(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 November 2011 (10.11.2011)

PCT

(10) International Publication Number
WO 2011/138421 A1

(51) International Patent Classification:
A61K 31/00 (2006.01) *A61P 3/04* (2006.01)
A61K 31/522 (2006.01) *A61P 3/10* (2006.01)
A61K 38/00 (2006.01)

(21) International Application Number:
PCT/EP2011/057256

(22) International Filing Date:
5 May 2011 (05.05.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10162036.7 5 May 2010 (05.05.2010) EP
11155154.5 21 February 2011 (21.02.2011) EP

(71) Applicant *(for all designated States except US)*: **BOEHRINGER INGELHEIM INTERNATIONAL GMBH** [DE/DE]; Binger Str. 173, 55216 Ingelheim Am Rhein (DE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **KLEIN, Thomas** [DE/DE]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Str. 173, 55216 Ingelheim Am Rhein (DE). **GREMPLER, Rolf** [DE/DE]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Str. 173, 55216 Ingelheim Am Rhein (DE). **MARK, Michael** [DE/DE]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Str. 173, 55216 Ingelheim Am Rhein (DE).

(74) Agents: **HAMMANN, et al, Heinz** et al.; Boehringer Ingelheim GmbH, Corporate Patents, Binger Str. 173, 55216 Ingelheim Am Rhein (DE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*

WO 2011/138421 A1

(54) **Title**: COMBINATION THERAPY

(57) **Abstract**: The present invention relates to methods for treating and/or preventing metabolic diseases comprising the combined administration of a GLP-1 receptor agonist and a DPP-4 inhibitor.

Combination therapy

The present invention relates to methods for treating and/or preventing metabolic diseases, especially type 2 diabetes mellitus, obesity and/or conditions related thereto (e.g. diabetic complications) comprising the combined administration of a GLP-1 receptor agonist (e.g. exogenous GLP-1 or a GLP-1 analogue) and a certain DPP-4 inhibitor, to pharmaceutical compositions and combinations comprising such active components, and to certain therapeutic uses thereof.

Further, the present invention relates to a method for reducing and maintaining body weight and/or body fat in a patient in need thereof, such as e.g. in an overweight or obesity patient with or without diabetes (particularly type 2 diabetes patient being obese or overweight), comprising the combined (e.g. separate, simultaneous or sequential) administration of a GLP-1 receptor agonist (e.g. GLP-1 or GLP-1 analogue) and a certain DPP-4 inhibitor; preferably said method comprising the sequential administration of a GLP-1 receptor agonist followed by a certain DPP-4 inhibitor.

Furthermore, the present invention relates to a method for reducing and maintaining body weight and/or body fat in a patient in need thereof, such as e.g. in an overweight or obesity patient with or without diabetes (particularly type 2 diabetes patient being obese or overweight), comprising i) inducing body weight loss (e.g. by administering an effective amount of a GLP-1 receptor agonist to the patient) and ii.) administering an effective amount of a certain DPP-4 inhibitor to the patient.

Moreover, the present invention relates to a certain DPP-4 inhibitor for use in preventing of body weight and/or body fat gain or controlling, stabilizing or maintaining a reduced body weight and/or body fat followed discontinuation of weight reducing treatment (such as e.g. diet, exercise and/or treatment with an anti-obesity or body weight reducing agent), particularly after discontinuation of treatment with a GLP-1 receptor agonist.

Further, the present invention relates to a certain DPP-4 inhibitor for use in delaying body weight and/or body fat gain and/or maintaining reduction in body weight and/or body fat in a subject (particularly an obesity patient with or without diabetes), particularly subsequent to cessation of or withdrawn from body weight reducing and/or fat reducing treatment.

Further, the present invention relates to a certain DPP-4 inhibitor for use in a method of delaying body weight and/or body fat gain and/or maintaining body weight and/or body fat loss induced by treatment with a GLP-1 receptor agonist in a subject, said method comprising cessation of GLP-1 receptor agonist treatment and transferring the subject from GLP-1 receptor agonist to DPP-4 inhibitor treatment.

Furthermore, the present invention relates to a DPP-4 inhibitor for use in reducing, maintaining loss of or delaying increase of body weight and/or body fat in a subject actively putting on weight.

Yet furthermore, the present invention relates to a DPP-4 inhibitor for use in reducing, maintaining loss of or delaying increase of body weight and/or body fat in a subject being in condition of actively putting on weight and/or increasing body weight through the deposition of fat, such as e.g. after withdrawing a weight loss treatment or under a treatment associated with weight gain (e.g. through the action of sulphonylureas, glinides, insulin and/or thiazolidinediones, the use of which is associated with weight gain).

Further, the present invention relates to a certain DPP-4 inhibitor for use in reducing intra-myocellular fat and/or hepatic fat in a patient in need thereof, such as e.g. in an overweight or obesity patient with or without diabetes (particularly type 2 diabetes patient being obese or overweight).

Further, the present invention relates to a DPP-4 inhibitor for use in achieving a reduction in the dose of GLP-1 receptor agonist medication, e.g. required for effective therapy of metabolic diseases (such as e.g. type 2 diabetes mellitus, obesity and/or conditions related thereto (e.g. diabetic complications)), e.g. in an overweight or obesity patient with or without diabetes (particularly type 2 diabetes patient being obese or overweight).

Moreover, the present invention relates to a certain DPP-4 inhibitor for use in treating, preventing or reducing the risk of skin necrosis, particularly associated with or induced by infusions or injections, e.g. of a GLP-1 receptor agonist, insulin or insulin analogue or other drugs administered subcutaneously and/or via needle or syringe, typically pierced through the skin.

Further, the present invention relates to the DPP-4 inhibitors and/or GLP-1 receptor agonists, each as defined herein, for use in the combination therapies as described herein.

Type 2 diabetes mellitus is a common chronic and progressive disease arising from a complex pathophysiology involving the dual endocrine effects of insulin resistance and impaired insulin secretion with the consequence not meeting the required demands to maintain plasma glucose levels in the normal range. This leads to chronic hyperglycaemia and its associated micro- and macrovascular complications or chronic damages, such as e.g. diabetic nephropathy, retinopathy or neuropathy, or macrovascular (e.g. cardio- or cerebro-vascular) complications. The vascular disease component plays a significant role, but is not the only factor in the spectrum of diabetes associated disorders. The high frequency of complications leads to a significant reduction of life expectancy. Diabetes is currently the

most frequent cause of adult-onset loss of vision, renal failure, and amputation in the Industrialised World because of diabetes induced complications and is associated with a two to five fold increase in cardiovascular disease risk.

Furthermore, diabetes (particularly type 2 diabetes) is often coexistent and interrelated with obesity and these two conditions together impose a particularly complex therapeutic challenge. Because of the effects of obesity on insulin resistance, weight loss and its maintainance is an important therapeutic objective in overweight or obese individuals with prediabetes, metabolic syndrome or diabetes. Studies have been demonstrated that weight reduction in subjects with type 2 diabetes is associated with descreased insulin resistance, improved measures of glycemia and lipemia, and reduced blood pressure. Maintainance of weight reduction over longer term is considered to improve glycemic control and prevent diabetic complications (e.g. reduction of risk for cardiovascular diseases or events). Thus, weight loss is recommended for all overweight or obese indivuduals who have or are at risk for diabetes. However, obese patients with type 2 diabetes have much greater difficulty losing weight and maintain the reduced weight than the general non-diabetic population.

Overweight may be defined as the condition wherein the individual has a body mass index (BMI) greater than or 25 kg/m² and less than 30 kg/m². The terms "overweight" and "pre-obese" are used interchangeably.

Obesity may be defined as the condition wherein the individual has a BMI equal to or greater than 30 kg/m². According to a WHO definition the term obesity may be categorized as follows: class I obesity is the condition wherein the BMI is equal to or greater than 30 kg/m² but lower than 35 kg/m²; class II obesity is the condition wherein the BMI is equal to or greater than 35 kg/m² but lower than 40 kg/m²; class III obesity is the condition wherein the BMI is equal to or greater than 40 kg/m². Obesity may include e.g. visceral or abdominal obesity.

Visceral obesity may be defined as the condition wherein a waist-to-hip ratio of greater than or equal to 1.0 in men and 0.8 in women is measured. It defines the risk for insulin resistance and the development of pre-diabetes.

Abdominal obesity may usually be defined as the condition wherein the waist circumference is > 40 inches or 102 cm in men, and is > 35 inches or 94 cm in women. With regard to a

Japanese ethnicity or Japanese patients abdominal obesity may be defined as waist circumference ≥ 85 cm in men and ≥ 90 cm in women (see e.g. investigating committee for the diagnosis of metabolic syndrome in Japan).

Diabetes patients within the meaning of this invention may include patients having obesity or overweight.

Obesity patients within the meaning of this invention may include, in one embodiment, patients with diabetes (particularly having type 2 diabetes).

Obesity patients within the meaning of this invention may include, in another embodiment, patients without diabetes (particularly without type 1 or type 2 diabetes).

The treatment of type 2 diabetes typically begins with diet and exercise, followed by oral antidiabetic monotherapy, and although conventional monotherapy may initially control blood glucose in some patients, it is however associated with a high secondary failure rate. The limitations of single-agent therapy for maintaining glycemic control may be overcome, at least in some patients, and for a limited period of time by combining multiple drugs to achieve reductions in blood glucose that cannot be sustained during long-term therapy with single agents. Available data support the conclusion that in most patients with type 2 diabetes current monotherapy will fail and treatment with multiple drugs will be required.
But, because type 2 diabetes is a progressive disease, even patients with good initial responses to conventional combination therapy will eventually require an increase of the dosage or further treatment with insulin because the blood glucose level is very difficult to maintain stable for a long period of time. Although existing combination therapy has the potential to enhance glycemic control, it is not without limitations (especially with regard to long term efficacy). Further, traditional therapies may show an increased risk for side effects, such as hypoglycemia or weight gain, which may compromise their efficacy and acceptability.
Thus, for many patients, these existing drug therapies result in progressive deterioriation in metabolic control despite treatment and do not sufficiently control metabolic status especially over long-term and thus fail to achieve and to maintain glycemic control in advanced or late stage type 2 diabetes, including diabetes with inadequate glycemic control despite conventional oral or non-oral antidiabetic medication.

Therefore, although intensive treatment of hyperglycemia can reduce the incidence of chronic damages, many patients with type 2 diabetes remain inadequately treated, partly because of limitations in long term efficacy, tolerability and dosing inconvenience of conventional antihyperglycemic therapies.

In addition, obesity, overweight or weight gain (e.g. as side or adverse effect of some conventional antidiabetic medications) further complicates the treatment of diabetes and its micorvascular or macrovascular complications.

This high incidence of therapeutic failure is a major contributor to the high rate of long-term hyperglycemia-associated complications or chronic damages (including micro- and makrovascular complications such as e.g. diabetic nephrophathy, retinopathy or neuropathy, or cardiovascular complications) in patients with type 2 diabetes.

Oral antidiabetic drugs conventionally used in therapy (such as e.g. first- or second-line, and/or mono- or (initial or add-on) combination therapy) include, without being restricted thereto, metformin, sulphonylureas, thiazolidinediones, glinides and α-glucosidase inhibitors.

Non-oral (typically injected) antidiabetic drugs conventionally used in therapy (such as e.g. first- or second-line, and/or mono- or (initial or add-on) combination therapy) include, without being restricted thereto, GLP-1 or GLP-1 analogues, and insulin or insulin analogues.

However, the use of these conventional antidiabetic or antihyperglycemic agents can be associated with various adverse effects. For example, metformin can be associated with lactic acidosis or gastrointestinal side effects; sulfonylureas, glinides and insulin or insulin analogues can be associated with hypoglycemia and weight gain; thiazolidinediones can be associated with edema, bone fracture, weight gain and heart failure/cardiac effects; and alpha-glucosidase blockers and GLP-1 or GLP-1 analogues can be associated with gastrointestinal adverse effects (e.g. dyspepsia, flatulence or diarrhea, or nausea or vomiting) and, most seriously (but rare), pancreatitis.

Therefore, it remains a need in the art to provide efficacious, safe and tolerable antidiabetic therapies, particularly for obese or overweight diabetes patients.

Further, it remains a need in the art to provide efficacious, safe and tolerable therapies for obesity patients with or without diabetes, particularly for reducing body weight and maintaining reduced body weight as well as for preventing rebound of weight gain following cessation of weight loss treatment in such patients.

Within the management of the dual epidemic of type 2 diabetes and obesity ("diabesity"), it is an objective to find therapies which are safe, tolerable and effective in the treatment or prevention of these conditions together, particularly in achieving long term weight reduction and improving glycemic control.

Further, within the therapy of type 2 diabetes, obesity or both, it is a need for treating the condition effectively, avoiding the complications inherent to the condition, and delaying disease progression.

Furthermore, it remains a need that antidiabetic treatments not only prevent the long-term complications often found in advanced stages of diabetes disease, but also are a therapeutic option in those diabetes patients who have developed complications, such as renal impairment.

Moreover, it remains a need to provide prevention or reduction of risk for adverse effects associated with conventional antidiabetic therapies.

The enzyme DPP-4 (dipeptidyl peptidase IV) also known as CD26 is a serine protease known to lead to the cleavage of a dipeptide from the N-terminal end of a number of proteins having at their N-terminal end a prolin or alanin residue. Due to this property DPP-4 inhibitors interfere with the plasma level of bioactive peptides including the peptide GLP-1 and are considered to be promising drugs for the treatment of diabetes mellitus.

For example, DPP-4 inhibitors and their uses are disclosed in WO 2002/068420, WO 2004/018467, WO 2004/018468, WO 2004/018469, WO 2004/041820, WO 2004/046148, WO 2005/051950, WO 2005/082906, WO 2005/063750, WO 2005/085246, WO 2006/027204, WO 2006/029769, WO2007/014886; WO 2004/050658, WO 2004/111051, WO 2005/058901, WO 2005/097798; WO 2006/068163, WO 2007/071738, WO 2008/017670; WO 2007/128721, WO 2007/128724, WO 2007/128761, or WO 2009/121945.

Glucagon-like peptide-1 (GLP-1) is a hormon secreted from enteroendocrine L cells of the intestine in response to food. Exogenous GLP-1 administration at pharmacological doses results in effects that are beneficial for treating type 2 diabetes. However, native GLP-1 is subject to rapid enzymatic degradation. The action of GLP-1 is mediated through the GLP-1 receptor (GLP-1R).

In the monitoring of the treatment of diabetes mellitus the HbA1c value, the product of a non-enzymatic glycation of the haemoglobin B chain, is of exceptional importance. As its formation depends essentially on the blood sugar level and the life time of the erythrocytes the HbA1c in the sense of a "blood sugar memory" reflects the average blood sugar level of the preceding 4-12 weeks. Diabetic patients whose HbA1c level has been well controlled over a long time by more intensive diabetes treatment (i.e. < 6.5 % of the total haemoglobin in the sample) are significantly better protected from diabetic microangiopathy. The available treatments for diabetes can give the diabetic an average improvement in their HbA1c level of the order of 1.0 – 1.5 %. This reduction in the HbA1C level is not sufficient in all diabetics to bring them into the desired target range of < 7.0 %, preferably < 6.5 % and more preferably < 6 % HbA1c.

Within the meaning of this invention, inadequate or insufficient glycemic control means in particular a condition wherein patients show HbA1c values above 6.5%, in particular above 7.0%, even more preferably above 7.5%, especially above 8%. An embodiment of patients with inadequate or insufficient glycemic control include, without being limited to, patients having a HbA1c value from 7.5 to 10% (or, in another embodiment, from 7.5 to 11%). A special sub-embodiment of inadequately controlled patients refers to patients with poor glycemic control including, without being limited, patients having a HbA1c value ≥ 9%.

Within glycemic control, in addition to improvement of the HbA1c level, other recommended therapeutic goals for type 2 diabetes mellitus patients are improvement of fasting plasma glucose (FPG) and of postprandial plasma glucose (PPG) levels to normal or as near normal as possible. Recommended desired target ranges of preprandial (fasting) plasma glucose are 70-130 mg/dL (or 90-130 mg/dL) or <110 mg/dL, and of two-hour postprandial plasma glucose are <180 mg/dL or <140 mg/dL.

In one embodiment, diabetes patients within the meaning of this invention may include patients who have not previously been treated with an antidiabetic drug (drug-naïve

patients). Thus, in an embodiment, the therapies described herein may be used in naïve patients. In another embodiment, diabetes patients within the meaning of this invention may include patients with advanced or late stage type 2 diabetes mellitus (including patients with failure to conventional antidiabetic therapy), such as e.g. patients with inadequate glycemic control on one, two or more conventional oral and/or non-oral antidiabetic drugs as defined herein, such as e.g. patients with insufficient glycemic control despite (mono-)therapy with metformin, a thiazolidinedione (particularly pioglitazone), a sulphonylurea, a glinide, GLP-1 or GLP-1 analogue, insulin or insulin analogue, or an α-glucosidase inhibitor, or despite dual combination therapy with metformin/sulphonylurea, metformin/thiazolidinedione (particularly pioglitazone), metformin/insulin, pioglitazone/sulphonylurea, pioglitazone/insulin, or sulphonylurea/insulin. Thus, in an embodiment, the therapies described herein may be used in patients experienced with therapy, e.g. with conventional oral and/or non-oral antidiabetic mono- or dual or triple combination medication as mentioned herein.

A further embodiment of diabetic patients within the meaning of this invention refers to patients ineligible for metformin therapy including

- patients for whom metformin therapy is contraindicated, e.g. patients having one or more contraindications against metformin therapy according to label, such as for example patients with at least one contraindication selected from:
  - renal disease, renal impairment or renal dysfunction (e.g., as specified by product information of locally approved metformin),
  - dehydration,
  - unstable or acute congestive heart failure,
  - acute or chronic metabolic acidosis, and
  - hereditary galactose intolerance;

and

- patients who suffer from one or more intolerable side effects attributed to metformin, particularly gastrointestinal side effects associated with metformin, such as for example patients suffering from at least one gastrointestinal side effect selected from:
  - nausea,
  - vomiting,
  - diarrhoea,
  - intestinal gas, and
  - severe abdominal discomfort.

A further embodiment of the diabetes patients which may be amenable to the therapies of this invention may include, without being limited, those diabetes patients for whom normal metformin therapy is not appropriate, such as e.g. those diabetes patients who need reduced dose metformin therapy due to reduced tolerability, intolerability or contraindication against metformin or due to (mildly) impaired/reduced renal function (including elderly patients, such as e.g. ≥ 60-65 years).

A further embodiment of diabetic patients within the meaning of this invention refers to patients having renal disease, renal dysfunction, or insufficiency or impairment of renal function (including mild, moderate and severe renal impairment), e.g. as suggested by elevated serum creatinine levels (e.g. serum creatinine levels above the upper limit of normal for their age, e.g. ≥ 130 - 150 µmol/l, or ≥ 1.5 mg/dl (≥ 136 µmol/l) in men and ≥ 1.4 mg/dl (≥ 124 µmol/l) in women) or abnormal creatinine clearance (e.g. glomerular filtration rate (GFR) ≤ 30 - 60 ml/min).

In this context, for more detailed example, mild renal impairment may be e.g. suggested by a creatinine clearance of 50-80 ml/min (approximately corresponding to serum creatine levels of ≤1.7 mg/dL in men and ≤1.5 mg/dL in women); moderate renal impairment may be e.g. suggested by a creatinine clearance of 30-50 ml/min (approximately corresponding to serum creatinine levels of >1.7 to ≤3.0 mg/dL in men and >1.5 to ≤2.5 mg/dL in women); and severe renal impairment may be e.g. suggested by a creatinine clearance of < 30 ml/min (approximately corresponding to serum creatinine levels of >3.0 mg/dL in men and >2.5 mg/dL in women). Patients with end-stage renal disease require dialysis (e.g. hemodialysis or peritoneal dialysis).

For other more detailed example, patients with renal disease, renal dysfunction or renal impairment include patients with chronic renal insufficiency or impairment, which can be stratified according to glomerular filtration rate (GFR, ml/min/1.73m^2) into 5 disease stages: stage 1 characterized by normal GFR ≥ 90 plus either persistent albuminuria or known structural or hereditary renal disease; stage 2 characterized by mild reduction of GFR (GFR 60-89) describing mild renal impairment; stage 3 characterized by moderate reduction of GFR (GFR 30-59) describing moderate renal impairment; stage 4 characterized by severe reduction of GFR (GFR 15-30) describing severe renal impairment; and terminal stage 5 characterized by requiring dialysis or GFR < 15 describing established kidney failure (end-stage renal disease, ESRD).

Within the scope of the present invention it has now been found that certain DPP-4 inhibitors as defined herein as well as pharmaceutical combinations, compositions or combined uses according to this invention of these DPP-4 inhibitors and GLP-1 receptor agonists (e.g. exogenous GLP-1 or GLP-1 analogues) as defined herein have unexpected and particularly advantageous properties, which make them suitable for the purpose of this invention and/or for fulfilling one or more of above needs.

The present invention thus relates to a combination comprising a certain DPP-4 inhibitor (particularly BI 1356) and a GLP-1 receptor agonist (e.g. exogenous GLP-1 or a GLP-1 analogue), each as defined herein, particularly for simultaneous, separate or sequential use in the therapies described herein.

The present invention further relates to a method for treating and/or preventing metabolic diseases, especially type 2 diabetes mellitus, obesity and/or conditions related thereto (e.g. diabetic complications) comprising the combined (e.g. simultaneous, separate or sequential) administration of an effective amount of a GLP-1 receptor agonist (e.g. exogenous GLP-1 or a GLP-1 analogue) as defined herein and of an effective amount of a DPP-4 inhibitor as defined herein to the patient (particularly human patient) in need thereof, such as e.g a patient as described herein.

The present invention further relates to at least one of the following methods:

- preventing, slowing the progression of, delaying or treating a metabolic disorder or disease, such as e.g. type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), hyperglycemia, postprandial hyperglycemia, overweight, obesity, dyslipidemia, hyperlipidemia, hypercholesterolemia, hypertension, atherosclerosis, endothelial dysfunction, osteoporosis, chronic systemic inflammation, non alcoholic fatty liver disease (NAFLD), retinopathy, neuropathy, nephropathy, polycystic ovarian syndrome, and/or metabolic syndrome;
- improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c;
- preventing, slowing, delaying or reversing progression from pre-diabetes, impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or from metabolic syndrome to type 2 diabetes mellitus;

- preventing, reducing the risk of, slowing the progression of, delaying or treating of complications of diabetes mellitus such as micro- and macrovascular diseases, such as nephropathy, micro- or macroalbuminuria, proteinuria, retinopathy, cataracts, neuropathy, learning or memory impairment, neurodegenerative or cognitive disorders, cardio- or cerebrovascular diseases, tissue ischaemia, diabetic foot or ulcus, atherosclerosis, hypertension, endothelial dysfunction, myocardial infarction, acute coronary syndrome, unstable angina pectoris, stable angina pectoris, peripheral arterial occlusive disease, cardiomyopathy, heart failure, heart rhythm disorders, vascular restenosis, and/or stroke;
- reducing body weight and/or body fat and/or liver fat and/or intra-myocellular fat or preventing an increase in body weight and/or body fat and/or liver fat and/or intra-myocellular fat or facilitating a reduction in body weight and/or body fat and/or liver fat and/or intra-myocellular fat;
- preventing, slowing, delaying or treating the degeneration of pancreatic beta cells and/or the decline of the functionality of pancreatic beta cells and/or for improving and/or restoring the functionality of pancreatic beta cells and/or stimulating and/or restoring or protecting the functionality of pancreatic insulin secretion;
- preventing, slowing, delaying or treating non alcoholic fatty liver disease (NAFLD) including hepatic steatosis, non-alcoholic steatohepatitis (NASH) and/or liver fibrosis (such as e.g. preventing, slowing the progression, delaying, attenuating, treating or reversing hepatic steatosis, (hepatic) inflammation and/or an abnormal accumulation of liver fat);
- preventing, slowing the progression of, delaying or treating type 2 diabetes with failure to conventional antidiabetic mono- or combination therapy;
- achieving a reduction in the dose of conventional antidiabetic medication required for adequate therapeutic effect;
- reducing the risk for adverse effects associated with conventional antidiabetic medication; and/or
- maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance;

in a patient in need thereof (such as e.g a patient as described herein), said method comprising combined (e.g. simultaneous, separate or sequential) administration of a DPP-4 inhibitor as defined herein and a GLP-1 receptor agonist as defined herein.

In addition, the present invention relates to the combination according to this invention comprising a DPP-4 inhibitor as defined herein and a GLP-1 receptor agonist as defined

herein for use in treating and/or preventing (including slowing the progession or delaying the onset) of metabolic diseases as defined herein, particularly diabetes (especially type 2 diabetes and obesity, or conditions related thereto, including diabetic complications), optionally in combination with one or more other therapeutic agents as described herein.

In addition, the present invention relates to the use of a combination according to this invention comprising a DPP-4 inhibitor as defined herein and a GLP-1 receptor agonist as defined herein for the manufacture of a medicament for use in a therapeutic method as described hereinbefore or hereinafter.

In addition, the present invention relates to a combination according to this invention comprising a DPP-4 inhibitor as defined herein and a GLP-1 receptor agonist as defined herein for use in a therapeutic method as described hereinbefore or hereinafter.

In addition, the present invention relates to a method of treating and/or preventing (including slowing the progession or delaying the onset) of a metabolic disease, particularly diabetes (especially type 2 diabetes or conditions related thereto, including diabetic complications) comprising administering to the patient in need thereof (such as e.g a patient as described herein) a combination according to this invention comprising a DPP-4 inhibitor as defined herein and a GLP-1 receptor agonist as defined herein.

In addition, the present invention relates to the use of a DPP-4 inhibitor as defined herein for the manufacture of a medicament for use in combination with a GLP-1 receptor agonist as defined herein for treating and/or preventing (including slowing the progession or delaying the onset) of metabolic diseases, particularly diabetes (especially type 2 diabetes and conditions related thereto, including diabetic complications).

In addition, the present invention relates to the use of a GLP-1 receptor agonist as defined herein for the manufacture of a medicament for use in combination with a DPP-4 inhibitor as defined herein for treating and/or preventing (including slowing the progession or delaying the onset) of metabolic diseases, particularly diabetes (especially type 2 diabetes and conditions related thereto, including diabetic complications).

In addition, the present invention relates a DPP-4 inhibitor as defined herein for use in a combination treatment according to the invention in a patient in need thereof (such as e.g a patient as described herein).

In addition, the present invention relates a GLP-1 receptor agonist as defined herein for use in a combination treatment according to the invention in a patient in need thereof (such as e.g a patient as described herein).

In addition, the present invention relates a DPP-4 inhibitor as defined herein, optionally in combination with one or more other active substances (such as e.g. metformin or pioglitazone), for use in a combination treatment according to the invention in a patient in need thereof.

In addition, the invention relates to a DPP-4 inhibitor as defined herein for use in a method as described hereinbefore or hereinafter, said method comprising administering the DPP-4 inhibitor, optionally in combination with one or more other active substances (e.g. which may selected from those mentioned herein, such as e.g. metformin or pioglitazone), to the patient.

In an embodiment, the present invention relates to a method for reducing and maintaining body weight and/or body fat in a patient in need thereof (particularly type 2 diabetes patient being obese or overweight) comprising administering a combination comprising a GLP-1 receptor agonist (e.g. GLP-1 or GLP-1 analogue as defined herein) and a DPP-4 inhibitor as defined herein to the patient.

In an embodiment, the present invention relates to a method for reducing and maintaining body weight and/or body fat in a patient in need thereof (particularly type 2 diabetes patient being obese or overweight) comprising i) inducing body weight and/or body fat loss (e.g. by diet, exercise and/or treatment with an anti-obesity or body weight reducing agent as described herein, particularly by administering an effective amount of the GLP-1 receptor agonist to the patient) and ii.) administering an effective amount of a certain DPP-4 inhibitor to the patient, wherein, optionally, said DPP-4 inhibitor may be used as replacement of the weight and/or fat loss treatment i) or as add-on or initial combination therapy with the weight and/or fat loss treatment i).

In a particular embodiment, the present invention relates to a DPP-4 inhibitor as defined herein, optionally in combination with one or more other therapeutic agents, for use in a method of preventing body weight and/or body fat gain or controlling, stabilizing or maintaining a reduced body weight and/or body fat after initial weight reducing treatment (such as e.g. diet, exercise and/or treatment with an anti-obesity or body weight reducing agent as described herein), particularly after discontinuation of initial treatment with a GLP-1 receptor agonist (e.g. GLP-1 or GLP-1 analogue as defined herein), in a patient in need thereof.

In a particular embodiment, the present invention relates to a method for reducing and maintaining body weight and/or body fat in a patient in need thereof (particularly type 2 diabetes patient being obese or overweight) comprising the combined (e.g. separate, simultaneous or sequential) administration of a GLP-1 receptor agonist (e.g. GLP-1 or GLP-1 analogue as defined herein) and a DPP-4 inhibitor as defined herein; preferably said method comprising the sequential administration of the GLP-1 receptor agonist followed by the DPP-4 inhibitor.

In a particular embodiment, the present invention relates to a method for reducing and maintaining body weight and/or body fat in a patient in need thereof (particularly type 2 diabetes patient being obese or overweight), said method comprising i) inducing body weight and/or body fat loss (e.g. by administering an effective amount of a GLP-1 receptor agonist (e.g. GLP-1 or GLP-1 analogue as defined herein) to the patient) and ii.) administering an effective amount of a DPP-4 inhibitor as defined herein to the patient for maintaining the body weight and/or body fat loss.

In a particular embodiment, the present invention relates to a method for reducing and maintaining body weight and/or body fat in a patient in need thereof (particularly type 2 diabetes patient being obese or overweight), said method comprising i) inducing initial body weight and/or body fat loss (e.g. by administering an effective amount of a GLP-1 receptor agonist (e.g. GLP-1 or GLP-1 analogue as defined herein) to the patient) and, subsequently, ii.) administering an effective amount of a DPP-4 inhibitor as defined herein to the patient, preferably thereby replacing the GLP-1 receptor agonist.

In a particular embodiment, the present invention relates to a DPP-4 inhibitor as defined herein for use in preventing of body weight and/or body fat gain or controlling, stabilizing or

maintaining a reduced body weight and/or body fat after discontinuation of a weight reducing treatment (such as e.g. diet, exercise and/or treatment with an anti-obesity or body weight reducing agent as described herein), particularly after discontinuation of treatment with a GLP-1 receptor agonist (e.g. GLP-1 or GLP-1 analogue as defined herein), in a patient in need thereof (such as e.g a patient as described herein).

In a particular embodiment, the present invention relates to the use of a DPP-4 inhibitor as defined herein for the manufacture of a medicament for use in preventing of body weight and/or body fat gain or controlling, stabilizing or maintaining a reduced body weight and/or body fat after initial weight reducing treatment (such as e.g. using diet, exercise and/or treatment with an anti-obesity or body weight reducing agent as described herein), particularly after initial treatment with a GLP-1 receptor agonist (e.g. GLP-1 or GLP-1 analogue as defined herein).

In a particular embodiment, the present invention relates to a method of preventing body weight gain and/or body fat gain or controlling, stabilizing or maintaining a reduced body weight and/or body fat after initial weight reducing treatment (such as e.g. using diet, exercise and/or treatment with an anti-obesity or body weight reducing agent as described herein), particularly after initial treatment with a GLP-1 receptor agonist (e.g. GLP-1 or GLP-1 analogue as defined herein), said method comprising administering an effective amount of a DPP-4 inhibitor as defined herein to the patient in need thereof.

In a particular embodiment, the present invention relates to a certain DPP-4 inhibitor for use in a method of reducing and maintaining body weight and/or body fat, or of attenuating, preventing or treating rebound of body weight gain and/or body fat gain following discontinuation of body weight loss treatment (particularly following discontinuation of treatment with a GLP-1 receptor agonist), particularly in obesity patients with or without diabetes, said method comprising administering a certain DPP-4 inhibitor (particularly linagliptin) subsequent to the body weight loss treatment (particularly subsequent to the treatment with the GLP-1 receptor agonist), optionally in combination with one or more other therapeutic agents.

In alternative to the use of a GLP-1 receptor agonist (e.g. GLP-1 or GLP-1 analogue as defined herein), the initial weight and/or fat loss may also be induced by using diet, exercise and/or treatment with an anti-obesity or body weight reducing agent, such as e.g. one or

more agents selected from sibutramine, tetrahydrolipstatin (orlistat), alizyme (cetilistat), a cannabinoid receptor 1 antagonist (e.g. rimonabant), a MC4 receptor agonist, a NPY receptor agonist such as e.g. a NPY2 antagonist (e.g. velneperit), a 5HT2c receptor agonist (e.g. lorcaserin), a Ghrelin antagonist, Pyy 3-36, leptin, a DGAT-1 inhibitor, a noradrenaline-dopamine-5HT reuptake inhibitor (e.g. tesofensine), bupropion/naltrexone, bupropion/zonisamide, topiramate/phentermine and pramlintide/metreleptin; or a MCH antagonist, a CCK inhibitor, a FAS inhibitor, an ACC inhibitor, a SCD inhibitor, a beta3 adrenoreceptor agonist, a MTP inhibitor (e.g. lomitapide) or amylin or an amylin analogue (e.g. davalintide or pramlintide).

Within an embodiment of the combination therapy of this invention (e.g. for treating type 2 diabetes, obesity or both, or for reducing and maintaining body weight), the GLP-1 receptor agonist may be used for inducing (initial) body weight loss, and/or the DPP-4 inhibitor may be used for maintaining body weight loss.

Another embodiment of the combination therapy of this invention (e.g. for treating type 2 diabetes, obesity or both, or for reducing and maintaining body weight and/or body fat), refers to a method comprising
i) administering an effective amount of a GLP-1 receptor agonist to the patient, particularly for inducing body weight and/or body fat loss in the patient,
ii) withdrawing the GLP-1 receptor agonist from the patient, particularly after the body weight and/or body fat is reduced in the patient, and
iii) administering an effective amount of a DPP-4 inhibitor to the patient, particularly for delaying body weight and/or body fat gain and/or maintaining reduction in body weight and/or in body fat in the patient.

Another embodiment of the combination therapy of this invention refers to the use of a certain DPP-4 inhibitor (particularly linagliptin) subsequent to body weight loss, particularly subsequent to a GLP-1 receptor agonist, optionally in combination with one or more other therapeutic agents.

Other aspects of the present invention become apparent to the skilled person from the foregoing and following remarks (including the examples and claims).

The aspects of the present invention, in particular the pharmaceutical compounds, compositions, combinations, methods and uses, refer to DPP-4 inhibitors and/or GLP-1 receptor agonists as defined hereinbefore and hereinafter.

A DPP-4 inhibitor within the meaning of the present invention includes, without being limited to, any of those DPP-4 inhibitors mentioned hereinabove and hereinbelow, preferably orally active DPP-4 inhibitors.

An embodiment of this invention refers to a DPP-4 inhibitor for use in the treatment and/or prevention of metabolic diseases (particularly type 2 diabetes mellitus) in type 2 diabetes patients, wherein said patients further suffering from renal disease, renal dysfunction or renal impairment, particularly characterized in that said DPP-4 inhibitor is administered to said patients in the same dose levels as to patients with normal renal function, thus e.g. said DPP-4 inhibitor does not require downward dosing adjustment for impaired renal function.

For example, a DPP-4 inhibitor according to this invention (especially one which may be suited for patients with impaired renal function) may be such an oral DPP-4 inhibitor, which and whose active metabolites have preferably a relatively wide (e.g. about > 100 fold) therapeutic window and/or, especially, that are primarily eliminated via hepatic metabolism or biliary excretion.

In more detailed example, a DPP-4 inhibitor according to this invention (especially one which may be suited for patients with impaired renal function) may be such an orally administered DPP-4 inhibitor, which has a relatively wide (e.g. > 100 fold) therapeutic window and/or which fulfils one or more of the following pharmacokinetic properties (preferably at its therapeutic oral dose levels):

- The DPP-4 inhibitor is substantially or mainly excreted via the liver (e.g. > 80 % or even > 90 % of the administered oral dose), and/or for which renal excretion represents no substantial or only a minor elimination pathway (e.g. < 10 %, preferably < 7 %, of the administered oral dose measured, for example, by following elimination of a radiolabelled carbon (^{14}C) substance oral dose);
- The DPP-4 inhibitor is excreted mainly unchanged as parent drug (e.g. with a mean of > 70%, or > 80%, or, preferably, 90% of excreted radioactivity in urine and faeces after oral dosing of radiolabelled carbon (^{14}C) substance), and/or which is eliminated to a non-

substantial or only to a minor extent via metabolism (e.g. < 30%, or < 20%, or, preferably, 10%);

- The (main) metabolite(s) of the DPP-4 inhibitor is/are pharmacologically inactive. Such as e.g. the main metabolite does not bind to the target enzyme DPP-4 and, optionally, it is rapidly eliminated compared to the parent compound (e.g. with a terminal half-life of the metabolite of ≤ 20 h, or, preferably, ≤ about 16 h, such as e.g. 15.9 h).

In one embodiment, the (main) metabolite in plasma (which may be pharmacologically inactive) of a DPP-4 inhibitor having a 3-amino-piperidin-1-yl substituent is such a derivative where the amino group of the 3-amino-piperidin-1-yl moiety is replaced by a hydroxyl group to form the 3-hydroxy-piperidin-1-yl moiety (e.g. the 3-(S)-hydroxy-piperidin-1-yl moiety, which is formed by inversion of the configuration of the chiral center).

Further properties of a DPP-4 inhibitor according to this invention may be one or more of the following: Rapid attainment of steady state (e.g. reaching steady state plasma levels (> 90% of the steady state plasma concentration) between second and fifth day of treatment with therapeutic oral dose levels), little accumulation (e.g. with a mean accumulation ratio $R_{A,AUC}$ ≤ 1.4 with therapeutic oral dose levels), and/or preserving a long-lasting effect on DPP-4 inhibition, preferably when used once-daily (e.g. with almost complete (> 90%) DPP-4 inhibition at therapeutic oral dose levels, > 80% inhibition over a 24h interval after once-daily intake of therapeutic oral drug dose), significant decrease in 2h postprandial blood glucose excursions by ≥ 80 % (already on first day of therapy) at therapeutic dose levels, and cumulative amount of unchanged parent compound excreted in urine on first day being below 1% of the administered dose and increasing to not more than about 3-6% in steady state.

Thus, for example, a DPP-4 inhibitor according to this invention may be characterized in that said DPP-4 inhibitor is excreted to a non-substantial or only to a minor extent (e.g. < 10 %, preferably < 7 % of administered oral dose) via the kidney (measured, for example, by following elimination of a radiolabelled carbon (^{14}C) substance oral dose).

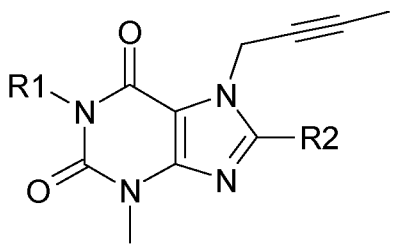
Further, a DPP-4 inhibitor according to this invention may be characterized in that said DPP-4 inhibitor is excreted substantially or mainly via the liver or faeces (measured, for example, by following elimination of a radiolabelled carbon (^{14}C) substance oral dose).

Further, a DPP-4 inhibitor according to this invention may be characterized in that
said DPP-4 inhibitor is excreted mainly unchanged as parent drug (e.g. with a mean of > 70%, or > 80%, or, preferably, 90 % of excreted radioactivity in urine and faeces after oral dosing of radiolabelled carbon (^{14}C) substance),
said DPP-4 inhibitor is eliminated to a non-substantial or only to a minor extent via metabolism, and/or
the main metabolite of said DPP-4 inhibitor is pharmacologically inactive or has a relatively wide therapeutic window.

Further, a DPP-4 inhibitor according to this invention may be characterized in that
said DPP-4 inhibitor does not significantly impair glomerular and/or tubular function of a type 2 diabetes patient with chronic renal insufficiency (e.g. mild, moderate or severe renal impairment or end stage renal disease), and/or
said DPP-4 inhibitor does not require to be dose-adjusted in a type 2 diabetes patient with impaired renal function (e.g. mild, moderate or severe renal impairment or end stage renal disease).

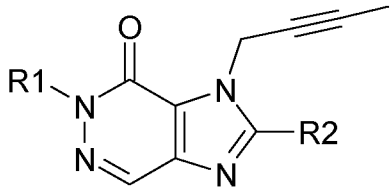
Further, a DPP-4 inhibitor according to this invention may be characterized in that
said DPP-4 inhibitor provides its minimally effective dose at that dose that results in >50% inhibition of DPP-4 activity at trough (24 h after last dose) in >80% of patients, and/or
said DPP-4 inhibitor provides its fully therapeutic dose at that dose that results in >80% inhibition of DPP-4 activity at trough (24 h after last dose) in >80% of patients.

In a first embodiment (embodiment **A**), a DPP-4 inhibitor in the context of the present invention is any DPP-4 inhibitor of
formula (I)



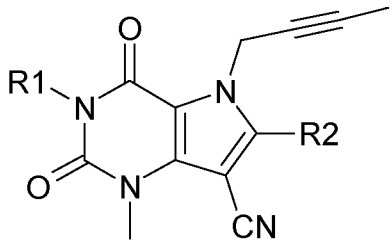
(I)

or formula (II)



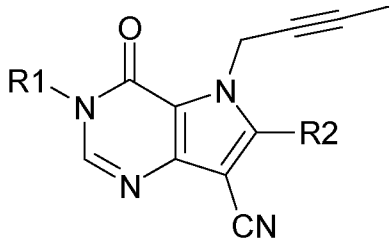
(II)

or formula (III)



(III)

or formula (IV)



(IV)

wherein **R1** denotes ([1,5]naphthyridin-2-yl)methyl, (quinazolin-2-yl)methyl, (quinoxalin-6-yl)methyl, (4-methyl-quinazolin-2-yl)methyl, 2-cyano-benzyl, (3-cyano-quinolin-2-yl)methyl, (3-cyano-pyridin-2-yl)methyl, (4-methyl-pyrimidin-2-yl)methyl, or (4,6-dimethyl-pyrimidin-2-yl)methyl and **R2** denotes 3-(*R*)-amino-piperidin-1-yl, (2-amino-2-methyl-propyl)-methylamino or (2-(*S*)-amino-propyl)-methylamino,

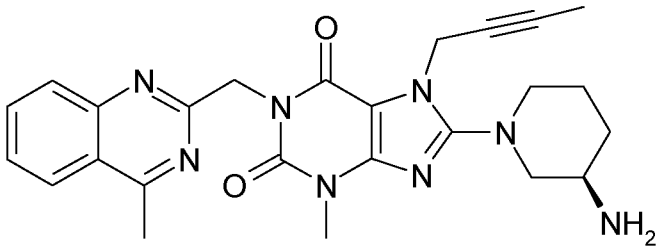
or its pharmaceutically acceptable salt.

In a second embodiment (embodiment **B**), a DPP-4 inhibitor in the context of the present invention is a DPP-4 inhibitor selected from the group consisting of
sitagliptin, vildagliptin, saxagliptin, alogliptin, gemigliptin,
(2*S*)-1-{[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethylamino]-acetyl}-pyrrolidine-2-carbonitrile,
(2*S*)-1-{[1,1,-Dimethyl-3-(4-pyridin-3-yl-imidazol-1-yl)-propylamino]-acetyl}-pyrrolidine-2-carbonitrile,

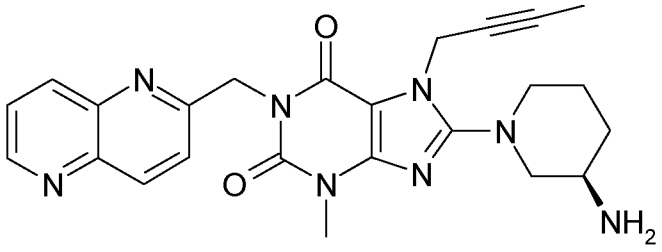
(*S*)-1-((2*S*,3*S*,11b*S*)-2-Amino-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-3-yl)-4-fluoromethyl-pyrrolidin-2-one,
(3,3-Difluoropyrrolidin-1-yl)-((2S,4S)-4-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrrolidin-2-yl)methanone,
(1((3S,4S)-4-amino-1-(4-(3,3-difluoropyrrolidin-1-yl)-1,3,5-triazin-2-yl)pyrrolidin-3-yl)-5,5-difluoropiperidin-2-one,
(2S,4S)-1-{2-[(3S,1R)-3-(1H-1,2,4-Triazol-1-ylmethyl)cyclopentylamino]-acetyl}-4-fluoropyrrolidine-2-carbonitrile,
(R)-2-[6-(3-Amino-piperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-4-fluoro-benzonitrile,
5-{(S)-2-[2-((S)-2-Cyano-pyrrolidin-1-yl)-2-oxo-ethylamino]-propyl}-5-(1H-tetrazol-5-yl)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-2,8-dicarboxylic acid bis-dimethylamide,
3-{(2S,4S)-4-[4-(3-Methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-ylcarbonyl}thiazolidine,
[(2R)-1-{[(3R)-pyrrolidin-3-ylamino]acetyl}pyrrolidin-2-yl]boronic acid,
(2S,4S)-1-[2-[(4-ethoxycarbonylbicyclo[2.2.2]oct-1-yl)amino]acetyl]-4-fluoropyrrolidine-2-carbonitrile,
2-({6-[(3R)-3-amino-3-methylpiperidin-1-yl]-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-d]pyrimidin-5-yl}methyl)-4-fluorobenzonitrile,
6-[(3R)-3-amino-piperidin-1-yl]-5-(2-chloro-5-fluoro-benzyl)-1,3-dimethyl-1,5-dihydro-pyrrolo[3,2-d]pyrimidine-2,4-dione, and
(S)-2-methylpyrazolo[1,5-a]primidine-6-carboxylic acid {2-[(2-cyanopyrrolidin-1-yl)-2-oxoethylamino]-2-methylpropyl}amide,
or its pharmaceutically acceptable salt.

Regarding the first embodiment (embodiment **A**), preferred DPP-4 inhibitors are any or all of the following compounds and their pharmaceutically acceptable salts:

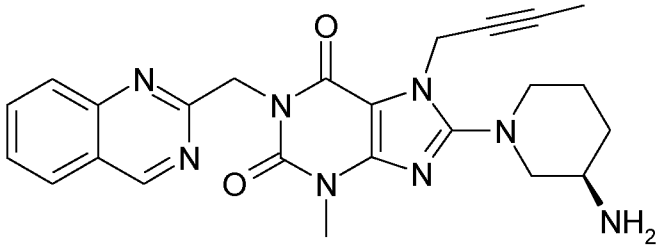
- 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine (compare WO 2004/018468, example 2(142)):



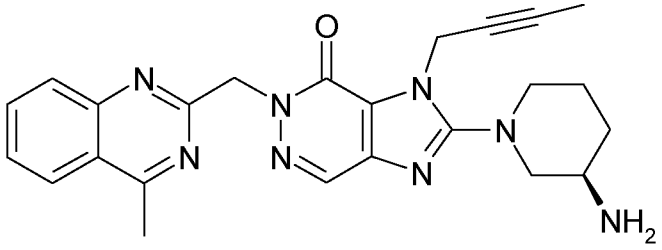
- 1-[([1,5]naphthyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine (compare WO 2004/018468, example 2(252)):



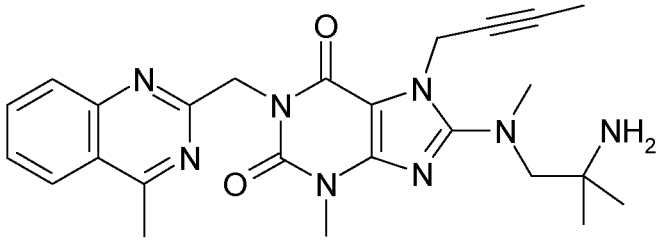
- 1-[(Quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine (compare WO 2004/018468, example 2(80)):



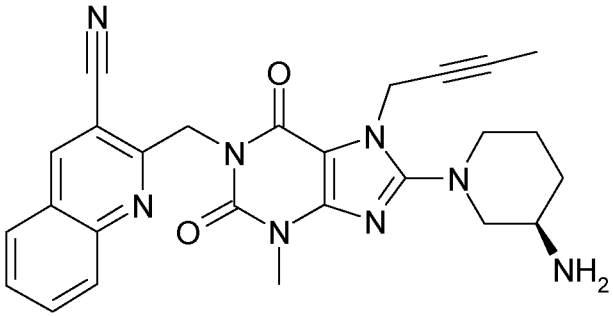
- 2-((R)-3-Amino-piperidin-1-yl)-3-(but-2-yinyl)-5-(4-methyl-quinazolin-2-ylmethyl)-3,5-dihydro-imidazo[4,5-d]pyridazin-4-one (compare WO 2004/050658, example 136):



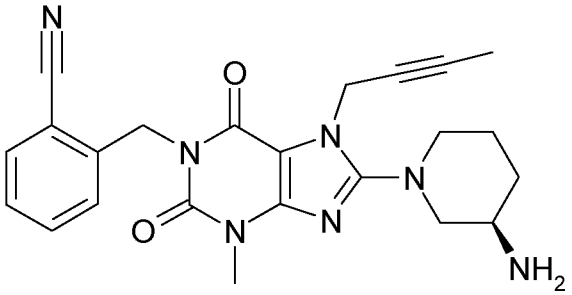
- 1-[(4-Methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyin-1-yl)-8-[(2-amino-2-methyl-propyl)-methylamino]-xanthine (compare WO 2006/029769, example 2(1)):



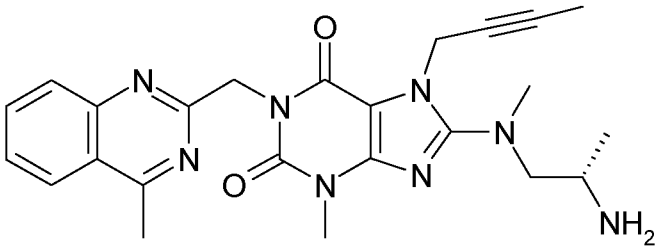
- 1-[(3-Cyano-quinolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine (compare WO 2005/085246, example 1(30)):



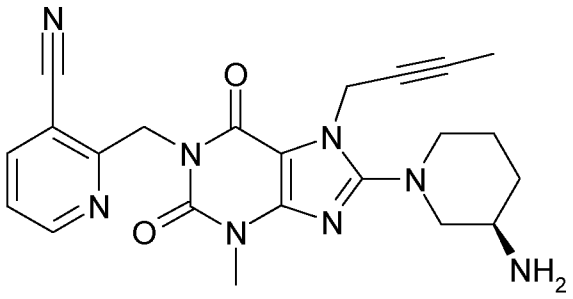
- 1-(2-Cyano-benzyl)-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine (compare WO 2005/085246, example 1(39)):



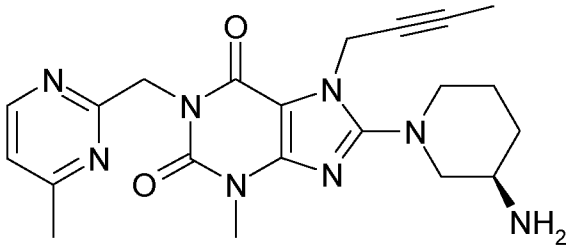
- 1-[(4-Methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(*S*)-(2-amino-propyl)-methylamino]-xanthine (compare WO 2006/029769, example 2(4)):



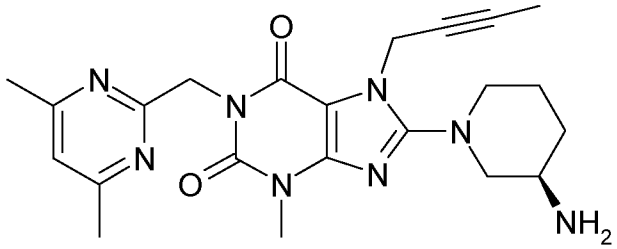
- 1-[(3-Cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine (compare WO 2005/085246, example 1(52)):



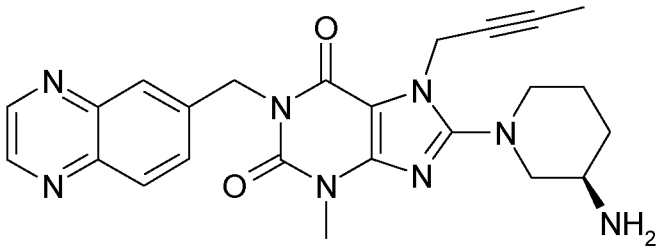
- 1-[(4-Methyl-pyrimidin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine (compare WO 2005/085246, example 1(81)):



- 1-[(4,6-Dimethyl-pyrimidin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine (compare WO 2005/085246, example 1(82)):



- 1-[(Quinoxalin-6-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine (compare WO 2005/085246, example 1(83)):



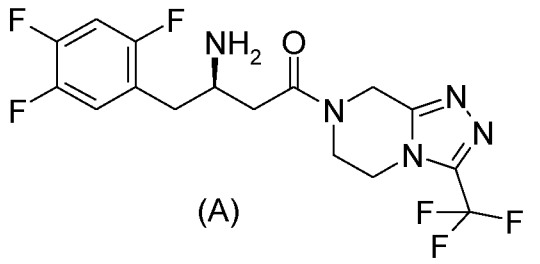
These DPP-4 inhibitors are distinguished from structurally comparable DPP-4 inhibitors, as they combine exceptional potency and a long-lasting effect with favourable pharmacological

properties, receptor selectivity and a favourable side-effect profile or bring about unexpected therapeutic advantages or improvements when combined with other pharmaceutical active substances. Their preparation is disclosed in the publications mentioned.

A more preferred DPP-4 inhibitor among the abovementioned DPP-4 inhibitors of embodiment **A** of this invention is 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine, particularly the free base thereof (which is also known as linagliptin or BI 1356).

As further DPP-4 inhibitors the following compounds can be mentioned:

- Sitagliptin (MK-0431) having the structural formula A below is (3*R*)-3-amino-1-[3-(trifluoromethyl)-5,6,7,8-tetrahydro-5H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one, also named (2*R*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine,

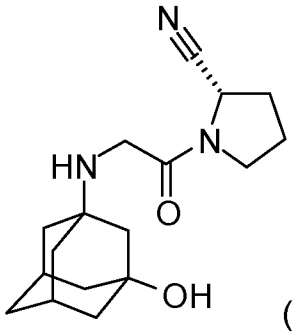


(A)

In one embodiment, sitagliptin is in the form of its dihydrogenphosphate salt, i.e. sitagliptin phosphate. In a further embodiment, sitagliptin phosphate is in the form of a crystalline anhydrate or monohydrate. A class of this embodiment refers to sitagliptin phosphate monohydrate. Sitagliptin free base and pharmaceutically acceptable salts thereof are disclosed in US Patent No. 6,699,871 and in Example 7 of WO 03/004498. Crystalline sitagliptin phosphate monohydrate is disclosed in WO 2005/003135 and in WO 2007/050485.
For details, e.g. on a process to manufacture, to formulate or to use this compound or a salt thereof, reference is thus made to these documents.

A tablet formulation for sitagliptin is commercially available under the trade name Januvia®. A tablet formulation for sitagliptin/metformin combination is commercially available under the trade name Janumet®.

- Vildagliptin (LAF-237) having the structural formula B below is (2S)-{[(3-hydroxyadamantan-1-yl)amino]acetyl}pyrrolidine-2-carbonitrile, also named (S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-pyrrolidine,

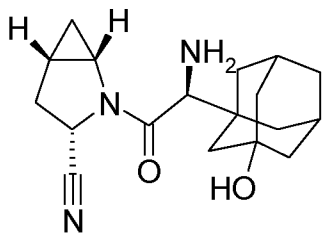


(B)

Vildagliptin is specifically disclosed in US Patent No. 6,166,063 and in Example 1 of WO 00/34241. Specific salts of vildagliptin are disclosed in WO 2007/019255. A crystalline form of vildagliptin as well as a vildagliptin tablet formulation are disclosed in WO 2006/078593. Vildagliptin can be formulated as described in WO 00/34241 or in WO 2005/067976. A modified release vildagliptin formulation is described in WO 2006/135723.
For details, e.g. on a process to manufacture, to formulate or to use this compound or a salt thereof, reference is thus made to these documents.

A tablet formulation for vildagliptin is expected to be commercially available under the trade name Galvus®. A tablet formulation for vildagliptin/metformin combination is commercially available under the trade name Eucreas®.

- Saxagliptin (BMS-477118) having the structural formula C below is (1S,3S,5S)-2-{(2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl}-2-azabicyclo[3.1.0]hexane-3-carbonitrile, also named (S)-3-hydroxyadamantylglycine-L-*cis*-4,5-methanoprolinenitrile,



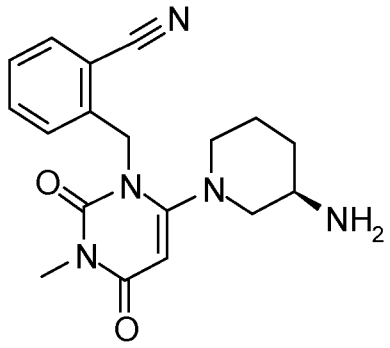
(C)

Saxagliptin is specifically disclosed in US Patent No. 6,395,767 and in Example 60 of WO 01/68603.

In one embodiment, saxagliptin is in the form of its HCl salt or its mono-benzoate salt as disclosed in WO 2004/052850. In a further embodiment, saxagliptin is in the form of the free base. In a yet further embodiment, saxagliptin is in the form of the monohydrate of the free base as disclosed in WO 2004/052850. Crystalline forms of the HCl salt and of the free base of saxagliptin are disclosed in WO 2008/131149. A process for preparing saxagliptin is also disclosed in WO 2005/106011 and WO 2005/115982. Saxagliptin can be formulated in a tablet as described in WO 2005/117841.

For details, e.g. on a process to manufacture, to formulate or to use this compound or a salt thereof, reference is thus made to these documents.

- Alogliptin (SYR-322) having the structural formula E below is 2-({6-[(3R)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl}methyl)benzonitrile



(E)

Alogliptin is specifically disclosed in US 2005/261271, EP 1586571 and in WO 2005/095381.

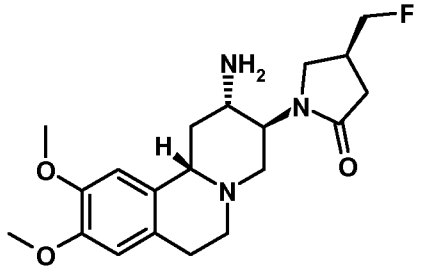
In one embodiment, alogliptin is in the form of its benzoate salt, its hydrochloride salt or its tosylate salt each as disclosed in WO 2007/035629. A class of this embodiment refers to alogliptin benzoate. Polymorphs of alogliptin benzoate are disclosed in WO 2007/035372. A process for preparing alogliptin is disclosed in WO 2007/112368 and, specifically, in WO 2007/035629. Alogliptin (namely its benzoate salt) can be formulated in a tablet and administered as described in WO 2007/033266. A solid preparation of alogliptin/pioglitazone and its preparation and use is described in WO 2008/093882. A solid preparation of alogliptin/metformin and its preparation and use is described in WO 2009/011451.

For details, e.g. on a process to manufacture, to formulate or to use this compound or a salt thereof, reference is thus made to these documents.

- (2*S*)-1-{[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethylamino]-acetyl}-pyrrolidine-2-carbonitrile or a pharmaceutically acceptable salt thereof, preferably the mesylate, or (2*S*)-1-{[1,1,-Dimethyl-3-(4-pyridin-3-yl-imidazol-1-yl)-propylamino]-acetyl}-pyrrolidine-2-carbonitrile or a pharmaceutically acceptable salt thereof:

These compounds and methods for their preparation are disclosed in WO 03/037327. The mesylate salt of the former compound as well as crystalline polymorphs thereof are disclosed in WO 2006/100181. The fumarate salt of the latter compound as well as crystalline polymorphs thereof are disclosed in WO 2007/071576. These compounds can be formulated in a pharmaceutical composition as described in WO 2007/017423.
For details, e.g. on a process to manufacture, to formulate or to use these compounds or salts thereof, reference is thus made to these documents.

- (*S*)-1-((2*S*,3*S*,11b*S*)-2-Amino-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-pyrido[2,1-a]isoquinolin-3-yl)-4-fluoromethyl-pyrrolidin-2-one (also named carmegliptin) or a pharmaceutically acceptable salt thereof:



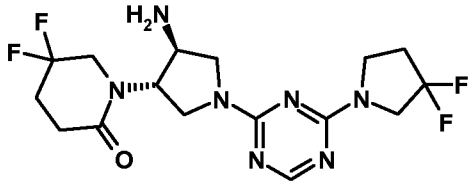
This compound and methods for its preparation are disclosed in WO 2005/000848. A process for preparing this compound (specifically its dihydrochloride salt) is also disclosed in WO 2008/031749, WO 2008/031750 and WO 2008/055814. This compound can be formulated in a pharmaceutical composition as described in WO 2007/017423.
For details, e.g. on a process to manufacture, to formulate or to use this compound or a salt thereof, reference is thus made to these documents.

- (3,3-Difluoropyrrolidin-1-yl)-((2S,4S)-4-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrrolidin-2-yl)methanone (also named gosogliptin) or a pharmaceutically acceptable salt thereof:

This compound and methods for its preparation are disclosed in WO 2005/116014 and US 7291618.

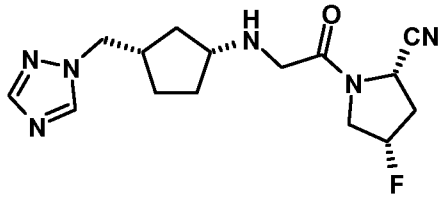
For details, e.g. on a process to manufacture, to formulate or to use this compound or a salt thereof, reference is thus made to these documents.

- (1((3S,4S)-4-amino-1-(4-(3,3-difluoropyrrolidin-1-yl)-1,3,5-triazin-2-yl)pyrrolidin-3-yl)-5,5-difluoropiperidin-2-one or a pharmaceutically acceptable salt thereof:



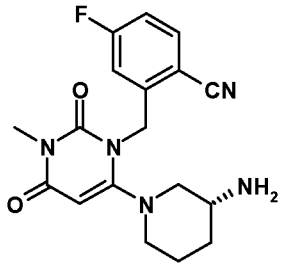
This compound and methods for its preparation are disclosed in WO 2007/148185 and US 20070299076. For details, e.g. on a process to manufacture, to formulate or to use this compound or a salt thereof, reference is thus made to these documents.

- (2S,4S)-1-{2-[(3S,1R)-3-(1H-1,2,4-Triazol-1-ylmethyl)cyclopentylamino]-acetyl}-4-fluoropyrrolidine-2-carbonitrile (alos named melogliptin) or a pharmaceutically acceptable salt thereof:



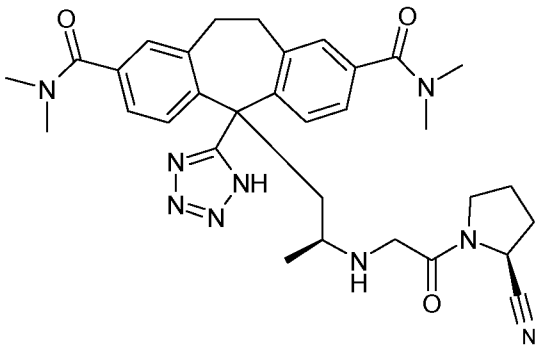
This compound and methods for its preparation are disclosed in WO 2006/040625 and WO 2008/001195. Specifically claimed salts include the methanesulfonate and p-toluenesulfonate. For details, e.g. on a process to manufacture, to formulate or to use this compound or a salt thereof, reference is thus made to these documents.

- (R)-2-[6-(3-Amino-piperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-4-fluoro-benzonitrile or a pharmaceutically acceptable salt thereof:



This compound and methods for its preparation and use are disclosed in WO 2005/095381, US 2007060530, WO 2007/033350, WO 2007/035629, WO 2007/074884, WO 2007/112368, WO 2008/033851, WO 2008/114800 and WO 2008/114807. Specifically claimed salts include the succinate (WO 2008/067465), benzoate, benzenesulfonate, p-toluenesulfonate, (R)-mandelate and hydrochloride. For details, e.g. on a process to manufacture, to formulate or to use this compound or a salt thereof, reference is thus made to these documents.

- 5-{(S)-2-[2-((S)-2-Cyano-pyrrolidin-1-yl)-2-oxo-ethylamino]-propyl}-5-(1H-tetrazol-5-yl)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-2,8-dicarboxylic acid bis-dimethylamide or a pharmaceutically acceptable salt thereof:



This compound and methods for its preparation are disclosed in WO 2006/116157 and US 2006/270701. For details, e.g. on a process to manufacture, to formulate or to use this compound or a salt thereof, reference is thus made to these documents.

- 3-{(2S,4S)-4-[4-(3-Methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-ylcarbonyl}thiazolidine (also named teneligliptin) or a pharmaceutically acceptable salt thereof:

This compound and methods for its preparation are disclosed in WO 02/14271. Specific salts are disclosed in WO 2006/088129 and WO 2006/118127 (including hydrochloride,

hydrobromide, inter alia). Combination therapy using this compound is described in WO 2006/129785. For details, e.g. on a process to manufacture, to formulate or to use this compound or a salt thereof, reference is thus made to these documents.

- [(2R)-1-{[(3R)-pyrrolidin-3-ylamino]acetyl}pyrrolidin-2-yl]boronic acid (also named dutogliptin) or a pharmaceutically acceptable salt thereof:

This compound and methods for its preparation are disclosed in WO 2005/047297, WO 2008/109681 and WO 2009/009751. Specific salts are disclosed in WO 2008/027273 (including citrate, tartrate). A formulation of this compound is described in WO 2008/144730. A formulation of dutogliptin (as its tartrate salt) with metformin is described in WO 2009/091663. For details, e.g. on a process to manufacture, to formulate or to use this compound or a salt thereof, reference is thus made to these documents.

- (2S,4S)-1-[2-[(4-ethoxycarbonylbicyclo[2.2.2]oct-1-yl)amino]acetyl]-4-fluoropyrrolidine-2-carbonitrile (also named bisegliptin) or a pharmaceutically acceptable salt thereof:

This compound and methods for its preparation are disclosed in WO 2005/075421, US 2008/146818 and WO 2008/114857. For details, e.g. on a process to manufacture, to formulate or to use this compound or a salt thereof, reference is thus made to these documents.

- 2-({6-[(3R)-3-amino-3-methylpiperidin-1-yl]-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-5H-pyrrolo[3,2-d]pyrimidin-5-yl}methyl)-4-fluorobenzonitrile or a pharmaceutically acceptable salt thereof, or 6-[(3R)-3-amino-piperidin-1-yl]-5-(2-chloro-5-fluoro-benzyl)-1,3-dimethyl-1,5-dihydro-pyrrolo[3,2-d]pyrimidine-2,4-dione or a pharmaceutically acceptable salt thereof:

These compounds and methods for their preparation are disclosed in WO 2009/084497 and WO 2006/068163, respectively. Combination therapy using the latter of these two compounds is described in WO 2009/128360. For details, e.g. on a process to manufacture, to formulate or to use these compounds or salts thereof, reference is thus made to these documents.

- (S)-2-methylpyrazolo[1,5-a]primidine-6-carboxylic acid {2-[(2-cyanopyrrolidin-1-yl)-2-oxoethylamino]-2-methylpropyl}amide (also named anagliptin) or a pharmaceutically acceptable salt:

This compound and methods for its preparation are disclosed in WO 2004/067509. Combination therapy using this compound is described in WO 2009/139362. For details, e.g. on a process to manufacture, to formulate or to use this compound or a salt thereof, reference is thus made to these documents.

Preferably the DPP-4 inhibitor of this invention is selected from the group (group **G1**) consisting of linagliptin, sitagliptin, vildagliptin, alogliptin, saxagliptin, teneligliptin and dutogliptin, or a pharmaceutically acceptable salt of one of the hereinmentioned DPP-4 inhibitors, or a prodrug thereof.

In another embodiment, the DPP-4 inhibitor of this invention is selected from the group (group **H1**) consisting of linagliptin, sitagliptin, vildagliptin, alogliptin, saxagliptin, teneligliptin, anagliptin, gemigliptin and dutogliptin, or a pharmaceutically acceptable salt of one of the hereinmentioned DPP-4 inhibitors, or a prodrug thereof.

A particularly preferred DPP-4 inhibitor within the present invention is linagliptin. The term "linagliptin" as employed herein refers to linagliptin or a pharmaceutically acceptable salt thereof, including hydrates and solvates thereof, and crystalline forms thereof, preferably linagliptin refers to 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine. Crystalline forms are described in WO 2007/128721. Methods for the manufacture of linagliptin are described in the patent applications WO 2004/018468 and WO 2006/048427 for example. Linagliptin is distinguished from structurally comparable DPP-4 inhibitors, as it combines exceptional potency and a long-lasting effect with favourable pharmacological properties, receptor selectivity and a favourable side-effect profile or bring about unexpected therapeutic advantages or improvements in mono- or dual or triple combination therapy.

For avoidance of any doubt, the disclosure of each of the foregoing and following documents cited above in connection with the specified DPP-4 inhibitors is specifically incorporated herein by reference in its entirety.

GLP-1 receptor agonists include, without being limited, exogenous GLP-1 (natural or synthetic), GLP-1 analogues (including longer acting analogues which are resistant to or have reduced susceptibility to enzymatic degradation by DPP-4 and NEP 24.11) and other substances (whether peptidic or non-peptidic, e.g. small molecules) which promote signalling through the GLP-1 receptor.

Examples of GLP-1 analogues may include (group **G2**): exenatide (synthetic exendin-4, e.g. formulated as Byetta); exenatide LAR (long acting release formulation of exenatide, e.g. formulated as Bydureon); liraglutide (e.g. formulated as Victoza); taspoglutide; semaglutide; albiglutide (e.g. formulated as Syncria); lixisenatide; dulaglutide; and the di-PEGylated GLP-1 compound comprising the amino acid sequence of the pegylated compound of Formula I (SEQ ID NO:1) according to WO 2006/124529 (the disclosure of which is incorporated herein), wherein Xaa_8 is Val, Xaa_{22} is Glu, Xaa_{33} is Ile, and Xaa_{46} is Cys-NH_2, and wherein one PEG molecule is covalently attached to Cys_{45} and one PEG molecule is covelently attached to Cys_{46}-NH_2, wherein each of the PEG molecules used for PEGylation reaction is a 20,000 dalton linear methoxy PEG maleimide (preferably the GLP-1 derivative consists of the amino acid sequence of Val^8-Glu^{22}-Ile^{33}-Cys-$NH_2{}^{46}$-GLP-1 (cf. SEQ ID NO:21 of WO 2009/020802, the disclosure of which is incorporated herein).

Preferred examples of GLP-1 receptor agonists (GLP-1 analogues) of this invention are exenatide, exenatide LAR, liraglutide, taspoglutide, semaglutide, albiglutide, lixisenatide and dulaglutide.

GLP-1 analogues have typically significant sequence identity to GLP-1 (e.g. greater than 50%, 75%, 90% or 95%) and may be derivatised, e.g. by conjunction to other proteins (e.g. albumin or IgG-Fc fusion protein) or through chemical modification.

Unless otherwise noted, according to this invention it is to be understood that the definitions of the active agents (including the DPP-4 inhibitors and GLP-1 receptor agonists) mentioned hereinabove and hereinbelow may also contemplate their pharmaceutically acceptable salts, and prodrugs, hydrates, solvates and polymorphic forms thereof. Particularly the terms of the therapeutic agents given herein refer to the respective active drugs. With respect to salts, hydrates and polymorphic forms thereof, particular reference is made to those which are referred to herein.

In an embodiment the combinations, compositions, methods and uses according to this invention relate to combinations wherein the DPP-4 inhibitor and the GLP-1 receptor agonist are preferably selected according to the entries in the Table 1:

Table 1

DPP-4 Inhibitor	GLP-1 receptor agonist
selected from embodiment B	selected from group G2
selected from embodiment B	exenatide
selected from embodiment B	exenatide LAR
selected from embodiment B	liraglutide
selected from embodiment B	taspoglutide
selected from embodiment B	semaglutide
selected from embodiment B	albiglutide
selected from embodiment B	lixisenatide
selected from embodiment B	dulaglutide
selected from group G1	selected from group G2
selected from group G1	exenatide
selected from group G1	exenatide LAR
selected from group G1	liraglutide
selected from group G1	taspoglutide
selected from group G1	semaglutide
selected from group G1	albiglutide
selected from group G1	lixisenatide
selected from group G1	dulaglutide
linagliptin	exenatide
linagliptin	exenatide LAR
linagliptin	liraglutide
linagliptin	taspoglutide
linagliptin	semaglutide
linagliptin	albiglutide
linagliptin	lixisenatide
linagliptin	dulaglutide
linagliptin	selected from group G2

In a particular embodiment (embodiement **E**) the combinations, compositions, methods and uses according to this invention relate to combinations wherein the DPP-4 inhibitor is linagliptin. According to this particular embodiment (embodiment **E**) the GLP-1 receptor agonist is preferably selected according to the entries E1 to E8 in the Table 2:

Table 2

Embodiment	GLP-1 receptor agonist
E1	exenatide
E2	exenatide LAR
E3	liraglutide
E4	taspoglutide
E5	semaglutide
E6	albiglutide
E7	lixisenatide
E8	dulaglutide

Within this invention it is to be understood that the combinations, compositions or combined uses according to this invention may envisage the simultaneous, sequential or separate administration of the active components or ingredients.

In this context, “combination” or “combined” within the meaning of this invention may include, without being limited, fixed and non-fixed (e.g. free) forms (including kits) and uses, such as e.g. the simultaneous, sequential or separate use of the components or ingredients.

The present invention also privides a kit-of-parts or combination therapeutic product comprising
a) a pharmaceutical composition comprising a DPP-4 inhibitor as defined herein, optionally together with one or more pharmaceutically acceptable carriers and/or diluents, and
b) a pharmaceutical composition comprising a GLP-1 receptor agonist as defined herein.

The present invention also privides a kit comprising
a) a DPP-4 inhibitor as defined herein, and
b) a GLP-1 receptor agonist as defined herein,

and, optionally, instructions directing use of the DPP-4 inhibitor and the GLP-1 receptor agonist in combination (e.g. simultaneously, separately, sequentially or chronologically staggered), e.g. for a purpose of this invention, such as e.g. for the treatment of type 2 diabetes, obesity and/or overweight, and/or for reducing and maintaining body weight in a (human) patient.

The combined administration of this invention may take place by administering the active components or ingredients together, such as e.g. by administering them simultaneously in one single or in two separate formulations or dosage forms. Alternatively, the administration may take place by administering the active components or ingredients sequentially, such as e.g. successively in two separate formulations or dosage forms.

For the combination therapy of this invention the active components or ingredients may be administered separately (which implies that they are formulated separately) or formulated altogether (which implies that they are formulated in the same preparation or in the same dosage form). Hence, the administration of one element of the combination of the present invention may be prior to, concurrent to, or subsequent to the administration of the other element of the combination. Preferably, for the combination therapy according to this invention the DPP-4 inhibitor and the GLP-1 receptor agonist are administered in different formulations.

Unless otherwise noted, combination therapy may refer to first line, second line or third line therapy, or initial or add-on combination therapy or replacement therapy.

With respect to embodiment **A**, the methods of synthesis for the DPP-4 inhibitors according to embodiment **A** of this invention are known to the skilled person. Advantageously, the DPP-4 inhibitors according to embodiment **A** of this invention can be prepared using synthetic methods as described in the literature. Thus, for example, purine derivatives of formula (I) can be obtained as described in WO 2002/068420, WO 2004/018468, WO 2005/085246, WO 2006/029769 or WO 2006/048427, the disclosures of which are incorporated herein. Purine derivatives of formula (II) can be obtained as described, for example, in WO 2004/050658 or WO 2005/110999, the disclosures of which are incorporated herein. Purine derivatives of formula (III) and (IV) can be obtained as described, for example, in WO 2006/068163, WO 2007/071738 or WO 2008/017670, the disclosures of which are incorporated herein. The preparation of those DPP-4 inhibitors, which are specifically

mentioned hereinabove, is disclosed in the publications mentioned in connection therewith. Polymorphous crystal modifications and formulations of particular DPP-4 inhibitors are disclosed in WO 2007/128721 and WO 2007/128724, respectively, the disclosures of which are incorporated herein in their entireties. Formulations of particular DPP-4 inhibitors with metformin or other combination partners are described in WO 2009/121945, the disclosure of which is incorporated herein in its entirety.

Typical dosage strengths of the dual fixed combination (tablet) of linagliptin / metformin IR (immediate release) are 2.5/500 mg, 2.5/850 mg and 2.5/1000 mg, which may be administered 1-3 times a day, particularly twice a day.

Typical dosage strengths of the dual fixed combination (tablet) of linagliptin / metformin XR (extended release) are 5/500 mg, 5/1000 mg and 5/1500 mg, or 2.5/500 mg, 2.5/750 mg and 2.5/1000 mg (each two tablets), which may be administered 1-2 times a day, particularly once a day, preferably to be taken in the evening with meal.

The present invention further provides a DPP-4 inhibitor as defined herein for use in (add-on or initial) combination therapy with metformin (e.g. in a total daily amount from 500 to 2000 mg metformin hydrochloride, such as e.g. 500 mg, 850 mg or 1000 mg once or twice daily).

With respect to embodiment **B**, the methods of synthesis for the DPP-4 inhibitors of embodiment **B** are described in the scientific literature and/ or in published patent documents, particularly in those cited herein.

Suitable doses and dosage forms of the DPP-4 inhibitors may be determined by a person skilled in the art and may include those described herein or in the relevant references.

For pharmaceutical application in warm-blooded vertebrates, particularly humans, the compounds of this invention are usually used in dosages from 0.001 to 100 mg/kg body weight, preferably at 0.1-15 mg/kg, in each case 1 to 4 times a day. For this purpose, the compounds, optionally combined with other active substances, may be incorporated together with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as

hard fat or suitable mixtures thereof into conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions or suppositories.

The pharmaceutical compositions according to this invention comprising the DPP-4 inhibitors as defined herein are thus prepared by the skilled person using pharmaceutically acceptable formulation excipients as described in the art. Examples of such excipients include, without being restricted to diluents, binders, carriers, fillers, lubricants, flow promoters, crystallisation retardants, disintegrants, solubilizers, colorants, pH regulators, surfactants and emulsifiers.

Examples of suitable diluents for compounds according to embodiment **A** include cellulose powder, calcium hydrogen phosphate, erythritol, low substituted hydroxypropyl cellulose, mannitol, pregelatinized starch or xylitol.

Examples of suitable lubricants for compounds according to embodiment **A** include talc, polyethyleneglycol, calcium behenate, calcium stearate, hydrogenated castor oil or magnesium stearate.

Examples of suitable binders for compounds according to embodiment **A** include copovidone (copolymerisates of vinylpyrrolidon with other vinylderivates), hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose (HPC), polyvinylpyrrolidon (povidone), pregelatinized starch, or low-substituted hydroxypropylcellulose (L-HPC).

Examples of suitable disintegrants for compounds according to embodiment **A** include corn starch or crospovidone.

Suitable methods of preparing pharmaceutical formulations of the DPP-4 inhibitors according to embodiment **A** of the invention are

- direct tabletting of the active substance in powder mixtures with suitable tabletting excipients;
- granulation with suitable excipients and subsequent mixing with suitable excipients and subsequent tabletting as well as film coating; or
- packing of powder mixtures or granules into capsules.

Suitable granulation methods are

- wet granulation in the intensive mixer followed by fluidised bed drying;

- one-pot granulation;
- fluidised bed granulation; or
- dry granulation (e.g. by roller compaction) with suitable excipients and subsequent tabletting or packing into capsules.

An exemplary composition (e.g. tablet core) of a DPP-4 inhibitor according to embodiment **A** of the invention comprises the first diluent mannitol, pregelatinized starch as a second diluent with additional binder properties, the binder copovidone, the disintegrant corn starch, and magnesium stearate as lubricant; wherein copovidone and/or corn starch may be optional.

A tablet of a DPP-4 inhibitor according to embodiment **A** of the invention may be film coated, preferably the film coat comprises hydroxypropylmethylcellulose (HPMC), polyethylene glycol (PEG), talc, titanium dioxide and iron oxide (e.g. red and/or yellow).

For details on dosage forms, formulations and administration of DPP-4 inhibitors of this invention and/or GLP-1 receptor agonists of this invention, reference is made to scientific literature and/or published patent documents, particularly to those cited herein.

In a preferred embodiment the element DPP-4 inhibitor of the combination according to the invention is preferably administered orally. In another preferred embodiment the component GLP-1 receptor agonist of the combination is preferably administered by injection.

Injectable formulations of the GLP-1 receptor agonists of this invention may be prepared according to known formulation techniques, e.g. using suitable liquid carriers, which usually comprise sterile water, and, optionally, further additives e.g. for aiding solubility or for preservation or the like, to obtain injectable solutions or suspensions.

The pharmaceutical compositions (or formulations) may be packaged in a variety of ways. Generally, an article for distribution includes a container that contains the pharmaceutical composition in an appropriate form. Tablets are typically packed in an appropriate primary package for easy handling, distribution and storage and for assurance of proper stability of the composition at prolonged contact with the environment during storage. Primary containers for tablets may be bottles or blister packs.

A suitable bottle, e.g. for a pharmaceutical composition or combination comprising a DPP-4 inhibitor according to embodiment **A** of the invention, may be made from glass or polymer (preferably polypropylene (PP) or high density polyethylene (HD-PE)) and sealed with a screw cap. The screw cap may be provided with a child resistant safety closure (e.g. press-and-twist closure) for preventing or hampering access to the contents by children. If required (e.g. in regions with high humidity), by the additional use of a desiccant (such as e.g. bentonite clay, molecular sieves, or, preferably, silica gel) the shelf life of the packaged composition can be prolonged.

A suitable blister pack, e.g. for a pharmaceutical composition or combination comprising a DPP-4 inhibitor according to embodiment **A** of the invention, comprises or is formed of a top foil (which is breachable by the tablets) and a bottom part (which contains pockets for the tablets). The top foil may contain a metalic foil, particularly an aluminium or aluminium alloy foil (e.g. having a thickness of 20µm to 45µm, preferably 20µm to 25µm) that is coated with a heat-sealing polymer layer on its inner side (sealing side). The bottom part may contain a multi-layer polymer foil (such as e.g. poly(vinyl choride) (PVC) coated with poly(vinylidene choride) (PVDC); or a PVC foil laminated with poly(chlorotriflouroethylene) (PCTFE)) or a multi-layer polymer-metal-polymer foil (such as e.g. a cold-formable laminated PVC/aluminium/polyamide composition).

To ensure a long storage period especially under hot and wet climate conditions an additional overwrap or pouch made of a multi-layer polymer-metal-polymer foil (e.g. a laminated polyethylen/aluminium/polyester composition) may be used for the blister packs. Supplementary desiccant (such as e.g. bentonite clay, molecular sieves, or, preferably, silica gel) in this pouch package may prolong the shelf life even more under such harsh conditions.

The article may further comprise a label or package insert, which refer to instructions customarily included in commercial packages of therapeutic products, that may contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products. In one embodiment, the label or package inserts indicates that the composition can be used for any of the purposes described herein.

With respect to the first embodiment (embodiment **A**), the dosage typically required of the DPP-4 inhibitors mentioned herein in embodiment **A** when administered intravenously is

0.1 mg to 10 mg, preferably 0.25 mg to 5 mg, and when administered orally is 0.5 mg to 100 mg, preferably 2.5 mg to 50 mg or 0.5 mg to 10 mg, more preferably 2.5 mg to 10 mg or 1 mg to 5 mg, in each case 1 to 4 times a day. Thus, e.g. the dosage of 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine when administered orally is 0.5 mg to 10 mg per patient per day, preferably 2.5 mg to 10 mg or 1 mg to 5 mg per patient per day.

A dosage form prepared with a pharmaceutical composition comprising a DPP-4 inhibitor mentioned herein in embodiment **A** contain the active ingredient in a dosage range of 0.1-100 mg. Thus, e.g. particular dosage strengths of 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine are 0.5 mg, 1 mg, 2.5 mg, 5 mg and 10 mg.

With respect to the second embodiment (embodiment **B**), the doses of DPP-4 inhibitors mentioned herein in embodiment **B** to be administered to mammals, for example human beings, of, for example, approximately 70 kg body weight, may be generally from about 0.5 mg to about 350 mg, for example from about 10 mg to about 250 mg, preferably 20-200 mg, more preferably 20-100 mg, of the active moiety per person per day, or from about 0.5 mg to about 20 mg, preferably 2.5-10 mg, per person per day, divided preferably into 1 to 4 single doses which may, for example, be of the same size. Single dosage strengths comprise, for example, 10, 25, 40, 50, 75, 100, 150 and 200 mg of the DPP-4 inhibitor active moiety.

A dosage strength of the DPP-4 inhibitor sitagliptin is usually between 25 and 200 mg of the active moiety. A recommended dose of sitagliptin is 100 mg calculated for the active moiety (free base anhydrate) once daily. Unit dosage strengths of sitagliptin free base anhydrate (active moiety) are 25, 50, 75, 100, 150 and 200 mg. Particular unit dosage strengths of sitagliptin (e.g. per tablet) are 25, 50 and 100 mg. An equivalent amount of sitagliptin phosphate monohydrate to the sitagliptin free base anhydrate is used in the pharmaceutical compositions, namely, 32.13, 64.25, 96.38, 128.5, 192.75, and 257 mg, respectively. Adjusted dosages of 25 and 50 mg sitagliptin are used for patients with renal failure. Typical dosage strengths of the dual combination of sitagliptin / metformin are 50/500 mg and 50/1000 mg.

A dosage range of the DPP-4 inhibitor vildagliptin is usually between 10 and 150 mg daily, in particular between 25 and 150 mg, 25 and 100 mg or 25 and 50 mg or 50 and 100 mg daily.

Particular examples of daily oral dosage are 25, 30, 35, 45, 50, 55, 60, 80, 100 or 150 mg. In a more particular aspect, the daily administration of vildagliptin may be between 25 and 150 mg or between 50 and 100 mg. In another more particular aspect, the daily administration of vildagliptin may be 50 or 100 mg. The application of the active ingredient may occur up to three times a day, preferably one or two times a day. Particular dosage strengths are 50 mg or 100 mg vildagliptin. Typical dosage strengths of the dual combination of vildagliptin / metformin are 50/850 mg and 50/1000 mg.

Alogliptin may be administered to a patient at a daily dose of between 5 mg/day and 250 mg/day, optionally between 10 mg and 200 mg, optionally between 10 mg and 150 mg, and optionally between 10 mg and 100 mg of alogliptin (in each instance based on the molecular weight of the free base form of alogliptin). Thus, specific dosage amounts that may be used include, but are not limited to 10 mg, 12.5 mg, 20 mg, 25 mg, 50 mg, 75 mg and 100 mg of alogliptin per day. Alogliptin may be administered in its free base form or as a pharmaceutically acceptable salt.

Saxagliptin may be administered to a patient at a daily dose of between 2.5 mg/day and 100 mg/day, optionally between 2.5 mg and 50 mg. Specific dosage amounts that may be used include, but are not limited to 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg , 40 mg, 50 mg and 100 mg of saxagliptin per day. Typical dosage strengths of the dual combination of saxagliptin / metformin are 2.5/500 mg and 2.5/1000 mg.

A special embodiment of the DPP-4 inhibitors of this invention refers to those orally administered DPP-4 inhibitors which are therapeutically efficacious at low dose levels, e.g. at oral dose levels < 100 mg or < 70 mg per patient per day, preferably < 50 mg, more preferably < 30 mg or < 20 mg, even more preferably from 1 mg to 10 mg, particularly from 1 mg to 5 mg (more particularly 5 mg), per patient per day (if required, divided into 1 to 4 single doses, particularly 1 or 2 single doses, which may be of the same size, preferentially, administered orally once- or twice daily (more preferentially once-daily), advantageously, administered at any time of day, with or without food. Thus, for example, the daily oral amount 5 mg BI 1356 can be given in an once daily dosing regimen (i.e. 5 mg BI 1356 once daily) or in a twice daily dosing regimen (i.e. 2.5 mg BI 1356 twice daily), at any time of day, with or without food.

The GLP-1 receptor agonist is typically administered by subcutaneous injection, e.g. ranging from thrice daily, twice daily, once daily to once weekly injection. Suitable doses and dosage forms of the GLP-1 receptor agonist may be determined by a person skilled in the art.
For example, exenatide is administered twice daily by subcutaneous injection (Byetta, 5-30 µg, particularly 5-20µg, preferably 5-10 µg, specific dosage strengths are 5 or 10 µg) before a main meal.
Exenatide LAR is administered once weekly by subcutaneous injection (0.1-3 mg, particularly 0.5 mg to 2.0 mg, specific dosage strengths are 0.8 mg or 2.0 mg).
Liraglutide is administered once daily by subcutaneous injection (Victoza, 0.5-3 mg, particularly 0.5 mg to 2 mg, specific dosage strengths are 0.6 mg, 0.9 mg, 1.2 mg or 1.8 mg).
Taspoglutide is administered once weekly by subcutaneous injection (1-30 mg, specific dosage strengths are 1 mg, 8 mg, 10 mg, 20 mg or 30 mg).
Semaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg).
Albiglutide is administered once weekly by subcutaneous injection (4-30 mg, specific dosage strengths are 4 mg, 15 mg or 30 mg).
Lixisenatide is administered once daily by subcutaneous injection (10-20 µg, specific dosage strengths are 10 µg, 15 µg or 20 µg).
Dulaglutide is administered once weekly by subcutaneous injection (0.25-3 mg, specific dosage strengths are 0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg, 1.5 mg, 2.0 mg or 3.0 mg).

Besides delivery by injection, other routes of administration of GLP-1 receptor agonists may be contemplated, for example, GLP-1 receptor agonists for use in combination therapy within the meaning of this invention also include, without being limited, such ones which are suited and/or formulated for oral delivery, continuous (subcutaneous) delivery, pulmonary (e.g. via inhalation) or nasal delivery, or transdermal delivery (e.g. via patch), with subcutaneous injection being preferred.

The dosage of the active ingredients in the combinations and compositions in accordance with the present invention may be varied, although the amount of the active ingredients shall be such that a suitable dosage form is obtained. Hence, the selected dosage and the selected dosage form shall depend on the desired therapeutic effect, the route of administration and the duration of the treatment. Suitable dosage ranges for the combination are from the maximal tolerated dose for the single agent to lower doses, e.g. to one tenth of the maximal tolerated dose.

A particularly preferred DPP-4 inhibitor to be emphasized within the meaning of this invention is 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine (also known as BI 1356 or linagliptin). BI 1356 exhibits high potency, 24h duration of action, and a wide therapeutic window. In patients with type 2 diabetes receiving multiple oral doses of 1, 2.5, 5 or 10 mg of BI 1356 once daily for 12 days, BI 1356 shows favourable pharmacodynamic and pharmacokinetic profile (see e.g. Table i below) with rapid attainment of steady state (e.g. reaching steady state plasma levels (> 90% of the pre-dose plasma concentration on Day 13) between second and fifth day of treatment in all dose groups), little accumulation (e.g. with a mean accumulation ratio $R_{A,AUC} \leq 1.4$ with doses above 1 mg) and preserving a long-lasting effect on DPP-4 inhibition (e.g. with almost complete (> 90%) DPP-4 inhibition at the 5 mg and 10 mg dose levels, i.e. 92.3 and 97.3% inhibition at steady state, respectively, and > 80% inhibition over a 24h interval after drug intake), as well as significant decrease in 2h postprandial blood glucose excursions by ≥ 80 % (already on Day 1) in doses ≥ 2.5 mg, and with the cumulative amount of unchanged parent compound excreted in urine on Day 1 being below 1% of the administered dose and increasing to not more than about 3-6% on Day 12 (renal clearance $CL_{R,ss}$ is from about 14 to about 70 mL/min for the administered oral doses, e.g. for the 5 mg dose renal clearance is about 70 ml/min). In people with type 2 diabetes BI 1356 shows a placebo-like safety and tolerability. With low doses of about ≥ 5 mg, BI 1356 acts as a true once-daily oral drug with a full 24 h duration of DPP-4 inhibition. At therapeutic oral dose levels, BI 1356 is mainly excreted via the liver and only to a minor extent (about < 7% of the administered oral dose) via the kidney. BI 1356 is primarily excreted unchanged via the bile. The fraction of BI 1356 eliminated via the kidneys increases only very slightly over time and with increasing dose, so that there will likely be no need to modify the dose of BI 1356 based on the patients' renal function. The non-renal elimination of BI 1356 in combination with its low accumulation potential and broad safety margin may be of significant benefit in a patient population that has a high prevalence of renal insufficiency and diabetic nephropathy.

Table i: Geometric mean (gMean) and geometric coefficient of variation (gCV) of pharmacokinetic parameters of BI 1356 at steady state (Day 12)

Parameter	**1 mg gMean (gCV)**	**2.5 mg gMean (gCV)**	**5 mg gMean (gCV)**	**10 mg gMean (gCV)**
AUC_{0-24} [nmol·h/L]	40.2 (39.7)	85.3 (22.7)	118 (16.0)	161 (15.7)

$AUC_{\tau,ss}$ [nmol·h/L]	81.7 (28.3)	117 (16.3)	158 (10.1)	190 (17.4)
C_{max} [nmol/L]	3.13 (43.2)	5.25 (24.5)	8.32 (42.4)	9.69 (29.8)
$C_{max,ss}$ [nmol/L]	4.53 (29.0)	6.58 (23.0)	11.1 (21.7)	13.6 (29.6)
t_{max}* [h]	1.50 [1.00 – 3.00]	2.00 [1.00 – 3.00]	1.75 [0.92 – 6.02]	2.00 [1.50 – 6.00]
$t_{max,ss}$* [h]	1.48 [1.00 – 3.00]	1.42 [1.00 – 3.00]	1.53 [1.00 – 3.00]	1.34 [0.50 – 3.00]
$T_{½,ss}$ [h]	121 (21.3)	113 (10.2)	131 (17.4)	130 (11.7)
Accumulation $t_{½,}$ [h]	23.9 (44.0)	12.5 (18.2)	11.4 (37.4)	8.59 (81.2)
$R_{A,Cmax}$	1.44 (25.6)	1.25 (10.6)	1.33 (30.0)	1.40 (47.7)
$R_{A,AUC}$	2.03 (30.7)	1.37 (8.2)	1.33 (15.0)	1.18 (23.4)
fe_{0-24} [%]	NC	0.139 (51.2)	0.453 (125)	0.919 (115)
$fe_{\tau,ss}$ [%]	3.34 (38.3)	3.06 (45.1)	6.27 (42.2)	3.22 (34.2)
$CL_{R,ss}$ [mL/min]	14.0 (24.2)	23.1 (39.3)	70 (35.0)	59.5 (22.5)

* median and range [min-max]

NC not calculated as most values below lower limit of quantification

As different metabolic functional disorders often occur simultaneously, it is quite often indicated to combine a number of different active principles with one another. Thus, depending on the functional disorders diagnosed, improved treatment outcomes may be obtained if a DPP-4 inhibitor is combined with active substances customary for the respective disorders, such as e.g. one or more active substances selected from among the other antidiabetic substances, especially active substances that lower the blood sugar level or the lipid level in the blood, raise the HDL level in the blood, lower blood pressure or are indicated in the treatment of atherosclerosis or obesity.

The DPP-4 inhibitors mentioned above – besides their use in mono-therapy – may also be used in conjunction with other active substances, by means of which improved treatment results can be obtained. Such a combined treatment may be given as a free combination of the substances or in the form of a fixed combination, for example in a tablet or capsule. Pharmaceutical formulations of the combination partner needed for this may either be obtained commercially as pharmaceutical compositions or may be formulated by the skilled man using conventional methods. The active substances which may be obtained commercially as pharmaceutical compositions are described in numerous places in the prior art, for example in the list of drugs that appears annually, the "Rote Liste ®" of the federal association of the pharmaceutical industry, or in the annually updated compilation of manufacturers' information on prescription drugs known as the "Physicians' Desk Reference".

Examples of antidiabetic combination partners are metformin; sulphonylureas such as glibenclamide, tolbutamide, glimepiride, glipizide, gliquidon, glibornuride and gliclazide; nateglinide; repaglinide; mitiglinide, thiazolidinediones such as rosiglitazone and pioglitazone; PPAR gamma modulators such as metaglidases; PPAR-gamma agonists such as mitoglitazone, INT-131, balaglitazone or rivoglitazone; PPAR-gamma antagonists; PPAR-gamma/alpha modulators such as tesaglitazar, muraglitazar, aleglitazar, indeglitazar and KRP297; PPAR-gamma/alpha/delta modulators such as e.g. lobeglitazone; AMPK-activators such as AICAR; acetyl-CoA carboxylase (ACC1 and ACC2) inhibitors; diacylglycerol-acetyltransferase (DGAT) inhibitors; pancreatic beta cell GCRP agonists such as SMT3-receptor-agonists and GPR119, such as the GPR119 agonists 5-ethyl-2-{4-[4-(4-tetrazol-1-yl-phenoxymethyl)-thiazol-2-yl]-piperidin-1-yl}-pyrimidine or 5-[1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-piperidin-4-ylmethoxy]-2-(4-methanesulfonyl-phenyl)-pyridine; 11ß-HSD-inhibitors; FGF19 agonists or analogues; alpha-glucosidase blockers such as acarbose, voglibose and miglitol; alpha2-antagonists; insulin and insulin analogues such as human insulin, insulin lispro, insulin glusilin, r-DNA-insulinaspart, NPH insulin, insulin detemir, insulin degludec, insulin tregopil, insulin zinc suspension and insulin glargin; Gastric inhibitory Peptide (GIP); amylin and amylin analogues (e.g. pramlintide or davalintide); GLP-1 and GLP-1 analogues such as Exendin-4, e.g. exenatide, exenatide LAR, liraglutide, taspoglutide, lixisenatide (AVE-0010), LY-2428757 (a PEGylated version of GLP-1), dulaglutide (LY-2189265), semaglutide or albiglutide; SGLT2-inhibitors such as e.g. dapagliflozin, sergliflozin (KGT-1251), atigliflozin, canagliflozin or (1S)-1,5-anhydro-1-[3-(1-benzothiophen-2-ylmethyl)-4-fluorophenyl]-D-glucitol, ipragliflozin, tofogliflozin, luseogliflozin;

inhibitors of protein tyrosine-phosphatase (e.g. trodusquemine); inhibitors of glucose-6-phosphatase; fructose-1,6-bisphosphatase modulators; glycogen phosphorylase modulators; glucagon receptor antagonists; phosphoenolpyruvatecarboxykinase (PEPCK) inhibitors; pyruvate dehydrogenasekinase (PDK) inhibitors; inhibitors of tyrosine-kinases (50 mg to 600 mg) such as PDGF-receptor-kinase (cf. EP-A-564409, WO 98/35958, US 5093330, WO 2004/005281, and WO 2006/041976) or of serine/threonine kinases; glucokinase/regulatory protein modulators incl. glucokinase activators; glycogen synthase kinase inhibitors; inhibitors of the SH2-domain-containing inositol 5-phosphatase type 2 (SHIP2) ; IKK inhibitors such as high-dose salicylate; JNK1 inhibitors; protein kinase C-theta inhibitors; beta 3 agonists such as ritobegron, YM 178, solabegron, talibegron, N-5984, GRC-1087, rafabegron, FMP825; aldosereductase inhibitors such as AS 3201, zenarestat, fidarestat, epalrestat, ranirestat, NZ-314, CP-744809, and CT-112; SGLT-1 or SGLT-2 inhibitors; KV 1.3 channel inhibitors; GPR40 modulators such as e.g. [(3S)-6-({2',6'-dimethyl-4'-[3-(methylsulfonyl)propoxy]biphenyl-3-yl}methoxy)-2,3-dihydro-1-benzofuran-3-yl]acetic acid; SCD-1 inhibitors; CCR-2 antagonists; dopamine receptor agonists (bromocriptine mesylate [Cycloset]); 4-(3-(2,6-dimethylbenzyloxy)phenyl)-4-oxobutanoic acid; sirtuin stimulants; and other DPP IV inhibitors.

Metformin is usually given in doses varying from about 500 mg to 2000 mg up to 2500 mg per day using various dosing regimens from about 100 mg to 500 mg or 200 mg to 850 mg (1-3 times a day), or about 300 mg to 1000 mg once or twice a day, or delayed-release metformin in doses of about 100 mg to 1000 mg or preferably 500 mg to 1000 mg once or twice a day or about 500 mg to 2000 mg once a day. Particular dosage strengths may be 250, 500, 625, 750, 850 and 1000 mg of metformin hydrochloride.

For children 10 to 16 years of age, the recommended starting dose of metformin is 500 mg given once daily. If this dose fails to produce adequate results, the dose may be increased to 500 mg twice daily. Further increases may be made in increments of 500 mg weekly to a maximum daily dose of 2000 mg, given in divided doses (e.g. 2 or 3 divided doses). Metformin may be administered with food to decrease nausea.

A dosage of pioglitazone is usually of about 1-10 mg, 15 mg, 30 mg, or 45 mg once a day.

Rosiglitazone is usually given in doses from 4 to 8 mg once (or divided twice) a day (typical dosage strengths are 2, 4 and 8 mg).

Glibenclamide (glyburide) is usually given in doses from 2.5-5 to 20 mg once (or divided twice) a day (typical dosage strengths are 1.25, 2.5 and 5 mg), or micronized glibenclamide in doses from 0.75-3 to 12 mg once (or divided twice) a day (typical dosage strengths are 1.5, 3, 4.5 and 6 mg).

Glipizide is usually given in doses from 2.5 to 10-20 mg once (or up to 40 mg divided twice) a day (typical dosage strengths are 5 and 10 mg), or extended-release glibenclamide in doses from 5 to 10 mg (up to 20 mg) once a day (typical dosage strengths are 2.5, 5 and 10 mg).

Glimepiride is usually given in doses from 1-2 to 4 mg (up to 8 mg) once a day (typical dosage strengths are 1, 2 and 4 mg).

A dual combination of glibenclamide/metformin is usually given in doses from 1.25/250 once daily to 10/1000 mg twice daily. (typical dosage strengths are 1.25/250, 2.5/500 and 5/500 mg).
A dual combination of glipizide/metformin is usually given in doses from 2.5/250 to 10/1000 mg twice daily (typical dosage strengths are 2.5/250, 2.5/500 and 5/500 mg).
A dual combination of glimepiride/metformin is usually given in doses from 1/250 to 4/1000 mg twice daily.
A dual combination of rosiglitazone/glimepiride is usually given in doses from 4/1 once or twice daily to 4/2 mg twice daily (typical dosage strengths are 4/1, 4/2, 4/4, 8/2 and 8/4 mg).
A dual combination of pioglitazone/glimepiride is usually given in doses from 30/2 to 30/4 mg once daily (typical dosage strengths are 30/4 and 45/4 mg).
A dual combination of rosiglitazone/metformin is usually given in doses from 1/500 to 4/1000 mg twice daily (typical dosage strengths are 1/500, 2/500, 4/500, 2/1000 and 4/1000 mg).
A dual combination of pioglitazone/metformin is usually given in doses from 15/500 once or twice daily to 15/850 mg thrice daily (typical dosage strengths are 15/500 and 15/850 mg).

The non-sulphonylurea insulin secretagogue nateglinide is usually given in doses from 60 to 120 mg with meals (up to 360 mg/day, typical dosage strengths are 60 and 120 mg); repaglinide is usually given in doses from 0.5 to 4 mg with meals (up to 16 mg/day, typical dosage strengths are 0.5, 1 and 2 mg). A dual combination of repaglinide/metformin is available in dosage strengths of 1/500 and 2/850 mg.

Acarbose is usually given in doses from 25 to 100 mg with meals. Miglitol is usually given in doses from 25 to 100 mg with meals.

Examples of combination partners that lower the lipid level in the blood are HMG-CoA-reductase inhibitors such as simvastatin, atorvastatin, lovastatin, fluvastatin, pravastatin, pitavastatin and rosuvastatin; fibrates such as bezafibrate, fenofibrate, clofibrate, gemfibrozil, etofibrate and etofyllinclofibrate; nicotinic acid and the derivatives thereof such as acipimox; PPAR-alpha agonists; PPAR-delta agonists such as e.g. {4-[(R)-2-ethoxy-3-(4-trifluoromethyl-phenoxy)-propylsulfanyl]-2-methyl-phenoxy}-acetic acid; inhibitors of acyl-coenzyme A:cholesterolacyltransferase (ACAT; EC 2.3.1.26) such as avasimibe; cholesterol resorption inhibitors such as ezetimib; substances that bind to bile acid, such as cholestyramine, colestipol and colesevelam; inhibitors of bile acid transport; HDL modulating active substances such as D4F, reverse D4F, LXR modulating active substances and FXR modulating active substances; CETP inhibitors such as torcetrapib, JTT-705 (dalcetrapib) or compound 12 from WO 2007/005572 (anacetrapib); LDL receptor modulators; MTP inhibitors (e.g. lomitapide); and ApoB100 antisense RNA.

A dosage of atorvastatin is usually from 1 mg to 40 mg or 10 mg to 80 mg once a day.

Examples of combination partners that lower blood pressure are beta-blockers such as atenolol, bisoprolol, celiprolol, metoprolol and carvedilol; diuretics such as hydrochlorothiazide, chlortalidon, xipamide, furosemide, piretanide, torasemide, spironolactone, eplerenone, amiloride and triamterene; calcium channel blockers such as amlodipine, nifedipine, nitrendipine, nisoldipine, nicardipine, felodipine, lacidipine, lercanipidine, manidipine, isradipine, nilvadipine, verapamil, gallopamil and diltiazem; ACE inhibitors such as ramipril, lisinopril, cilazapril, quinapril, captopril, enalapril, benazepril, perindopril, fosinopril and trandolapril; as well as angiotensin II receptor blockers (ARBs) such as telmisartan, candesartan, valsartan, losartan, irbesartan, olmesartan, azilsartan and eprosartan.

A dosage of telmisartan is usually from 20 mg to 320 mg or 40 mg to 160 mg per day.

Examples of combination partners which increase the HDL level in the blood are Cholesteryl Ester Transfer Protein (CETP) inhibitors; inhibitors of endothelial lipase; regulators of ABC1; LXRalpha antagonists; LXRbeta agonists; PPAR-delta agonists; LXRalpha/beta regulators,

and substances that increase the expression and/or plasma concentration of apolipoprotein A-I.

Examples of combination partners for the treatment of obesity are sibutramine; tetrahydrolipstatin (orlistat); alizyme (cetilistat); dexfenfluramine; axokine; cannabinoid receptor 1 antagonists such as the CB1 antagonist rimonobant; MCH-1 receptor antagonists; MC4 receptor agonists; NPY5 as well as NPY2 antagonists (e.g. velneperit); beta3-AR agonists such as SB-418790 and AD-9677; 5HT2c receptor agonists such as APD 356 (lorcaserin); myostatin inhibitors; Acrp30 and adiponectin; steroyl CoA desaturase (SCD1) inhibitors; fatty acid synthase (FAS) inhibitors; CCK receptor agonists; Ghrelin receptor modulators; Pyy 3-36; orexin receptor antagonists; and tesofensine; as well as the dual combinations bupropion/naltrexone, bupropion/zonisamide, topiramate/phentermine and pramlintide/metreleptin.

Examples of combination partners for the treatment of atherosclerosis are phospholipase A2 inhibitors; inhibitors of tyrosine-kinases (50 mg to 600 mg) such as PDGF-receptor-kinase (cf. EP-A-564409, WO 98/35958, US 5093330, WO 2004/005281, and WO 2006/041976); oxLDL antibodies and oxLDL vaccines; apoA-1 Milano; ASA; and VCAM-1 inhibitors.

The present invention is not to be limited in scope by the specific embodiments described herein. Various modifications of the invention in addition to those described herein may become apparent to those skilled in the art from the present disclosure. Such modifications are intended to fall within the scope of the appended claims.

All patent applications cited herein are hereby incorporated by reference in their entireties.

Further embodiments, features and advantages of the present invention may become apparent from the following examples. The following examples serve to illustrate, by way of example, the principles of the invention without restricting it.

Examples

The aim of this study is to evaluate the effects of repeated administration of a GLP-1 receptor agonist, such as e.g. exenatide (30 µg/kg/day sc) by subcutaneous minipump for 10 or 28 days and exenatide (30 µg/kg/day sc) for 10 days followed by vehicle or BI 1356 (3 mg/kg po) given orally on body weight in dietary-induced obese (DIO) female Wistar rats (ie in an animal model of obesity). BI 1356 is a novel compound with potential for the treatment of obesity/diabetes. All experimental procedures concerning the use of laboratory animals are carried out under a Home Office Certificate of Designation.

Methodology:
Obesity is induced-in female Wistar rats for 20 weeks by giving the animals free access to powdered high fat diet (VRF1 plus 20% lard), ground chocolate, ground peanuts and tap water at all times. Two weeks before the start of the baseline readings, animals are housed singly in polypropylene cages with wire grid floors to enable the food intake of each rat to be recorded. Following a 5-day baseline period, osmotic minipumps (2ML2) delivering either vehicle or exenatide are implanted subcutaneously (sc) under anaesthetic. The surgery is performed over two days and therefore the study was divided into two arms (staggered by one day) and the data pooled. On day 11, the osmotic minipumps are removed from all animals and replaced with a new pump (2ML4) containing vehicle or exenatide for 10 days. In addition animals are treated orally with either vehicle (0.5% Natrosol) or BI 1356 and body weight is recorded daily as shown in Figure 1.
When the osmotic mini-pumps start to emerge through the wound clips, animals are re-clipped on one occasion per animal only. Rats are removed from the feeding laboratory for approximately 30 min and the wound resealed under brief (~10 min) anaesthesia. If the wound re-opened the rat is terminated.

Results: Exenatide leads to significant weight loss during the first 11 days. When the animals receive vehicle + vehicle from day 11 on, they gain weight again. However, the animals treated further with the DPP 4 inhibitor BI 1356 stabilize their body weight at the new weight level and are significantly lighter than the vehicle-treated control animals (see Figure1).

Specific surgical procedures: Animals are anaesthetised using gaseous anaesthesia (isoflurane). Specifically, anaesthesia is induced with isoflurane (5%), O_2 (2 l/min), N_2O (2 l/min). During this time the implant site is shaved. All surgery will use aseptic technique.

During surgery, anaesthesia is maintained with isoflurane at 2%, with O_2 (1 l/min) and N_2O (1 l/min). The incision is sited at the flank, and a pocket of suitable size is created and the pump inserted. Pumps are filled with vehicle or exenatide shortly before implantation. The wound is sealed by the use of one or more wound clips (VetTech Solutions). Betadine spray and Opsite dressing are applied to the wound. Immediately post surgery, the N_2O gas stream is removed and O_2 increased to a flow rate of 2 l/min. After approximately 1 min, isoflurane is turned off. Once animals begin to show signs of recovery (e.g. faster breathing rate, tail and/or limb movement) they are placed into the home cage on a heat mat with a heat lamp present. Animals are carefully monitored for up to 2 h following surgery and until they are fully recovered. As soon as the rats recover from the anaesthetic they have free access to food and water.

Figure 1: Body weight development

Figure 1: Results are adjusted means + sem; n=5-51 (n values in brackets are the number remaining on day 21.)SEMs are calculated from the residuals of the statistical model. Data analysed by ANCOVA with body weight on Day 1 as covariate. Multiple comparisons versus the vehicle control group are by multiple t test. Significant differences from vehicle control: *p<0.05, **p<0.01, ***p<0.001. Significant differences from Exenatide 30 µg/kg/day (Day 1-10) + vehicle (from Day 11): #p<0.05, ##p<0.01 (multiple t test). Percent values are weight loss compared to Vehicle on Day 21.

Exenatide-treated animals show higher incidence for skin alterations, which lead often to euthanization of the respective animals. Linagliptin-treated animals show better survival (see Figure 2, e.g. after about 22-23 days treatment, vehicle treated animals (A) show about 65% survival, exenatide+vehicle-treated animals (B) show about 67% survival, exenatide+BI 1356-treated animals (E) show about 75% survival, and exenatide-treated animals (F) show about 45% survival).

Figure 2: Survival plots

Figure 3: Linagliptin attenuates rebound of body weight (including body fat) gain following discontinuation of GLP-1R agonist (e.g. exendin-4) treatment

Figure 3: Results are mean change in body weight of obese female Wistar rats treated with exenatide for either a 10 or 21 day period (n=5-11; Day 1-11 data with exenatide are pooled and include all data for animals treated with exenatide over this period). Means are adjusted for differences between the body weights of the different treatment groups at baseline (Day 1). SEMs are calculated from the residuals of the statistical model. On day 11, the mini-pump was removed and replaced with a second mini-pump. Animals treated with exenatide for 10 days were switched to vehicle treatment for the rest of the study. The change in body weight of animals treated with the DPP-4 inhibitor, linagliptin (3 mg/kg po), on exenatide withdrawal are illustrated on the figure (first bar from right: Exenatide; second bar from right: Exenatide followed by Linagliptin; third bar from right: Exenatide followed by Vehicle). Multiple comparisons versus the vehicle control group were by the multiple t test. Significant differences from vehicle control: *p<0.05; **p<0.01. Significant differences from Exenatide 30 µg/kg/day (Day 1-10) + vehicle s.c. and p.o. (from Day 11): #p=0.07 (multiple t test).

Figure 4: GLP-1R agonist (e.g. exendin-4) cessation and replacement with linagliptin prevents body fat weight regain

5

Table (a): Carcass composition and final body weight (prior to tissue dissection) of animals at the study conclusion

	Water (g)			Fat (g)			Protein (g)			Final Weight (g)	
	Mean	SEM		Mean	SEM		Mean	SEM		Mean	SEM
Vehicle (Day 1-10) + Vehicle (from Day 11); Vehicle po from Day 11	204.2	5.3		123.0	6.5		62.7	1.4		438.2	4.6
Exenatide 30 µg/kg/day (Day 1-10) + Vehicle (from Day 11); Vehicle po from Day 11	194.6	4.3		132.0	6.3		59.7	1.8		424.4	4.5
Exenatide 30 µg/kg/day (Day 1-10) + Vehicle (from Day 11); linagliptin 3 mg/kg po from Day 11	198.0	4.4		117.6	5.0		61.6	2.1		419.1	5.7
Exenatide 30 µg/kg/day (Day 1-10) + Exenatide (30 µg/kg/day from Day 11);	202.1	5.2		103.9	7.5	*$$	61.4	1.5		410.5	8.3

Table (a): Table detailing the carcass composition and final body weight (prior to tissue dissection) of animals at the study conclusion, n=6-10. Data are adjusted for differences between treatment groups in body weight at baseline (Day 1). SEMs are calculated from the residuals of the statistical model. Comparisons against the control group were by the multiple t test: * $p < 0.05$. Comparisons against the vehicle-treated exenatide withdrawal group by multiple t test: $$ $p < 0.01$.

The effect of linagliptin (BI 1356, 3mg/kg po, once daily for 28 days) either alone or in combination with a low dose of exenatide (3µg/kg/day sc) on body weight, carcass composition and relevant plasma markers of obese female Wistar rats fed a high-fat cafeteria diet (DIO) rats for approximately 20 weeks is assessed. Linagliptin has no effect on body weight, daily food intake, plasma glucose, insulin or carcass fat in DIO rats compared to vehicle-treated controls and does not augment the effect of a low dose of exenatide (delivered via a subcutaneously implanted osmotic minipump), when dosed in combination.

In a follow on study (21 days duration), a high dose of exenatide (30µg/kg/day sc) is shown to reduce body weight (6%; $p<0.001$) and body fat (16% $p<0.05$) in DIO rats compared to vehicle-treated controls. Carcass protein ($p=0.8$) and water ($p=0.7$) are not affected. In DIO rats where the osmotic minipump delivering exenatide is removed (Day 10) and replaced by an osmotic minipump delivering saline, weight regain is observed such that the body weight of these animals is not significantly different to controls ($p=0.239$) after 21 days. In contrast, linagliptin (3mg/kg po) reduces weight regain after withdrawal of exenatide such that a significant difference from controls is evident ($p<0.05$). This weight regain is characterized principally by fat deposition and linagliptin-treated animals put on 10.6% less fat than vehicle-treated counterparts during exenatide withdrawal ($p=0.07$). In this context, please see also Figure 3, Figure 4 and Table (a).

These data demonstrate that linagliptin has no weight reducing effect per se in untreated DIO rats or in DIO rats treated with exenatide but in DIO rats where weight loss is induced by a high dose of a GLP-1 receptor agonist or exenatide and then withdrawn, linagliptin reduces or delays subsequent weight regain. Linagliptin can therefore be used in controlling weight rebound during intermittent courses of treatment with a GLP-1 receptor agonist or exenatide.

Diabetic patients may switch from one treatment to another in an effort to avoid unpleasant side effects like nausea that are frequently reported with a GLP-1 receptor agonist or exenatide treatment.

In conclusion, the present study demonstrates that linagliptin (BI 1356) does not significantly alter body weight, food intake or carcass composition in an established and validated animal model of obesity, i.e. drug-naïve female Wistar rats allowed continuous exposure to a simplified three-component cafeteria diet in order to develop marked obesity, insulin resistance (e.g. hyperinsulinaemia) and/or impaired glucose tolerance.

Although exhibiting dietary-induced obesity, the rats used in the present studies do not exhibit a diabetic phenotype and, accordingly, their plasma glucose and HbA1c levels are within a normal range.

Accordingly, the present data shows that treatment with linagliptin is a useful strategy for the weight-neutral treatment of diabetes since, in contrast to other drug classes (e.g. thiazolidinediones, sulphonylureas, insulin etc,) linagliptin is unlikely to promote weight gain, a major causative factor in the development of diabetes.

Further, the present data are the first to demonstrate that dietary-induced obese rats treated with exenatide lose weight compared to vehicle controls but put this weight back on once withdrawn from the drug. Importantly, this body weight gain does not increase beyond the level of vehicle-treated controls and there is evidence that this weight gain, especially the increase in fat, may be reduced by treatment with linagliptin. Thus, the present invention provides a treatment regimen comprising inducing initial weight loss, e.g. via GLP-1 receptor agonism, and subsequently being replaced by or switching to a DPP-4 inhibitor (preferably linagliptin) treatment, which is favourable for reducing, preventing or delaying subsequent weight regain after weight loss, particularly the concomitant increase in body fat.

It is further shown that also the direct combination of linagliptin and low dose of a GLP-1 receptor agonist (exenatide) has a positive effect on body fat which is greater than for the respective single agents (see Table (b)).

Table (b): Effect of linagliptin and exenatide combination on plasma parameters and body composition in DIO rats

	Day 29				
Pump treatment (SC)	Vehicle	Exenatide (3 µg/kg/day)	Exenatide (30 µg/kg/day)	Vehicle	Exenatide (3 µg/kg/day)
Oral treatment	Vehicle	Vehicle	Vehicle	Linagliptin (3 mg/kg PO)	Linagliptin (3 mg/kg PO)
Glucose (mM)	8.14 ± 0.33	8.06 ± 0.31	7.70 ± 0.21	8.72 ± 0.22	8.51 ± 0.21
Insulin (ng/mL)	2.12 ± 0.34	1.89 ± 0.32	1.61 ± 0.64	1.82 ± 0.36	1.89 ± 0.31

Leptin (ng/mL)	26.7 ± 2.6	20.5 ± 2.3	14.4 ± 1.2[c] ***	23.9 ± 2.5	21.1 ± 1.6
GLP-1 (pM)	3.67 ± 1.1	3.52 ± 0.3	4.58 ± 0.5	5.72 ± 0.9[b]	5.44 ± 1.3[b,d]
Carcass Protein (g)	60.8 ± 4.6	55.6 ± 5.2	54.3 ± 3.5	63.8 ± 4.0	63.7 ± 5.1
Carcass Water (g)	206.8 ± 5.9	209.9 ± 7.7	207.5 ± 3.5	212.6 ± 3.4	213.6 ± 3.8
Carcass Fat (g)	161.1 ± 5.9	144.7 ± 10.0	127.3 ± 9.3 **	151.1 ± 7.3	**139.5 ± 7.1[a]**

Table (b): Data are mean ± SEM (*n* = 7–10). Multiple comparisons vs. vehicle are by Williams' test for groups treated solely with exenatide, and the multiple *t* test for all other groups: [a]***P* = 0.050,** [b]*P* < 0.05, [c]*P* < 0.001. [d]*P* < 0.05 from the exenatide (3 µg/kg/day) group. GLP-1, glucagon-like peptide-1.

These data show that adding linagliptin to a GLP-1 receptor agonist (e.g. exenatide) provides a dose-sparing effect on the use of the GLP-1 receptor agonist.

In a further study the efficacy of chronic treatment with linagliptin on body weight, total body fat, intra-myocellular fat, and hepatic fat in a non-diabetic model of diet induced obesity (DIO) in comparison to the appetite suppressant subutramine is investigated:

Rats are fed a high-fat diet for 3 months and received either vehicle, linagliptin (10 mg/kg), or sibutramine (5 mg/kg) for 6 additional weeks, while continuing the high-fat diet. Magnetic resonance spectroscopy (MRS) analysis of total body fat, muscle fat, and liver fat is performed before treatment and at the end of the study.
Sibutramine causes a significant reduction of body weight (-12%) versus control, whereas linagliptin has no significant effect (-3%). Total body fat is also significantly reduced by sibutramine (-12%), whereas linagliptin-treated animals show no significant reduction (-5%). However, linagliptin and sibutramine result both in a potent reduction of intramyocellular fat (-

24% and -34%, respectively). In addition, treatment with linagliptin results in a profound decrease of hepatic fat (-39%), whereas the effect of sibutramine (-30%) does not reach significance (see Table (c)). Thus, linagliptin is weight neutral but improves intra-myocellular and hepatic lipid accumulation.

Table (c): Effect of linagliptin on body weight total body fat, liver fat and intramyocellular fat

	Body weight		Total body fat		Liver fat		Intra-myocellular fat	
	% contr.	% baseli.	% contr.	% baseli.	% contr.	% baseli.	% contr.	% baseli.
Control	-	**+15%** p=0.016	-	**+11%** p=0.001	-	**+27%** p=0.09	-	**+23%** p=0.49
Linagliptin	**-3%** p=0.56	**+12%** p=0.001	**-5%** p=0.27	**+5%** p=0.06	**-39%** p=0.022	**-30%** p=0.05	**-36%** p=0.14	**-24%** p=0.039
Sibutramine	**-12%** p=0.018	**+1%** p=0.64	**-12%** p=0.008	**-0.4%** p =0.86	**-30%** p=0.13	**-29%** p=0.12	**-55%** p=0.037	**-34%** p=0.007

In conclusion, linagliptin treatment provokes a potent reduction of intramyocellular lipids and hepatic fat, which are both independent of weight loss. The effects of sibutramine on muscular and hepatic fat are attributed mainly to the known weight reduction induced by this compound.

Claims

1) A combination comprising
a GLP-1 receptor agonist and a DPP-4 inhibitor which is linagliptin,
for separate, sequential or simultaneous therapeutic use of the active components.

2) The combination according to claim 1, wherein the GLP-1 receptor agonist is selected from exenatide, exenatide LAR, liraglutide, taspoglutide, semaglutide, albiglutide, lixisenatide and dulaglutide.

3) The combination according to claim 1 or 2, wherein the GLP-1 receptor agonist and the DPP-4 inhibitor are present each in separate dosage forms.

4) The combination according to claim 1, 2 or 3 for sequential use of the active components.

5) The combination according to claim 1, 2 or 3 for sequential use of the GLP-1 receptor agonist followed by the DPP-4 inhibitor.

6) The combination according to any one of the claims 1 to 5 for use in a method for reducing and maintaining body weight and/or body fat in a patient, such as e.g. in an overweight or obesity patient with or without diabetes, particularly in a type 2 diabetes patient being obese or overweight.

7) The combination according to any one of the claims 1 to 5 for use in the treatment of type 2 diabetes, obesity or both, said treatment comprising
administering an effective amount of the GLP-1 receptor agonist to the patient, e.g. for inducing body weight loss and/or body fat loss, and
administering an effective amount of the DPP-4 inhibitor to the patient, e.g. for maintaining the reduced body weight and/or body fat.

8) The combination according to any one of the claims 1 to 5 for use in the treatment of type 2 diabetes, obesity or both, said treatment comprising the steps
i) administering an effective amount of the GLP-1 receptor agonist to the patient, e.g. for inducing body weight loss and/or body fat loss, and

ii) administering an effective amount of the DPP-4 inhibitor to the patient, e.g. for maintaining the reduced body weight and/or body fat,
wherein the DPP-4 inhibitor treatment ii) is subsequent to the GLP-1 receptor agonist treatment i).

9) The combination according to any one of the claims 1 to 5 for use in a method for reducing and maintaining body weight and/or body fat in a patient, such as e.g. in an overweight or obesity patient with or without diabetes, particularly in a type 2 diabetes patient being obese or overweight, said method comprising the sequential administration of the GLP-1 receptor agonist for inducing initial body weight and/or body fat loss, followed by administration of the DPP-4 inhibitor for maintaining body weight and/or body fat loss.

10) The combination according to any one of the claims 1 to 5 for use in one or more of the following methods:

- preventing, slowing the progression of, delaying or treating a metabolic disorder or disease, such as e.g. type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), hyperglycemia, postprandial hyperglycemia, overweight, obesity, dyslipidemia, hyperlipidemia, hypercholesterolemia, hypertension, atherosclerosis, endothelial dysfunction, osteoporosis, chronic systemic inflammation, non alcoholic fatty liver disease (NAFLD), retinopathy, neuropathy, nephropathy, polycystic ovarian syndrome, and/or metabolic syndrome;
- improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c;
- preventing, slowing, delaying or reversing progression from pre-diabetes, impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or from metabolic syndrome to type 2 diabetes mellitus;
- preventing, reducing the risk of, slowing the progression of, delaying or treating of complications of diabetes mellitus such as micro- and macrovascular diseases, such as nephropathy, micro- or macroalbuminuria, proteinuria, retinopathy, cataracts, neuropathy, learning or memory impairment, neurodegenerative or cognitive disorders, cardio- or cerebrovascular diseases, tissue ischaemia, diabetic foot or ulcus, atherosclerosis, hypertension, endothelial dysfunction, myocardial infarction, acute coronary syndrome, unstable angina pectoris, stable angina pectoris, peripheral arterial occlusive disease, cardiomyopathy, heart failure, heart rhythm disorders, vascular restenosis, and/or stroke;

- reducing body weight and/or body fat and/or liver fat and/or intra-myocellular fat or preventing an increase in body weight and/or body fat and/or liver fat and/or intra-myocellular fat or facilitating a reduction in body weight and/or body fat and/or liver fat and/or intra-myocellular fat;
- preventing, slowing, delaying or treating the degeneration of pancreatic beta cells and/or the decline of the functionality of pancreatic beta cells and/or for improving and/or restoring the functionality of pancreatic beta cells and/or stimulating and/or restoring or protecting the functionality of pancreatic insulin secretion;
- preventing, slowing, delaying or treating non alcoholic fatty liver disease (NAFLD) including hepatic steatosis, non-alcoholic steatohepatitis (NASH) and/or liver fibrosis (such as e.g. preventing, slowing the progression, delaying, attenuating, treating or reversing hepatic steatosis, (hepatic) inflammation and/or an abnormal accumulation of liver fat);
- preventing, slowing the progression of, delaying or treating type 2 diabetes with failure to conventional antidiabetic mono- or combination therapy;
- achieving a reduction in the dose of conventional antidiabetic medication required for adequate therapeutic effect;
- reducing the risk for adverse effects associated with conventional antidiabetic medication; and/or
- maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance.

11) A DPP-4 inhibitor, which is preferably linagliptin, for use in preventing of body weight and/or body fat gain or controlling, stabilizing or maintaining a reduced body weight and/or body fat after initial weight reducing treatment.

12) The DPP-4 inhibitor of claim 11, which is preferably linagliptin, for use in preventing of body weight and/or body fat gain or controlling, stabilizing or maintaining a reduced body weight and/or body fat after initial weight reducing treatment, wherein the weight reducing treatment is selected from diet, exercise and/or treatment with an anti-obesity or weight reducing agent selected from sibutramine, tetrahydrolipstatin (orlistat), alizyme (cetilistat), a cannabinoid receptor 1 antagonist (e.g. rimonabant), a MC4 receptor agonist, a NPY2 antagonist (e.g. velneperit), a 5HT2c receptor agonist (e.g. lorcaserin), a Ghrelin antagonist, Pyy 3-36, leptin, a DGAT-1 inhibitor, a noradrenaline-dopamine-5HT reuptake inhibitor (e.g.

tesofensine), bupropion/naltrexone, bupropion/zonisamide, topiramate/phentermine and pramlintide/metreleptin.

13) The DPP-4 inhibitor of claim 11, which is preferably linagliptin, for use in preventing of body weight and/or body fat gain or controlling, stabilizing or maintaining a reduced body weight and/or body fat after initial weight reducing treatment, wherein the weight reducing treatment is selected from diet, exercise and/or treatment with a GLP-1 receptor agonist.

14) The DPP-4 inhibitor of claim 13, which is preferably linagliptin, for use in preventing of body weight and/or body fat gain or controlling, stabilizing or maintaining a reduced body weight and/or body fat after initial weight reducing treatment, which is treatment with a GLP-1 receptor agonist selected from exenatide, exenatide LAR, liraglutide, taspoglutide, semaglutide, albiglutide, lixisenatide and dulaglutide.

15) A DPP-4 inhibitor, which is preferably linagliptin, for use in preventing of body weight and/or body fat gain or controlling, stabilizing or maintaining a reduced body weight and/or body fat after discontinuation of treatment with a GLP-1 receptor agonist selected from exenatide, exenatide LAR, liraglutide, taspoglutide, semaglutide, albiglutide, lixisenatide and dulaglutide.

16) A DPP-4 inhibitor which is preferably linagliptin for use in a method of treating type 2 diabetes, obesity or both, said method comprising administration (e.g. separate, sequential or simultaneous administration) of the DPP-4 inhibitor and a GLP-1 receptor agonist selected from exenatide, exenatide LAR, liraglutide, taspoglutide, semaglutide, albiglutide, lixisenatide and dulaglutide.

17) A GLP-1 receptor agonist selected from exenatide, exenatide LAR, liraglutide, taspoglutide, semaglutide, albiglutide, lixisenatide and dulaglutide, for use in a method of treating type 2 diabetes, obesity or both, said method comprising administration (e.g. separate, sequential or simultaneous administration) of the GLP-1 receptor agonist and a DPP-4 inhibitor which is preferably linagliptin.

18) A DPP-4 inhibitor which is preferably linagliptin for use in a method of attenuating or preventing rebound of weight and/or fat gain following discontinuation of weight reducing treatment, particularly in obesity patients with or without diabetes, said method comprising

administering the DPP-4 inhibitor subsequent to the weight reducing treatment, optionally in combination with one or more other therapeutic agents.

19) A DPP-4 inhibitor which is preferably linagliptin for use in a method according to claim 18, wherein the weight reducing treatment is selected from diet, exercise and/or treatment with an anti-obesity or weight reducing agent selected from a GLP-1 receptor agonist, a lipase inhibitor such as e.g. tetrahydrolipstatin (orlistat) or alizyme (cetilistat), a cannabinoid receptor 1 antagonist, a MC4 receptor agonist, a NPY2 antagonist (e.g. velneperit), a 5HT2c receptor agonist (e.g. lorcaserin), a Ghrelin antagonist, Pyy 3-36, leptin, a DGAT-1 inhibitor, a noradrenaline-dopamine-5HT reuptake inhibitor (e.g. tesofensine), bupropion/naltrexone (Contrave), bupropion/zonisamide (Empatic), topiramate/phentermine (Qnexa), pramlintide/metreleptin, a MCH antagonist, a CCK inhibitor, a FAS inhibitor, an ACC inhibitor, a SCD inhibitor, a beta3 adrenoreceptor agonist, a MTP inhibitor, and amylin or an amylin analogue (e.g. davalintide or pramlintide).

20) A DPP-4 inhibitor which is preferably linagliptin for use in a method of attenuating or preventing rebound of weight and/or fat gain following discontinuation of treatment with a GLP-1 receptor agonist, such as e.g. selected from exenatide, exenatide LAR, liraglutide, taspoglutide, semaglutide, albiglutide, lixisenatide and dulaglutide, particularly in obesity patients with or without diabetes, said method comprising administering the DPP-4 inhibitor subsequent to the treatment with the GLP-1 receptor agonist, optionally in combination with one or more other therapeutic agents.

21) A DPP-4 inhibitor which is preferably linagliptin for use in reducing, maintaining loss of or delaying increase of body weight and/or body fat in a subject being in condition of actively putting on weight and/or increasing body weight through the deposition of fat.

22) A DPP-4 inhibitor which is preferably linagliptin for use in treating, preventing or reducing the risk of skin necrosis, particularly associated with or induced by injections or infusions, e.g. injections by a needle or syringe pierced through the skin, such as e.g. subcutaneous injections of a GLP-1 receptor agonist.

23) The combination according to any one of the claims 1 to 5 for use in achieving a reduction in the dose of the GLP-1 receptor agonist required for effective treatment, particularly of overweight or obesity patients with or without diabetes.

Drawings:

Figure 1: Body weight development

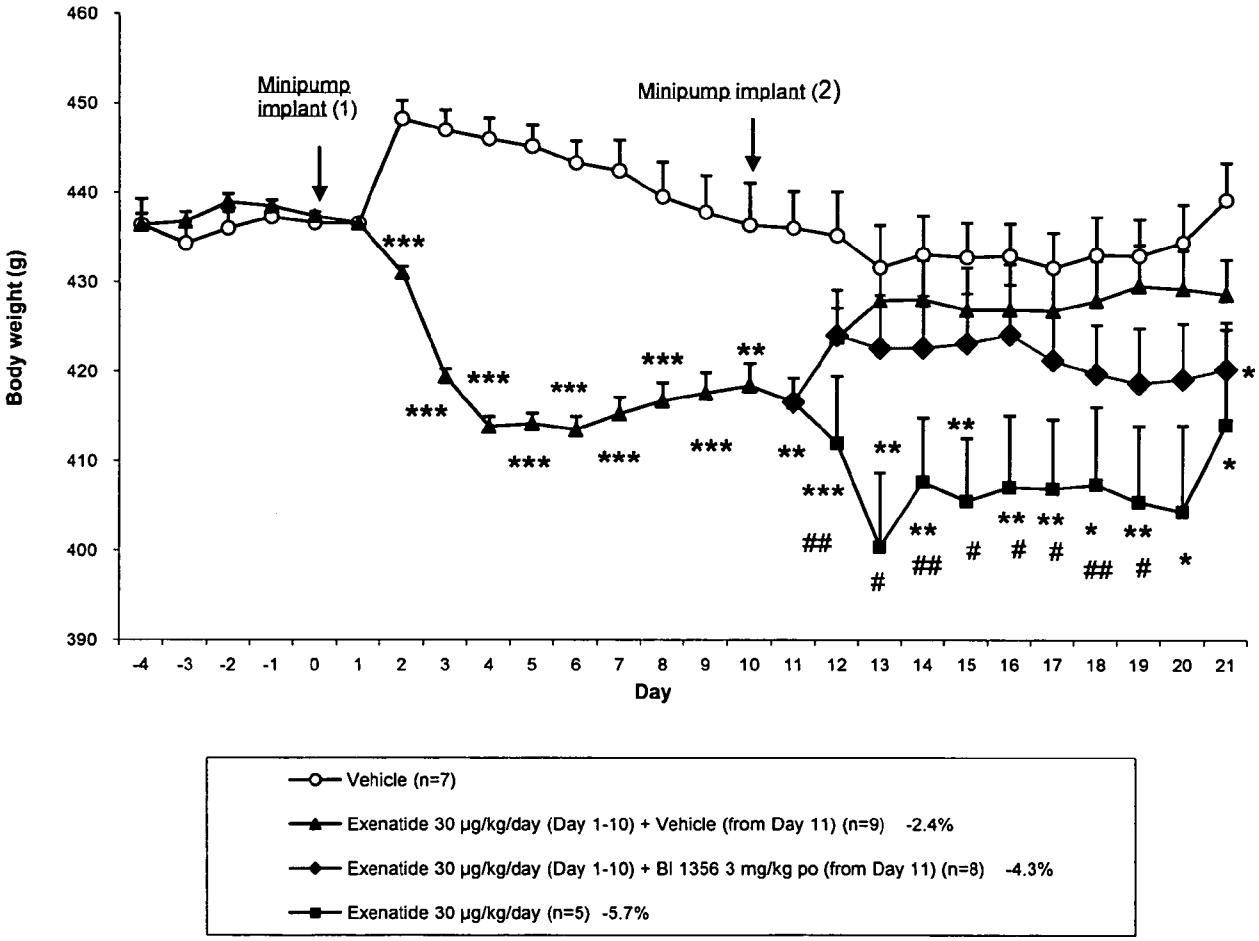


Figure 2: Survival plots

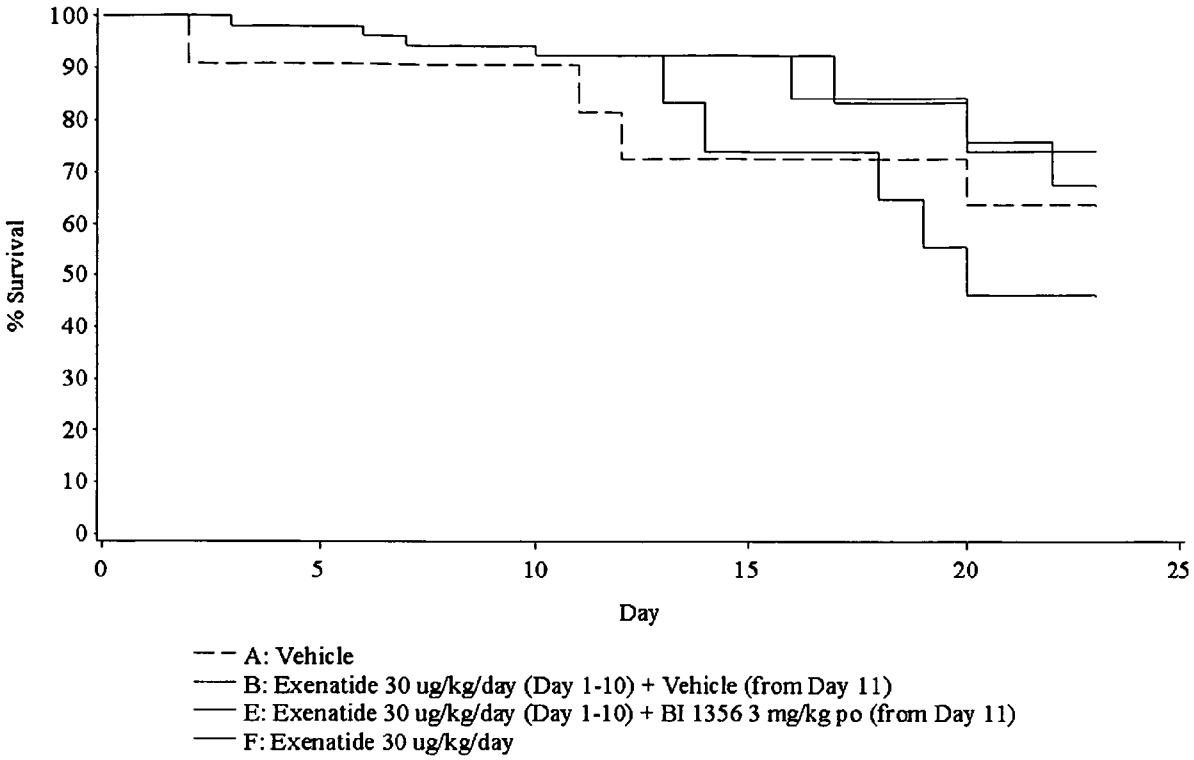


Figure 3: Linagliptin attenuates rebound of body weight (including body fat) gain following discontinuation of GLP-1R agonist (e.g. exendin-4) treatment

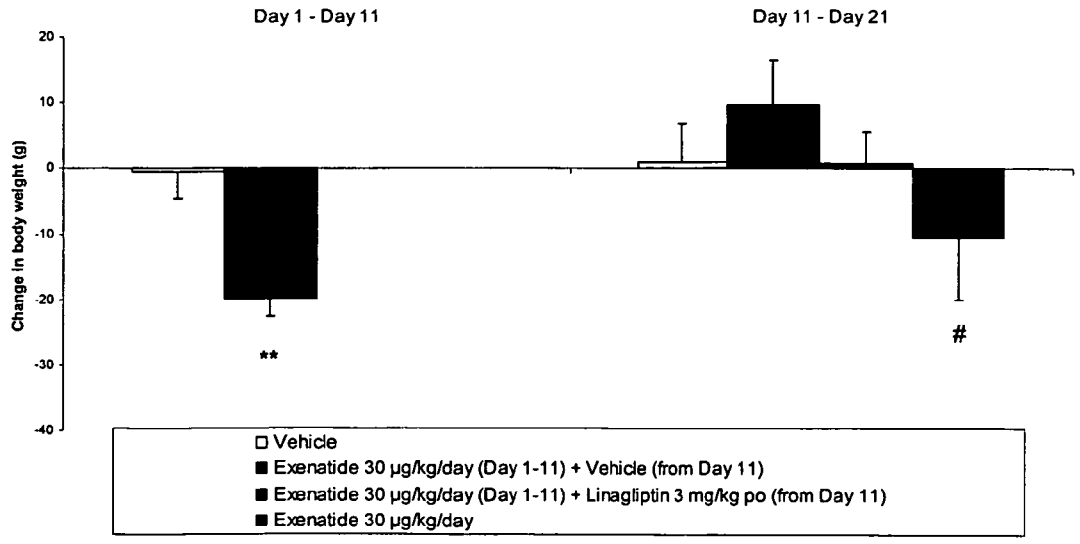
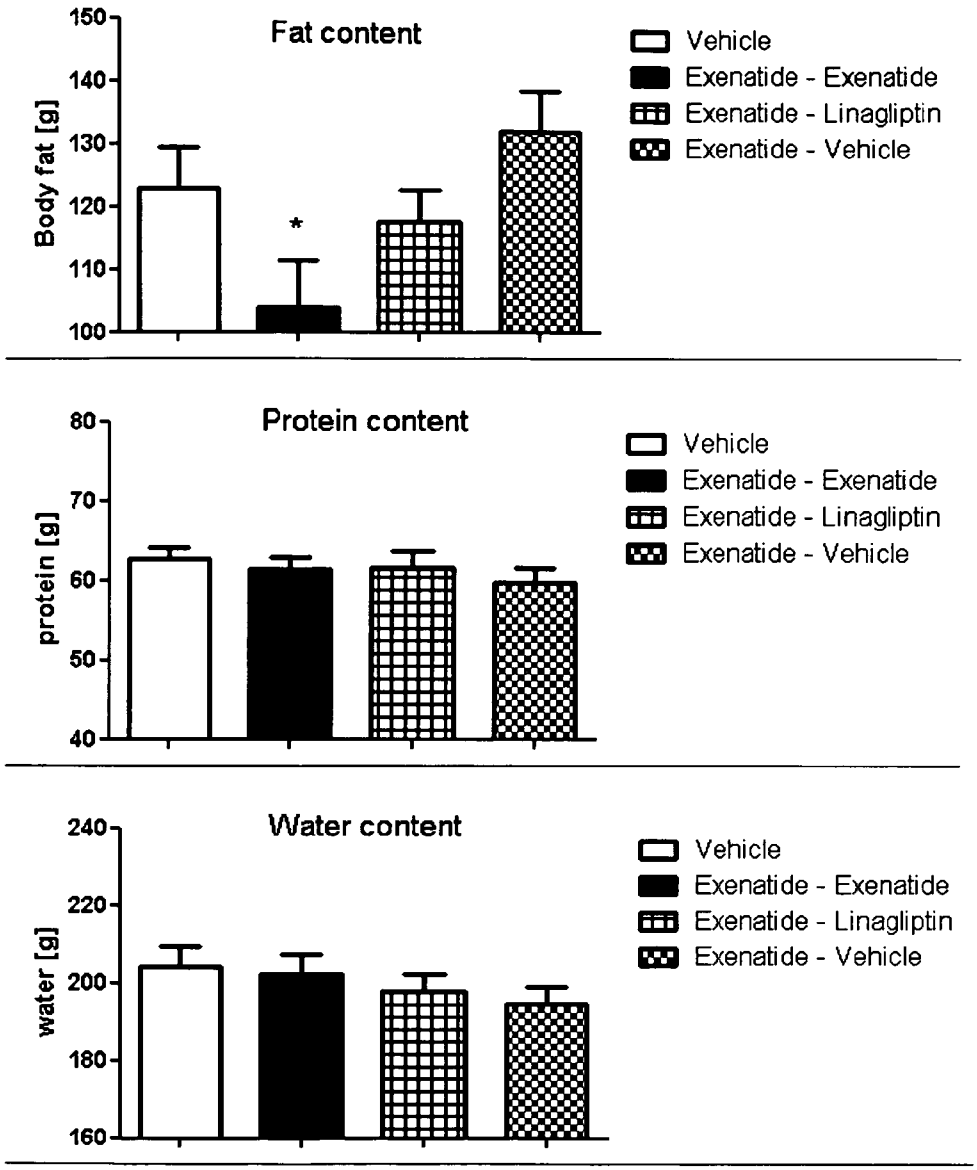


Figure 4: GLP-1R agonist (e.g. exendin-4) cessation and replacement with linagliptin prevents body fat weight regain



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/057256

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/00 A61K31/522 A61K38/00 A61P3/04 A61P3/10
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AULINGER BENEDIKT A ET AL: "Ex-4 and the DPP-IV inhibitor vildagliptin have additive effects to suppress food intake in rodents", DIABETES, AMERICAN DIABETES ASSOCIATION, US, vol. 57, no. suppl. 1, 1 June 2008 (2008-06-01), page A433, XP009135884, ISSN: 0012-1797 the whole document	1-23
X	EP 2 143 443 A1 (MITSUBISHI TANABE PHARMA CORP [JP]) 13 January 2010 (2010-01-13) claims 24-28; figures 5a-c	1-23

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 July 2011	22/07/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Loher, Florian

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CONARELLO S L ET AL: "Mice lacking dipeptidyl peptidase IV are protected against obesity and insulin resistance", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES (PNAS), NATIONAL ACADEMY OF SCIENCE, US LNKD-DOI:10.1073/PNAS.0631828100, vol. 100, no. 11, 27 May 2003 (2003-05-27) , pages 6825-6830, XP003003538, ISSN: 0027-8424 page 6825, left-hand column, last paragraph - right-hand column, paragraph 1 page 6826, left-hand column, last paragraph -----	1-23
X	US 2007/060530 A1 (CHRISTOPHER RONALD J [US] ET AL) 15 March 2007 (2007-03-15) paragraph [0017] paragraph [0068] claim 72 -----	1-23
E	WO 2011/064352 A1 (BOEHRINGER INGELHEIM INT [DE]; DUGI KLAUS [DE]; GRAEFE-MODY EVA ULRIKE) 3 June 2011 (2011-06-03) page 44, line 31 page 11, paragraph 3 - page 17, paragraph 1 -----	1-23

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2011/057256

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 2143443 A1	13-01-2010	AU 2008233548 A1	09-10-2008
		CA 2682736 A1	09-10-2008
		CN 101652147 A	17-02-2010
		WO 2008120813 A1	09-10-2008
		KR 20090127946 A	14-12-2009
		US 2010113382 A1	06-05-2010
US 2007060530 A1	15-03-2007	NONE	
WO 2011064352 A1	03-06-2011	NONE	