinical data suggest that the glucose lowering that occurs in response to treatment with DPIV inhibitors is not accompanied by significant side effects such as weight gain and hypoglycaemia. In addition, pre-clinical data exist which suggest that DPIV inhibitors preserve beta-cell mass, see International Patent Application No. WO01/72290, raising the possibility that treatment with a DPIV inhibitor would decrease the rate of decline of beta-cell function that occurs with time in type 2 diabetes.

The current treatment paradigm in type 2 diabetes is to commence therapy with one class of oral agent, following 'failure' of diet and exercise, with addition of a second (and later a third) class of agent only when glycaemic control is no longer adequate on the initial agent(s), i.e. the treatment comprises first-line monotherapy followed by second-line combination therapy followed by third-line combination therapy. Thus, for example, the DPIV inhibitor sitagliptin phosphate (Januvia™) is approved for use in the US in combination with metformin or a PPARγ agonist only when the metformin or PPARγ agonist alone, with diet and exercise, does not provide adequate glycaemic control. Currently, no DPIV inhibitors are licensed for simultaneous commencement of therapy with a second class of anti-diabetic agent on initiation of oral therapy, after 'failure' of diet and exercise, in type 2 diabetes.

There is a need to find new and improved regimens for the treatment of type 2 diabetes. The present invention provides a novel first line, i.e. initial, combination therapy for the treatment of type 2 diabetes i.e. for the treatment of type 2 diabetes after 'failure' of diet and exercise. This method has the potential to provide greater efficacy than current monotherapy given alone without introducing any side-effect liability.

## SUMMARY ~~OF THE INVENTION~~

The present ~~invention~~ disclosure provides the use of a combination of a DPIV inhibitor and metformin or a thiazolidinedione as first-line combination therapy for treatment of type 2 diabetes, i.e. to be used in patients who do not have adequate glycaemic control on treatment with diet and exercise alone.

In one aspect, there is provided the use of a DPIV inhibitor, which binds to DPIV and inhibits DPIV activity, in combination with metformin or a thiazolidinedione in the manufacture of a medicament for the treatment of type 2 diabetes in a human, wherein the DPIV inhibitor in combination with metformin or a thiazolidinedione is a first-line therapy for the treatment of type 2 diabetes in a human, wherein the human has not previously been treated with a pharmaceutical antidiabetic agent.

## DETAILED DESCRIPTION ~~OF THE INVENTION~~

The present invention provides a method for the treatment of type 2 diabetes in a mammal, such as a human, which method comprises administering a combination of a DPIV inhibitor and metformin or a thiazolidinedione as first-line therapy, to a mammal in need thereof.

The invention also provides the use of combination of a DPIV inhibitor and metformin or a thiazolidinedione as first-line therapy for the treatment of type 2 diabetes.

The invention also provides the use of a DPIV inhibitor in the manufacture of a medicament for use in combination with metformin or a thiazolidinedione as first-line therapy, for the treatment of type 2 diabetes.

First-line therapy is defined as the first course of pharmaceutical treatment used against a disease, thus in the present case it represents the first pharmacological intervention to treat type 2 diabetes in a patient diagnosed as having inadequate glycaemic control. In a type 2 diabetic patient this will generally

CLAIMS:

1. A method for the treatment of type 2 diabetes in a mammal which method comprises administering a combination of a DPIV inhibitor and metformin or a thiazolidinedione as first-line therapy, to a mammal in need thereof.

2. The method according to claim 1 wherein the mammal is a human.

3. The method according to claim 2 wherein the human has failed to achieve adequate glycaemic control using diet, weight reduction and/or exercise alone.

4. A method for the treatment of type 2 diabetes in a mammal, such as a human, which mammal has not previously been treated with an antidiabetic agent, which method comprises administering a combination of a DPIV inhibitor and metformin or a thiazolidinedione to said a mammal.

5. The method according to any one of the preceding claims wherein the DPIV inhibitor and metformin or a thiazolidinedione are administered simultaneously, sequentially or separately.

6. The method according to any one of the preceding claims wherein the DPIV inhibitor and metformin or a thiazolidinedione are administered orally.

7. The method according to any one of the preceding claims wherein the DPIV inhibitor is glutaminyl thiazolidine or a pharmaceutically acceptable salt thereof.

8. The method according to claim 6 wherein the DPIV inhibitor is glutaminyl thiazolidine hydrochloride.

9. The method according to any one of the preceding claims wherein DPIV inhibitor is administered in combination with metformin.

10. The method according to any one of claims 1 to 8 wherein the thiazolidinedione is troglitazone, ciglitazone, pioglitazone, englitazone or rosiglitazone.

11. The method according to claim 10 wherein the thiazolidinedione is rosiglitazone.

12. A method for the treatment of type 2 diabetes in a mammal which method comprises administering a combination of glutaminyl thiazolidine or a pharmaceutically acceptable salt thereof, and metformin as first-line therapy, to a human that has failed to achieve adequate glycaemic control using diet, weight reduction and/or exercise alone.

13. A method for the treatment of type 2 diabetes in a mammal which method comprises administering a combination of glutaminyl thiazolidine or a pharmaceutically acceptable salt thereof, and a thiazolidinedione as first-line therapy, to a human that has failed to achieve adequate glycaemic control using diet, weight reduction and/or exercise alone.

14. A method for the treatment of type 2 diabetes in a mammal, which mammal has not previously been treated with an antidiabetic agent, which method comprises administering a combination of glutaminyl thiazolidine or a pharmaceutically acceptable salt thereof, and metformin to said a mammal.

15. A method for the treatment of type 2 diabetes in a mammal, which mammal has not previously been treated with an antidiabetic agent, which method comprises administering a combination of glutaminyl thiazolidine or a pharmaceutically acceptable salt thereof, and a thiazolidinedione to said a mammal.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. The use of a DPIV inhibitor, which binds to DPIV and inhibits DPIV activity, in combination with metformin or a thiazolidinedione in the manufacture of a medicament for the treatment of type 2 diabetes in a human, wherein the DPIV inhibitor in combination with metformin or a thiazolidinedione is a first-line therapy for the treatment of type 2 diabetes in a human, wherein the human has not previously been treated with a pharmaceutical antidiabetic agent.

2. The use according to claim 1, wherein the human has failed to achieve adequate glycaemic control using diet, weight reduction and/or exercise alone.

3. The use according to any one of the preceding claims, wherein the DPIV inhibitor and metformin or a thiazolidinedione are administered simultaneously, sequentially or separately.

4. The use according to any one of the preceding claims, wherein the DPIV inhibitor and metformin or a thiazolidinedione are administered in a formulation which includes both the DPIV inhibitor and metformin or a thiazolidinedione.

5. The use according to any one of the preceding claims, wherein the DPIV inhibitor and metformin or a thiazolidinedione are administered orally.

6. The use according to any one of the preceding claims, wherein the DPIV inhibitor is glutaminyl thiazolidine or a pharmaceutically acceptable salt thereof.

7. The use according to any one of claims 1 to 5, wherein the DPIV inhibitor is selected from the group consisting of sitagliptin, vildagliptin, saxagliptin, denagliptin and alogliptin and pharmaceutically acceptable salts thereof.

8. The use according to any one of the preceding claims, wherein the DPIV inhibitor and metformin or a thiazolidinedione are administered once, twice or three times a day.

9. The use according to any one of the preceding claims, wherein the DPIV inhibitor is administered in combination with metformin.

10. The use according to any one of claims 1 to 8, wherein the thiazolidinedione is selected from the group consisting of troglitazone, ciglitazone, pioglitazone, englitazone and rosiglitazone.

11. A DPIV inhibitor for use according to claim 10, wherein the thiazolidinedione is rosiglitazone.