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(54) **Title:** A XANTHINE DERIVATIVE AS DPP -4 INHIBITOR FOR USE IN THE TREATMENT OF AUTOIMMUNE DIABETES, PARTICULARLY LADA

(57) **Abstract:** The present invention relates to methods for treating and/or preventing autoimmune diabetes, particularly LADA, as well as diseases related or associated therewith, comprising the administration of an effective amount of a certain DPP-4 inhibitor, as well as to the use of a certain DPP-4 inhibitor for modifying disease trajectory of autoimmune diabetes (particularly LADA).

**A XANTHINE DERIVATIVE AS DPP -4 INHIBITOR FOR USE IN THE TREATMENT OF  
AUTOIMMUNE  
DIABETES, PARTICULARLY LADA**

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Field of the Invention

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The present invention relates to a certain DPP-4 inhibitor, preferably linagliptin (optionally in combination with one or more other active agents) for use in treating and/or preventing autoimmune diabetes, particularly LADA (latent autoimmune diabetes of adults), particularly in those (LADA) patients in whom one or more autoantibodies selected from GAD (GAD-65, anti-GAD), ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA are present, especially in those (LADA) patients in whom antibodies towards GAD (GAD-65) are present, and/or diseases related or associated therewith (e.g. diabetic complications), to pharmaceutical compositions and combinations comprising such active components, and to certain therapeutic uses thereof.

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15 Background of the Invention

Latent autoimmune diabetes of adults (LADA) is also known as slowly progressive type 1 diabetes mellitus (T1DM), "mild" T1DM, non-insulin dependent type 1 DM, type 1 ½ DM, double diabetes or antibody positive type 2 DM (T2DM). LADA is often not clearly defined and, opposed to T1DM, seldom or never presents with significant weight loss and ketoacidosis due to rapidly progressive  $\beta$ -cell failure.

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Summary of the Invention

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The present invention relates to a certain DPP-4 inhibitor, preferably linagliptin (optionally in combination with one or more other active agents) for use in treating and/or preventing autoimmune diabetes, particularly LADA (latent autoimmune diabetes of adults), particularly in those (LADA) patients in whom one or more autoantibodies selected from GAD (GAD-65, anti-GAD), ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA are present, especially in those (LADA) patients in whom antibodies towards GAD (GAD-65) are present, and/or diseases related or associated therewith (e.g. diabetic complications, such as e.g. micro- or macrovascular diseases such as cardio- or cerebrovascular diseases, nephropathy, retinopathy or neuropathy), to pharmaceutical compositions and combinations comprising such active components, and to certain therapeutic uses thereof.

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Further, the present invention relates to a certain DPP-4 inhibitor, preferably linagliptin (optionally in combination with one or more other active agents, such as e.g. selected from

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other antidiabetics, including e.g. metformin, thiazolidinediones (pioglitazone) and/or insulin or insulin analogues) for use in modifying disease trajectory of autoimmune diabetes, particularly LADA (latent autoimmune diabetes of adults), particularly in those (LADA) patients in whom one or more autoantibodies selected from GAD (GAD-65, anti-GAD), ICA, 5 IA-2A, anti-ZnT8 and IAA are present, especially in those (LADA) patients who have antibodies towards GAD (GAD-65).

Further, the present invention relates to a certain DPP-4 inhibitor, preferably linagliptin (optionally in combination with one or more other active agents, such as e.g. selected from 10 other antidiabetics, including e.g. metformin, thiazolidinediones (pioglitazone) and/or insulin or insulin analogues) for use in preserving pancreatic beta cells and/or their function in patients with autoimmune diabetes, particularly LADA, especially in early diabetes.

Further, the present invention relates to a certain DPP-4 inhibitor, preferably linagliptin 15 (optionally in combination with one or more other active agents, such as e.g. selected from other antidiabetics, including e.g. metformin, thiazolidinediones (pioglitazone) and/or insulin or insulin analogues) for use in preserving C-peptide, pancreatic beta cells and/or pancreatic beta cell function in patients with or at risk of autoimmune diabetes, particularly LADA, such as e.g. LADA patients in whom one or more autoantibodies selected from GAD (GAD-65, 20 anti-GAD), ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA are present, especially LADA patients with antibodies towards GAD (GAD-65).

Further, the present invention relates to a certain DPP-4 inhibitor, preferably linagliptin 25 (optionally in combination with one or more other active agents, such as e.g. selected from other antidiabetics, including e.g. metformin, thiazolidinediones (pioglitazone) and/or insulin or insulin analogues) for use in increasing or preserving C-peptide level in patients with or at risk of autoimmune diabetes, particularly LADA, such as e.g. in those LADA patients in whom one or more autoantibodies selected from GAD (GAD-65, anti-GAD), ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA are present, especially in LADA patients with antibodies towards GAD (GAD- 30 65).

Further, the present invention relates to a certain DPP-4 inhibitor, preferably linagliptin (optionally in combination with one or more other active agents, such as e.g. selected from 35 other antidiabetics, including e.g. metformin, thiazolidinediones (pioglitazone) and/or insulin or insulin analogues) for use in preventing, slowing, delaying or treating the degeneration of

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pancreatic beta cells and/or the decline of the functionality of pancreatic beta cells and/or for improving, preserving and/or restoring the functionality of pancreatic beta cells and/or stimulating and/or restoring or protecting the functionality of pancreatic insulin secretion in patients with or at risk of autoimmune diabetes, particularly LADA, such as e.g. in those

5 LADA patients in whom one or more autoantibodies selected from GAD (GAD-65, anti-GAD), ICA, IA-2A and IAA are present, especially in LADA patients with antibodies towards GAD (GAD-65).

Further, the present invention relates a certain DPP-4 inhibitor (preferably linagliptin, optionally in combination with one or more other active agents, such as e.g. selected from

10 other antidiabetics, including e.g. metformin, thiazolidinediones (pioglitazone) and/or insulin or insulin analogues) for use in treating and/or preventing metabolic diseases, in a patient (particularly human patient) with or at risk of autoimmune diabetes, particularly LADA, such as e.g. in such LADA patient in whom one or more autoantibodies selected from GAD (GAD-

15 65, anti-GAD), ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA are present, especially in a LADA patient with antibodies towards GAD (GAD-65).

Further, the present invention relates a certain DPP-4 inhibitor (preferably linagliptin, optionally in combination with one or more other active agents, such as e.g. selected from

20 other antidiabetics) for use in delaying the onset of rescue therapy (e.g. insulin therapy) in a patient (particularly human patient) with or at risk of autoimmune diabetes, particularly LADA, such as e.g. in such LADA patient in whom one or more autoantibodies selected from GAD (GAD-65, anti-GAD), ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA are present, especially in a

25 LADA patient with antibodies towards GAD (GAD-65).

In particular, diabetes within the meaning of this invention refers to autoimmune diabetes, particularly LADA.

In a special embodiment, the autoimmune diabetes (particularly LADA) of this invention presents one or more autoantibodies selected from GAD (GAD-65, anti-GAD), ICA, IA-2A,

30 ZnT8 (anti-ZnT8) and IAA, especially GAD (GAD-65, anti-GAD) antibodies, as diagnosed in the patient.

In a further special embodiment, the autoimmune diabetes (particularly LADA) of this invention presents autoantibodies towards GAD (GAD-65), and optionally one or more further autoantibodies as mentioned above.

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In a particular embodiment, the patient described herein is a subject having autoimmune diabetes, particularly LADA, in whom one or more autoantibodies selected from GAD (GAD-65, anti-GAD), ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA are present.

- 5 In a more particular embodiment, the patient described herein is a subject having autoimmune diabetes, particularly LADA, in whom GAD (GAD-65, anti-GAD) autoantibodies are present.

Especially, the patient within this invention is a human.

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Further, the present invention relates to a method of treating and/or preventing autoimmune diabetes, particularly LADA (latent autoimmune diabetes of adults), and/or diseases related or associated therewith (e.g. diabetic complications), in a patient (particularly human patient) in need thereof (such as e.g. a LADA patient in whom one or more autoantibodies selected from GAD (GAD-65, anti-GAD), ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA are present, especially a LADA patient in whom antibodies to GAD (GAD-65) are present), comprising administering an effective amount of a certain DPP-4 inhibitor, preferably linagliptin, optionally in combination with one or more other active agents, to the patient.

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Further, the present invention relates to a method of modifying disease trajectory of autoimmune diabetes, particularly LADA (latent autoimmune diabetes of adults), in a patient (particularly human patient) in need thereof (such as e.g. a LADA patient in whom one or more autoantibodies selected from GAD (GAD-65, anti-GAD), ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA are present, especially a LADA patient in whom antibodies to GAD (GAD-65) are present), comprising administering an effective amount of a certain DPP-4 inhibitor, preferably linagliptin, optionally in combination with one or more other active agents, to the patient.

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Further, the present invention relates to a method of preserving C-peptide, pancreatic beta cells and/or pancreatic beta cell function in patients (particularly human patients) with autoimmune diabetes, particularly LADA, such as e.g. LADA patients in whom one or more autoantibodies selected from GAD (GAD-65, anti-GAD), ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA are present, especially LADA patients in whom antibodies to GAD (GAD-65) are present, comprising administering an effective amount of a certain DPP-4 inhibitor, preferably

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linagliptin, optionally in combination with one or more other active agents (such as e.g. selected from other antidiabetics), to the patients.

Further, the present invention relates to a method of increasing or preserving C-peptide level  
5 in patients (particularly human patients) with autoimmune diabetes, particularly LADA, such  
as e.g. LADA patients in whom one or more autoantibodies selected from GAD (GAD-65,  
anti-GAD), ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA are present, especially LADA patients in  
whom antibodies to GAD (GAD-65) are present, comprising administering an effective  
10 amount of a certain DPP-4 inhibitor, preferably linagliptin, optionally in combination with one  
or more other active agents (such as e.g. selected from other antidiabetics), to the patients.

Further, the present invention relates to a method of 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, preserving and/or restoring the functionality of pancreatic  
15 beta cells and/or stimulating and/or restoring or protecting the functionality of pancreatic  
insulin secretion in patients with autoimmune diabetes, particularly LADA (such as e.g. a  
LADA patient in whom one or more autoantibodies selected from GAD (GAD-65, anti-GAD),  
ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA are present, especially a LADA patient in whom  
antibodies to GAD (GAD-65) are present), comprising administering an effective amount of a  
20 certain DPP-4 inhibitor, preferably linagliptin, optionally in combination with one or more  
other active agents (such as e.g. selected from other antidiabetics), to the patient.

Further, the present invention relates a method of treating and/or preventing metabolic  
diseases, in a patient (particularly human patient) with or at risk of autoimmune diabetes,  
25 particularly LADA (such as e.g. a LADA patient in whom one or more autoantibodies selected  
from GAD (GAD-65, anti-GAD), ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA are present, especially  
a LADA patient in whom antibodies to GAD (GAD-65) are present), comprising administering  
an effective amount of a certain DPP-4 inhibitor, preferably linagliptin, optionally in  
combination with one or more other active agents, to the patient.

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

Detailed Description of the Invention

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Usually three criteria are needed fulfilled for diagnosis of LADA:

- 1) adult age at onset of diabetes (> 30 years),
- 2) the presence of circulating islet autoantibodies (markers of beta cell autoimmunity to distinguish LADA from T2DM, e.g. islet cell antibodies (ICA, against cytoplasmic proteins in the beta cell, islet-cell cytoplasm), antibodies to glutamic acid decarboxylase (GAD-65, anti-GAD), insulin autoantibodies (IAA), and/or IA-2A antibodies to the intracytoplasmic domain of the tyrosine phosphatase-like protein IA-2), and
- 3) lack of a requirement for insulin for at least 6 months after diagnosis (to distinguish LADA from classic T1DM).

10 However, alternative definitions of LADA include GAD (glutamic acid decarboxylase) antibody titer  $\geq 0.08$  U/mL and 1) lifestyle and oral therapy or 2) insulin treatment started later than 12 months after diagnosis or 3) insulin therapy started before 12 months after diagnosis, but with fasting C-peptide levels > 150 pmol/l.

15 One prerequisite in the definition is the presence of one or more circulating autoantibodies. For this reasons it is sometimes argued that LADA is just a "low-titer T1DM condition". However, the LADA population often shares phenotypical traits with T2DM, more so than with T1DM; therefore LADA etiologically may represent a unique disease entity that is characterized by a more rapid decline of  $\beta$ -cell function than common T2DM.

20 It has been demonstrated, in several studies, that insulin dependency occurs at higher rate in LADA than in subjects with common T2DM.

One assumes that the LADA prevalence in a general type 2 diabetes population is at least 5-10%. Moreover, adults with LADA are frequently initially misdiagnosed as having type 2 diabetes, based on age; not etiology. In a survey conducted by Australia's Type 1 Diabetes Network, one third of all Australians with type 1 diabetes reported being initially misdiagnosed as having the more common type 2 diabetes mellitus.

30 Currently, there is no "gold standard" for LADA treatment or management. In general, the treatment of LADA should focus not only on controlling glycemia and preventing the onset of any complications, but also allow preservation of residual beta cell function. Insulin therapy in LADA is often efficacious; but might be of most benefit in patients with both a high titer of GAD (> 10 U/mL) and preserved insulin secretion (C-peptide > 10 ng/mL). This also seems to apply to thiazolidinediones (glitazones), in particular if combined with insulin when islet beta cell function is preserved. Sulfonylureas (SUs) (and glinides) have in some studies been

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shown to be detrimental on beta cell function in LADA. This is supported by that metabolic control by SUs when compared to insulin also is often less.

5 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  $\alpha$ -glucosidase inhibitors.

10 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.

15 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).

20 Therefore, it remains a need in the art to provide efficacious, safe and tolerable antidiabetic therapies.

25 Further, within the therapy of diabetes, it is a need for treating the condition effectively, avoiding the complications inherent to the condition, and delaying disease progression, e.g. in order to achieve a long-lasting therapeutic benefit.

30 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 or are at risk of developing complications, such as renal impairment.

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



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Within the scope of the present invention it has now been found that a certain DPP-4 inhibitor, preferably linagliptin, as defined herein as well as pharmaceutical combinations, compositions, uses or methods according to this invention of that DPP-4 inhibitor, preferably linagliptin, optionally in combination with one or more other active agents as defined herein  
5 have properties, which make them suitable for the purpose of this invention and/or for fulfilling one or more of the needs mentioned herein.

Linagliptin holds some inherent characteristics that potentially could modulate the LADA process as well as preserve the beta cell function; in particular in early autoimmune diabetes.

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For example, clinical studies show a significant increase in homeostasis model assessment beta-cell function index (HOMA-b) and fasting proinsulin/insulin ratio when using a DPP-4 inhibitor.

15 Reducing glycaemic excursions might be beta cell protective; reducing hyperglycaemia is definitely beta-cell protective.

As DPP-4 cleaves other peptides aside GLP-1 and GIP, inhibition of DPP-4 by linagliptin may also prolong the active half-life of these peptides that through their receptor interactions may be beneficial for glucose control and beta-cell function or other aspects of the disease.

20 Linagliptin may be involved in immune response and inflammation, thereby being beneficial in LADA.

There is a potential antioxidative potential of linagliptin, e.g. based on its unique xanthine structure, for reducing oxidative stress, which is interlinked with inflammation and is detrimental for the beta cells.

25 C-peptide originates from proinsulin and is produced in the body along with insulin. It is an accepted biomarker for proof of beta-cell preservation. Persons with LADA typically have low, although sometimes moderate, levels of C-peptide as the disease progresses.

30 Human C-peptide is a biologically active peptide hormone that can stimulate specific intracellular processes and modulate cellular function. C-peptide has been shown to bind to the surface of a number of cell types such as neuronal, endothelial, fibroblast and renal tubular, at nanomolar concentrations to a receptor that is likely G-protein-coupled.

35 In vivo studies in animal models that have C-peptide deficiency (type 1 diabetes model) have established that C-peptide administration results in significant improvements in nerve and

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kidney function. Thus, in animals with early signs of diabetes-induced neuropathy, C-peptide treatment in replacement dosage results in improved peripheral nerve function and significant amelioration of nerve structural changes. Likewise, C-peptide administration in animals that had C-peptide deficiency (type 1 diabetes model) with nephropathy improves renal function and structure; it decreases urinary albumin excretion and prevents or decreases diabetes-induced glomerular changes secondary to mesangial matrix expansion. C-peptide also has been reported to have anti-inflammatory effects (e.g. on inflammatory processes of vascular damage, such as e.g. endothelial dysfunction) as well as aid repair of smooth muscle cells.

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Thus, chronic administration of "replacement doses" of C-peptide can ameliorate the microvascular complications in a C-peptide deficiency model (type 1 diabetes), for example diabetic neuropathy, nephropathy and retinopathy. An opinion is that C-peptide may have beneficial effects on the complications of diabetes on the kidneys, nerves and eyes, and/or on macrovascular complications in such patients. Therefore, it may be suggested that C-peptide based therapy (replacement therapy) may offer an approach to prevent, retard or treat diabetic vascular complications in such patients.

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Thus, the present invention provides a certain DPP-4 inhibitor as defined herein, preferably linagliptin (optionally in combination with one or more other active agents) for use in treating, preventing and/or modifying disease trajectory of autoimmune diabetes, particularly LADA (latent autoimmune diabetes of adults), and/or diseases related or associated therewith (e.g. diabetic complications); particularly in such patients in whom one or more autoantibodies selected from GAD (GAD65, anti-GAD), ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA, especially GAD (GAD65) autoantibodies, are present.

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Further, the present invention relates to a certain DPP-4 inhibitor, preferably linagliptin (optionally in combination with one or more other active agents) for use in preserving pancreatic beta cells and/or pancreatic beta cell function in patients with autoimmune diabetes, particularly LADA, such as e.g. LADA patients in whom one or more autoantibodies selected from GAD (GAD65, anti-GAD), ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA, especially GAD (GAD65) autoantibodies, are present.

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Further, the present invention relates to a certain DPP-4 inhibitor, preferably linagliptin (optionally in combination with one or more other active agents) for use in treating and/or

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preventing metabolic disorders in patients with autoimmune diabetes, particularly with LADA, such as e.g. LADA patients in whom one or more autoantibodies selected from GAD (GAD65, anti-GAD), ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA, especially GAD (GAD65) autoantibodies, are present.

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Examples of metabolic disorders or diseases amenable by the therapy of this invention may include, without being limited to, type 1 diabetes, type 2 diabetes, impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), hyperglycemia, postprandial hyperglycemia, postabsorptive hyperglycemia, latent autoimmune diabetes in adults (LADA), overweight, obesity, dyslipidemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, hyperNEFA-emia, fasting or postprandial hyperlipidemia such as postprandial lipemia (e.g. postprandial hypertriglyceridemia), hypertension, atherosclerosis, endothelial dysfunction, osteoporosis, chronic systemic inflammation, non alcoholic fatty liver disease (NAFLD), retinopathy, neuropathy, nephropathy, nephrotic syndrome, polycystic ovarian syndrome, and/or metabolic syndrome.

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The present invention further relates to a certain DPP-4 inhibitor, preferably linagliptin (optionally in combination with one or more other active agents) for use in at least one of the following methods:

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- preventing, slowing the progression of, delaying the onset of 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, postabsorptive hyperglycemia, latent autoimmune diabetes in adults (LADA), overweight, obesity, dyslipidemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, hyperNEFA-emia, postprandial lipemia (e.g. postprandial hypertriglyceridemia), hypertension, atherosclerosis, endothelial dysfunction, osteoporosis, chronic systemic inflammation, non alcoholic fatty liver disease (NAFLD), retinopathy, neuropathy, nephropathy, nephrotic syndrome, polycystic ovarian syndrome, and/or metabolic syndrome;

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- improving and/or maintaining glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose, of postabsorptive plasma glucose and/or of glycosylated hemoglobin HbA1c, or preventing, reducing the risk of, slowing the progression of, delaying the onset of or treating worsening or deterioration of glycemic control, need for insulin therapy or elevated HbA1c despite treatment;

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- preventing, slowing, delaying the onset of or reversing progression from pre-diabetes, impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or from metabolic syndrome to diabetes;
- preventing, reducing the risk of, slowing the progression of, delaying the onset of or  
5 treating of complications of diabetes such as micro- and macrovascular diseases, such as nephropathy, micro- or macroalbuminuria, proteinuria, nephrotic syndrome, retinopathy, cataracts, neuropathy, learning or memory impairment, neurodegenerative or cognitive disorders, cardio- or cerebrovascular diseases, tissue ischaemia, diabetic foot or ulcer, atherosclerosis, hypertension, endothelial dysfunction, myocardial infarction, acute  
10 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-  
15 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 the onset of or treating the degeneration of pancreatic beta cells and/or the decline of the functionality of pancreatic beta cells and/or for improving, preserving and/or restoring the functionality of pancreatic beta cells and/or stimulating  
20 and/or restoring or protecting the functionality of pancreatic insulin, proinsulin, and/or C-peptide secretion;
- preventing, slowing, delaying the onset of 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 the onset of,  
25 attenuating, treating or reversing hepatic steatosis, (hepatic) inflammation and/or an abnormal accumulation of liver fat);
- preventing, slowing the progression of, delaying the onset of or treating diabetes with failure to conventional antidiabetic mono- or combination therapy;
- achieving a reduction in the dose of conventional antidiabetic medication required for  
30 adequate therapeutic effect;
- reducing the risk for adverse effects associated with conventional antidiabetic medication (e.g. hypoglycemia or weight gain);
- delaying initiation of rescue or insulin therapy; and/or
- maintaining and/or improving the insulin sensitivity and/or for treating or preventing  
35 hyperinsulinemia and/or insulin resistance;

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in a patient in need thereof (such as e.g. a patient as described herein, for example a human patient having autoimmune diabetes, particularly LADA), such as e.g. a (LADA) patient in whom one or more autoantibodies selected from GAD (GAD-65, anti-GAD), ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA are present, especially a LADA patient in whom antibodies to GAD  
5 (GAD-65) are present.

The present invention thus relates to a certain DPP-4 inhibitor as defined herein, preferably linagliptin (BI 1356), for use in the therapies (treatments and/or preventions) described herein.  
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The present invention further relates to a certain DPP-4 inhibitor as defined herein, preferably linagliptin (BI 1356), in combination with metformin, for use in the therapies (treatments and/or preventions) described herein.

15 The present invention further relates to a certain DPP-4 inhibitor as defined herein, preferably linagliptin (BI 1356), in combination with pioglitazone, for use in the therapies (treatments and/or preventions) described herein.

The present invention further relates to a certain DPP-4 inhibitor as defined herein, preferably linagliptin (BI 1356), in combination with telmisartan, for use in the therapies  
20 (treatments and/or preventions) described herein.

The present invention further relates to a certain DPP-4 inhibitor as defined herein, preferably linagliptin (BI 1356), in combination with insulin or an insulin analogue for use in  
25 the therapies (treatments and/or preventions) described herein.

The present invention further relates to a certain DPP-4 inhibitor as defined herein, preferably linagliptin (BI 1356), in combination with a GLP-1 receptor agonist (such as e.g. exenatide, exenatide LAR, liraglutide, taspoglutide, semaglutide, albiglutide, lixisenatide or  
30 dulaglutide) for use in the therapies (treatments and/or preventions) described herein.

The present invention further relates to a certain DPP-4 inhibitor as defined herein, preferably linagliptin (BI 1356), in combination with one or more other antidiabetic agents selected from metformin, a sulphonylurea, nateglinide, repaglinide, a thiazolidinedione, a  
35 PPAR-gamma agonist, an alpha-glucosidase inhibitor, insulin or an insulin analogue, and

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GLP-1 or a GLP-1 analogue, for use in the therapies (treatments and/or preventions) described herein.

The present invention further relates to a certain DPP-4 inhibitor as defined herein,  
5 preferably linagliptin (BI 1356), in combination with one or more other active agents, e.g. selected from other antidiabetic substances, active substances that lower the blood sugar level, active substances that lower the lipid level in the blood, active substances that raise the HDL level in the blood, active substances that lower blood pressure, and active substances that are indicated in the treatment of atherosclerosis or obesity, for use in the  
10 therapies (treatments and/or preventions) described herein.

The present invention further relates to a certain DPP-4 inhibitor as defined herein, preferably linagliptin (BI 1356), in combination with one or more other antidiabetics selected from the group consisting of metformin, a sulphonylurea, nateglinide, repaglinide, a  
15 thiazolidinedione, a PPAR-gamma-agonist, an alpha-glucosidase inhibitor, insulin or an insulin analogue, and GLP-1 or a GLP-1 analogue, optionally in combination with one or more further active agents (e.g. selected from a diuretic, ACE inhibitor and/or ARB, such as e.g. telmisartan), for use in the therapies (treatments and/or preventions) described herein.

20 The present invention further relates to a pharmaceutical composition comprising a certain DPP-4 inhibitor as defined herein, preferably linagliptin (BI 1356), for use in the therapies described herein.

The present invention further relates to a pharmaceutical composition comprising a certain  
25 DPP-4 inhibitor as defined herein, preferably linagliptin (BI 1356), and metformin, for use in the therapies described herein.

The present invention further relates to a pharmaceutical composition comprising a certain  
30 DPP-4 inhibitor as defined herein, preferably linagliptin (BI 1356), and pioglitazone, for use in the therapies described herein.

The present invention further relates to a combination comprising a certain DPP-4 inhibitor (particularly linagliptin) and one or more other active agents selected from those mentioned herein, e.g. selected from other antidiabetic substances, active substances that lower the  
35 blood sugar level, active substances that lower the lipid level in the blood, active substances

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that raise the HDL level in the blood, active substances that lower blood pressure, active substances that are indicated in the treatment of atherosclerosis or obesity, e.g. each as described herein; particularly for simultaneous, separate or sequential use in the therapies described herein.

5

The present invention further relates to a combination comprising a certain DPP-4 inhibitor (particularly linagliptin) and one or more other antidiabetics selected from the group consisting of metformin, a sulphonylurea, nateglinide, repaglinide, a thiazolidinedione, a PPAR-gamma-agonist, an alpha-glucosidase inhibitor, insulin or an insulin analogue, and  
10 GLP-1 or a GLP-1 analogue, particularly for simultaneous, separate or sequential use in the therapies described herein, optionally in combination with a diuretic, ACE inhibitor and/or ARB, such as e.g. telmisartan.

15

The present invention further relates to therapies or therapeutic or preventive methods or uses as described herein, such as e.g. to a method for treating and/or preventing a metabolic disease, such as e.g. autoimmune diabetes, particularly LADA, and/or conditions related thereto (e.g. diabetic complications), comprising administering (e.g. simultaneously, separately or sequentially) an effective amount of a certain DPP-4 inhibitor (particularly linagliptin) as defined herein and, optionally, one or more other active agents, such as e.g.  
20 one or more other antidiabetics selected from the group consisting of metformin, a sulphonylurea, nateglinide, repaglinide, a thiazolidinedione, a PPAR-gamma-agonist, an alpha-glucosidase inhibitor, insulin or an insulin analogue, and GLP-1 or a GLP-1 analogue, optionally in combination with one or more further active agents (e.g. a diuretic, ACE inhibitor and/or ARB, such as e.g. telmisartan), to the patient (particularly human patient) in need  
25 thereof, such as e.g. a patient as described herein, particularly a (LADA) patient in whom one or more autoantibodies selected from GAD (GAD-65, anti-GAD), ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA are present, especially a LADA patient in whom antibodies to GAD (GAD-65) are present.

30

The present invention further relates to therapies or therapeutic or preventive methods or uses as described herein, such as e.g. a method for treating and/or preventing a metabolic disease, autoimmune diabetes, particularly LADA, and/or conditions related thereto (e.g. diabetic complications), comprising administering an effective amount of linagliptin (BI 1356) and metformin, and optionally one or more further active agents, to the patient (particularly  
35 human patient) in need thereof, such as e.g. a patient as described herein, particularly a

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(LADA) patient in whom one or more autoantibodies selected from GAD (GAD-65, anti-GAD), ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA are present, especially a LADA patient in whom antibodies to GAD (GAD-65) are present.

5 The present invention further relates to therapies or therapeutic or preventive methods or uses as described herein, such as e.g. a method for treating and/or preventing a metabolic disease, such as e.g. autoimmune diabetes, particularly LADA, and/or conditions related thereto (e.g. diabetic complications), comprising administering an effective amount of linagliptin (BI 1356) and pioglitazone, and optionally one or more further active agents, to the  
10 patient (particularly human patient) in need thereof, such as e.g. a patient as described herein, particularly a (LADA) patient in whom one or more autoantibodies selected from GAD (GAD-65, anti-GAD), ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA are present, especially a LADA patient in whom antibodies to GAD (GAD-65) are present.

15 The present invention further relates to therapies or therapeutic or preventive methods or uses as described herein, such as e.g. a method for treating and/or preventing a metabolic disease, such as e.g. autoimmune diabetes, particularly LADA, and/or conditions related thereto (e.g. diabetic complications), comprising administering an effective amount of linagliptin (BI 1356) and insulin or insulin analogue, and optionally one or more further active  
20 agents, to the patient (particularly human patient) in need thereof, such as e.g. a patient as described herein, particularly a (LADA) patient in whom one or more autoantibodies selected from GAD (GAD-65, anti-GAD), ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA are present, especially a LADA patient in whom antibodies to GAD (GAD-65) are present.

25 Further, the present invention relates to a method of treating, preventing and/or modifying disease trajectory of autoimmune diabetes, particularly LADA, in a patient (particularly a human patient) in need thereof, particularly a (LADA) patient in whom one or more autoantibodies selected from GAD (GAD-65, anti-GAD), ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA are present, especially a LADA patient in whom antibodies to GAD (GAD-65) are  
30 present, comprising administering an effective amount of linagliptin, optionally in combination with one or more other active agents to the patient.

Further, the present invention relates to a method of treating, preventing and/or modifying disease trajectory of autoimmune diabetes, particularly LADA, in a patient (particularly a  
35 human patient) in need thereof, particularly a (LADA) patient in whom one or more



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autoantibodies selected from GAD (GAD-65, anti-GAD), ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA are present, especially a LADA patient in whom antibodies to GAD (GAD-65) are present, comprising administering an effective amount of linagliptin, optionally in combination with one or more other active agents, e.g. selected from other antidiabetic substances, active  
5 substances that lower the blood sugar level, active substances that lower the lipid level in the blood, active substances that raise the HDL level in the blood, active substances that lower blood pressure, active substances that are indicated in the treatment of atherosclerosis or obesity, to the patient.

10 Further, the present invention relates to a method of treating, preventing and/or modifying disease trajectory of autoimmune diabetes, particularly LADA, in a patient (particularly a human patient) in need thereof, particularly a (LADA) patient in whom one or more autoantibodies selected from GAD (GAD-65, anti-GAD), ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA are present, especially a LADA patient in whom antibodies to GAD (GAD-65) are  
15 present, comprising administering an effective amount of linagliptin and one or more other antidiabetics selected from the group consisting of metformin, a sulphonylurea, nateglinide, repaglinide, a thiazolidinedione, a PPAR-gamma-agonist, an alpha-glucosidase inhibitor, insulin or an insulin analogue, and GLP-1 or a GLP-1 analogue, optionally in combination with one or more further active agents to the patient.

20

Further on, the present invention relates to a certain DPP-4 inhibitor (preferably linagliptin) for treating and/or preventing oxidative stress, as well as to the use of such DPP-4 inhibitors in treatment and/or prevention of diabetic (autoimmune diabetes, particularly LADA) patients, including patient groups at risk of cardiovascular and/or renal disease.

25

The present invention further relates to a certain DPP-4 inhibitor (preferably linagliptin) for treating and/or preventing endothelial dysfunction in such patients.

The present invention further relates to a certain DPP-4 inhibitor (preferably linagliptin) for  
30 use as antioxidants and/or anti-inflammatories in such patients.

The present invention further relates to a certain DPP-4 inhibitor (preferably linagliptin) for treating and/or preventing oxidative stress, vascular stress and/or endothelial dysfunction in autoimmune diabetes (particularly LADA) patients, particularly independently from or beyond  
35 glycemic control.

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5 The present invention further relates to a certain DPP-4 inhibitor (preferably linagliptin) for treating and/or preventing hyperglycemia-induced or -associated oxidative stress (e.g. beyond glycemic control), as well as to the use of such DPP-4 inhibitors in antidiabetic therapy.

10 The present invention further relates to a certain DPP-4 inhibitor (preferably linagliptin) for treating and/or preventing autoimmune diabetes, particularly LADA, and/or diseases related thereto (e.g. diabetic complications), particularly in patients having or being at risk of oxidative stress, vascular stress and/or endothelial dysfunction, or diseases or conditions related or associated therewith.

15 Further, the present invention relates to a certain DPP-4 inhibitor (preferably linagliptin) for treating and/or preventing autoimmune diabetes, particularly LADA, and/or diseases related thereto (e.g. diabetic complications), in patients having or being at risk of cardiovascular and/or renal disease, such as e.g. myocardial infarction, stroke or peripheral arterial occlusive disease and/or diabetic nephropathy, micro- or macroalbuminuria, or acute or chronic renal impairment.

20 Further, the present invention relates to a certain DPP-4 inhibitor (preferably linagliptin) for treating and/or preventing autoimmune diabetes, particularly LADA, mellitus and/or diseases related thereto, in patients having or being at risk of micro- or macrovascular diabetic complications, such as e.g. diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, or cardio- or cerebrovascular diseases (such as e.g. myocardial infarction, stroke or  
25 peripheral arterial occlusive disease).

30 Further, the present invention relates to a certain DPP-4 inhibitor (preferably linagliptin) for modulating, blocking or reducing deleterious metabolic memory effect of (chronic or transient episodes of) hyperglycemia, particularly on diabetic complications.

Further, the present invention relates to a certain DPP-4 inhibitor (preferably linagliptin) for treating, preventing or reducing risk for micro- or macrovascular diseases which may be induced, memorized by or associated with exposure to oxidative stress.

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Furthermore, the present invention relates to a certain DPP-4 inhibitor (preferably linagliptin) for treating and/or preventing autoimmune diabetes, particularly LADA, and/or diseases related thereto (e.g. diabetic complications), in patients with or at risk of cardiovascular and/or renal disease, particularly in those diabetes patients being at risk of cardio- or  
5 cerebrovascular events, such as diabetes patients with one or more risk factors selected from A), B), C) and D):

A) previous or existing vascular disease (such as e.g. myocardial infarction (e.g. silent or non-silent), coronary artery disease, percutaneous coronary intervention, coronary artery by-  
10 pass grafting, ischemic or hemorrhagic stroke, congestive heart failure (e.g. NYHA class I or II, e.g. left ventricular function <40%), or peripheral occlusive arterial disease),

B) vascular related end-organ damage (such as e.g. nephropathy, retinopathy, neuropathy, impaired renal function, chronic kidney disease, and/or micro- or macroalbuminuria),

C) advanced age (such as e.g. age  $\geq$  60-70 years), and

D) one or more cardiovascular risk factors selected from

15 - advanced diabetes (such as e.g. > 10 years duration),

- hypertension (such as e.g. > 130/80 mm Hg, or systolic blood pressure >140 mmHg or on at least one blood pressure lowering treatment),

- current daily cigarette smoking,

- dyslipidemia (such as e.g. atherogenic dyslipidemia, postprandial lipemia, or high level of  
20 LDL cholesterol (e.g. LDL cholesterol  $\geq$ 130-135 mg/dL), low level of HDL cholesterol (e.g. <35-40 mg/dL in men or <45-50 mg/dL in women) and/or high level of triglycerides (e.g. >200-400 mg/dL) in the blood, or on at least one treatment for lipid abnormality),

- obesity (such as e.g. abdominal and/or visceral obesity, or body mass index  $\geq$ 45  
kg/m<sup>2</sup>),

25 - age  $\geq$  40 and  $\leq$  80 years,

- metabolic syndrome, hyperinsulinemia or insulin resistance, and

- hyperuricemia, erectile dysfunction, polycystic ovary syndrome, sleep apnea, or family history of vascular disease or cardiomyopathy in first-degree relative,

said method comprising administering a therapeutically effective amount of the DPP-4

30 inhibitor, optionally in combination with one or more other therapeutic substances, to the patient.

Moreover, the present invention relates to a certain DPP-4 inhibitor (preferably linagliptin) for use in a method of preventing, reducing the risk of or delaying the occurrence of cardio- or  
35 cerebrovascular events, such as cardiovascular death, (fatal or non-fatal) myocardial

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infarction (e.g. silent or non-silent MI), (fatal or non-fatal) stroke, or hospitalisation (e.g. for acute coronary syndrome, leg amputation, (urgent) revascularization procedures, heart failure or for unstable angina pectoris), such as e.g. in autoimmune diabetes (particularly LADA) patients, particularly those patients being at risk of cardio- or cerebrovascular events, such as those patients with one or more risk factors selected from A), B), C) and D):

5 A) previous or existing vascular disease (such as e.g. myocardial infarction (e.g. silent or non-silent), coronary artery disease, percutaneous coronary intervention, coronary artery bypass grafting, ischemic or hemorrhagic stroke, congestive heart failure (e.g. NYHA class I or II, e.g. left ventricular function <40%), or peripheral occlusive arterial disease),

10 B) vascular related end-organ damage (such as e.g. nephropathy, retinopathy, neuropathy, impaired renal function, chronic kidney disease, and/or micro- or macroalbuminuria),

C) advanced age (such as e.g. age  $\geq 60$ -70 years), and

D) one or more cardiovascular risk factors selected from

- advanced diabetes (such as e.g.  $> 10$  years duration),

15 - hypertension (such as e.g.  $> 130/80$  mm Hg, or systolic blood pressure  $>140$  mmHg or on at least one blood pressure lowering treatment),

- current daily cigarette smoking,

- dyslipidemia (such as e.g. atherogenic dyslipidemia, postprandial lipemia, or high level of LDL cholesterol (e.g. LDL cholesterol  $\geq 130$ -135 mg/dL), low level of HDL cholesterol

20 (e.g.  $<35$ -40 mg/dL in men or  $<45$ -50 mg/dL in women) and/or high level of triglycerides (e.g.  $>200$ -400 mg/dL) in the blood, or on at least one treatment for lipid abnormality),

- obesity (such as e.g. abdominal and/or visceral obesity, or body mass index  $\geq 45$  kg/m<sup>2</sup>),

- age  $\geq 40$  and  $\leq 80$  years,

25 - metabolic syndrome, hyperinsulinemia or insulin resistance, and

- hyperuricemia, erectile dysfunction, polycystic ovary syndrome, sleep apnea, or family history of vascular disease or cardiomyopathy in first-degree relative,

said method comprising administering a therapeutically effective amount of the DPP-4 inhibitor, optionally in combination with one or more other therapeutic substances, to the patient.

Yet moreover, the present invention relates to a certain DPP-4 inhibitor (preferably linagliptin) for use in a method of preventing, reducing the risk of or delaying the occurrence of cardio- or cerebrovascular events, such as cardiovascular death, (fatal or non-fatal) myocardial infarction (e.g. silent or non-silent MI), (fatal or non-fatal) stroke, or hospitalisation (e.g. for

35

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acute coronary syndrome, leg amputation, (urgent) revascularization procedures, heart failure or for unstable angina pectoris) in autoimmune diabetes (particularly LADA) patients with vascular related end-organ damage, particularly nephropathy, impaired renal function, chronic kidney disease, micro- or macroalbuminuria,

5 said method comprising administering a therapeutically effective amount of the DPP-4 inhibitor, optionally in combination with one or more other therapeutic substances, to the patient.

Yet moreover, the present invention relates to a certain DPP-4 inhibitor (preferably linagliptin)  
10 for use in a method of improving cognitive function (e.g. attenuating, reversing or treating cognitive decline), improving  $\beta$ -cell function (e.g. improving insulin secretion rate derived from a 3h meal tolerance test, improving long term  $\beta$ -cell function), improving diurnal glucose pattern (e.g. improving ambulatory glucose profile, glycemic variability, biomarkers of  
15 oxidation, inflammation or endothelial function), and/or improving durability of glucose control according to  $\beta$ -cell autoantibody status (e.g., glutamic acid decarboxylase GAD), said method comprising administering a therapeutically effective amount of the DPP-4 inhibitor, optionally in combination with one or more other therapeutic substances, to the patient.

Yet moreover, the present invention relates to a certain DPP-4 inhibitor (preferably linagliptin)  
20 for use in a method of preventing, reducing the risk of, slowing the progression of, delaying the onset of, attenuating, reversing or treating cognitive dysfunction or cognitive decline, said method comprising administering a therapeutically effective amount of the DPP-4 inhibitor, optionally in combination with one or more other therapeutic substances, to the patient.

25 Yet moreover, the present invention relates to a certain DPP-4 inhibitor (preferably linagliptin) for use in a method of preventing, reducing the risk of, slowing the progression of, delaying the onset of, attenuating, reversing or treating latent autoimmune diabetes in adults (LADA), said method comprising administering a therapeutically effective amount of the DPP-4  
30 inhibitor, optionally in combination with one or more other therapeutic substances, to the patient.

Further, the present invention relates to a certain DPP-4 inhibitor (preferably linagliptin) for use in a method (e.g. with the joint aims) of

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preventing, reducing the risk of, slowing the progression of, delaying the onset of, attenuating, reversing or treating cardio- or cerebrovascular disease or events (such as e.g. those described herein), and/or

preventing, reducing the risk of, slowing the progression of, delaying the onset of,

5 attenuating, reversing or treating diabetic nephropathy,

in a patient in need thereof (such as e.g. a patient as described herein, such as autoimmune diabetes (particularly LADA) patient),

said method comprising administering a therapeutically effective amount of the DPP-4 inhibitor, optionally in combination with one or more other therapeutic substances, to the  
10 patient.

Further, the present invention relates to one or more of the following methods of

- treating, reducing, preventing and/or protecting against oxidative stress, such as e.g. non-diabetes- or diabetes- (hyperglycemia-) induced or -associated oxidative stress;

15 - treating, preventing, reducing the risk of, slowing the progression of, delaying the onset of, attenuating or reversing endothelial dysfunction or improving endothelial function;

- treating, preventing, reducing the risk of, slowing the progression of, delaying the onset of, attenuating or reversing diseases or conditions associated with oxidative stress, such as those described herein;

20 - treating, preventing, reducing the risk of, slowing the progression of, delaying the onset of, attenuating or reversing (renal, cardiac, cerebral or hepatic) ischemia/reperfusion injuries and/or reducing myocardial infarct size in the heart (e.g. after myocardial ischemia/reperfusion);

25 - treating, preventing, reducing the risk of, slowing the progression of, delaying the onset of, attenuating or reversing (adverse) vascular remodeling such as cardiac remodeling (particularly after myocardial infarction), which may be characterized by cardiomyocyte hypertrophy, interstitial fibrosis, ventricular dilation, contractile dysfunction and/or cell death/apoptosis;

30 - treating, preventing, reducing the risk of, slowing the progression of, delaying the onset of, attenuating or reversing chronic or acute renal failure and/or peripheral arterial occlusion;

- treating, preventing, reducing the risk of, slowing the progression of, delaying the onset, attenuating or reversing congestive heart failure (e.g. NYHA class I, II, III or IV) and/or cardiac hypertrophy (e.g. left ventricular hypertrophy), and/or nephropathy and/or albuminuria;

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- treating, preventing, reducing the risk of, slowing the progression of, delaying the onset of, attenuating or reversing uremic cardiomyopathy, interstitial expansion and/or (cardiac) fibrosis (particularly in patients with chronic kidney and heart diseases often associated with diabetes);
- 5 - modulating, blocking, preventing, reducing or protecting against deleterious metabolic memory effect of (chronic, early or transient episodes of) hyperglycemia, particularly on diabetic complications;
  - preventing or protecting against oxidation of atherogenic or pro-atherogenic low density lipoprotein (particularly, small dense LDL particles) and/or atherosclerotic plaque formation;
- 10 - preventing or protecting against oxidative-stress induced impairment of function or viability of pancreatic beta cells;
  - treating, preventing, ameliorating or improving pancreatic islet inflammation or lipotoxicity and glucotoxicity in islets, or increasing beta cell/alpha cell ratio, protecting beta cell or normalizing/improving pancreatic islet morphology or function; and/or
- 15 - preventing, reducing the risk of, slowing the progression of, delaying the onset of, attenuating, reversing or treating complications of diabetes, such as micro- and macrovascular diseases, such as e.g. nephropathy, micro- or macroalbuminuria, proteinuria, retinopathy, cataracts, neuropathy, learning or memory impairment, neurodegenerative or cognitive disorders, cardio- or cerebrovascular diseases, endothelial dysfunction, tissue
- 20 ischaemia, diabetic foot or ulcer, atherosclerosis, hypertension, myocardial infarction, acute coronary syndrome, unstable angina pectoris, stable angina pectoris, peripheral arterial occlusive disease, cardiomyopathy (including e.g. uremic cardiomyopathy), heart failure, heart rhythm disorders, vascular restenosis, and/or stroke;
  - particularly independently from or beyond glycemic control;
- 25 in a patient in need thereof (e.g. autoimmune diabetes, particularly LADA, patient);  
said methods comprising administering an effective amount of a certain DPP-4 inhibitor (preferably linagliptin), optionally in combination with an effective amount of one or more other active substances to the patient.
- 30 Further, the present invention relates to a certain DPP-4 inhibitor (preferably linagliptin) for use in a method of  
preventing, reducing the risk of, slowing the progression of, delaying the onset of, attenuating, reversing or treating diabetic nephropathy,  
in a patient (such as e.g. a patient as described herein, such as autoimmune diabetes,
- 35 particularly LADA, patient),

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who does not adequately respond to therapy with an angiotensin receptor blocker (ARB such as e.g. telmisartan),  
said method comprising administering a therapeutically effective amount of the DPP-4 inhibitor, optionally in combination with one or more other therapeutic substances (e.g. an  
5 ARB such as e.g. telmisartan), to the patient.

Features of diabetic nephropathy may include hyperfiltration (in early stage), micro- or macroalbuminuria, nephrotic syndrome, proteinuria, hypertension, fluid retention, edema, and/or progressively impaired or decreased kidney and renal filter function (e.g. glomerular  
10 filtration rate GFR) leading finally to renal failure or end-stage renal disease. Further features may include diffuse or nodular glomerulosclerosis, afferent and efferent hyaline arteriosclerosis, and/or tubulointerstitial fibrosis and atrophy. Further features may include abnormal albumin/creatinine or protein/creatinine ratio and/or abnormal glomerular filtration rate.

15

The present invention further relates to a certain DPP-4 (preferably linagliptin) for use in a method of preventing or treating diabetic nephropathy in a patient with inadequate response to therapy with an angiotensin receptor blocker (ARB such as e.g. telmisartan). The method may comprise administering a therapeutically effective amount of the DPP-4 inhibitor and  
20 telmisartan to the patient.

Accordingly, in a particular embodiment, a preferred DPP-4 inhibitor within the meaning of this invention is linagliptin.

25 Pharmaceutical compositions or combinations for use in these therapies (treatments or preventions) comprising a certain DPP-4 inhibitor (preferably linagliptin) as defined herein optionally together with one or more other active agents are also contemplated.

Further, the present invention relates to a certain DPP-4 inhibitor (preferably linagliptin),  
30 optionally in combination with one, two or more further active agents, each as defined herein, for use in the therapies (treatments or preventions) as described herein.

Further, the present invention relates to the use of a certain DPP-4 inhibitor (preferably linagliptin), optionally in combination with one, two or more further active agents, each as



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defined herein, for preparing a pharmaceutical composition which is suitable for the treatment and/or prevention purposes of this invention.

Further, the present invention relates to a therapeutic (treatment or prevention) method as  
5 described herein, said method comprising administering an effective amount of a certain  
DPP-4 inhibitor (preferably linagliptin) and, optionally, one or more other active or therapeutic  
agents to the patient in need thereof, each as described herein.

Other aspects of the present invention become apparent to the skilled person from the  
10 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 a certain DPP-4 inhibitor (preferably  
linagliptin), optionally in combination with one or more other active agents, as defined  
15 hereinbefore and hereinafter.

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  
20 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,  
25 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.

30 In the monitoring of the treatment of diabetes 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  
35 over a long time by more intensive diabetes treatment (i.e. < 6.5 % of the total haemoglobin

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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 glycaemic 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 glycaemic 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 glycaemic control including, without being limited, patients having a HbA1c value  $\geq$  9%.

Within glycaemic control, in addition to improvement of the HbA1c level, other recommended therapeutic goals for diabetes 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 diabetes (including patients with failure to conventional antidiabetic therapy), such as e.g. patients with inadequate glycaemic control on one, two or more conventional oral and/or non-oral antidiabetic drugs as defined herein, such as e.g. patients with insufficient glycaemic 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  $\alpha$ -glucosidase inhibitor, or despite dual combination therapy with metformin/sulphonylurea, metformin/thiazolidinedione (particularly pioglitazone), sulphonylurea/  $\alpha$ -glucosidase inhibitor, pioglitazone/sulphonylurea, metformin/insulin, pioglitazone/insulin or sulphonylurea/insulin. Thus, in an embodiment, the therapies described herein may be used in patients experienced with therapy, e.g. with

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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

5 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

10 information of locally approved metformin),

dehydration,

unstable or acute congestive heart failure,

acute or chronic metabolic acidosis, and

hereditary galactose intolerance;

15 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,

20 vomiting,

diarrhoea,

intestinal gas, and

severe abdominal discomfort.

25 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

30 as e.g.  $\geq 60$ -65 years).

A further embodiment of patients (e.g. which may be diabetic or non-diabetic) 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

35 impairment), e.g. as suggested by elevated serum creatinine levels (e.g. serum creatinine

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levels above the upper limit of normal for their age, e.g.  $\geq 130 - 150 \mu\text{mol/l}$ , or  $\geq 1.5 \text{ mg/dl}$  ( $\geq 136 \mu\text{mol/l}$ ) in men and  $\geq 1.4 \text{ mg/dl}$  ( $\geq 124 \mu\text{mol/l}$ ) in women) or abnormal creatinine clearance (e.g. glomerular filtration rate (GFR)  $\leq 30 - 60 \text{ ml/min}$ ).

5 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  $\leq 1.7 \text{ mg/dL}$  in men and  $\leq 1.5 \text{ mg/dL}$  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  $\leq 3.0 \text{ mg/dL}$  in men and  $>1.5$  to  $\leq 2.5 \text{ mg/dL}$  in women); and severe  
10 renal impairment may be e.g. suggested by a creatinine clearance of  $< 30 \text{ ml/min}$  (approximately corresponding to serum creatinine levels of  $>3.0 \text{ mg/dL}$  in men and  $>2.5 \text{ mg/dL}$  in women). Patients with end-stage renal disease require dialysis (e.g. hemodialysis or peritoneal dialysis).

15 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,  $\text{ml/min}/1.73\text{m}^2$ ) into 5 disease stages: stage 1 characterized by normal GFR  $\geq 90$  plus either persistent albuminuria or known structural or hereditary renal disease; stage 2 characterized by mild reduction of GFR (GFR  
20 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 15-29) describing severe renal impairment; and terminal stage 5 characterized by requiring dialysis or GFR  $< 15$  describing established kidney failure (end-stage renal disease, ESRD).

25 A further embodiment of diabetic patients within the meaning of this invention refers to diabetes patients with or at risk of developing micro- or macrovascular diabetic complications, such as e.g. described herein (e.g. such at-risk patients as described as follows).

30 A further embodiment of patients within the meaning of this invention refers to diabetes patients with or at risk of developing renal complications, such as diabetic nephropathy (including chronic and progressive renal insufficiency, albuminuria, proteinuria, fluid retention in the body (edema) and/or hypertension).

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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 with or at risk of developing retinal complications, such as diabetic retinopathy.

5 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 with or at risk of developing macrovascular complications, such as myocardial infarction, coronary artery disease, ischemic or hemorrhagic stroke, and/or peripheral occlusive arterial disease.

10 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 with or at risk of cardio- or cerebrovascular diseases or events (such as e.g. those cardiovascular risk patients described herein).

15 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 with advanced age and/or with advanced diabetes disease, such as e.g. patients on insulin treatment, patients on triple antidiabetic oral therapy, patients with pre-existing cardio- and/or cerebrovascular events and/or patients with advanced disease duration (e.g.  $\geq 5$  to 10 years).

20

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 with one or more cardiovascular risk factors selected from A), B), C) and D):

25 A) previous or existing vascular disease (such as e.g. myocardial infarction (e.g. silent or non-silent), coronary artery disease, percutaneous coronary intervention, coronary artery bypass grafting, ischemic or hemorrhagic stroke, congestive heart failure (e.g. NYHA class I or II, e.g. left ventricular function  $<40\%$ ), or peripheral occlusive arterial disease),

B) vascular related end-organ damage (such as e.g. nephropathy, retinopathy, neuropathy, impaired renal function, chronic kidney disease, and/or micro- or macroalbuminuria),

30 C) advanced age (such as e.g. age  $\geq 60-70$  years), and

D) one or more cardiovascular risk factors selected from

- advanced diabetes (such as e.g.  $> 10$  years duration),

- hypertension (such as e.g.  $> 130/80$  mm Hg, or systolic blood pressure  $>140$  mmHg or on at least one blood pressure lowering treatment),

35 - current daily cigarette smoking,

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- dyslipidemia (such as e.g. atherogenic dyslipidemia, postprandial lipemia, or high level of LDL cholesterol (e.g. LDL cholesterol  $\geq 130$ -135 mg/dL), low level of HDL cholesterol (e.g.  $< 35$ -40 mg/dL in men or  $< 45$ -50 mg/dL in women) and/or high level of triglycerides (e.g.  $> 200$ -400 mg/dL) in the blood, or on at least one treatment for lipid abnormality),
- 5 - obesity (such as e.g. abdominal and/or visceral obesity, or body mass index  $\geq 45$  kg/m<sup>2</sup>),
- age  $\geq 40$  and  $\leq 80$  years,
- metabolic syndrome, hyperinsulinemia or insulin resistance, and
- hyperuricemia, erectile dysfunction, polycystic ovary syndrome, sleep apnea, or family
- 10 history of vascular disease or cardiomyopathy in first-degree relative.

In certain embodiments, the patients which may be amenable to the therapies of this invention may have or are at-risk of one or more of the following diseases, disorders or conditions: type 1 diabetes, type 2 diabetes, impaired glucose tolerance (IGT), impaired

15 fasting blood glucose (IFG), hyperglycemia, postprandial hyperglycemia, postabsorptive hyperglycemia, latent autoimmune diabetes in adults (LADA), overweight, obesity, dyslipidemia (including e.g. atherogenic dyslipidemia), hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, hyperNEFA-emia, postprandial lipemia, hypertension, atherosclerosis, endothelial dysfunction, osteoporosis, chronic systemic inflammation, non alcoholic fatty liver

20 disease (NAFLD), polycystic ovarian syndrome, hyperuricemia, metabolic syndrome, nephropathy, micro- or macroalbuminuria, proteinuria, nephrotic syndrome, retinopathy, cataracts, neuropathy, learning or memory impairment, neurodegenerative or cognitive disorders, cardio- or cerebrovascular diseases, tissue ischaemia, diabetic foot or ulcer, atherosclerosis, hypertension, endothelial dysfunction, myocardial infarction, acute coronary

25 syndrome, unstable angina pectoris, stable angina pectoris, peripheral arterial occlusive disease, cardiomyopathy (including e.g. uremic cardiomyopathy), heart failure, cardiac hypertrophy, heart rhythm disorders, vascular restenosis, stroke, (renal, cardiac, cerebral or hepatic) ischemia/reperfusion injuries, (renal, cardiac, cerebral or hepatic) fibrosis, (renal, cardiac, cerebral or hepatic) vascular remodelling; a diabetic disease, e.g. autoimmune

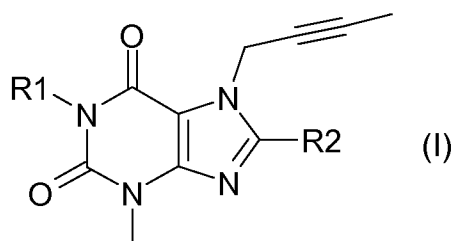
30 diabetes (particularly LADA) being particularly to be noted (e.g. as an underlying disease), particularly autoimmune diabetes (LADA) with one or more positive autoantibodies selected from GAD (GAD-65, anti-GAD), ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA, especially GAD (GAD-65, anti-GAD) positive LADA.

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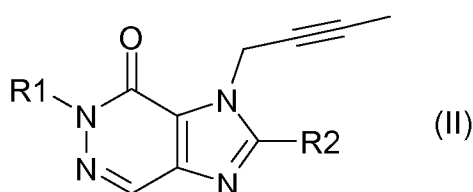
In a further embodiment, the patients which may be amenable to the therapies of this invention have a diabetic disease, such as e.g. autoimmune diabetes (particularly LADA), particularly autoimmune diabetes (LADA) with one or more positive autoantibodies selected from GAD (GAD-65, anti-GAD), ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA, especially GAD  
 5 (GAD-65, anti-GAD) positive LADA, and, optionally, may have or are at-risk of one or more other diseases, disorders or conditions, such as e.g. selected from those mentioned immediately above.

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

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

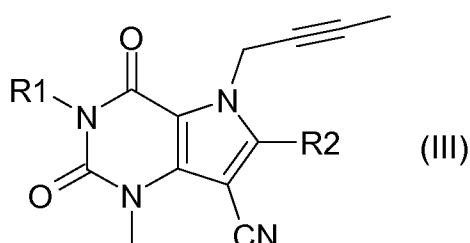


or formula (II)



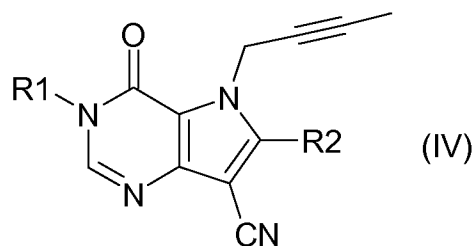
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or formula (III)



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or formula (IV)



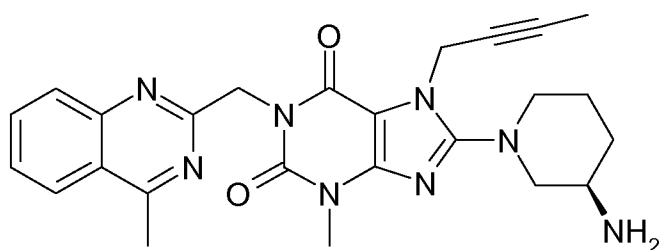
wherein **R1** denotes ([1,5]naphthyridin-2-yl)methyl, (quinazolin-2-yl)methyl, (quinoxalin-6-yl)methyl, (4-methyl-quinazolin-2-yl)methyl, 2-cyano-benzyl, (3-cyano-quinolin-2-yl)methyl, (3-cyano-pyridin-2-yl)methyl, (4-methyl-pyrimidin-2-yl)methyl, or (4,6-dimethyl-pyrimidin-2-yl)methyl and **R2** denotes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

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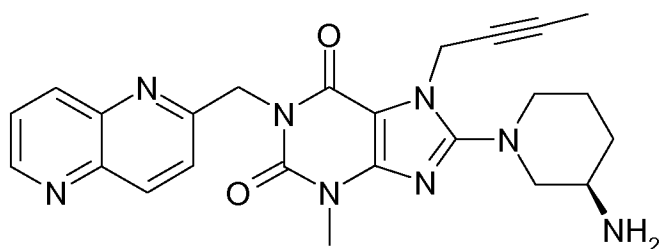
Regarding the first embodiment (embodiment **A**), preferred DPP-4 inhibitors are any or all of the following compounds and their pharmaceutically acceptable salts:

- 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)):

15



- 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)):

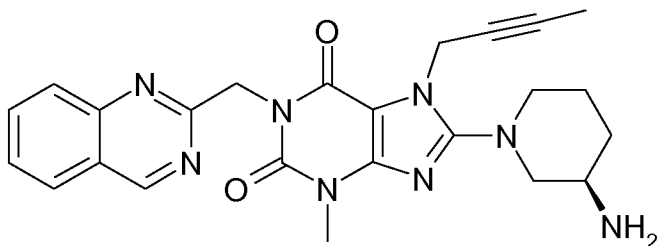


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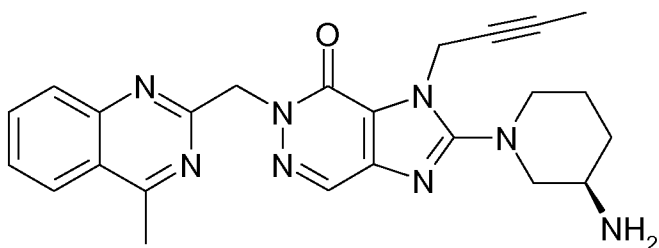


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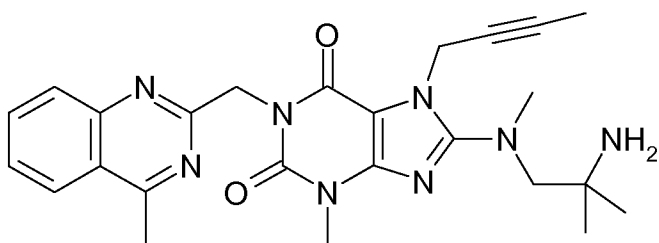
- 1-[(Quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine (compare WO 2004/018468, example 2(80)):



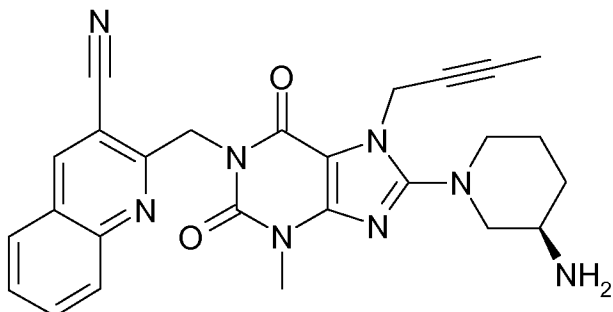
- 5 • 2-((*R*)-3-Amino-piperidin-1-yl)-3-(but-2-ynyl)-5-(4-methyl-quinazolin-2-ylmethyl)-3,5-dihydro-imidazo[4,5-d]pyridazin-4-one (compare WO 2004/050658, example 136):



- 10 • 1-[(4-Methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-[(2-amino-2-methyl-propyl)-methylamino]-xanthine (compare WO 2006/029769, example 2(1)):

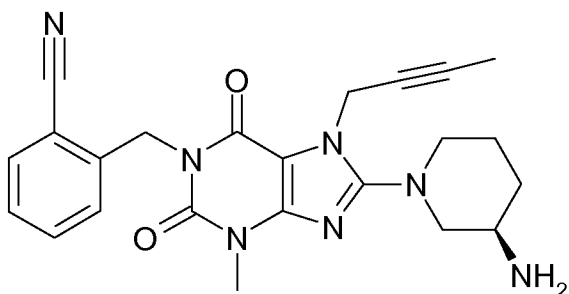


- 1-[(3-Cyano-quinolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine (compare WO 2005/085246, example 1(30)):



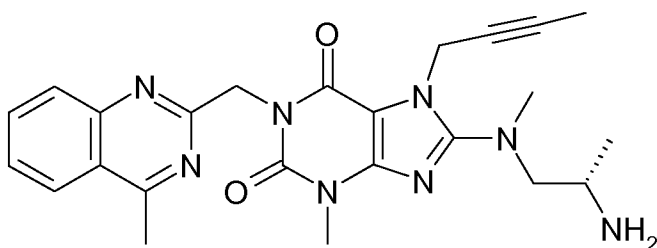
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- 1-(2-Cyano-benzyl)-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine (compare WO 2005/085246, example 1(39)):

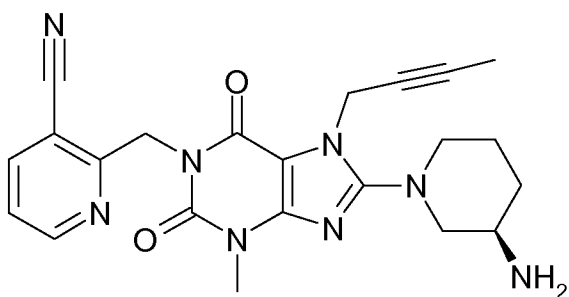


5

- 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)):

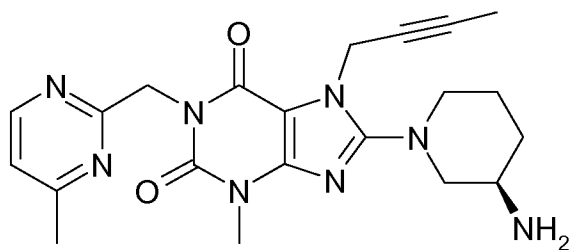


- 10 • 1-[(3-Cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine (compare WO 2005/085246, example 1(52)):

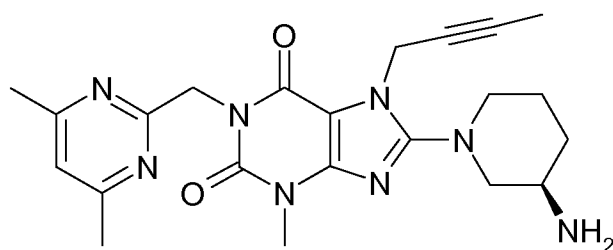


- 15 • 1-[(4-Methyl-pyrimidin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine (compare WO 2005/085246, example 1(81)):

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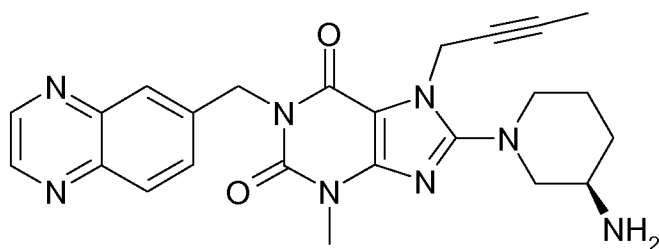


- 1-[(4,6-Dimethyl-pyrimidin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine (compare WO 2005/085246, example 1(82)):



5

- 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)):



10

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.

15

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, omarigliptin, evogliptin, (2*S*)-1-[[2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethylamino]-acetyl]-pyrrolidine-2-carbonitrile,

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- (2S)-1-[[1,1-Dimethyl-3-(4-pyridin-3-yl-imidazol-1-yl)-propylamino]-acetyl]-pyrrolidine-2-carbonitrile,  
 (S)-1-((2S,3S,11bS)-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,  
 5 (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-  
 10 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,  
 15 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,  
 20 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-  
 25 oxoethylamino]-2-methylpropyl}amide,  
 or its pharmaceutically acceptable salt.

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  
 30 known as linagliptin or BI 1356).

Preferably the DPP-4 inhibitor of this invention is selected from the group consisting of linagliptin, sitagliptin, vildagliptin, alogliptin, saxagliptin, teneligliptin, anagliptin, gemigliptin

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and dutogliptin, or a pharmaceutically acceptable salt of one of the herein mentioned DPP-4 inhibitors, or a prodrug thereof.

A particularly preferred DPP-4 inhibitor to be emphasized within the present invention is  
5 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  
10 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.

15

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.

20 An embodiment of this invention refers to a DPP-4 inhibitor suitable for use in the treatment and/or prevention of metabolic diseases (particularly diabetes) in 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  
25 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)  
30 therapeutic window and/or, especially, that are primarily eliminated via hepatic metabolism or biliary excretion (preferably without adding additional burden to the kidney).

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  
35 DPP-4 inhibitor, which has a relatively wide (e.g. > 100 fold) therapeutic window (preferably a

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safety profile comparable to placebo) and/or which fulfils one or more of the following pharmacokinetic properties (preferably at its therapeutic oral dose levels):

- 5 - 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 (<sup>14</sup>C) substance oral dose);
- 10 - 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 (<sup>14</sup>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%);
- 15 - 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).

20 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).

25 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  $R_{A,AUC} \leq 1.4$  with therapeutic oral dose levels), and/or preserving a long-lasting effect on DPP-4  
30 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

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below 1% of the administered dose and increasing to not more than about 3-6% in steady state.

5 Thus, for example, a DPP-4 inhibitor according to this invention may be characterized in that said DPP-4 inhibitor has a primarily non-renal route of excretion, i.e. said DPP-4 inhibitor is excreted to a non-substantial or only to a minor extent (e.g. < 10 %, preferably < 7 %, e.g. about 5 %, of administered oral dose, preferably of oral therapeutic dose) via the kidney (measured, for example, by following elimination of a radiolabelled carbon (<sup>14</sup>C) substance oral dose).

10

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, bile or faeces (measured, for example, by following elimination of a radiolabelled carbon (<sup>14</sup>C) substance oral dose).

15

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 (<sup>14</sup>C) substance),

20

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.

25

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 diabetes patient with chronic renal insufficiency (e.g. mild, moderate or severe renal impairment or end stage renal disease), and/or

30

said DPP-4 inhibitor trough levels in the blood plasma of diabetes patients with mild or moderate renal impairment are comparable to the levels in patients with normal renal function, and/or

said DPP-4 inhibitor does not require to be dose-adjusted in a diabetes patient with impaired renal function (e.g. mild, moderate or severe renal impairment or end stage renal disease, preferably regardless of the stage of renal impairment).

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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.

Further, a DPP-4 inhibitor according to this invention may be characterized in that being suitable for use in diabetes patients who are with diagnosed renal impairment or complication and/or who are at risk of developing renal complications, e.g. patients with or at risk of diabetic nephropathy (including chronic and progressive renal insufficiency, albuminuria, proteinuria, fluid retention in the body (edema) and/or hypertension).

GLP-1 receptor agonists include, without being limited, exogenous GLP-1 (natural or synthetic), GLP-1 mimetics or 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: 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<sub>8</sub> is Val, Xaa<sub>22</sub> is Glu, Xaa<sub>33</sub> is Ile, and Xaa<sub>46</sub> is Cys-NH<sub>2</sub>, and wherein one PEG molecule is covalently attached to Cys<sub>45</sub> and one PEG molecule is covalently attached to Cys<sub>46</sub>-NH<sub>2</sub>, 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<sup>8</sup>-Glu<sup>22</sup>-Ile<sup>33</sup>-Cys-NH<sub>2</sub><sup>46</sup>-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.

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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.

- 5 In an embodiment, the GLP-1 receptor agonist is preferably administered by injection (preferably subcutaneously).

10 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 herein below 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.

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An effective amount of a compound as used herein means an amount sufficient to affect, e.g. cure, alleviate or partially arrest the clinical manifestations of a given state or condition, such as a disease or disorder, and its complications. An amount adequate to accomplish this is defined as "effective amount". Effective amounts for each purpose will depend on the severity of the condition, disease or injury as well as the weight and general state of the subject and mode of administration, or the like. It will be understood that determining an appropriate dosage may be achieved using routine experimentation, e.g. by constructing a matrix of values and testing different points in the matrix, which is all within the ordinary skills of a trained physician or veterinary.

20

25 In the present context, treatment or treating mean the management and care of a patient or subject for the purpose of combating a condition, a disease or a disorder. The term is intended to include the full spectrum of treatments for a given condition from which the patient or subject is suffering, such as administration of the active compound to alleviate the symptoms or complications, to delay the progression of the disease, disorder or condition, to alleviate or relief the symptoms and complications, to improve patient's status or outcome, and/or to cure or eliminate the disease, disorder or condition as well as to prevent the condition, wherein prevention is to be understood as the management and care of a patient for the purpose of combating the disease, condition, or disorder and includes the

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administration of the active compounds to prevent or delay the onset of the symptoms or complications.

5 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.

10 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.

15 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.

20 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.

25 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.

30 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  
35 2004/050658 or WO 2005/110999, the disclosures of which are incorporated herein.

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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.

5 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.

10

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.

15 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 (each one tablet) 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.

20 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).

25 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.

30 The elements of the combination of this invention may be administered by various ways, for example by oral, buccal, sublingual, enterical, parenteral (e.g., transdermal, intramuscular or subcutaneous), inhalative (e.g., liquid or powder inhalation, aerosol), pulmonary, intranasal (e.g. spray), intraperitoneal, vaginal, rectal, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration.

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In an embodiment, the DPP-4 inhibitor according to the invention is preferably administered orally.

5 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.

10 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 0.01-15 mg/kg or 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, 15 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.

20 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 and appropriate for the desired route of administration. 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.

25 Oral formulations or dosage forms of the DPP-4 inhibitor of this invention may be prepared according to known techniques.

30 A pharmaceutical composition or dosage form (e.g. oral tablet) of a DPP-4 inhibitor according to embodiment **A** of the invention may typically contain as excipients (in addition to an active ingredient), for example: one or more diluents, a binder, a disintegrant, and a lubricant, preferably each as disclosed herein-below. In an embodiment, the disintegrant may be optional.

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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.

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

- 10 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).

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

Suitable methods of preparing (oral) preparations or dosage forms of the DPP-4 inhibitors according to embodiment **A** of the invention are

- 20
- direct tableting of the active substance in powder mixtures with suitable tableting excipients;
  - granulation with suitable excipients and subsequent mixing with suitable excipients and subsequent tableting as well as film coating; or
  - packing of powder mixtures or granules into capsules.

25 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
- 30 tableting 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

35 magnesium stearate as lubricant; wherein copovidone and/or corn starch may be optional.

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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).

5

In a further embodiment, the DPP-4 inhibitor according to the invention may be administered by injection (preferably subcutaneously). In another embodiment, the GLP-1 receptor agonist is preferably administered by injection (preferably subcutaneously) as well.

10

Injectable formulations of the GLP-1 receptor agonist and/or the DPP-4 inhibitor of this invention (particularly for subcutaneous use) may be prepared according to known formulation techniques, e.g. using suitable liquid carriers, which usually comprise sterile water, and, optionally, further additives such as e.g. preservatives, pH adjusting agents, buffering agents, isotoning agents, solubility aids and/or tensides or the like, to obtain

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injectable solutions or suspensions. In addition, injectable formulations may comprise further additives, for example salts, solubility modifying agents or precipitating agents which retard release of the drug(s). In further addition, injectable GLP-1 formulations may comprise GLP-1 stabilizing agents (e.g. a surfactant).

20

For example, an injectable formulation (particularly for subcutaneous use) containing the GLP-1 receptor agonist (e.g. exenatide), optionally together with the DPP-4 inhibitor of this invention, may further comprise the following additives: a tonicity-adjusting agent (such as e.g. mannitol), an antimicrobial preservative (such as e.g. metacresol), a buffer or pH adjusting agent (such as e.g. glacial acetic acid and sodium acetate trihydrate in water for

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injection as a buffering solution at pH 4.5), and optionally a solubilizing and/or stabilizing agent (such as e.g. a surfactant or detergent).

30

In a further embodiment, the DPP-4 inhibitor according to the invention may be administered by a transdermal delivery system. In another embodiment, the GLP-1 receptor agonist is preferably administered by a transdermal delivery system as well.

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Transdermal formulations (e.g. for transdermal patches or gels) of the GLP-1 receptor agonist and/or the DPP-4 inhibitor of this invention may be prepared according to known formulation techniques, e.g. using suitable carriers and, optionally, further additives. To facilitate transdermal passage, different methodologies and systems may be used, such as

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e.g. techniques involving formation of microchannels or micropores in the skin, such as e.g. iontophoresis (based on low-level electrical current), sonophoresis (based on low-frequency ultrasound) or microneedling, or the use of drug-carrier agents (e.g. elastic or lipid vesicles such as transfersomes) or permeation enhancers.

5

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

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The pharmaceutical compositions (or formulations) may be packaged in a variety of ways. Generally, an article for distribution includes one or more containers that contain the one or more pharmaceutical compositions 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.

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Primary containers for tablets may be bottles or blister packs.

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A suitable bottle, e.g. for a pharmaceutical composition or combination (tablet) 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.

25

A suitable blister pack, e.g. for a pharmaceutical composition or combination (tablet) 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 metallic foil, particularly 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 chloride) (PVC) coated with poly(vinylidene chloride) (PVDC); or a PVC foil laminated with poly(chlorotrifluoroethylene) (PCTFE)) or a multi-layer polymer-metal-polymer foil (such as e.g. a cold-formable laminated PVC/aluminium/polyamide composition).

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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 polyethylene/aluminium/polyester composition) may be used for the blister packs.

5 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.

Solutions for injection may be available in typical suitable presentation forms such as vials, cartridges or prefilled (disposable) pens, which may be further packaged.

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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  
15 package inserts indicates that the composition can be used for any of the purposes described herein.

15

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  
20 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  
25 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.

25

For example, doses of linagliptin when administered subcutaneously or i.v. for human patients are in the range of 0.3-10 mg, preferably from 1 to 5 mg, particularly 2.5 mg, per patient per day.

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In a further embodiment, for example, doses of linagliptin when administered subcutaneously for human patients (such as e.g. in obese human patients or for treating obesity) are in the range of 0.1-30 mg, preferably from 1 to 10 mg, particularly 5 mg, per patient per day.



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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 oral 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  
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  
10 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 oral dosage strengths comprise, for example, 10, 25, 40, 50, 75, 100, 150 and 200 mg of the DPP-4 inhibitor active moiety.

An oral 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  
20 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  
25 mg and 50/1000 mg.

An oral 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  
30 150 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  
35 of vildagliptin / metformin are 50/850 mg and 50/1000 mg.

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Alogliptin may be administered to a patient at an oral 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  
5 molecular weight of the free base form of alogliptin). Thus, specific oral 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.

10 Saxagliptin may be administered to a patient at an oral daily dose of between 2.5 mg/day and 100 mg/day, optionally between 2.5 mg and 50 mg. Specific oral 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.

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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  
20 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  
25 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 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  
30 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. Dosage ranges for the combination may be from the maximal tolerated dose for the single agent to lower doses.

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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 3 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  $\geq 80\%$  (already on Day 1) in doses  $\geq 2.5$  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  $\geq 5$  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 3:** 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 <sub>0-24</sub> [nmol·h/L]	40.2 (39.7)	85.3 (22.7)	118 (16.0)	161 (15.7)

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AUC <sub>T,ss</sub> [nmol·h/L]	81.7 (28.3)	117 (16.3)	158 (10.1)	190 (17.4)
C <sub>max</sub> [nmol/L]	3.13 (43.2)	5.25 (24.5)	8.32 (42.4)	9.69 (29.8)
C <sub>max,ss</sub> [nmol/L]	4.53 (29.0)	6.58 (23.0)	11.1 (21.7)	13.6 (29.6)
t <sub>max</sub> * [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 <sub>max,ss</sub> * [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 <sub>½,ss</sub> [h]	121 (21.3)	113 (10.2)	131 (17.4)	130 (11.7)
Accumulation t <sub>½</sub> [h]	23.9 (44.0)	12.5 (18.2)	11.4 (37.4)	8.59 (81.2)
R <sub>A,Cmax</sub>	1.44 (25.6)	1.25 (10.6)	1.33 (30.0)	1.40 (47.7)
R <sub>A,AUC</sub>	2.03 (30.7)	1.37 (8.2)	1.33 (15.0)	1.18 (23.4)
fe <sub>0-24</sub> [%]	NC	0.139 (51.2)	0.453 (125)	0.919 (115)
fe <sub>T,ss</sub> [%]	3.34 (38.3)	3.06 (45.1)	6.27 (42.2)	3.22 (34.2)
CL <sub>R,ss</sub> [mL/min]	14.0 (24.2)	23.1 (39.3)	70 (35.0)	59.5 (22.5)

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\* 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 one or more active substances which may be 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.

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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.

5 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  
10 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  
15 glibenclamide, tolbutamide, glimepiride, glipizide, gliquidone, glibornuride and gliclazide; nateglinide; repaglinide; mitiglinide; thiazolidinediones such as rosiglitazone and pioglitazone; PPAR gamma modulators such as metaglitazones; PPAR-gamma agonists such as e.g. rivoglitazone, mitoglitazone, INT-131 and balaglitazone; PPAR-gamma antagonists; PPAR-gamma/alpha modulators such as tesaglitazar, muraglitazar, aleglitazar, indeglitazar  
20 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 GPR119 agonists (SMT3-receptor-agonists), such as the GPR119 agonists 5-ethyl-2-[4-[4-(4-tetrazol-1-yl-phenoxy)methyl]-thiazol-2-yl]-piperidin-1-yl]-pyrimidine or 5-[1-(3-isopropyl-  
25 [1,2,4]oxadiazol-5-yl)-piperidin-4-ylmethoxy]-2-(4-methanesulfonyl-phenyl)-pyridine; 11 $\beta$ -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 glulisin, r-DNA-insulinaspart, NPH insulin, insulin detemir, insulin degludec, insulin tregopil, insulin zinc suspension and insulin glargin; Gastric inhibitory  
30 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, ipragliflozin, luseogliflozin or  
35 tofogliflozin; inhibitors of protein tyrosine-phosphatase (e.g. trodusquemine); inhibitors of

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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 5 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, 10 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 15 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 20 (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.

25 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.

30

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).

35

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).

5

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).

10 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).

15

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.

20 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).

25

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).

30 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.

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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.

5 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-  
10 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  
15 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.

20 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,  
25 lercanipidine, manidipine, isradipine, nilvadipine, verapamil, gallopamil and diltiazem; ACE inhibitors such as ramipril, lisinopril, cilazapril, quinapril, captopril, enalapril, benazepril, perindopril, fosinopril andtrandolapril; as well as angiotensin II receptor blockers (ARBs) such as telmisartan, candesartan, valsartan, losartan, irbesartan, olmesartan, azilsartan and eprosartan.

30

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

35 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,



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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;

5 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  
10 (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.

15 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.

20 Further, the certain DPP-4 inhibitor of this invention may be used in combination with a  
substrate of DPP-4 (particularly with an anti-inflammatory substrate of DPP-4), which may be  
other than GLP-1, for the purposes according to the present invention, such substrates of  
DPP-4 include, for example – without being limited to, one or more of the following:

Incretins:

25 Glucagon-like peptide (GLP)-1  
Glucose-dependent insulinotropic peptide (GIP)

Neuroactive:

Substance P

Neuropeptide Y (NPY)

30 Peptide YY

Energy homeostasis:

GLP-2

Prolactin

Pituitary adenylate cyclase activating peptide (PACAP)

35 Other hormones:

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PACAP 27

Human chorionic gonadotrophin alpha chain

Growth hormone releasing factor (GHRF)

Luteinizing hormone alpha chain

5 Insulin-like growth factor (IGF-1)

CCL8/eotaxin

CCL22/macrophage-derived chemokine

CXCL9/interferon-gamma-induced monokine

Chemokines:

10 CXCL10/interferon-gamma-induced protein-10

CXCL11/interferon-inducible T cell a chemoattractant

CCL3L1/macrophage inflammatory protein 1alpha isoform

LD78beta

CXCL12/stromal-derived factor 1 alpha and beta

15 Other:

Enkephalins, gastrin-releasing peptide, vasostatin-1,  
peptide histidine methionine, thyrotropin alpha

20 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.

25

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**

β-Cell function in latent autoimmune diabetes in adults (LADA) treated with linagliptin versus glimepiride: exploratory results from a two year double-blind, randomized, controlled study:

5

Latent autoimmune diabetes in adults (LADA) is associated with a more rapid decline in β-cell function compared to common type 2 diabetes (T2D). Presently, no treatment modality is drug of choice in LADA.

10 It is compared the impact of treatment with the DPP4-inhibitor linagliptin (lina) 5mg/d and the sulphonylurea glimepiride (glim) 1-4mg/d on β-cell function in patients retrospectively identified with LADA who had insufficient glycaemic control despite metformin therapy in a two year study.

15 Patients were classified as LADA if one or more of the autoantibodies assessed (GAD65, ICA, IA-2A, IAA) were present at baseline or any on-treatment visit. GAD was assessed using RIA methodology (cut-off 0.05 [sensitivity 82%/specificity 98.89% in the Diabetes Autoantibody Standardization Program 2010]).

20 The study cohort comprised 1519 patients (16 countries), with assumed common T2D. The prevalence of LADA was 7.8% (n=118). GAD65 was the most prevalent autoantibody (6.5%) whereas ICA (0.3%), IA-2A (1.2%) and IAA (0.2%) were rare. Proportion of patients with ≥ 2 positive antibodies was 0.4%. Baseline characteristics in GAD65 + LADA patients treated with lina (n=65) or glim (n=53) were fairly well balanced (respective age 59/63 yrs, BMI 30.3/31.7 kg/m<sup>2</sup> and diabetes duration > 5 years 62%/59%).

25 C-peptide was available in a subset and as indicated, GAD65+ patients treated with lina preserved C-peptide significantly better than those treated with glim over a 2 yr trajectory (table). HbA1c reductions were of similar magnitude in the groups.

In conclusion, treatment with lina or glim in LADA could have differing impacts on long term β-cell function.

Table. Changes in fasting C-peptide over time by treatment and GAD65 autoimmune status

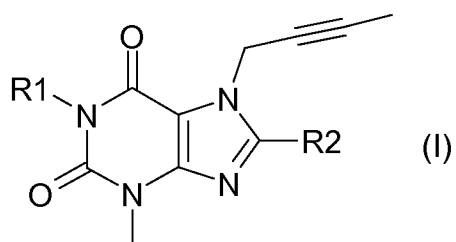
	28 weeks		52 weeks		104 weeks	
	Lina GAD+	Glim GAD+	Lina GAD+	Glim GAD+	Lina GAD+	Glim GAD+
n	21	17	14	14	9	9
Baseline C-peptide	821	1326	835	1425	944	1374

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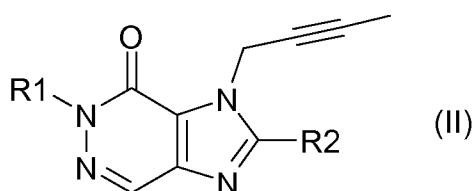
Follow-up C-peptide	917	1221	978	1246	1146	1345
$\Delta$ C- peptide	+96***##	-105	+143***##	-179	+202***	-29
Baseline HbA1c (%)	7.62	7.75	7.50	7.46	7.40	7.40
$\Delta$ HbA1c	-0.25	-0.75	-0.49	-0.52	-0.41	-0.49
***p<0.001 vs baseline; ##p<0.01 vs glim						

## Claims

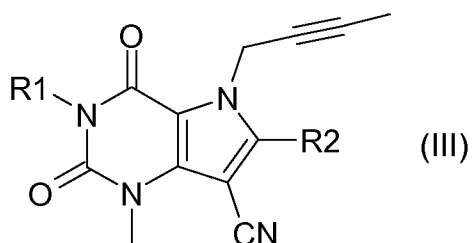
1. A DPP-4 inhibitor which is of formula (I)



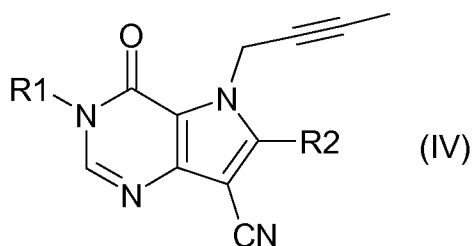
or formula (II)



10 or formula (III)



or formula (IV)



15

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-

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yl)methyl and **R2** denotes 3-(*R*)-amino-piperidin-1-yl, (2-amino-2-methyl-propyl)-methylamino or (2-(*S*)-amino-propyl)-methylamino,

or a pharmaceutically acceptable salt thereof;

optionally in combination with one or more other active agents,

5 for use in treating and/or preventing autoimmune diabetes, particularly LADA (latent autoimmune diabetes of adults), particularly in those (LADA) human patients in whom one or more autoantibodies selected from GAD (GAD-65, anti-GAD), ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA are present, especially in those (LADA) human patients in whom antibodies towards GAD (GAD-65) are present, and/or diseases related or associated therewith (e.g. diabetic  
10 complications).

2. The DPP-4 inhibitor according to claim 1, preferably linagliptin, optionally in combination with one or more other active agents, such as e.g. selected from other antidiabetics,

including e.g. metformin, thiazolidinediones (pioglitazone) and/or insulin or insulin analogues,  
15 for use in modifying disease trajectory of autoimmune diabetes, particularly LADA (latent autoimmune diabetes of adults), particularly in those (LADA) human patients in whom one or more autoantibodies selected from GAD (GAD-65, anti-GAD), ICA, IA-2A, anti-ZnT8 and IAA are present, especially in those (LADA) human patients who have antibodies towards GAD (GAD-65).

20

3. The DPP-4 inhibitor according to claim 1 or 2, preferably linagliptin, optionally in combination with one or more other active agents, such as e.g. selected from other antidiabetics, including e.g. metformin, thiazolidinediones (pioglitazone) and/or insulin or insulin analogues, for use in preserving C-peptide, pancreatic beta cells and/or pancreatic

25 beta cell function in patients with or at risk of autoimmune diabetes, particularly LADA, such as e.g. LADA human patients in whom one or more autoantibodies selected from GAD (GAD-65, anti-GAD), ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA are present, especially LADA human patients with antibodies towards GAD (GAD-65).

30 4. The DPP-4 inhibitor according to claim 1, 2 or 3, preferably linagliptin, optionally in combination with one or more other active agents, such as e.g. selected from other antidiabetics, including e.g. metformin, thiazolidinediones (pioglitazone) and/or insulin or insulin analogues, for use in treating and/or preventing a metabolic disease, in a patient with or at risk of autoimmune diabetes, particularly LADA, such as e.g. in a LADA human patient  
35 in whom one or more autoantibodies selected from GAD (GAD-65, anti-GAD), ICA, IA-2A,

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ZnT8 (anti-ZnT8) and IAA are present, especially in a LADA human patient with antibodies towards GAD (GAD-65).

5 5. The DPP-4 inhibitor according to claim 1, preferably linagliptin, optionally in combination  
with one or more other active agents, such as e.g. selected from other antidiabetics, for use  
in delaying the onset of rescue therapy (e.g. insulin therapy) in a patient with or at risk of  
autoimmune diabetes, particularly LADA, such as e.g. in a LADA human patient in whom one  
or more autoantibodies selected from GAD (GAD-65, anti-GAD), ICA, IA-2A, ZnT8 (anti-  
ZnT8) and IAA are present, especially in a LADA human patient with antibodies towards  
10 GAD (GAD-65).

6. The DPP-4 inhibitor according to claim 1, preferably linagliptin, optionally in combination  
with one or more other active agents, for use in at least one of the following methods:

- 15 - preventing, slowing the progression of, delaying the onset of 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, postabsorptive hyperglycemia, latent autoimmune diabetes in  
adults (LADA), overweight, obesity, dyslipidemia, hyperlipidemia, hypercholesterolemia,  
hypertriglyceridemia, hyperNEFA-emia, postprandial lipemia (e.g. postprandial  
20 hypertriglyceridemia), hypertension, atherosclerosis, endothelial dysfunction,  
osteoporosis, chronic systemic inflammation, non alcoholic fatty liver disease (NAFLD),  
retinopathy, neuropathy, nephropathy, nephrotic syndrome, polycystic ovarian syndrome,  
and/or metabolic syndrome;
- 25 - improving and/or maintaining glycemic control and/or for reducing of fasting plasma  
glucose, of postprandial plasma glucose, of postabsorptive plasma glucose and/or of  
glycosylated hemoglobin HbA1c, or preventing, reducing the risk of, slowing the  
progression of, delaying the onset of or treating worsening or deterioration of glycemic  
control, need for insulin therapy or elevated HbA1c despite treatment;
- 30 - preventing, slowing, delaying the onset of or reversing progression from pre-diabetes,  
impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance  
and/or from metabolic syndrome to diabetes;
- 35 - preventing, reducing the risk of, slowing the progression of, delaying the onset of or  
treating of complications of diabetes such as micro- and macrovascular diseases, such as  
nephropathy, micro- or macroalbuminuria, proteinuria, nephrotic syndrome, retinopathy,  
cataracts, neuropathy, learning or memory impairment, neurodegenerative or cognitive

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disorders, cardio- or cerebrovascular diseases, tissue ischaemia, diabetic foot or ulcer, 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

5

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;

10

- preventing, slowing, delaying the onset of or treating the degeneration of pancreatic beta cells and/or the decline of the functionality of pancreatic beta cells and/or for improving, preserving and/or restoring the functionality of pancreatic beta cells and/or stimulating and/or restoring or protecting the functionality of pancreatic insulin, proinsulin, and/or C-peptide secretion;

15

- preventing, slowing, delaying the onset of 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 the onset of, attenuating, treating or reversing hepatic steatosis, (hepatic) inflammation and/or an abnormal accumulation of liver fat);

20

- preventing, slowing the progression of, delaying the onset of or treating 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 (e.g. hypoglycemia or weight gain);

25

- delaying initiation of rescue or insulin therapy; 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, particularly in a patient having autoimmune diabetes, particularly LADA, such as e.g. in a (LADA) human patient in whom one or more autoantibodies selected from GAD (GAD-65, anti-GAD), ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA are present, especially in a LADA human patient in whom antibodies to GAD (GAD-65) are present.

30

7) The DPP-4 inhibitor (preferably linagliptin, optionally in combination with one or more other active agents) for use according to any one of claims 1 to 6, wherein the patient is a

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autoimmune diabetes patient with or at risk of a cardiovascular and/or renal disease, such as e.g. selected from myocardial infarction, stroke, peripheral arterial occlusive disease, diabetic nephropathy, micro- or macroalbuminuria, acute or chronic renal impairment, hyperuricemia and/or hypertension.

5

8) The DPP-4 inhibitor (preferably linagliptin, optionally in combination with one or more other active agents) for use according to at least one of claims 1 to 7, wherein the autoimmune diabetes patient has nephropathy, impaired renal function, chronic kidney disease, and/or micro- or macroalbuminuria.

10

9) The DPP-4 inhibitor (preferably linagliptin, optionally in combination with one or more other active agents) for use according to at least one of claims 1 to 8, wherein the autoimmune diabetes patient has mild, moderate or severe renal impairment, or end stage renal disease.

15

10) The DPP-4 inhibitor (preferably linagliptin, optionally in combination with one or more other active agents) for use according to at least one of claims 1 to 9, wherein the autoimmune diabetes patient has microalbuminuria or diabetic nephropathy.

20

11) The DPP-4 inhibitor (preferably linagliptin, optionally in combination with one or more other active agents) for use according to claim 1, wherein the diabetic complications are selected from micro- and macrovascular diseases such as e.g. diabetic nephropathy, retinopathy or neuropathy, or cerebro- or cardiovascular events such as e.g. myocardial infarction, stroke, or vascular mortality or morbidity (e.g. CV death, non-fatal MI, non-fatal stroke, or hospitalisation for unstable angina pectoris).

25

12) The DPP-4 inhibitor (preferably linagliptin) for use according to any one of the preceding claims, wherein the one or more other active agents include one or more other antidiabetics selected from metformin, sulphonylureas, nateglinide, repaglinide, thiazolidinediones (pioglitazone), PPAR-gamma agonists, alpha-glucosidase inhibitors, insulin or insulin analogues, and GLP-1 or GLP-1 analogues.

30

13) The DPP-4 inhibitor according to claim 1, preferably linagliptin, optionally in combination with one or more other active agents, for use in treating and/or preventing nephropathy, impaired renal function, chronic kidney disease, and/or micro- or macroalbuminuria, particularly in a patient having autoimmune diabetes, particularly LADA, such as e.g. in a

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(LADA) human patient in whom one or more autoantibodies selected from GAD (GAD-65, anti-GAD), ICA, IA-2A, ZnT8 (anti-ZnT8) and IAA are present, especially in a LADA human patient in whom antibodies to GAD (GAD-65) are present.

5 14) The DPP-4 inhibitor for use according to any one of the preceding claims, wherein the DPP-4 inhibitor is 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine.

10 15) The DPP-4 inhibitor for use according to claim 14, wherein 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine (linagliptin) is administered orally in a total daily amount of 5 mg to the patient.

INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2013/060311

A. CLASSIFICATION OF SUBJECT MATTER  
INV. A61K31/522 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

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 practicable, search terms used)  
EPO-Internal, CHEM ABS Data, 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	US 2012/121530 A1 (KLEIN THOMAS [DE] ET AL) 17 May 2012 (2012-05-17) paragraphs [0032] - [0043] paragraph [0051] paragraphs [0333] - [0335] claims 1,2,4,26	1-15
X	WO 2009/147125 A1 (BOEHRINGER INGELHEIM INT [DE]; KLEIN THOMAS [DE]; MARK MICHAEL [DE]; N) 10 December 2009 (2009-12-10) page 8, line 25 - page 11, line 12	1-15
X	WO 2011/064352 A1 (BOEHRINGER INGELHEIM INT [DE]; DUGI KLAUS [DE]; GRAEFE-MODY EVA ULRIKE) 3 June 2011 (2011-06-03) example 11 claims 14-22	1-15
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Further documents are listed in the continuation of Box C.

See patent family annex.

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

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Date of the actual completion of the international search  31 July 2013	Date of mailing of the international search report  09/08/2013
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer  Renard, Delphine
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## INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2013/060311

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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E	<p>WO 2013/098372 A1 (BOEHRINGER INGELHEIM INT [DE]) 4 July 2013 (2013-07-04) page 46, line 19 - page 47, line 19 page 48, line 16 - page 49, line 23 claim 8</p> <p style="text-align: center;">-----</p>	1-15
X,P	<p>ODD ERIK JOHANSEN et al.: "Cell Function in Latent Autoimmune Diabetes in Adults (LADA) Treated with Linagliptin Versus Glimpiride: Exploratory Results from a Two Year Double-Blind, Randomized, Controlled Study",</p> <p>8 June 2012 (2012-06-08), XP002708003, Retrieved from the Internet: URL:<a href="http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=b266eaf6-c060-450a-9a54-ae244aae03af&amp;cKey=4cdfccc3-7a39-416c-acd9-49e063e85d6f&amp;mKey={0F70410F-8DF3-49F5-A63D-3165359F5371}">http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=b266eaf6-c060-450a-9a54-ae244aae03af&amp;cKey=4cdfccc3-7a39-416c-acd9-49e063e85d6f&amp;mKey={0F70410F-8DF3-49F5-A63D-3165359F5371}</a> [retrieved on 2013-07-29] the whole document</p> <p style="text-align: center;">-----</p>	1-15

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Information on patent family members

International application No

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