Title: USE OF ORGANIC COMPOUNDS

Abstract: A method to prevent, delay the progression or reduce, the Gastrointestinal disorders or Gastrointestinal side effects induced by metformin, comprising administering a therapeutically effective amount of metformin or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of a DPP-IV inhibitor, preferably vildagliptin, or a pharmaceutically acceptable salt thereof, to a patient in need thereof.
Use of Organic compounds

The invention relates to a method of treatment, wherein a Dipeptidyl peptidase IV inhibitor (DPP-IV inhibitor) or a pharmaceutically acceptable salt thereof is administered to a patient treated with metformin or a pharmaceutically acceptable salt thereof, to prevent, delay the progression or reduce, the Gastrointestinal disorders or Gastronintestinal side effects induced by metformin.

The treated patients are preferably suffering from hyperglycemia such as diabetes mellitus preferably non-insulin-dependent diabetes mellitus or Impaired Glucose Metabolism (IGM) preferably Impaired Glucose Tolerance (IGT).

Diabetes mellitus is a relatively common disorder (estimated at about 1% prevalence in the general population) which is characterized by hyperglycemia. There are three basic types of diabetes mellitus, type I or insulin-dependent diabetes mellitus (IDDM), type II or non-insulin-dependent diabetes mellitus (NIDDM), and type A insulin resistance. Patients with either type I or type II diabetes can become insensitive to the effects of exogenous insulin ("insulin resistant") through a variety of mechanisms. Type A insulin resistance results from either mutations in the insulin receptor gene or defects in post-receptor sites of action critical for glucose metabolism. Diabetes is generally controlled through administration of exogenous insulin (especially in type I diabetics), dietary control and exercise (especially in type II diabetics) or both.

Impaired Glucose Metabolism (IGM) is defined by blood glucose levels that are above the normal range but are not high enough to meet the diagnostic criteria for type 2 diabetes mellitus. The incidence of IGM varies from country to country, but usually occurs 2-3 times more frequently than overt diabetes. Until recently, individuals with IGM were felt to be pre-diabetics, but data from several epidemiologic studies argue that subjects with IGM are heterogeneous with respect to their risk of diabetes and their risk of cardiovascular morbidity and mortality. The data suggest that subjects with IGM, in particular IGT, do not always develop diabetes, but whether they are diabetic or not, they are, nonetheless, at high risk for cardiovascular morbidity and mortality. Among subjects with IGM, about 58% have Impaired Glucose Tolerance (IGT), another 29% have Impaired Fasting Glucose (IFG), and 13% have both abnormalities (IFG/IGT). IGT is characterized by elevated postprandial (post-meal) hyperglycemia while IFG has been defined by the ADA (see Table below) on the basis of fasting glycemic values.
The categories of Normal Glucose Tolerance (NGT), IGM and type 2 diabetes mellitus were defined by the ADA (American Diabetes Association) in 1997.

The fact that IGT is an independent risk factor in non-diabetics as well as diabetics justifies it as a new indication, separate from diabetes, for prevention and treatment of cardiovascular morbidity and mortality as well as cancer. Furthermore the stage between normoglycemia and type 2 diabetes mellitus, especially the glycemic stage, is becoming of major interest and there is a strong need for a method to inhibit or delay the progression to type 2 diabetes mellitus, and also the variety of cardiovascular and microvascular conditions and diseases as well as cancer that have been associated with IGM and especially IFG and/or IGT.

Type 2 diabetes is a progressive disease, and although monotherapy may initially control blood glucose in some patients, it is associated with a high secondary failure rate. This high incidence of therapeutic failure is a major contributor to the high rate of long-term hyperglycemia-associated complications in patients with type 2 diabetes.

Metformin is an effective and commonly administered drug for controlling plasma glucose concentrations in patients with type 2 diabetes mellitus. Metformin is the most commonly used oral antidiabetic compound and is the current gold standard. 51% of new type 2 diabetic patients in the US received Metformin. However, metformin has significant safety/tolerability issues that limit its use or safe use.

Indeed, it is well known that metformin’s main safety issue is to induce gastrointestinal side effects and gastrointestinal disorders. Gastrointestinal adverse effects such as abdominal pain, abdominal cramping, nausea, dyspepsia, anorexia, and diarrhea are common and widely accepted to be associated to metformin therapy. Or explosive watery diarrhea that occasionally caused incontinence after several years of stable metformin therapy.

Metformin-induced diarrhea is differentiated from diabetic diarrhea, which is clinically similar, except diabetic diarrhea is rare in patients with type 2 diabetes. Patients with type 2 diabetes who are taking metformin and experience diarrhea deserve a drug-free interval before undergoing expensive and uncomfortable diagnostic tests, even when the dosage has been stable over a long period.

The applicant has surprisingly discovered that DPP-IV inhibitors especially LAF237, or a pharmaceutically acceptable salt thereof, can be used in combination with Metformin or a pharmaceutically acceptable salt thereof, to reduce gastrointestinal side effects and gastrointestinal disorders induced by metformin. Thus the long term treatment with such a
combination has significantly less inconvenient gastrointestinal side effects than other combinations.

Metformin, i.e. N,N-dimethylimidocarbonimide diamide, is a known compound approved by the U.S. Food & Drug Administration for the therapeutic treatment of diabetes. The compound and its preparation are disclosed, for example, in U.S. Pat. No. 3,174,901, issued May 23, 1965. It is known that metformin is effective in the treatment of type 2 diabetes, otherwise known as non-insulin-dependent diabetes mellitus (NIDDM).

In the present context the term "metformin" is also intended to comprise any salt or crystal form, especially the metformin hydrochloride salt.

The term "DPP-IV inhibitor" is intended to indicate a molecule that exhibits inhibition of the enzymatic activity of DPP-IV and functionally related enzymes, such as from 1-100% inhibition, and specially preserves the action of substrate molecules, including but not limited to glucagon-like peptide-1, gastric inhibitory polypeptide, peptide histidine methionine, substance P, neuropeptide Y, and other molecules typically containing alanine or proline residues in the second aminoterminal position. Treatment with DPP-IV inhibitors prolongs the duration of action of peptide substrates and increases levels of their intact, undegraded forms leading to a spectrum of biological activities relevant to the disclosed invention.

DPP-IV can be used in the control of glucose metabolism because its substrates include the insulinotropic hormones Glucagon like peptide-1 (GLP-1) and Gastric inhibitory peptide (GIP). GLP-1 and GIP are active only in their intact forms; removal of their two N-terminal amino acids inactivates them. In vivo administration of synthetic inhibitors of DPP-IV prevents N-terminal degradation of GLP-1 and GIP, resulting in higher plasma concentrations of these hormones, increased insulin secretion and, therefore, improved glucose tolerance. For that purpose, chemical compounds are tested for their ability to inhibit the enzyme activity of purified CD26/DPP-IV. Briefly, the activity of CD26/DPP-IV is measured in vitro by its ability to cleave the synthetic substrate Gly-Pro-p-nitroanilide (Gly-Pro-pNA). Cleavage of Gly-Pro-pNA by DPP-IV liberates the product p-nitroanilide (pNA), whose rate of appearance is directly proportional to the enzyme activity. Inhibition of the enzyme activity by specific enzyme inhibitors slows down the generation of pNA. Stronger interaction between an inhibitor and the enzyme results in a slower rate of generation of pNA. Thus, the degree of inhibition of the rate of accumulation of pNA is a direct measure of the strength of enzyme inhibition. The accumulation of pNA is measured with a spectrophotometer. The inhibition constant, Ki, for each compound is determined by
incubating fixed amounts of enzyme with several different concentrations of inhibitor and substrate.

In the present context "a DPP-IV inhibitor" is also intended to comprise active metabolites and prodrugs thereof, such as active metabolites and prodrugs of DPP-IV inhibitors. A "metabolite" is an active derivative of a DPP-IV inhibitor produced when the DPP-IV inhibitor is metabolised. A "prodrug" is a compound that is either metabolised to a DPP-IV inhibitor or is metabolised to the same metabolite(s) as a DPP-IV inhibitor. In the present context the term "a DPP-IV inhibitor" is also intended to comprise pharmaceutical salts thereof.

DPP-IV inhibitors are known in the art. In the following reference is made to representatives of DPP-IV inhibitors:

Preferred DPP-IV inhibitors are described in the following patent applications; WO 02053548 especially compounds 1001 to 1293 and examples 1 to 124, WO 02067918 especially compounds 1000 to 1278 and 2001 to 2159, WO 02066627 especially the described examples, WO 02/068420 especially all the compounds specifically listed in the examples I to LXIII and the described corresponding analogues, even preferred compounds are 2(28), 2(88), 2(119), 2(136) described in the table reporting IC50, WO 02083128 such as in the claims 1 to 5 especially compounds described in examples 1 to 13 and the claims 6 to 10, US 2003096846 especially the specifically described compounds, WO 2004/037181 especially examples 1 to 33, WO 0168603 especially compounds of examples 1 to 109, EP 1258480 especially compounds of examples 1 to 60, WO 0181337 especially examples 1 to 118, WO 20083109 especially examples 1A to 1D, WO 03003250 especially compounds of examples 1 to 166, most preferably 1 to 8, WO 03035067 especially the compounds described in the examples, WO 03/035057 especially the compounds described in the examples, US 2003216450 especially examples 1 to 450, WO 99/46272 especially compounds of claims 12, 14, 15 and 17, WO 0197808 especially compounds of claim 2, WO 03002553 especially compounds of examples 1 to 33, WO 01/34594 especially the compounds described in the examples 1 to 4, WO 20051836 especially examples 1 to 712, EP 1245568 especially examples 1 to 7, EP 1258476 especially examples 1 to 32, US 2003087950 especially the described examples, WO 02/076450 especially examples 1 to 128, WO 03000180 especially examples 1 to 162, WO 03000181 especially examples 1 to 66, WO 0304498 especially examples 1 to 33, WO 0302942 especially examples 1 to 68, US 6482844 especially the described examples, WO 0155105 especially the compounds listed in the examples 1 and 2, WO 0202560 especially examples 1 to 166, WO 03004496
especially examples 1 to 103, WO 03/024965 especially examples 1 to 54, WO 0303727 especially examples 1 to 209, WO 0368757 especially examples 1 to 88, WO 03074500 especially examples 1 to 72, examples 4.1 to 4.23, examples 5.1 to 5.10, examples 6.1 to 6.30, examples 7.1 to 7.23, examples 8.1 to 8.10, examples 9.1 to 9.30, WO 02038541 especially examples 1 to 53, WO 02062764 especially examples 1 to 293, preferably the compound of example 95 (2-[[3-(Aminomethyl)-4-butoxy-2-neopentyl-1-oxo-1,2 dihydro-6-isoquinolinyloxy]acetamide hydrochloride), WO 02308090 especially examples 1-1 to 1-109, examples 2-1 to 2-9, example 3, examples 4-1 to 4-19, examples 5-1 to 5-39, examples 6-1 to 6-4, examples 7-1 to 7-10, examples 8-1 to 8-8, examples 7-1 to 7-7 of page 90, examples 8-1 to 8-59 of pages 91 to 95, examples 9-1 to 9-33, examples 10-1 to 10-20, US 2003225102 especially compounds 1 to 115, compounds of examples 1 to 121, preferably compounds a) to z), aa) to az), ba) to bz), ca) to cz) and da) to dk), WO 0214271 especially examples 1 to 320, US 2003096857, U.S. application Serial No. 09/788,173 filed February 16, 2001 (attorney file LA50) especially the described examples, WO99/38501 especially the described examples, W099/46272 especially the described examples and DE19616 486 A1 especially val-pyr, val-thiazolidide, isoleucyl-thiazolidide, isoleucyl-pyrrolidide, and fumar salts of isoleucyl-thiazolidide and isoleucyl-pyrrolidide.


In a further preferred embodiment, the DPP-IV inhibitor is a N-peptidyl-O-aroyl hydroxylamine or a pharmaceutically acceptable salt thereof. The peptidyl moiety comprises preferably two α-amino acids, e.g. glycine, alanine, leucine, phenylalanine, lysine or proline, of which the one attached directly to the hydroxylamine nitrogen atom is preferably proline.

In each case in particular in the compound claims and the final products of the working examples, the subject matter of the final products, the pharmaceutical preparations and the claims are hereby incorporated into the present application by reference to these publications.

Preferred compounds described in WO03/002553 are listed on pages 9 to 11 and are incorporated into the present application by reference.


WO 0034241 and US 6110949 disclose N-substituted adamantyl-amino-acetyl-2-cyano pyrrolidines and W (substituted glycyl)-4-cyano pyrrolidines respectively.

WO9515309 discloses amino acid 2-cyanopyrrolidine amides as inhibitors of DPP-IV and WO 9529691 discloses peptidyl derivates of diesters of alpha-aminoalkylphosphonic acids, particularly those with proline or related structures. DPP-IV inhibitors of interest are specially those cited in Table 1 to 8.

In WO 01/72290 DPP-IV inhibitors of interest are specially those cited in example 1 and claims 1, 4, and 6.


WO 9310127 discloses proline boronic esters useful as DPP-IV inhibitors. DPP-IV inhibitors of interest are specially those cited in examples 1 to 19.

Published patent application WO 9925719 discloses sulphostin, a DPP-IV inhibitor prepared by culturing a Streptomyces microorganism.

WO 9938501 discloses N-substituted 4- to 8-membered heterocyclic rings. DPP-IV inhibitors of interest are specially those cited in claims 15 to 20.

WO 9946272 discloses phosphoric compounds as inhibitors of DPP-IV. DPP-IV inhibitors of interest are specially those cited in claims 1 to 23.

Other preferred DPP-IV inhibitors are the compounds of formula I, II or III disclosed in the patent application WO 03/057200 on page 14 to 27. Most preferred DPP-IV inhibitors are the compounds specifically described on pages 28 and 29.

Published patent applications WO 9967278 and WO 9967279 disclose DPP-IV prodrugs and inhibitors of the form A-B-C where C is either a stable or unstable inhibitor of DPP-IV. Preferably, the N-peptidyl-O-aroyl hydroxylamine is a compound of formula VII
wherein

\( j \) is 0, 1 or 2;

\( R_{\varepsilon 1} \) represents the side chain of a natural amino acid; and

\( R_{\varepsilon 2} \) represents lower alkoxy, lower alkyl, halogen or nitro;
or a pharmaceutically acceptable salt thereof.

In a very preferred embodiment of the invention, the N-peptidyl-O-aroyl hydroxylamine is a compound of formula Vila

\[
\begin{align*}
\text{NH}_2 \quad & \quad \text{O} \\
\text{H} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\text{C} & \quad \text{O}
\end{align*}
\]

or a pharmaceutically acceptable salt thereof.

N-Peptidyl-O-aroyl hydroxylamines, e.g. of formula VII or Vila, and their preparation are described by H.U. Demuth et al. in J. Enzyme Inhibition 1988, Vol. 2, pages 129-142, especially on pages 130-132.

Preferred DPP-IV inhibitors are those described by Mona Patel and col. (Expert Opinion Investig Drugs. 2003 Apr;12(4):623-33) on the paragraph 5, especially P32/98, K-364, FE-99901, BDPX, NVP-DDP-728 and others, which publication is hereby incorporated by reference especially the described DPP-IV inhibitors.

Another preferred DPP-IV inhibitor is the No.815541 (T 6666) from Tanabe.

Preferred DPP-IV inhibitors are also described in the patent applications WO 02/083128, especially the compounds described in the examples 1 to 13, US 6,395,767 examples 1 to 109 and WO 03/033671 all the specifically described compounds e.g. compounds 1 to 393, compounds of pages 67-70.

FE-99901 1 is described in WO 95/15309 page 14, as compound No. 18.

Another preferred inhibitor is the compound BMS-4771 18 disclosed in WO 2001068603 or U.S. Patent No. 6,395,767 (compound of example 60) also known as is (1S,3S,5S)-2-{(2S)-2-amino-2-(3-hydroxvtricyclo[3.3.1].1.1^{3,7})dec-1-yl}-1-oxoethyl]-2-azabicyclo[3.1.0]hexane-3-
carbonitrile, benzoate (1:1) as depicted in Formula M of the patent application WO 2004/052850 on page 2, and the corresponding free base, \((S,3S,5S)-2-(2S)-2\text{-amino}-2-(3\text{-hydroxy-tricyclo[3.3.1.1^{3,7}]}\text{dec-1-yl})-1\text{-oxoethyl}2\text{-azabicyclo[3.1.0]}\text{hexane-3-carbonitrile \(M'\)}\) and its monohydrate \((M'')\) as depicted in Formula M of the patent application WO 2004/052850 on page 3. The compound BMS-477118 is also known as saxagliptin.

Another preferred inhibitor is the compound GSK23A disclosed in WO 03/002531 (example 9) also known as \((2S,4S)-1\text{-((2R)-2-Amino-3-[(4-methoxybenzyl)sulfonyl]-3-methylbutanoyl)-4-fluoropyrrolidine-2-carbonitrile hydrochloride. P32/98 (CAS number: 251572-86-8) also known as 3-\([2S,3S]-2\text{-amino}-3\text{-methyl-1-oxopentyl}\)]\text{thiazolidine} can be used as 3-\([2S,3S]-2\text{-amino}-3\text{-methyl-1-oxopentyl}\)]\text{thiazolidine and (2E)-2-butenedioate (2:1) mixture and is described in WO 99/61431 and the below formula,}

\[
\text{is described in WO 99/61431 and also in Diabetes 1998, 47, 1253-1258, in the name of Probiodrug, as well as the compound P93/01 described by the same company.}

Other very preferred DPP-IV inhibitors are the compounds disclosed in the patent application WO 02/083128 such as in the claims 1 to 5. Most preferred DPP-IV inhibitors are the compounds specifically described by the examples 1 to 13 and the claims 6 to 10.

Other very preferred DPP-IV inhibitors are the compounds disclosed by Bristol-Myers Squibb such as Saxagliptin (BMS477118).

Other very preferred DPP-IV inhibitors of the invention are described in the International patent application WO 02/076450 (especially the examples 1 to 128) and by Wallace T. Ashton (Bioorganic & Medicinal Chemistry Letters 14 (2004) 859-863) especially the compound 1 and the compounds listed in the tables 1 and 2. The preferred compound is the compound 21e (table 1) of formula :
Other preferred DPP-IV inhibitors are described in the patent applications WO 2004/037169 especially those described in the examples 1 to 48 and WO 02/062764 especially the described examples 1 to 293, even preferred are the compounds 3-<aminomethyl)-2-isobuthyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide and 2-{[3-(aminomethyl)-2-isobuthyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]oxy}acetamide described on page 7 and also in the patent application WO2004/024184 especially in the reference examples 1 to 4.

Other preferred DPP-IV inhibitors are described in the patent application WO 03/004498 especially examples 1 to 33 and most preferably the compound of the formula

\[ \text{MK-0431} \]

described by the example 7 and also known as MK-0431.

In each case in particular in the compound claims and the final products of the working examples, the subject matter of the final products, the pharmaceutical preparations and the claims are hereby incorporated into the present application by reference to these publications.

Preferred DPP-IV inhibitors are also described in the patent application WO 2004/037181 especially examples 1 to 33 and most preferably the compounds described in the claims 3 to 5.

Most preferred DPP-IV inhibitors are selected from [S]-1-[2-(5-cyano-2-pyridinylamino)ethylamino]acetyl-2-pyrolidine carbonitrile monohydrochloride, <S>-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-pyrrolidine and L-threo-isoleucyl thiazolidine (compound code according to Probiodrug: P32/98 as described above), MK-0431, 3-(aminomethyl)-2-isobuthyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide and 2-[[3-(aminomethyl)-2-isobuthyl-4-phenyl-1-oxo-1,2-dihydro-6-isoquinolyl]oxy]acetamide and optionally pharmaceutical salts thereof.

[S]-1-[2-(5-cyano-2-pyridinylamino)ethylamino]acetyl-2-pyrolidine carbonitrile monohydrochloride and (S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-pyrrolidine are specifically disclosed in Example 3 of WO 98/19998 and Example 1 of WO 00/34241, respectively. The DPP-IV inhibitor P32/98 (see above) is specifically described in Diabetes 1998, 47, 1253-1258. [S]-1-[2-(5-cyano-2-pyridinylamino)ethylamino]acetyl-2-pyrolidine carbonitrile monohydrochloride and (S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-pyrrolidine can be formulated as described on page 20 of WO 98/19998 or in WO 00/34241.

Especially preferred are 1-[(5-cyanopyridin-2-yl) amino] ethylamino] acetyl-2-<S>-cyano-pyrrolidine (also named [S]-1-[2-(5-cyano-2-pyridinylamino)ethylamino]acetyl-2-pyrolidine carbonitrile monohydrochloride), of formula:

![Chemical Structure](image)

especially the dihydrochloride and monohydrochloride form thereof.

pyrrolidine, 1-[(3-hydroxy-1-adamantyl) amino] acetyl-2-cyano-, <S> (also named <S>-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-pyrrolidine, LAF237 or vildagliptin) of formula

![Chemical Structure](image)

and L-threo-isoleucyl thiazolidine (compound code according to Probiodrug: P32/98 as described above), MK-0431 , GSK23A, saxagliptin, 3-(aminomethyl)-2-isobuthyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinecarboxamide and 2-[[3-(aminomethyl)-2-isobuthyl-4-phenyl-
1-oxo-1,2-dihydro-6-isoquinolyl[oxy]acetamide and optionally in any case pharmaceutical salts thereof.

DPP728 and LAF237 are specifically disclosed in Example 3 of WO 98/19998 and Example 1 of WO 00/34241, respectively. The DPP-IV inhibitor P32/98 (see above) is specifically described in Diabetes 1998, 47, 1253-1258. DPP728 and LAF237 can be formulated as described on page 20 of WO 98/19998 or in WO 00/34241, or in the International Patent Application No. EP2005/000400 (application number).

Any of the substances disclosed in the above mentioned patent documents or scientific publications, hereby included by reference, are considered potentially useful as DPP-IV inhibitors to be used in carrying out the present invention.

DPP-IV inhibitor to be used alone according to the present invention can be used in association with a carrier.

A carrier in the instant context is a tool (natural, synthetic, peptidic, non-peptidic) for example a protein which transports specific substances through the cell membrane in which it is embedded and into the cell. Different carriers (natural, synthetic, peptidic, non-peptidic) are required to transport different substances, as each one is designed to recognize only one substance, or group of similar substances.

Any means of detection known by the person skilled in the art can be used to detect the association of the DPP-IV with a carrier, for example, by labelling the carrier.

The DPP-IV inhibitor can be a peptidic or, preferably, non-peptidic one.

Most preferred are orally active DPP-IV inhibitors and pharmaceutical salts thereof.

The active ingredients (metformin or DPP-IV inhibitors) or pharmaceutically acceptable salts thereof according to the present invention may also be used in form of a solvate, such as a hydrate or including other solvents, used for crystallization.

It has now been surprisingly found that DPP-IV inhibitors especially vildagliptin or pharmaceutically acceptable salt thereof, can be used in combination with Metformin to prevent, delay the progression or reduce, the Gastrointestinal disorders or Gastrointestinal side effects induced by metformin.

Thus in a first embodiment, this invention provides a method to prevent, delay the progression or reduce, the Gastrointestinal disorders or Gastrointestinal side effects induced by metformin, comprising administering a therapeutically effective amount of metformin or a
pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of a DPP-IV inhibitor, preferably vildagliptin or a DPP-IV inhibitor as hereinabove described, or in any case a pharmaceutically acceptable salt thereof, to a patient in need thereof.

The invention furthermore relates to the use of metformin or pharmaceutically acceptable salt thereof in combination with a DPP-IV inhibitor, preferably vildagliptin or a DPP-IV inhibitor as hereinabove described, or pharmaceutically acceptable salt thereof, for the manufacture of a medicament to prevent, delay the progression or reduce, the Gastrointestinal disorders or Gastrointestinal side effects induced by metformin.

Preferably the treated patient in the herein claimed methods or uses, is selected from a metformin treated patient suffering from metformin-induced gastrointestinal side effects.

Preferably the treated patient in the herein claimed methods or uses, is selected from a metformin treated patient suffering from metformin-induced diarrhea.

Preferably the DPP-IV inhibitor is (S)-1-[(3-hydroxy-1-adamantyl) amino] acetyl-2-cyano-pyrrolidine (LAF237 or vildagliptin).

In the present context the terms "(S)-1-[(3-hydroxy-1-adamantyl) amino] acetyl-2-cyano-pyrrolidine" or "LAF237" or "vildagliptin" is also intended to comprise any salt or crystal form thereof.

Preferably the treated patient is suffering from hyperglycemia. Most preferably the patient is suffering from a disease selected from diabetes mellitus, type I or insulin-dependent diabetes mellitus (IDDM), type II or non-insulin-dependent diabetes mellitus (NIDDM), type A insulin resistance, IGM, IFG or IGT. In a preferred embodiment the patient is suffering from type II diabetes or IGT.

In a most preferred embodiment the DPP-IV inhibitor is added to the standard diabetes treatment in patients whose disease was not adequately controlled by metformin alone.

The present methods or uses are particularly useful for the prevention or delay of progression of conditions associated with type II diabetes or IGT, particularly cardiovascular and microvascular conditions.

The term "reduce the Gastrointestinal disorders or Gastrointestinal side effects" means to reduce the frequency or severity of Gastrointestinal disorders or Gastrointestinal side effects.
The term "Gastrointestinal disorders or Gastrointestinal side effects" include but are not limited to abdominal pain, abdominal cramping, nausea, dyspepsia, anorexia, diarrhea, or explosive watery diarrhea. A preferred side effect according to the present invention is the Metformin-induced diarrhea.

Furthermore as used herein, "a daily dose" means the dose given within a 24-hour period.

The term "prevention" means prophylactic administration of the combination to healthy patients to prevent the outbreak of the conditions mentioned herein. Moreover, the term "prevention" means prophylactic administration of such combination to patients being in a pre-stage of the conditions, to be treated.

The term "delay of progression" used herein means administration of the combination, such as a combined preparation or pharmaceutical composition, to patients being in a pre-stage of the condition to be treated in which patients a pre-form of the corresponding condition is diagnosed.

By the term "treatment" is understood the management and care of a patient for the purpose of combating the disease, condition, or disorder.

As used herein, the term "patient" refers to an animal who is suffering from hyperglycemia or diabetes or IGM. The preferred animal is a mammal, such as dogs, cats, horses, cows and humans. It is preferred that the patient is a human.

The term "whose disease was not adequately controlled by metformin alone" used herein means preferably a hypoglycemia related disease such as diabetes, type 2 diabetes, IGT or IGM.

In this field the preferred patient population age is from 45 years onwards, most preferred from 65 years onwards.

The person skilled in the pertinent art is fully enabled to select a relevant test model and protocols to prove the beneficial effects of the invention.

The invention in a further aspect relates to a method to prevent, delay the progression or reduce, the Gastrointestinal disorders or Gastrointestinal side effects induced by metformin, comprising administering daily, a therapeutically effective amount of metformin, preferably 1500 to 3000 mg of metformin or a pharmaceutically acceptable salt thereof and 50 mg to 150 mg of vildagliptin or a pharmaceutically acceptable salt thereof to a patient in need thereof.
The invention in a further aspect relates to a method to prevent, delay the progression or reduce, the Gastrointestinal disorders or Gastrointestinal side effects induced by metformin, comprising administering daily, a therapeutically effective amount of metformin, preferably 1500 to 3000 mg of metformin or a pharmaceutically acceptable salt thereof and 25 mg to 100 mg of vildagliptin or a pharmaceutically acceptable salt thereof to a patient in need thereof.

The invention in a further aspect relates to the use of 50 mg to 150 mg of vildagliptin or a pharmaceutically acceptable salt thereof, in combination with metformin preferably 1500 to 3000 mg of metformin or a pharmaceutically acceptable salt thereof, daily, for the manufacture of a medicament to prevent, delay the progression or reduce, the Gastrointestinal disorders or Gastrointestinal side effects induced by metformin.

The invention in a further aspect relates to the use of 25 mg to 100 mg of vildagliptin or a pharmaceutically acceptable salt thereof, in combination with metformin preferably 1500 to 3000 mg of metformin or a pharmaceutically acceptable salt thereof, daily, for the manufacture of a medicament to prevent, delay the progression or reduce, the Gastrointestinal disorders or Gastrointestinal side effects induced by metformin.

The invention also relates to a treatment regimen, wherein,

i) 50 mg of vildagliptin or a pharmaceutically acceptable salt thereof, is to be administered in combination to metformin or a pharmaceutically acceptable salt thereof, preferably 1500 to 3000 mg of metformin, daily, to a patient in need thereof,

ii) the treated patient is selected from a patient suffering from Gastrointestinal disorders or Gastrointestinal side effects induced by metformin.

The invention also relates to a treatment regimen, wherein,

i) 50 mg of vildagliptin or a pharmaceutically acceptable salt thereof, is to be administered in combination to metformin or a pharmaceutically acceptable salt thereof, preferably 1500 to 3000 mg of metformin, daily, to a patient in need thereof,

ii) the treated patient is a patient whose disease was not adequately controlled by metformin alone, and
iii) the treated patient is selected from a patient suffering from Gastrointestinal disorders or Gastrointestinal side effects induced by metformin.

The invention also relates to a treatment regimen, wherein,

i) 25 mg of vildagliptin or a pharmaceutically acceptable salt thereof, is to be administered in combination to metformin or a pharmaceutically acceptable salt thereof, preferably 1500 to 3000 mg of metformin, daily, to a patient in need thereof,

ii) the treated patient is selected from a patient suffering from Gastrointestinal disorders or Gastrointestinal side effects induced by metformin.

The invention also relates to a treatment regimen, wherein,

i) 25 mg of vildagliptin or a pharmaceutically acceptable salt thereof, is to be administered in combination to metformin or a pharmaceutically acceptable salt thereof, preferably 1500 to 3000 mg of metformin, daily, to a patient in need thereof,

ii) the treated patient is a patient whose disease was not adequately controlled by metformin alone, and

iii) the treated patient is selected from a patient suffering from Gastrointestinal disorders or Gastrointestinal side effects induced by metformin.

The invention also relates to a treatment regimen, wherein,

i) 100 mg of vildagliptin or a pharmaceutically acceptable salt thereof, is to be administered in combination to metformin or a pharmaceutically acceptable salt thereof, preferably 1500 to 3000 mg of metformin, daily, to a patient in need thereof,

ii) the treated patient is selected from a patient suffering from Gastrointestinal disorders or Gastrointestinal side effects induced by metformin.

The invention also relates to a treatment regimen, wherein,

i) 100 mg of vildagliptin or a pharmaceutically acceptable salt thereof, is to be administered in combination to metformin or a pharmaceutically acceptable salt thereof, preferably 1500 to 3000 mg of metformin, daily, to a patient in need thereof,
ii) the treated patient is a patient whose disease was not adequately controlled by metformin alone, and

iii) the treated patient is selected from a patient suffering from Gastrointestinal disorders or Gastrointestinal side effects induced by metformin.

The invention also relates to a treatment regimen, wherein,

i) 150 mg of vildagliptin or a pharmaceutically acceptable salt thereof, is to be administered in combination to metformin, preferably 1500 to 3000 mg of metformin, daily, to a patient in need thereof,

ii) the treated patient is a patient whose disease was not adequately controlled by metformin alone, and

iii) the treated patient is selected from a patient suffering from Gastrointestinal disorders or Gastrointestinal side effects induced by metformin.

The invention also relates to a treatment regimen, wherein,

i) 150 mg of vildagliptin or a pharmaceutically acceptable salt thereof, is to be administered in combination to metformin or a pharmaceutically acceptable salt thereof, preferably 1500 to 3000 mg of metformin, daily, to a patient in need thereof,

ii) the treated patient is a patient whose disease was not adequately controlled by metformin alone, and

iii) the treated patient is selected from a patient suffering from Gastrointestinal disorders or Gastrointestinal side effects induced by metformin.

When 100 mg of vildagliptin or a pharmaceutically acceptable salt thereof, is administered daily, it can be in the form of a once a day administration of 100 mg of vildagliptin (OD), or a twice daily administration of 50 mg (i.e. bid) of vildagliptin.

When 50 mg of vildagliptin or a pharmaceutically acceptable salt thereof, is administered daily, it can be in the form of a once a day administration of 50 mg of vildagliptin <OD), or a twice daily administration of 25 mg (i.e. bid) of vildagliptin.

When metformin or a pharmaceutically acceptable salt thereof, is administered daily, it can be in the form of a once a day administration of metformin (OD), or a twice daily administration of (i.e. bid) of metformin e.g. twice daily administration of 750 mg, 850 mg, 1000 mg or 1500 mg (i.e. bid) of metformin, or three-times-daily dosing (500, 750, 850 or 1000 mg tablet 3 times a day).
Preferably metformin is taken before (up to 30 minutes before) or with (concomitantly with) the meal.

A treatment regimen, a method of treatment or a use as previously described, wherein between 250 mg and 3000 mg of metformin or a salt thereof, is administered twice daily (i.e. bid), and between 25 mg and 50 mg of vildagliptin or a salt thereof, is administered twice daily (i.e. bid).

A treatment regimen, a method of treatment or a use as previously described, wherein 750 mg, 850 mg, 1000 mg or 1500 mg of metformin or a salt thereof, is administered twice daily (i.e. bid), and between 25 mg or 50 mg of vildagliptin or a salt thereof, is administered twice daily (i.e. bid). Preferably metformin and vildagliptin are taken together before (up to 30 minutes before) or with (concomitantly with) the meal. In one embodiment, metformin and vildagliptin are taken together with the morning and evening meal.

A treatment regimen, a method of treatment or a use as previously described, wherein metformin or a pharmaceutically acceptable salt thereof and vildagliptin or a pharmaceutically acceptable salt thereof, are taken together before (up to 30 minutes before) or with (concomitantly with) the morning meal and/or together before (up to 30 minutes before) or with (concomitantly with) the evening meal.

In the above described treatment regimen, the term "daily", applies to metformin and (S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-pyrrolidine or a pharmaceutically acceptable salt thereof (vildagliptin).

Preferably the treated patient in the above described methods or uses or treatment regimens, is suffering from hyperglycemia. Most preferably the patient suffering from hyperglycemia, is suffering from a disease selected from diabetes mellitus, type I or insulin-dependent diabetes mellitus (IDDM), type II or non-insulin-dependent diabetes mellitus (NIDDM), type A insulin resistance, IGM, IFG or IGT. In a preferred embodiment the patient is suffering from type II diabetes or IGT. In another preferred embodiment the treated patient is a patient whose disease was not adequately controlled by metformin alone.

Preferably the treated patient in the herein claimed treatment regimen, is selected from a metformin treated patient suffering from metformin-induced diarrhea.

The structure of the active agents identified by code nos., generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications). The corresponding
content thereof is hereby incorporated by reference. Any person skilled in the art is fully enabled to identify the active agents and, based on these references, likewise enabled to manufacture and test the pharmaceutical indications and properties in standard test models, both in vitro and in vivo.

The herein described pharmaceutical preparations are for enteral, such as oral, and also rectal or parenteral, administration to homeotherms, with the preparations comprising the pharmacological active compound either alone or together with customary pharmaceutical auxiliary substances. For example, the pharmaceutical preparations consist of from about 0.1 % to 90 %, preferably from about 1 % to about 80 %, of the active compound.

Pharmaceutical preparations for enteral or parenteral, and also for ocular, administration are, for example, in unit dose forms, such as coated tablets, tablets, capsules or suppositories and also ampoules. These are prepared in a manner that is known per se, for example using conventional mixing, granulation, coating, solubulizing or lyophilising processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compound with solid excipients, if desired granulating a mixture which has been obtained, and, if required or necessary, processing the mixture or granulate into tablets or coated tablet cores after having added suitable auxiliary substances.

The dosage of the active compound can depend on a variety of factors, such as mode of administration, homeothermic species, age and/or individual condition.

Preferred dosages, for those active ingredients of the pharmaceutical combination according to the present invention that are commercially available, are especially therapeutically effective commercially available dosages.

The dosage of the active compound can depend on a variety of factors, such as mode of administration, homeothermic species, age and/or individual condition.

The corresponding active ingredient or a pharmaceutically acceptable salt thereof may also be used in form of a hydrate or include other solvents used for crystallization.

The exact dosage will of course vary depending upon the compound employed, mode of administration and treatment desired. The compound may be administered by any conventional route, non-oral or preferably orally.

For the larger mammals, an indicated total daily dosage is in the range from about 0.01 to 100mg/kg of the compound, conveniently administered in divided doses 2 to 4 times a day in
unit dosage form containing for example from about 0.1 to about 50 mg of the compound in sustained release form.

Preferably for the DPP-IV inhibitor especially LAF237 an indicated total daily dosage is in the range from between 1 and 500 mg, preferably between 10 and 200 mg of active ingredient.

Another preferred DPP-IV inhibitor especially LAF237 daily oral dosage is between 1 and 100 mg preferably between 10 and 100 mg e.g. 10 mg, most preferably between 25 and 100 mg e.g. 25 mg or 30 or 40 or 50, 61, 70, 90, 100 mg. The very preferred daily oral dosage of LAF237 is between 50 and 150 mg.

Appropriate unit doses for oral administration contain for example about 25 to about 150 mg of DPP-IV inhibitor especially LAF237, such as preferably 25, 50, 100 or 150 mg.

Appropriate doses for parenteral administration contain for example about 1 to about 150 mg of the compound, e.g. from 10 to 50 mg.

The DPP-IV inhibitor can also be administered every day (e.g. twice a day (BiD) or once a day (OD)), or only every two days, or twice a week.

The preparation of metformin (dimethylbiguanide) and its hydrochloride salt is state of the art and was disclosed first by Emil A. Werner and James Bell, J. Chem. Soc. 121, 1922, 1790-1794. In general, satisfactory results are obtained when Metformin is administered at a daily dosage of from about 50 mg to about 3000 mg, preferably from about 500 mg to about 2000 mg. Metformin can be administered e.g. in the form as marketed e.g. as 500 mg tablets. If the drug metformin shall be administered in a separate pharmaceutical composition, it can be administered in the form as it is launched e.g. under the trademark DIABETOSAN™ or GLUCOPHAGE™. If the drug metformin shall be administered in a separate pharmaceutical composition in the form of its hydrochloride salt, the metformin hydrochloride salt can be administered in the form as it is launched e.g. under the trademarks DIABETASE 500™, DIABETASE 850™ or GLUCOPHAGE S™. Metformin can also be administered only every two days, or twice a week.

A treatment regimen, a method of treatment or a use as previously described, wherein between 250 mg and 3000 mg of metformin or a salt thereof, is administered daily.

Metformin has been widely prescribed for lowering blood glucose in patients with NIDDM and is marketed in 500, 750, 850 and 1000 mg strengths. However, because it is a short acting drug, metformin requires often twice-daily or three-times-daily dosing (500 - 850 mg tab 2-3/day or 1000 mg bid with meals). The biguanide antihyperglycemic agent metformin
disclosed in U.S. Patent No. 3,174,901 is currently marketed in the U.S. in the form of its hydrochloride salt (Glucophage®), Bristol-Myers Squibb Company). The preparation of metformin (dimethylbiguanide) and its hydrochloride salt is state of the art and was disclosed first by Emil A. Werner and James Bell, J. Chem. Soc. 121, 1922, 1790-1794. Metformin, can be administered e.g. in the form as marketed under the trademarks GLUCOPHAGE™. Metformin, increases the sensitivity to insulin in peripheral tissues of the hosts. Metformin is also involved in inhibition of glucose absorption from the intestine, suppression of hepatic gluconeogenesis, and inhibition of fatty acid oxidation. Suitable dosage regimens of Metformin include unit doses of 500 mg two to three times daily and can even be build up to five times daily or 850 mg once or twice daily. [Martindale, The Complete Drug Reference. Certain controlled or sustained release formulations that employ antihyperglycemic drugs such as metformin hydrochloride have been limited to the use of an expanding or gelling agent to control the release of the drug from the dosage form. This research is exemplified by the teachings of WO 96/08243 and by the GLUCOPHAGE XR product insert which is a controlled release metformin product commercially available from Bristol-Myers Squibb. GLUCOPHAGE (metformin hydrochloride tablets) should be given in divided doses with meals while GLUCOPHAGE XR (metformin hydrochloride extended-release tablets) should generally be given once daily with the evening meal. Metformin is preferably in the form of metformin HCl.

The term "metformin" as employed herein refers to metformin or a pharmaceutically acceptable salt thereof such as the hydrochloride salt, the metformin (2:1) fumarate salt, and the metformin (2:1) succinate salt as disclosed in U.S. application Serial No. 09/262,526 filed March 4, 1999, the hydrobromide salt, the p-chlorophenoxy acetate or the embonate, and other known metformin salts of mono and dibasic carboxylic acids including those disclosed in U.S. Patent No. 3, 174,901, all of which salts are collectively referred to as metformin. It is preferred that the metformin employed herein be the metformin hydrochloride salt, namely, that marketed as GLUCOPHAGE-D or GLUCOPHAGE XR (trademark of Bristol-Myers Squibb Company).

The compounds may be administered in similar manner to known standards for uses in these utilities. The suitable daily dosage for a particular compound will depend on a number of factors such as its relative potency of activity. A person skilled in the pertinent art is fully enabled to determine the therapeutically effective dosage.
The compound of the invention may be administered in free base for or as a
pharmacologically acceptable acid addition or quaternary ammonium salt. Such salts may be
prepared in conventional manner and exhibit the same order of activity as the free forms.
If these compounds have, for example, at least one basic center, they can form acid addition
salts. Corresponding acid addition salts can also be formed having, if desired, an
additionally present basic center. The compounds having an acid group (for example COOH)
can also form salts with bases. For example, the compounds to be combined can be present
as a sodium salt, as a maleate or as a dihydrochloride. The active ingredient or a
pharmacologically acceptable salt thereof may also be used in form of a hydrate or include
other solvents used for crystallization.

The present invention refers to a combination which comprises a DPP-IV inhibitor in free or
pharmacologically acceptable salt form, and metformin or the pharmacologically acceptable
salt thereof and optionally at least one pharmacologically acceptable carrier; wherein the
active ingredients can be administered simultaneously or sequentially in any order,
separately or in a fixed combination (same galenic formulation).

A combined preparation which comprises a DPP-IV inhibitor in free or pharmacologically
acceptable salt form and metformin and optionally at least one, i.e., one or more, e.g. two,
pharmacologically acceptable carrier for simultaneous, separate or sequential use is
especially a "kit of parts" in the sense that the components, a DPP-IV inhibitor in free or
pharmacologically acceptable salt form and metformin, can be dosed independently or by use
of different fixed combinations with distinguished amounts of the components, i.e. at different
time points or simultaneously. The parts of the kit of parts can then, e.g., be administered
simultaneously or chronologically staggered, that is at different time points and with equal or
different time intervals for any part of the kit of parts. Preferably, the time intervals are
chosen such that the effect on the treated disease or condition in the combined use of the
parts is larger than the effect which would be obtained by use of only any one of the
components.

A therapeutically effective amount of each of the components of the combination of the
present invention may be administered simultaneously or sequentially and in any order, and
the components may be administered separately or as a fixed combination. For example, the
method of treatment of the invention may comprise (i) administration of a DPP-IV inhibitor in
free or pharmacologically acceptable salt form and (ii) administration of metformin
simultaneously or sequentially in any order, in jointly therapeutically effective amounts,
preferably in synergistically effective amounts, e.g. in daily dosages corresponding to the ratios described herein.

The pharmaceutical compositions according to the invention can be prepared in a manner known per se and are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals (warm-blooded animals), including man, comprising a therapeutically effective amount of the pharmacologically active compound, alone or in combination with one or more pharmaceutically acceptable carries, especially suitable for enteral or parenteral application.

To further illustrate the invention, but not by way of limitation, the following clinical study is provided. Further experimental protocols are described in the patent application WO 01/52825 describing combinations comprising a DPP-IV inhibitor and an antidiabetic compound e.g. metformin.

The invention has been described above by reference to preferred embodiments but, as those skilled in the art will appreciate, many additions, omissions and modifications are possible all within the scope of the claims below.

All patents and literature references cited in this specification are hereby incorporated by reference in their entirety. In case of inconsistencies, the present description, including the definitions and interpretations, will prevail.

Example 1:

CLINICAL STUDY
List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA</td>
<td>American Diabetes Association</td>
</tr>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>ALT</td>
<td>alanine aminotransferase/glutamic pyruvic transaminase/GPT</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>Analysis of covariance</td>
</tr>
<tr>
<td>AST</td>
<td>aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the plasma-concentration time curve</td>
</tr>
<tr>
<td>bid</td>
<td>bis in diem/twice a day</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>bpm</td>
<td>Beats Per Minute</td>
</tr>
<tr>
<td>BUN</td>
<td>Blood Urea Nitrogen</td>
</tr>
<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
</tr>
<tr>
<td>CPK</td>
<td>Creatinine phosphokinase</td>
</tr>
<tr>
<td>CPK-MB</td>
<td>Creatinine phosphokinase muscle-brain fraction</td>
</tr>
<tr>
<td>CPO</td>
<td>Country Pharma Organization</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report/Record Form</td>
</tr>
<tr>
<td>CS&amp;E</td>
<td>Clinical Safety and Epidemiology</td>
</tr>
<tr>
<td>CRD</td>
<td>Clinical Research and Development</td>
</tr>
<tr>
<td>DPP-4</td>
<td>Dipeptidyl peptidase IV</td>
</tr>
<tr>
<td>DSC-R</td>
<td>Diabetes Symptom Checklist</td>
</tr>
<tr>
<td>DTSQc</td>
<td>Diabetes Treatment Satisfaction Questionnaire, change version</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case Report/Record Form</td>
</tr>
<tr>
<td>EDC</td>
<td>Electronic Data capture</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FPG</td>
<td>Fasting Plasma Glucose</td>
</tr>
<tr>
<td>GLP-1</td>
<td>Glucagon-like peptide 1</td>
</tr>
<tr>
<td>HbA1c</td>
<td>Hemoglobin A1C</td>
</tr>
<tr>
<td>HDL</td>
<td>High density lipoprotein</td>
</tr>
<tr>
<td>HOMA B</td>
<td>Homeostatic model assessment - beta cell</td>
</tr>
<tr>
<td>HOMA IR</td>
<td>Homeostatic model assessment - insulin resistance</td>
</tr>
<tr>
<td>HPLC</td>
<td>High pressure liquid chromatography</td>
</tr>
<tr>
<td>HRQoL</td>
<td>Health-related Quality of Life</td>
</tr>
<tr>
<td>IB</td>
<td>Investigator Brochure</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>ITT</td>
<td>Intent to treat</td>
</tr>
<tr>
<td>IUD</td>
<td>Intrauterine contraceptive device</td>
</tr>
<tr>
<td>LC-MS/MS</td>
<td>Liquid chromatography/tandem mass spectrometry</td>
</tr>
<tr>
<td>LDL</td>
<td>Low density lipoprotein</td>
</tr>
<tr>
<td>LOCF</td>
<td>Last Observation Carried Forward</td>
</tr>
<tr>
<td>LOQ</td>
<td>Limit of quantification</td>
</tr>
</tbody>
</table>
MedDRA  Medical dictionary for regulatory activities
MI  Myocardial infarction
mmHg  Millimeters of mercury
PD  Pharmacodynamics
PK  Pharmacokinetics
PP  Per Protocol
qd  Qua'que di'el every day
RAN  Randomized
REB  Research Ethics Board
SAE  Serious adverse event
SAF  Safety
SF-36  Short-Form 36
TSH  Thyroid Stimulating Hormone
ULN  Upper limit of normal
VLDL  Very low density lipoprotein
WHO  World Health Organization
WPAI-GH  Work Productivity and Activity Impairment Questionnaire: General Health
**Glossary of terms**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment</td>
<td>A procedure used to generate data required by the study</td>
</tr>
<tr>
<td>Control; control drug</td>
<td>A study drug used as a comparator to reduce assessment bias, preserve blindness of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug</td>
</tr>
<tr>
<td>Enrollment</td>
<td>Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e., prior to starting any of the procedures described in the protocol)</td>
</tr>
<tr>
<td>Investigational drug</td>
<td>The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”</td>
</tr>
<tr>
<td>Medication number</td>
<td>A unique identifier on the label of each medication package in studies that dispense medication using an IVR system</td>
</tr>
<tr>
<td>Patient number</td>
<td>A unique identifier assigned to each patient who enrolls in the study</td>
</tr>
<tr>
<td>Phase</td>
<td>A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.</td>
</tr>
<tr>
<td>Period</td>
<td>A minor subdivision of the study timeline; divides phases into smaller functional segments</td>
</tr>
<tr>
<td>Premature patient withdrawal</td>
<td>Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned</td>
</tr>
<tr>
<td>Randomization number</td>
<td>A unique identifier assigned to each randomized patient, corresponding to a specific treatment group assignment</td>
</tr>
<tr>
<td>Study drug</td>
<td>Any drug administered to the patient as part of the required study procedures; includes investigational drug and any control drugs</td>
</tr>
<tr>
<td>Study drug discontinuation</td>
<td>Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal</td>
</tr>
<tr>
<td>Variable</td>
<td>Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints</td>
</tr>
</tbody>
</table>

**Title of study:**

A multicenter, double-blind, randomized, parallel-group study to compare the effect of 24 weeks treatment with vildagliptin (LAF237) (50 mg qd or bid) to placebo as add-on therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy.

**Study purpose:**

The present study is designed to demonstrate the efficacy and safety of add-on therapy with LAF237 (50 mg qd or bid) in patients with type 2 diabetes inadequately controlled with prior metformin monotherapy (HbA1c 7.5-11%). This study will support the global regulatory approval of LAF237 as combination therapy with metformin in the treatment of type 2 diabetes.
Objectives:

Primary: To confirm the efficacy of add-on therapy with LAF237 in patients with type 2 diabetes inadequately controlled with prior metformin monotherapy by testing the hypothesis that the HbA1c reduction with LAF237 (50mg qd or bid) is superior to that with placebo after 24 weeks of treatment. Secondary: Critical variables 1- To confirm the efficacy of add-on therapy with LAF237 in patients with type 2 diabetes inadequately controlled with prior metformin monotherapy by testing the hypothesis that the FPG reduction with LAF237 (50 mg qd or bid) is superior to that with placebo after 24 weeks of treatment. 2- To demonstrate the safety of LAF237 in patients with type 2 diabetes inadequately controlled with prior metformin monotherapy by showing that add-on therapy with LAF237 (50 mg qd or bid) has comparable adverse event profiles including GI tolerability at the two dose levels and these are similar to placebo after 24 weeks of treatment. 3- To demonstrate the efficacy of add-on therapy with LAF237 in patients with type 2 diabetes inadequately controlled with prior metformin monotherapy by showing that the responder rates with LAF237 (50 mg qd or bid) are greater than those with placebo after 24 weeks of treatment. 4- To demonstrate the efficacy of add-on therapy with LAF237 in patients with type 2 diabetes inadequately controlled with prior metformin monotherapy across baseline HbA1c subgroups to assess whether or not the therapeutic efficacy of LAF237 (lowering of HbA1c with 50 mg qd or bid vs placebo) is greater in patients with a high baseline HbA1c (> 9%) than patients with a lower baseline HbA1c (≤ 9%) after 24 weeks of treatment. Exploratory variables 1- To explore the mechanism of action of LAF237 in add-on therapy in patients with type 2 diabetes inadequately controlled with prior metformin monotherapy by testing the hypotheses that LAF237 (50 mg qd or bid) improves beta-cell function (indexed by the fasting proinsulin concentration, fasting proinsulin/insulin ratio and HOMA B) and reduces insulin resistance (indexed by the fasting insulin concentration and HOMA IR) relative to placebo after 24 weeks of treatment. 2- To explore the ancillary clinical benefits of add-on therapy with LAF237 in patients with type 2 diabetes inadequately controlled with prior metformin monotherapy by testing the hypotheses that LAF237 (50 mg qd or bid) has a beneficial effect on fasting plasma lipid profiles and is body weight neutral relative to placebo after 24 weeks of treatment. 3- To explore the efficacy of add-on therapy with LAF237 in patients with type 2 diabetes inadequately controlled with prior metformin monotherapy by testing the hypotheses that LAF237 (50 mg qd or bid) has favorable effects relative to placebo on the area under the 0-4 hour prandial curve (AUC0-4hr) for plasma glucose, insulin and C-peptide, and 2-hour absolute glucose level following a standard meal challenge after 24 weeks of
treatment, in a subset of patients. 4- To explore the pharmacokinetics of LAF237 in add-on therapy in patients with type 2 diabetes inadequately controlled with prior metformin monotherapy, in a subset of patients, by evaluating the effects of demographic variables such as age, weight, gender and race on the elimination clearance. 5- To explore the ancillary benefits of add-on therapy with LAF237 in patients with type 2 diabetes inadequately controlled with prior metformin monotherapy by showing that LAF237 (50 mg qd or bid) has a favorable impact on quality of life, patient satisfaction and work productivity relative to placebo after 24 weeks of treatment.

**Population:**

Patients with type 2 diabetes who are inadequately controlled on metformin are candidates for combination therapy with a second oral antidiabetic agent. Patients with type 2 diabetes treated with metformin for at least three months and at a stable dose of at least 1500 mg daily for a minimum of 4 weeks prior to visit 1 are eligible to participate in the trial. If patients at visit 1 are treated with their maximum tolerated dose of metformin but it is < 2000 mg daily, a note must be entered in the source document confirming that higher doses have previously been tried but were not tolerated. Patients treated with < 2000 mg who have not been previously titrated to a higher dose does start 2000 mg daily at visit 1; if the higher dose is not tolerated, the dose can be adjusted downward to the previous dose. The dose of metformin used at randomization must be maintained unchanged throughout the trial. This was based on a prospective study that indicated that maximal efficacy for metformin is achieved with a total daily dose of around 2000 mg (Garber, et al 1997 - Garber AJ, Duncan TG, Goodman AM, et al (1997) - Efficacy of metformin in type 2 diabetes: Results of a double-blind, placebo controlled, dose-response trial. Am J Med 102:491-497), whereas a dose of 1500 mg per day also provided good efficacy, preserving approximately 85% of the maximal efficacy. This study also demonstrated that gastrointestinal symptoms such as nausea, diarrhea, and abdominal pain limit the metformin dose in some patients, even at lower doses.

In this study, the population consists of males and females (non-fertile or of childbearing potential using a medically approved birth control method) aged 18-78 years, with an HbA$_{1c}$ of 7.5-11%.

This is an outpatient multicenter study conducted in approximately 70 study centers in the US and 25 study centers in Europe. Approximately 690 patients are screened in order to randomize 345 patients.
Inclusion/Exclusion criteria:

**Inclusion criteria:** Male or female (non-fertile or using a medically approved birth control method); age range 18-78 years inclusive; patients with type 2 diabetes who have received metformin for at least three months and have been on a stable dose of at least 1500 mg daily for a minimum of 4 weeks prior to visit 1. If patients are currently treated with their maximum tolerated dose of metformin but it is < 2000 mg daily, a note must be entered in the source document confirming that higher doses have previously been tried but were not tolerated. Patients treated with < 2000 mg who have not previously been tried at a higher dose of metformin must agree to increase the metformin dose to 2000 mg at visit 1; agreement to maintain the same dose of metformin from randomization to the end of the study; body mass index of 22-45 kg/m² inclusive; HbA₁₀ 7.5 to 11% inclusive; FPG <270 mg/dL (15 mmol/L); and agreement to maintain prior diet and exercise.

**Exclusion criteria:** Pregnant or lactating female; a history of type 1 diabetes, diabetes that is a result of pancreatic injury or secondary forms of diabetes; acute metabolic diabetic complications within the past 6 months; evidence of significant diabetic complications; acute infections which may affect blood glucose control within 4 weeks prior to visit 1; a history of Torsades de Pointes, sustained and clinically relevant ventricular tachycardia or ventricular fibrillation; percutaneous coronary intervention within the past 3 months; myocardial infarction, coronary artery bypass surgery, or unstable angina within the past 6 months; congestive heart failure requiring pharmacologic treatment; second degree AV block (Mobitz 1 and 2), third degree AV block, prolonged QTc; malignancy including leukemia and lymphoma (not including basal cell skin cancer) within the last 5 years; liver disease; renal disease or renal dysfunction; acromegaly or treatment with growth hormone or similar drugs; concurrent medical condition that may interfere with the interpretation of efficacy and safety data during the study; donation of one unit (500mL) or more of blood, significant blood loss equaling at least one unit of blood within the past two weeks or a blood transfusion within the past eight weeks; contraindications and warnings according to the country specific label for metformin not listed in the other exclusion criteria; treatment with any oral anti-diabetic other than metformin within 3 months prior to visit 1; chronic insulin treatment (> 4 weeks of treatment in the absence of an intercurrent illness) within the past 6 months; chronic oral or parenteral corticosteroid treatment within 8 weeks prior to visit 1; treatment with class Ia, Ib, Ic, or III anti-arrhythmics; investigational drug treatment within 4 weeks prior to visit 1 unless local health authority guidelines mandate a longer period; treatment with any drug with known and frequent toxicity to a major organ system within the past 3 months; any of the
following significant laboratory abnormalities: ALT, AST greater than three times the upper limit of the normal range, direct bilirubin greater than 1.3 times the upper limit of the normal range, serum creatinine levels \( \geq 1.5 \text{ mg/dL} \) (132 \( \mu \text{mol/L} \)) males, \( \geq 1.4 \text{ mg/dL} \) (123 \( \mu \text{mol/L} \)) females or abnormal creatinine clearance, TSH outside of normal range at visit 1, clinically significant laboratory abnormalities, confirmed by repeat measurement, that may interfere with the assessment of safety and/or efficacy of the study drug (other than hyperglycemia, hyperinsulinemia, and glycosuria), fasting triglycerides \( > 700 \text{ mg/dL} \) (\( > 7.9 \text{ mmol/L} \)); history of active substance abuse (including alcohol) within the past 2 years; and potentially unreliable patients, and those judged by the investigator to be unsuitable for the study.

**Investigational and reference therapy:**

In addition to their continued metformin treatment patients are assigned to double-blind treatment of either LAF237 50 mg qd, 50 mg bid or placebo in a ratio of 1:1:1.

**Study design:**

This is a multicenter, randomized, double-blind, placebo-controlled study. Patients with type 2 diabetes inadequately controlled on metformin monotherapy (HbA1c 7.5-11%) are included in the trial. Eligible patients are randomized equally to LAF237 50 mg qd, 50 mg bid or placebo in addition to their continued metformin treatment. Each patient attend one screening visit (Week -4) where the inclusion/exclusion criteria are assessed. Eligible patients are then be randomized at Visit 2 (Baseline; Day 1) and complete 4 additional visits over a period of 24 weeks of treatment with LAF237 or placebo added to metformin.

**Efficacy assessments:**

**Primary efficacy assessments:** HbA1c.

**Secondary efficacy assessments:** Fasting plasma glucose, fasting lipids (triglycerides, total cholesterol, calculated LDL, HDL, calculated non-HDL, calculated VLDL), body weight, beta-cell function (fasting proinsulin, fasting proinsulin/insulin ratio, HOMA B), insulin resistance (fasting insulin, HOMA IR), and responder rates. In a subset of patients, prandial glucose, insulin, and C-peptide are measured following a standard meal challenge.

**Other assessments:**

Safety assessments include the monitoring of adverse events (e.g. gastrointestinal side effects), vital signs, physical examinations, laboratory evaluations (hematology,
biochemistry, and urinalysis) and electrocardiograms. Other assessments include pharmacokinetics of LAF237 and quality of life questionnaires.

Safety

The assessment of safety is based mainly on the frequency of treatment emergent adverse events, on the number of post baseline laboratory values that fall outside of pre-determined ranges and on the frequency and severity of hypoglycemic events during the double-blind, randomized treatment period. Summaries for safety assessment are presented for the SAF population. Unless specified otherwise, comparison are made to Baseline, which are the measurement taken at Day 1 (Visit 2) or the screening measurement (Visit 1, Week -4) if Day 1 measurement is missing.

Adverse events are summarized by presenting, for each treatment group, the number and percentage of patients having any adverse event, having an adverse event in each primary system organ class and having each individual adverse event. Any other information collected (e.g. severity or relatedness to study medication) are presented as appropriate. In addition, the incidence of gastrointestinal (GI) adverse events are summarized for each treatment group and compared.

Laboratory data are summarized by presenting scatter plots (baseline vs. endpoint value), by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges) and by presenting the number and percentage of patients having notable lab values or having endpoint change from baseline meeting pre-specified percent change criteria. The identification of notable values are based on the pre-specified criteria provided in the investigator binder (are also included in the analysis plan), and the percent change from baseline criteria in selected lab tests are pre-defined in the analysis plan.

Hypoglycemia events are included in all AE summaries. In addition, events are characterized by event profile, such as ability to self-treat, self monitoring of plasma glucose level, precipitating event, time from last meal, time from last dose, and time of the day.

Data from other tests (e.g. vital signs, ECGs) are summarized as appropriate, incidences of notable values are presented in the tables and notable values are flagged in the listings.

Data analysis:
The hypotheses for testing superiority of LAF237 to placebo, both LAF237 and placebo combined with metformin, for the effect of reducing HbA$_1c$ is be H$_0$: $\delta_{\text{LAF}}^{50 \text{ mgqd}} = \delta_{\text{placebo}}$

$\mathit{H}_{\text{a1}}$: $\delta_{\text{LAF}}^{50 \text{ mgqd}} \neq \delta_{\text{placebo}}$ and $\mathit{H}_{\text{a2}}$: $\delta_{\text{LAF}}^{50 \text{ mg bid}} = \delta_{\text{placebo}}$

where $\delta$ is the mean change from baseline in the treatment group indicated by the subscript.

The least squares mean ("adjusted mean") change from baseline for each treatment group, the difference in the least squares mean changes between the two treatment groups (LAF237 - placebo), and the two-sided 95% confidence intervals along with the $p$ values for the treatment differences are obtained from the primary analysis model and presented.

Secondary efficacy variables are assessed using a simNar model. Hochberg's multiple-testing step-up procedure are used to ensure an overall significance level of 0.05 for the primary efficacy analysis (HbA$_1c$) with two statistical tests combined.

**Results:**

The applicant has surprisingly discovered that vildagliptin does reduce the Gastrointestinal (GI) disorders or side effects associated with metformin.

**Frequency in GI Disorders (in %)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo + Vildagliptin</th>
<th>Vildagliptin 50 mg daily + Metformin</th>
<th>Vildagliptin 100 mg daily + Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>18.2%</td>
<td>9.6%</td>
<td>14.2%</td>
</tr>
<tr>
<td>Metformin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
What is claimed is:

1) A method to prevent, delay the progression or reduce, the Gastrointestinal disorders or Gastrointestinal side effects induced by metformin, comprising administering a therapeutically effective amount of metformin or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of vildagliptin or a pharmaceutically acceptable salt thereof, to a patient in need thereof.

2) Use of metformin or a pharmaceutically acceptable salt thereof, in combination with vildagliptin or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament to prevent, delay the progression or reduce, the Gastrointestinal disorders or Gastrointestinal side effects induced by metformin.

3) A method to prevent, delay the progression or reduce, the Gastrointestinal disorders or Gastrointestinal side effects induced by metformin, comprising administering daily, a therapeutically effective amount of metformin, preferably 1500 to 3000 mg of metformin or a pharmaceutically acceptable salt thereof and 50 mg to 150 mg of vildagliptin or a pharmaceutically acceptable salt thereof to a patient in need thereof.

4) A method to prevent, delay the progression or reduce, the Gastrointestinal disorders or Gastrointestinal side effects induced by metformin, comprising administering daily, a therapeutically effective amount of metformin, preferably 1500 to 3000 mg of metformin or a pharmaceutically acceptable salt thereof and 25 mg to 100 mg of vildagliptin or a pharmaceutically acceptable salt thereof to a patient in need thereof.

5) Use of 50 mg to 150 mg of vildagliptin or a pharmaceutically acceptable salt thereof, in combination with metformin preferably 1500 to 3000 mg of metformin or a pharmaceutically acceptable salt thereof, daily, for the manufacture of a medicament to prevent, delay the progression or reduce, the Gastrointestinal disorders or Gastrointestinal side effects induced by metformin.

6) Use of 25 mg to 100 mg of vildagliptin or a pharmaceutically acceptable salt thereof, in combination with metformin preferably 1500 to 3000 mg of metformin or a pharmaceutically acceptable salt thereof, daily, for the manufacture of a medicament to prevent, delay the progression or reduce, the Gastrointestinal disorders or Gastrointestinal side effects induced by metformin.
7) Method according to any of claims 3, 4 or 1, use according to any of claims 2, 5 or 6, wherein the treated patient is selected from a metformin treated patient suffering from metformin-induced gastrointestinal side effects or a metformin treated patient suffering from metformin-induced diarrhea.

8) Method according to any of claims 1, 3, 4 or 7, use according to any of claims 2, 5, 6 or 7, wherein the treated patient is suffering from hyperglycemia or is a patient whose disease was not adequately controlled by metformin alone.

9) A treatment regimen, wherein,
   i) 50 mg of vildagliptin or a pharmaceutically acceptable salt thereof, is to be administered in combination to metformin or a pharmaceutically acceptable salt thereof, preferably 1500 to 3000 mg of metformin, daily, to a patient in need thereof,
   ii) the treated patient is selected from a patient suffering from Gastrointestinal disorders or Gastrointestinal side effects induced by metformin.

10) A treatment regimen, wherein,
    i) 50 mg of vildagliptin or a pharmaceutically acceptable salt thereof, is to be administered in combination to metformin or a pharmaceutically acceptable salt thereof, preferably 1500 to 3000 mg of metformin, daily, to a patient in need thereof,
    ii) the treated patient is a patient whose disease was not adequately controlled by metformin alone, and
    iii) the treated patient is selected from a patient suffering from Gastrointestinal disorders or Gastrointestinal side effects induced by metformin.

11) A treatment regimen, wherein,
    i) 100 mg of vildagliptin or a pharmaceutically acceptable salt thereof, is to be administered in combination to metformin or a pharmaceutically acceptable salt thereof, preferably 1500 to 3000 mg of metformin, daily, to a patient in need thereof,
    ii) the treated patient is selected from a patient suffering from Gastrointestinal disorders or Gastrointestinal side effects induced by metformin.

12) A treatment regimen, wherein,
i) 100 mg of vildagliptin or a pharmaceutically acceptable salt thereof, is to be administered in combination to metformin or a pharmaceutically acceptable salt thereof, preferably 1500 to 3000 mg of metformin, daily, to a patient in need thereof,

ii) the treated patient is a patient whose disease was not adequately controlled by metformin alone, and

iii) the treated patient is selected from a patient suffering from Gastrointestinal disorders or Gastrointestinal side effects induced by metformin.

13) A treatment regimen, wherein,

i) 150 mg of vildagliptin or a pharmaceutically acceptable salt thereof, is to be administered in combination to metformin or a pharmaceutically acceptable salt thereof, preferably 1500 to 3000 mg of metformin, daily, to a patient in need thereof,

ii) the treated patient is selected from a patient suffering from Gastrointestinal disorders or Gastrointestinal side effects induced by metformin.

14) A treatment regimen, wherein,

i) 150 mg of vildagliptin or a pharmaceutically acceptable salt thereof, is to be administered in combination to metformin or a pharmaceutically acceptable salt thereof, preferably 1500 to 3000 mg of metformin, daily, to a patient in need thereof,

ii) the treated patient is a patient whose disease was not adequately controlled by metformin alone, and

iii) the treated patient is selected from a patient suffering from Gastrointestinal disorders or Gastrointestinal side effects induced by metformin.

15) A treatment regimen, wherein,

i) 25 mg of vildagliptin or a pharmaceutically acceptable salt thereof, is to be administered in combination to metformin or a pharmaceutically acceptable salt thereof, preferably 1500 to 3000 mg of metformin, daily, to a patient in need thereof,

ii) the treated patient is selected from a patient suffering from Gastrointestinal disorders or Gastrointestinal side effects induced by metformin.
16) A treatment regimen, wherein,

i) 25 mg of vildagliptin or a pharmaceutically acceptable salt thereof, is to be
administered in combination to metformin or a pharmaceutically acceptable salt
thereof, preferably 1500 to 3000 mg of metformin, daily, to a patient in need
thereof,

ii) the treated patient is a patient whose disease was not adequately controlled by
metformin alone, and

iii) the treated patient is selected from a patient suffering from Gastrointestinal
disorders or Gastrointestinal side effects induced by metformin.

17) A treatment regimen according to any of claims 9 to 16, wherein the treated patient is
selected from a metformin treated patient suffering from metformin-induced diarrhea.

18) A treatment regimen according to any of claims 9 to 17, wherein the treated patient is
suffering from hyperglycemia.

19) A treatment regimen, a method of treatment or a use according to any of the previous
claims, wherein between 250 mg and 3000 mg of metformin or a salt thereof is administered
daily.

20) A treatment regimen, a method of treatment or a use according to any of the previous
claims, wherein metformin is administered daily, twice daily or three-times-daily.

21) A treatment regimen, a method of treatment or a use according to any of the previous
claims, wherein 750 mg, 850 mg, 1000 mg or 1500 mg of metformin or a salt thereof, is
administered twice daily.

22) A treatment regimen, a method of treatment or a use according to any of the previous
claims, wherein 500, 750, 850 or 1000 mg of metformin or a salt thereof, is administered
three-times-daily.

23) A treatment regimen according to any of claims 9 to 12, a method of treatment or a
use according to any of the previous claims, wherein 50 mg or 100 mg of vildagliptin or a
pharmaceutically acceptable salt thereof, is administered daily, in the form of a once a day
administration of vildagliptin.

24) A treatment regimen according to any of claims 9, 10, 17, 18, 19, 20, 21, or 22, a
method of treatment or a use according to any of the previous claims, wherein 50 mg of
vildagliptin or a pharmaceutically acceptable salt thereof, is administered daily, in the form of
a twice daily administration of 25 mg of vildagliptin.

25) A treatment regimen according to any of claims 11, 12, 17, 18, 19, 20, 21 or 22, a
method of treatment or a use according to any of the previous claims, wherein 100 mg of
vildagliptin or a pharmaceutically acceptable salt thereof, is administered daily, in the form of
a twice daily administration of 50 mg of vildagliptin.

26) A treatment regimen, a method of treatment or a use according to any of the previous
claims, wherein metformin or a pharmaceutically acceptable salt thereof, is taken before (up
to 30 minutes before) or with (concomitantly with) the meal.

27) A treatment regimen, a method of treatment or a use according to any of the previous
claims, wherein metformin or a pharmaceutically acceptable salt thereof and vildagliptin or a
pharmaceutically acceptable salt thereof, are taken together before (up to 30 minutes
before) or with (concomitantly with) the meal.

28) A treatment regimen, a method of treatment or a use according to any of the previous
claims, wherein metformin or a pharmaceutically acceptable salt thereof and vildagliptin or a
pharmaceutically acceptable salt thereof, are taken together before (up to 30 minutes
before) or with (concomitantly with) the morning meal and/or together before (up to 30
minutes before) or with (concomitantly with) the evening meal.

29) A treatment regimen, a method of treatment or a use according to any of the previous
claims, wherein the treated patient is selected from a metformin treated patient suffering
from metformin-induced diarrhea.