Abstract:
The invention relates to the finding that certain DPP-4 inhibitors are particularly suitable for treating and/or preventing metabolic diseases, particularly diabetes, in pediatric patients.
The present invention relates to certain DPP-4 inhibitors for treating and/or preventing metabolic diseases, particularly diabetes (especially type 2 diabetes mellitus and diseases related thereto), in paediatric type 2 diabetes patients, as well as to the use of these DPP-4 inhibitors in antidiabetic therapy. Pharmaceutical compositions for use in these therapies comprising a DPP-4 inhibitor as defined herein optionally together with one or more other active substances are also contemplated.

Type 2 diabetes mellitus (T2DM) is a polygenic disorder where insulin secretion does not meet the required demands to maintain plasma glucose levels in the normal range. This leads to chronic hyperglycaemia and its associated micro- and macrovascular complications or chronic damages, such as e.g. diabetic nephropathy, retinopathy or neuropathy, or macrovascular (e.g. cardio- or cerebro-vascular) complications. The vascular disease component plays a significant role, but is not the only factor in the spectrum of diabetes associated disorders. The high frequency of complications leads to a significant reduction of life expectancy. Diabetes is currently the most frequent cause of adult-onset loss of vision, renal failure, and amputation in the Industrialised World because of diabetes induced complications and is associated with a two to five fold increase in cardiovascular disease risk.

Oral or non-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, α-glucosidase inhibitors, GLP-1 or GLP-1 analogues, and insulin or insulin analogues, or (dual or triple) combinations thereof.

As in adults, type 2 diabetes in children and youth appears to be due to the combination of insulin resistance and a relative β-cell secretory failure. There seems to be a host of genetic and environmental risk factors for insulin resistance and limited β-cell reserve: family history of type 2 diabetes, ethnicity, pubertal augmentation of growth hormone/IGF secretory dynamics, intrauterine exposure to maternal diabetes, low birth weight, sedentary lifestyle and female gender in association with hyperandrogenism.
However, the most important risk factor for the development of type 2 diabetes in children and adolescents appears to be obesity and the increasing prevalence of childhood obesity is likely the main cause for the increase in type 2 diabetes cases in children and adolescents.

Another important risk factor for the development of type 2 diabetes in childhood is ethnicity. In North America, for instance, cases of type 2 diabetes occur mainly in ethnic minorities including African American, Mexican American, Native American and Asian American children and youth.

Prior to the development of frank diabetes, there is a period of pre-diabetes that children experience which can be defined as either elevated fasting glucose or impaired glucose tolerance.

The vast majority of type 2 diabetes cases in children and adolescents occurs in the 12-17 year of age group. In children younger than 10 years, the prevalence of type 2 diabetes is extremely low.

The diagnosis of diabetes in children and youth is made as per the same American Diabetes Association criteria as those established for adults. The diagnosis can be made when the subject is symptomatic and has a plasma glucose \( \geq 200 \) mg/dl, or by screening asymptomatic children and youth and finding a fasting plasma glucose \( >126 \) mg/dl, or a 2-hour plasma glucose \( >200 \) mg/dl during an oral glucose tolerance test.

The populations being at high risk for paediatric type 2 diabetes include children and adolescents at risk of overweight (e.g. body mass index > 85th percentile for age and sex; or weight for age, sex, and height > 85th percentile; or weight > 120% of ideal for height) or with overweight (BMI > 85th percentile) or, particularly, with obesity (including mild, moderate and, particularly, severe obesity), and/or a positive (first to second degree) family history of type 2 diabetes, and/or those belonging to certain race/ethnic groups such as American Indians/Native Americans, black Africans/African Americans, Hispanic (e.g. Mexican) Americans, Asians, East Asians, South Asians (Indian Peninsula) or Pacific Islanders, and/or those having insulin resistance or metabolic syndrome particularly with hypertension, acanthosis nigricans, dyslipidemia, polycystic ovarian disease, hyperandrogenism and/or non alcoholic fatty liver disease (NAFLD).
The therapeutic goals for glycemic control in pediatric type 2 diabetes patients may be as defined for adults with type 2 diabetes: 1. HbA1c <6-7%, and 2. Fasting plasma glucose levels <126 mg/dl.

If pharmacotherapy is required in pediatric type 2 diabetes patients, although there are many agents available to improve the metabolic abnormalities seen in subjects with type 2 diabetes, there are little data concerning their use in pediatrics. Metformin is the only oral agent that has been approved in pediatrics.

However, there remain some drawbacks to metformin therapy, such as e.g.
- currently available standard antidiabetic agents including metformin may be associated with a loss of glycaemic control over time,
- the posology of metformin is two to three times daily, which may lead to compliance issues,
- metformin tablets are of large dimensions which may be difficult for some children to swallow,
- metformin therapy is associated with a 20-30% incidence of gastrointestinal symptoms which may not be well tolerated in children and may lead to compliance issues,
- caution regarding the risk of lactic acidosis with metformin needs to be taken,
- metformin is contraindicated in patients with renal insufficiency, and
- metformin monotherapy may not result in the achievement of glycaemic goals in all children / adolescents.

In addition to oral antihyperglycemic agents, insulin can also be used to lower plasma glucose levels and return HbA1c levels to normal. However, insulin use can be rigorous and is often unwanted in the pediatric population due to its subcutaneous injectable route of delivery. Also, insulin is associated with a higher rate of hypoglycaemia and weight gain.

Therefore, it remains a need in the art to provide efficacious, safe and tolerable antidiabetic therapies for pediatric type 2 diabetes patients.

Further, it remains a need in the art to also provide antidiabetic therapies that are convenient for pediatric type 2 diabetes patients.
Further, it remains a need in the art to improve efficacy, safety, tolerability and/or convenience of existing antidiabetic therapies for paediatric type 2 diabetes patients.

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

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

An embodiment of paediatric diabetic patients within the meaning of this invention refers to patients ineligible for metformin therapy including - patients for whom metformin therapy is contraindicated, e.g. patients having one or more contraindications against metformin therapy according to label, such as for example patients with at least one contraindication selected from:

- renal disease, renal impairment or renal dysfunction (e.g., as specified by product information of locally approved metformin),
- dehydration,
- unstable or acute congestive heart failure,
- acute or chronic metabolic acidosis, and
- hereditary galactose intolerance;

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

A further embodiment of paediatric diabetic patients within the meaning of this invention refers to patients having renal disease, renal dysfunction, or insufficiency or impairment of renal function (including mild, moderate and severe renal impairment), e.g. as suggested by elevated serum creatinine levels (e.g. serum creatinine levels above the upper limit of normal for their age) or abnormal creatinine clearance.

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

In this context, for example, mild renal impairment in paediatric patients (e.g. < 40 kg) may be e.g. suggested by a creatinine clearance of >30 ml/min; moderate renal impairment may be e.g. suggested by a creatinine clearance of 10-30 ml/min; and severe renal impairment may be e.g. suggested by a creatinine clearance of < 10 ml/min. Patients with end-stage renal disease require dialysis.

A particular group of paediatric type 2 diabetes patients within the meaning of this invention refers to adolescent patients, particularly to the 10-17 year of age group (i.e. from 10 to less than 18 years of age).

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 proline or alanine residue. Due to this property DPP-4 inhibitors interfere with the plasma level of bioactive peptides including the peptide GLP-1 and are considered to be promising drugs for the treatment of diabetes mellitus.


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

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

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\text{(A)}
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In one embodiment, sitagliptin is in the form of its dihydrogenphosphate salt, i.e. sitagliptin phosphate. In a further embodiment, sitagliptin phosphate is in the form of a crystalline anhydrate or monohydrate. A class of this embodiment refers to sitagliptin phosphate monohydrate. Sitagliptin free base and pharmaceutically acceptable salts thereof are disclosed in US Patent No. 6,699,871 and in Example 7 of WO 03/004498. Crystalline sitagliptin phosphate monohydrate is disclosed in WO 2005/003135 and in WO 2007/050485.

For details, e.g. on a process to manufacture, to formulate or to use this compound or a salt thereof, reference is thus made to these documents.
A tablet formulation for sitagliptin is commercially available under the trade name Januvia®. A tablet formulation for sitagliptin/metformin combination is commercially available under the trade name Janumet®.

- Vildagliptin (LAF-237) having the structural formula B below is (2S)-[((3-hydroxyadamantan-1-y1)amino)acetyl]pyrrolidine-2-carbonitrile, also named (S)-1-[(3-hydroxy-1-adamantyl)amino]acetyl-2-cyano-pyrrolidine,

![Formula B]

Vildagliptin is specifically disclosed in US Patent No. 6,166,063 and in Example 1 of WO 00/34241. Specific salts of vildagliptin are disclosed in WO 2007/019255. A crystalline form of vildagliptin as well as a vildagliptin tablet formulation are disclosed in WO 2006/078593.

Vildagliptin can be formulated as described in WO 00/34241 or in WO 2005/067976. A modified release vildagliptin formulation is described in WO 2006/135723.

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

- Saxagliptin (BMS-4771 18) having the structural formula C below is (1S,3S,5S)-2-((2S)-2-amino-2-(3-hydroxyadamantan-1-yl)acetyl)-2-azabicyclo[3.1.0]hexane-3-carbonitrile, also named (S)-3-hydroxyadamantylglycine-L-c/s-4,5-methanoprolinenitrile,
Saxagliptin is specifically disclosed in US Patent No. 6,395,767 and in Example 60 of WO 01/68603.

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

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

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

In one embodiment, alogliptin is in the form of its benzoate salt, its hydrochloride salt or its tosylate salt each as disclosed in WO 2007/035629. A class of this embodiment refers to alogliptin benzoate. Polymorphs of alogliptin benzoate are disclosed in WO 2007/035372. A process for preparing alogliptin is disclosed in WO 2007/1 12368 and, specifically, in WO 2007/035629. Alogliptin (namely its benzoate salt) can be formulated in a tablet and administered as described in WO 2007/033266. Formulations of Aloglipitin with pioglitazone or metformin are described in WO 2008/093882 or WO 2009/01 1451, respectively. For details, e.g. on a process to manufacture, to formulate or to use this compound or a salt thereof, reference is thus made to these documents.

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

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

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

This compound and methods for its preparation are disclosed in WO 2005/000848. A process for preparing this compound (specifically its dihydrochloride salt) is also disclosed in
For details, e.g. on a process to manufacture, to formulate or to use this compound or a salt thereof, reference is thus made to these documents.

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

This compound and methods for its preparation are disclosed in WO 2005/1 6014 and US 7291618.
For details, e.g. on a process to manufacture, to formulate or to use this compound or a salt thereof, reference is thus made to these documents.

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

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

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

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

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

![Chemical Structure 1](image1)


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

![Chemical Structure 2](image2)

This compound and methods for its preparation are disclosed in WO 2006/16157 and US 2006/270701. For details, e.g. on a process to manufacture, to formulate or to use this compound or a salt thereof, reference is thus made to these documents.
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- 3-\{(2S,4S)-4-[4-(3-Methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-ylcarbonyl\}thiazolidine (also named teneligliptin) or a pharmaceutically acceptable salt thereof:

This compound and methods for its preparation are disclosed in WO 02/14271. Specific salts are disclosed in WO 2006/088129 and WO 2006/1 8127 (including hydrochloride, hydrobromide, inter alia). Combination therapy using this compound is described in WO 2006/129785. For details, e.g. on a process to manufacture, to formulate or to use this compound or a salt thereof, reference is thus made to these documents.

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

This compound and methods for its preparation are disclosed in WO 2005/047297, WO 2008/1 09681 and WO 2009/009751. Specific salts are disclosed in WO 2008/027273 (including citrate, tartrate). A formulation of this compound is described in WO 2008/144730. For details, e.g. on a process to manufacture, to formulate or to use this compound or a salt thereof, reference is thus made to these documents.

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

This compound and methods for its preparation are disclosed in WO 2005/075421, US 2008/146818 and WO 2008/1 4857. For details, e.g. on a process to manufacture, to formulate or to use this compound or a salt thereof, reference is thus made to these documents.

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

These compounds and methods for their preparation are disclosed in WO 2009/084497 and WO 2006/068163, respectively. For details, e.g. on a process to manufacture, to formulate or to use these compounds or salts thereof, reference is thus made to these documents.
For avoidance of any doubt, the disclosure of each of the foregoing documents cited above is specifically incorporated herein by reference in its entirety.

Within the scope of the present invention it has now surprisingly been found that DPP-4 inhibitors as defined herein have unexpected and advantageous properties, which make them particularly suitable for treating and/or preventing (including preventing or slowing the progression or delaying the onset) of metabolic diseases, particularly diabetes (especially type 2 diabetes mellitus and conditions related thereto, including diabetic complications), in paediatric type 2 diabetes patients.

Thus, the present invention provides a DPP-4 inhibitor as defined herein for use in the treatment and/or prevention of metabolic diseases, particularly type 2 diabetes mellitus, in paediatric patients, particularly from 10 to less than 18 years of age.

The present invention further provides a DPP-4 inhibitor as defined herein for use in the treatment and/or prevention of paediatric type 2 diabetes.

The present invention further provides the use of a DPP-4 inhibitor as defined herein for the manufacture of a pharmaceutical composition for treating and/or preventing metabolic diseases, particularly type 2 diabetes mellitus, in paediatric patients, including, for example, in patient populations being at high risk for paediatric type 2 diabetes as described herein.

The present invention further provides a pharmaceutical composition for use in the treatment and/or prevention of metabolic diseases, particularly type 2 diabetes mellitus, in paediatric patients, said pharmaceutical composition comprising a DPP-4 inhibitor as defined herein and optionally one or more pharmaceutically acceptable carriers and/or diluents.

The present invention further provides a fixed or non-fixed combination including a kit-of-parts for use in the treatment and/or prevention of metabolic diseases, particularly type 2 diabetes mellitus, in paediatric patients, said combination comprising a DPP-4 inhibitor as defined herein and one or more other active substances, e.g. any of those mentioned herein, especially metformin.
The present invention further provides the use of a DPP-4 inhibitor as defined herein in combination with one or more other active substances, such as e.g. any of those mentioned herein, especially metformin, for the manufacture of a pharmaceutical composition for treatment and/or prevention of metabolic diseases, particularly type 2 diabetes mellitus, in paediatric patients.

The present invention further provides a pharmaceutical composition for use in the treatment and/or prevention of metabolic diseases, particularly type 2 diabetes mellitus, in paediatric patients, said pharmaceutical composition comprising a DPP-4 inhibitor as defined herein and, optionally, one or more other active substances, such as e.g. any of those mentioned herein, especially metformin.

The present invention further provides a method of treating and/or preventing metabolic diseases, particularly type 2 diabetes mellitus, in paediatric patients, said method comprising administering to a subject in need thereof (particularly a human paediatric patient) an effective amount of a DPP-4 inhibitor as defined herein, optionally alone or in combination, such as e.g. separately, sequentially, simultaneously, concurrently or chronologically staggered with an effective amount of one or more other active substances, such as e.g. any of those mentioned herein, especially metformin.

The present invention further provides the use of a DPP-4 inhibitor as defined herein optionally in (add-on or initial) combination with one or more other active substances, such as e.g. selected from those mentioned herein, for the therapies described herein.

The present invention further provides the use of a DPP-4 inhibitor as defined herein in combination with (e.g. as initial combination or as add-on to) one or more standard medications, such as e.g. selected from those mentioned herein, for the therapies described herein.

The present invention further provides a DPP-4 inhibitor as defined herein for use in monotherapy or in (add-on or initial) combination therapy.

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).
Unless otherwise noted, combination within the meaning of this invention may include fixed or free combination.

Further, within the meaning of this invention, the DPP-4 inhibitors as defined herein may be useful in one or more of the following methods:
- for preventing, slowing progression of, delaying, or treating a metabolic disorder;
- for improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c;
- for preventing, slowing, delaying or reversing progression from impaired glucose tolerance, impaired fasting blood glucose, insulin resistance and/or from metabolic syndrome to type 2 diabetes mellitus;
- for preventing, reducing the risk of, slowing progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus;
- for reducing body weight or preventing an increase in body weight or facilitating a reduction in body weight;
- for reducing the risk for adverse effects associated with conventional (oral) antihyperglycemic medication;
- for preventing or treating the degeneration of pancreatic beta cells and/or for improving and/or restoring the functionality of pancreatic beta cells and/or stimulating and/or restoring the functionality of pancreatic insulin secretion; and/or
- for maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance;

particularly in paediatric diabetes (especially type 2 diabetes) patients.

Examples of such metabolic diseases or disorders amenable by the therapy of this invention particularly in paediatric patients may include, without being restricted to, Type 1 diabetes, Type 2 diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypercholesterolemia, dyslipidemia, metabolic syndrome, obesity, hypertension, chronic systemic inflammation, retinopathy, neuropathy, nephropathy, atherosclerosis, endothelial dysfunction and osteoporosis.
The present invention further provides a DPP-4 inhibitor as defined herein, optionally in combination with one or more other active substances, such as e.g. any of those mentioned herein, for use in one or more of the following methods:

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

- improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbAlc;

- preventing, slowing, delaying or reversing progression from pre-diabetes, impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or from metabolic syndrome to type 2 diabetes mellitus;

- preventing, reducing the risk of, slowing the progression of, delaying or treating of complications of diabetes mellitus such as micro- and macrovascular diseases, such as nephropathy, micro- or macroalbuminuria, proteinuria, retinopathy, cataracts, neuropathy, learning or memory impairment, neurodegenerative or cognitive disorders, cardio- or cerebrovascular diseases, tissue ischaemia, diabetic foot or ulcus, atherosclerosis, hypertension, endothelial dysfunction, myocardial infarction, acute coronary syndrome, unstable angina pectoris, stable angina pectoris, peripheral arterial occlusive disease, cardiomyopathy, heart failure, heart rhythm disorders, vascular restenosis, and/or stroke;

- reducing body weight and/or body fat or preventing an increase in body weight and/or body fat or facilitating a reduction in body weight and/or body fat;

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

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

particularly in a paediatric diabetes (especially type 2 diabetes) patient, especially from 10 to less than 18 years of age.

In one embodiment, the therapies described herein may be used in naïve patients. In another embodiment, the therapies described herein may be used in patients experienced with therapy, e.g. with conventional (oral) antidiabetic medication (e.g. insulin and/or, particularly, metformin).

In a further embodiment, the therapies described herein may be used in paediatric type 2 diabetes patients who are without associated islet cell autoimmunity, e.g. negative for islet cell antigen auto-antibodies and/or glutamic acid decarboxylase auto-antibodies and/or insulin auto-antibodies, and, optionally, with persistent elevation of C-peptide levels, e.g. stimulated serum C-peptide levels ≥1.5 ng/ml (at 90 min following a boost challenge).

In a further embodiment, the therapies described herein may be used in paediatric type 2 diabetes patients (particularly from 10 to below 18 years of age) who are obese and, optionally, with high fasting C-peptide concentrations and/or residual insulin production.

In a further embodiment, the therapies described herein may be used in paediatric type 2 diabetes patients (particularly from 10 to below 18 years of age) who are non-obese, without associated islet cell autoimmunity, and with high fasting C-peptide concentrations and/or residual insulin production.

In a further embodiment, the therapies described herein may be used in at-risk paediatric type 2 diabetes patient groups, e.g. in those paediatric type 2 diabetes patients who are associated with obesity and/or a positive (first to second degree) family history of type 2 diabetes, and/or those belonging to certain race/ethnic groups such as those of American
Indian/Native American descent, black African descent, Hispanic (e.g. Mexican) Americans, Asians, East Asians, South Asians (Indian Peninsula) or Pacific Islanders, and/or those having insulin resistance or metabolic syndrome particularly with hypertension, acanthosis nigricans, dyslipidemia, polycystic ovarian disease, hyperandrogenism and/or non alcoholic fatty liver disease (NAFLD).

A special embodiment of this invention refers to a DPP-4 inhibitor as defined herein for use in improving glycemic control in paediatric patients with type 2 diabetes mellitus, especially in adolescent patients, particularly in the 10-17 year of age group (or from 10 to less than 18 years of age).

Another special embodiment of this invention refers to a DPP-4 inhibitor as defined herein for use in the treatment of paediatric type 2 diabetes mellitus, especially in at-risk patient groups, e.g. as disclosed herein.

Another special embodiment of this invention refers to a DPP-4 inhibitor as defined herein for improving glycemic control in paediatric type 2 diabetes patients 10-17 years of age (or from 10 to less than 18 years of age) with inadequate glycemic control (e.g. HbA1c >7%) despite therapy with metformin alone, for example despite maximal tolerated dose of oral therapy with metformin.

Another special embodiment of this invention refers to a DPP-4 inhibitor as defined herein for improving glycemic control in paediatric type 2 diabetes patients 10-17 years of age (or from 10 to less than 18 years of age) with inadequate glycemic control (e.g. HbA1c >7%), e.g. despite diet, exercise and/or therapy with metformin alone, wherein said DPP-4 inhibitor may be used as replacement of metformin or as add-on or initial combination therapy with metformin, particularly as add-on combination therapy with metformin.

Another special embodiment of this invention refers to a DPP-4 inhibitor as defined herein for use in obese adolescent type 2 diabetes patients, particularly 10-17 years of age (or from 10 to less than 18 years of age).

Another special embodiment of this invention refers to a DPP-4 inhibitor as defined herein for use in reducing the risk of complications of diabetes mellitus in paediatric type 2 diabetes.
In another special embodiment, the therapies described herein may be used in paediatric type 2 diabetes patients (particularly from 10 to below 18 years of age) who are obese.

Other aspects of the present invention become apparent to the skilled person from the foregoing and following remarks.

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

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

Another embodiment of this invention refers to a DPP-4 inhibitor for use in the treatment and/or prevention of metabolic diseases (particularly type 2 diabetes mellitus) in paediatric type 2 diabetes patients with secondary oral antidiabetic drug failure, wherein said patients are also with failure in or ineligible for metformin therapy or in need of metformin dose reduction due to intolerability or contraindication against metformin, such as e.g. any of those intolerabilities or contraindications defined hereinbefore or hereinafter.

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

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

- 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 radiolabeled carbon (^14C) substance oral dose);

- The DPP-4 inhibitor is excreted mainly unchanged as parent drug (e.g. with a mean of > 70%, or > 80%, or, preferably, 90% of excreted radioactivity in urine and faeces after oral dosing of radiolabeled carbon (^14C) substance), and/or which is eliminated to a non-substantial or only to a minor extent via metabolism (e.g. < 30%, or < 20%, or, preferably, 10%);

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

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

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

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

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

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

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

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

\[
\begin{array}{c}
\text{R}_1 \text{N} \text{O} \text{N} \text{R}_2 \\
\text{O} \text{N} \text{N} \text{R}_2 \\
\end{array}
\]

(I)

or formula (II)

\[
\begin{array}{c}
\text{R}_1 \text{N} \text{O} \text{N} \text{R}_2 \\
\text{O} \text{N} \text{N} \text{CN} \text{R}_2 \\
\end{array}
\]

(II)

or formula (III)

\[
\begin{array}{c}
\text{R}_1 \text{N} \text{O} \text{N} \text{R}_2 \\
\text{O} \text{N} \text{N} \text{CN} \text{R}_2 \\
\end{array}
\]

(III)

or formula (IV)

\[
\begin{array}{c}
\text{R}_1 \text{N} \text{O} \text{N} \text{R}_2 \\
\text{O} \text{N} \text{N} \text{CN} \text{R}_2 \\
\end{array}
\]

(IV)

wherein \( R_1 \) denotes \((1,5)\text{naphthyridin-2-yl})\text{methyl}, (\text{quinazolin-2-yl})\text{methyl}, (\text{quinoxalin-6-yl})\text{methyl}, (\text{4-methyl-quinazolin-2-yl})\text{methyl}, 2-\text{cyano-benzyl}, (\text{3-cyano-quinolin-2-yl})\text{methyl}, (\text{3-cyano-pyridin-2-yl})\text{methyl}, (\text{4-methyl-pyrimidin-2-yl})\text{methyl}, (\text{4,6-dimethyl-pyrimidin-2-yl})\text{methyl} and \( R_2 \) denotes 3-\((R)\)-amino-piperidin-1-yl, (2-\text{amino-2-methyl-propyl})-methylamino
or (2-(S)-amino-propyl)-methylamino,
or its pharmaceutically acceptable salt.

In a second embodiment (embodiment B), a DPP-4 inhibitor in the context of the present invention is a DPP-4 inhibitor selected from the group consisting of sitagliptin, vildagliptin, saxagliptin, alogliptin,
(2S)-1-[(2-(5-Methyl-2-phenyl-oxazol-4-yl)-ethylamino)-acetyl]-pyrrolidine-2-carbonitrile,
(2S)-1-[[1,1,1,-Dimethyl-3-(4-pyridin-3-yl-imidazol-1-yl)-propylamino]-acetyl]-pyrrolidine-2-carbonitrile,
(S)-1-[(2S,3S,1 1bS)-2-Amino-9,10-dimethoxy-1,3,4,6,7,1 1b-hexahydro-2H-pyrido[2,1-a]-isoquinolinin-3-yl)-4-fluoromethyl-pyrrolidin-2-one,
(3,3-Difluoropyrrolidin-1-yl)-(2S,4S)-4-(4-(pyrimidin-2-yl)piperazin-1-yl)pyrrolidin-2-yl)methanone,
(1(3S,4S)-4-amino-1 -(4-(3,3-difluoropyrrolidin-1-y1)pyrrolidin-3-yl)-5,5-difluoropiperidin-2-one,
(2S,4S)-1-[2-[(3S,1R)-3-(1H-1,2,4-Triazol-1-ylmethyl)cyclopentylamino]-acetyl]-4-fluoropyrrolidine-2-carbonitrile,
(R)-2-[6-(3-Amino-piperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-4-fluoro-benzonitrile,
5-[(S)-2-[(S)-2-Cyano-pyrrolidin-1-yl)-2-oxo-ethylamino]-propyl]-5-(1 H-tetrazol-5-yl)-10,1 1-dihydro-5H-dibenzo[a,d]cycloheptene-2,8-dicarboxylic acid bis-dimethylamide,
3-[(2S,4S)-4-[4-(3-Methyl-1-phenyl-1H-pyrazol-5-yl)piperazin-1-yl]pyrrolidin-2-ylcarbonyl]thiazolidine,
[(2R)-1-[(3R)-pyrrolidin-3-ylamino]acetyl]pyrrolidin-2-yl]boronic acid,
(2S,4S)-1-[(4-ethoxycarbonylbicyclo[2.2.2]oct-1-yl)amino]acetyl]-4-fluoropyrrolidine-2-carbonitrile,
2-[(6-[(3R)-3-amino-3-methylpiperidin-1 -yl]-1,3-dimethyl-2,4-dioxo-1 ,2,3,4-tetrahydro-5H-pyrrolo[3,2-d]pyrimidin-5-yl]methyl]-4-fluorobenzonitrile, and
6-[(3R)-3-amino-piperidin-1 -yl]-(5-(2-chloro-5-fluoro-benzyl)-1 ,3-dimethyl-1 ,5-dihydro-
pyrrolo[3,2-d]pyrimidine-2,4-dione,
or its pharmaceutically acceptable salt.

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

![Chemical Structure](image1)

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

![Chemical Structure](image2)

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

![Chemical Structure](image3)

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

![Chemical Structure](image4)
• 1-[(4-Methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyin-1-yl)-8-[(2-amino-2-methyl-propyl)-methylamino]-xanthine (compare WO 2006/029769, example 2(1)):

![Chemical Structure 1](image1)

5 • 1-[(3-Cyano-quinolin-2-yl)methyl]-3-methyl-7-(2-butyin-1-yl)-8-((R)-3-amino-piperidin-1-yl)-xanthine (compare WO 2005/085246, example 1(39)):

![Chemical Structure 2](image2)

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

![Chemical Structure 3](image3)

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

![Chemical Structure 4](image4)
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- 1-[(3-Cyano-pyridin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((R)-3-amino-piperidin-1-yl)-xanthine (compare WO 2005/085246, example 1(52)):

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

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

- 1-[(Quinoxalin-6-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-((R)-3-amino-piperidin-1-yl)-xanthine (compare WO 2005/085246, example 1(83)): 
These DPP-4 inhibitors are distinguished from structurally comparable DPP-4 inhibitors, as they combine exceptional potency and a long-lasting effect with favourable pharmacological properties, receptor selectivity and a favourable side-effect profile or bring about unexpected therapeutic advantages or improvements when combined with other pharmaceutical active substances. Their preparation is disclosed in the publications mentioned.

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

Unless otherwise noted, according to this invention it is to be understood that the definitions of the active compounds (including the DPP-4 inhibitors) mentioned hereinabove and hereinbelow also comprise their pharmaceutically acceptable salts as well as hydrates, solvates and polymorphic forms thereof. With respect to salts, hydrates and polymorphic forms thereof, particular reference is made to those which are referred to herein.

With respect to embodiment A, the methods of synthesis for the DPP-4 inhibitors according to embodiment A of this invention are known to the skilled person. Advantageously, the DPP-4 inhibitors according to embodiment A of this invention can be prepared using synthetic methods as described in the literature. Thus, for example, purine derivatives of formula (I) can be obtained as described in WO 2002/068420, WO 2004/018468, WO 2005/085246, WO 2006/029769 or WO 2006/048427, the disclosures of which are incorporated herein.

Purine derivatives of formula (II) can be obtained as described, for example, in WO 2004/050658 or WO 2005/110999, the disclosures of which are incorporated herein. Purine derivatives of formula (III) and (IV) can be obtained as described, for example, in WO 2006/068163, WO 2007/071738 or WO 2008/017670, the disclosures of which are incorporated herein. The preparation of those DPP-4 inhibitors, which are specifically mentioned hereinabove, is disclosed in the publications mentioned in connection therewith. Polymorphous crystal modifications and formulations of particular DPP-4 inhibitors are disclosed in WO 2007/128721 and WO 2007/128724, respectively, the disclosures of which are incorporated herein in their entireties. Formulations of particular DPP-4 inhibitors with metformin or other combination partners are described in WO 2009/121945, the disclosure of which is incorporated herein in its entirety. Typical dosage strengths of the dual fixed
combination of BI 1356 / metformin 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.

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.

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

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

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

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

Examples of suitable binders for compounds according to embodiment A include copovidone
(copolymerisates of vinylpyrrolidon with other vinylderivates), hydroxypropyl methylcellulose
Examples of suitable disintegrants for compounds according to embodiment A include corn starch or crospovidone.

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

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

Suitable granulation methods are

- wet granulation in the intensive mixer followed by fluidised bed drying;
- one-pot granulation;
- fluidised bed granulation; or
- dry granulation (e.g. by roller compaction) with suitable excipients and subsequent tabletting or packing into capsules.

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

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

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

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

A suitable blister pack, e.g. for a pharmaceutical composition or combination comprising a DPP-4 inhibitor according to embodiment A of the invention, comprises or is formed of a top foil (which is breachable by the tablets) and a bottom part (which contains pockets for the tablets). The top foil may contain a metallic foil, particularly an aluminium or aluminium alloy foil (e.g. having a thickness of 20µm to 45µm, preferably 20µm to 25µm) that is coated with a heat-sealing polymer layer on its inner side (sealing side). The bottom part may contain a multi-layer polymer foil (such as e.g. polyvinyl 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).

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

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

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

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

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

A dosage range of the DPP-4 inhibitor vildagliptin is usually between 10 and 150 mg daily, in particular between 25 and 150 mg, 25 and 100 mg or 25 and 50 mg or 50 and 100 mg daily. Particular examples of daily oral dosage are 25, 30, 35, 45, 50, 55, 60, 80, 100 or 150 mg. In a more particular aspect, the daily administration of vildagliptin may be between 25 and 150 mg or between 50 and 100 mg. In another more particular aspect, the daily administration of
vildagliptin may be 50 or 100 mg. The application of the active ingredient may occur up to
three times a day, preferably one or two times a day. Particular dosage strengths are 50 mg
or 100 mg vildagliptin. Typical dosage strengths of the dual combination of vildagliptin /
metformin are 50/850 mg and 50/1000 mg.

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

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

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

Particular daily oral doses of BI 1356 for paediatric use may be 1 mg or 5 mg, each
preferably administered orally once daily.
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). BI 1356 exhibits high potency, 24h duration of action, and a wide therapeutic window. In adult 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 1 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_{AUC} ≤ 1.4 with doses above 1 mg) and preserving a long-lasting effect on DPP-4 inhibition (e.g. with almost complete (> 90%) DPP-4 inhibition at the 5 mg and 10 mg dose levels, i.e. 92.3 and 97.3% inhibition at steady state, respectively, and > 80% inhibition over a 24h interval after drug intake), as well as significant decrease in 2h postprandial blood glucose excursions by ≥ 80% (already on Day 1) in doses ≥ 2.5 mg, and with the cumulative amount of unchanged parent compound excreted in urine on Day 1 being below 1% of the administered dose and increasing to not more than about 3-6% on Day 12 (renal clearance CL_{A,SS} is from about 14 to about 70 mL/min for the administered oral doses, e.g. for the 5 mg dose renal clearance is about 70 mL/min). In people with type 2 diabetes BI 1356 shows a placebo-like safety and tolerability. With low doses of about ≥ 5 mg, BI 1356 acts as a true once-daily oral drug with a full 24 h duration of DPP-4 inhibition. At therapeutic oral dose levels, BI 1356 is mainly excreted via the liver and only to a minor extent (about < 7% of the administered oral dose) via the kidney. BI 1356 is primarily excreted unchanged via the bile. The fraction of BI 1356 eliminated via the kidneys increases only very slightly over time and with increasing dose, so that there will likely be no need to modify the dose of BI 1356 based on the patients’ renal function. The non-renal elimination of BI 1356 in combination with its low accumulation potential and broad safety margin may be of significant benefit in a patient population that has a high prevalence of renal insufficiency and diabetic nephropathy.
Table 1: Geometric mean (gMean) and geometric coefficient of variation (gCV) of pharmacokinetic parameters of BI 1356 at steady state (Day 12)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1 mg gMean (gCV)</th>
<th>2.5 mg gMean (gCV)</th>
<th>5 mg gMean (gCV)</th>
<th>10 mg gMean (gCV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUCo-24 [nmol-h/L]</td>
<td>40.2 (39.7)</td>
<td>85.3 (22.7)</td>
<td>118 (16.0)</td>
<td>161 (15.7)</td>
</tr>
<tr>
<td>AUC_{T_{ss}} [nmol-h/L]</td>
<td>81.7 (28.3)</td>
<td>117 (16.3)</td>
<td>158 (10.1)</td>
<td>190 (17.4)</td>
</tr>
<tr>
<td>C_{max} [nmol/L]</td>
<td>3.13 (43.2)</td>
<td>5.25 (24.5)</td>
<td>8.32 (42.4)</td>
<td>9.69 (29.8)</td>
</tr>
<tr>
<td>C_{max,ss} [nmol/L]</td>
<td>4.53 (29.0)</td>
<td>6.58 (23.0)</td>
<td>11.1 (21.7)</td>
<td>13.6 (29.6)</td>
</tr>
<tr>
<td>t_{max} [h]</td>
<td>1.50 [1.00 - 3.00]</td>
<td>2.00 [1.00 - 3.00]</td>
<td>1.75 [0.92 - 6.02]</td>
<td>2.00 [1.50 - 6.00]</td>
</tr>
<tr>
<td>t_{max,ss} [h]</td>
<td>1.48 [1.00 - 3.00]</td>
<td>1.42 [1.00 - 3.00]</td>
<td>1.53 [1.00 - 3.00]</td>
<td>1.34 [0.50 - 3.00]</td>
</tr>
<tr>
<td>T_{v4,es} [h]</td>
<td>121 (21.3)</td>
<td>113 (10.2)</td>
<td>131 (17.4)</td>
<td>130 (11.7)</td>
</tr>
<tr>
<td>Accumulation</td>
<td>23.9 (44.0)</td>
<td>12.5 (18.2)</td>
<td>11.4 (37.4)</td>
<td>8.59 (81.2)</td>
</tr>
<tr>
<td>t_{vi} [h]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>f_{A,C_{max}}</td>
<td>1.44 (25.6)</td>
<td>1.25 (10.6)</td>
<td>1.33 (30.0)</td>
<td>1.40 (47.7)</td>
</tr>
<tr>
<td>RA_{AUC}</td>
<td>2.03 (30.7)</td>
<td>1.37 (8.2)</td>
<td>1.33 (15.0)</td>
<td>1.18 (23.4)</td>
</tr>
<tr>
<td>f_{e_{O24}} [%]</td>
<td>NC</td>
<td>0.139 (51.2)</td>
<td>0.453 (125)</td>
<td>0.919 (115)</td>
</tr>
<tr>
<td>f_{e_{ss}} [%]</td>
<td>3.34 (38.3)</td>
<td>3.06 (45.1)</td>
<td>6.27 (42.2)</td>
<td>3.22 (34.2)</td>
</tr>
<tr>
<td>CLR_{ss} [mL/min]</td>
<td>14.0 (24.2)</td>
<td>23.1 (39.3)</td>
<td>70 (35.0)</td>
<td>59.5 (22.5)</td>
</tr>
</tbody>
</table>

* median and range [min-max]
NC not calculated as most values below lower limit of quantification
As different metabolic functional disorders often occur simultaneously, it is quite often indicated to combine a number of different active principles with one another. Thus, depending on the functional disorders diagnosed, improved treatment outcomes may be obtained if a DPP-4 inhibitor is combined with active substances customary for the respective disorders, such as e.g. one or more active substances selected from among the other antidiabetic substances, especially active substances that lower the blood sugar level or the lipid level in the blood, raise the HDL level in the blood, lower blood pressure or are indicated in the treatment of atherosclerosis or obesity.

The DPP-4 inhibitors mentioned above - besides their use in mono-therapy - may also be used in conjunction with other active substances, by means of which improved treatment results can be obtained. Such a combined treatment may be given as a free combination of the substances or in the form of a fixed combination, for example in a tablet or capsule.

Pharmaceutical formulations of the combination partner needed for this may either be obtained commercially as pharmaceutical compositions or may be formulated by the skilled man using conventional methods. The active substances which may be obtained commercially as pharmaceutical compositions are described in numerous places in the prior art, for example in the list of drugs that appears annually, the "Rote Liste®" of the federal association of the pharmaceutical industry, or in the annually updated compilation of manufacturers' information on prescription drugs known as the "Physicians' Desk Reference".

Examples of antidiabetic combination partners are metformin; sulphonylureas such as glibenclamide, tolbutamide, glimepiride, glipizide, gliclodon, glibornuride and gliclazide; nateglinide; repaglinide; thiazolidinediones such as rosiglitazone and pioglitazone; PPAR gamma modulators such as metaglidades; PPAR-gamma agonists such as GI 262570; PPAR-gamma antagonists; PPAR-gamma/alpha modulators such as tesaglitzar, muraglitzar, aleglitzar, indeglitzar and KRP297; PPAR-gamma/alpha/delta modulators; AMPK-activators such as AICAR; acetyl-CoA carboxylase (ACC1 and ACC2) inhibitors; diacylglycerol-acetyltransferase (DGAT) inhibitors; pancreatic beta cell GCRP agonists such as SMT3-receptor-agonists and GPR1 19; 11β-HSD-inhibitors; FGF19 agonists or analogues; alpha-glucosidase blockers such as acarbose, voglibose and miglitol; alpha2-agonists; insulin and insulin analogues such as human insulin, insulin lispro, insulin glulisin, r-DNA-insulinaspart, NPH insulin, insulin detemir, insulin zinc suspension and insulin glargin;
Gastric inhibitory Peptide (GIP); amylin and amylin analogues (e.g. pramlintide or
davalintide); GLP-1 and GLP-1 analogues such as Exendin-4, e.g. exenatide, exenatide
LAR, liraglutide, taspoglutide, lixisenatide (AVE-0010), LY-2428757 (a PEGylated version of
GLP-1), LY-2189265 (GLP-1 analogue linked to IgG4-Fc heavy chain), semaglutide or
albiglutide; SGLT2-inhibitors such as e.g. dapagliflozin, sergliflozin (KGT-1251), atigliflozin,
canagliflozin or (1S)-1,5-anhydro-1-[3-(1-benzothiophen-2-ylmethyl)-4-fluorophenyl]-D-
glucitol; inhibitors of protein tyrosine-phosphatase (e.g. trodusquemeine); inhibitors of glucose-
6-phosphatase; fructose-1,6-bisphosphatase modulators; glycogen phosphorylase
modulators; glucagon receptor antagonists; phosphoanpyruvatecarboxykinase (PEPCK)
inhibitors; pyruvate dehydrogenasekinase (PDK) inhibitors; inhibitors of tyrosine-kinases
(50 mg to 600 mg) such as PDGF-receptor-kinase (cf. EP-A-564409, WO 98/35958, US
5093330, WO 2004/005281 , and WO 2006/041976); 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, solabeegron, talibegron, N-5984, GRC-1087, rafabegron, FMP825;
aldosereuctase inhibitors such as AS 3201, zenaresetat, fidarestat, epalrestat, ranirestat,
NZ-314, CP-744809, and CT-112; SGLT-1 or SGLT-2 inhibitors; KV 1.3 channel inhibitors;
GPR40 modulators; SCD-1 inhibitors; CCR-2 antagonists; dopamine receptor agonists
(bromocriptine mesylate [Cycloset]); sirtuin stimulants; and other DPP IV inhibitors.

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

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

A dosage of pioglitazone is usually of about 1-10 mg, 15 mg, 30 mg, or 45 mg once a day.
Rosiglitazone is usually given in doses from 4 to 8 mg once (or divided twice) a day (typical dosage strengths are 2, 4 and 8 mg).

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

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

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

A dual combination of glibenclamide/metformin is usually given in doses from 1.25/250 once daily to 10/1000 mg twice daily. (typical dosage strengths are 1.25/250, 2.5/500 and 5/500 mg).

A dual combination of glipizide/metformin is usually given in doses from 2.5/250 to 10/1000 mg twice daily (typical dosage strengths are 2.5/250, 2.5/500 and 5/500 mg).

A dual combination of glimepiride/metformin is usually given in doses from 1/250 to 4/1000 mg twice daily.

A dual combination of rosiglitazone/glimepiride is usually given in doses from 4/1 once or twice daily to 4/2 mg twice daily (typical dosage strengths are 4/1, 4/2, 4/4, 8/2 and 8/4 mg).

A dual combination of pioglitazone/glimepiride is usually given in doses from 30/2 to 30/4 mg once daily (typical dosage strengths are 30/4 and 45/4 mg).

A dual combination of rosiglitazone/metformin is usually given in doses from 1/500 to 4/1000 mg twice daily (typical dosage strengths are 1/500, 2/500, 4/500, 2/1000 and 4/1000 mg).

A dual combination of pioglitazone/metformin is usually given in doses from 15/500 once or twice daily to 15/850 mg thrice daily (typical dosage strengths are 15/500 and 15/850 mg).

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

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

Examples of combination partners that lower the lipid level in the blood are HMG-CoA-reductase inhibitors such as simvastatin, atorvastatin, lovastatin, fluvastatin, pravastatin, pitavastatin and rosuvastatin; fibrates such as bezafibrate, fenofibrate, clofibrate, gemfibrozil, etofibrate and etofyllinclofibrate; nicotinic acid and the derivatives thereof such as acipimox; PPAR-alpha agonists; PPAR-delta agonists; inhibitors of acyl-coenzyme A:cholesterol acyltransferase (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 colesvelam; 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 (dalce trapib) or compound 12 from WO 2007/005572 (anacetrapib); LDL receptor modulators; MTP inhibitors (e.g. lomitapide); and ApoBIOO antisense RNA.

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

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

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

Examples of combination partners which increase the HDL level in the blood are Cholesteryl Ester Transfer Protein (CETP) inhibitors; inhibitors of endothelial lipase; regulators of ABC1;
LXRalpha antagonists; LXRbeta agonists; PPAR-delta agonists; LXRalpha/beta regulators, and substances that increase the expression and/or plasma concentration of apolipoprotein A-I.

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

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

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

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

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

B1356, a Potent and Selective DPP-4 Inhibitor, is safe and efficacious in Patients with Inadequately Controlled Type 2 Diabetes despite Metformin Therapy

Efficacy and safety of B1 1356 (1, 5, or 10 mg qd), a potent and selective dipeptidyl peptidase-4 (DPP-4) inhibitor, was examined in inadequately controlled, metformin-treated (MET, ≥1 g daily) adult type 2 diabetic patients (T2DM; HbA1c at baseline 7.5-10.0%).

Effects were compared to add-on of placebo (PBO) or of open label glimepiride (GLIM; 1 to 3 mg qd) in a 12-week randomized, double-blind study. Antidiabetic medication other than metformin was washed out for 6 weeks (34.7% of the patients).

The primary endpoint was change from baseline in HbA1c, adjusted for prior antidiabetic medication. 333 patients (mean baseline HbA1c 8.3%; fasting plasma glucose [FPG] 185 mg/dL) were randomized to B1 1356, PBO or open-label GLIM. After 12 weeks, B1 1356 treatment resulted in significant placebo corrected mean reductions in HbA1c (B1 1356 1 mg, n=65, -0.39%; 5 mg, n=66, -0.75%; 10 mg, n=66, -0.73%). Patients receiving GLIM demonstrated a slightly greater mean PBO corrected reduction in HbA1c at Week 12 (n=64, -0.90%). Reductions in FPG from baseline to Week 12 with B1 1356 were statistically significant (1 mg, -19 mg/dL; 5 mg, -35 mg/dL; 10 mg, -30 mg/dL). Hence, a dose-response relationship was demonstrated for HbA1c and FPG, reaching an effect plateau at 5 mg of B1 1356. For this dose, >80% DPP-4 inhibition at trough in >80% of the patients at week 12 was achieved.

In total, 106 patients (43.1%) experienced adverse events (AEs) with similar incidences across all treatments. Most frequently reported episodes were nasopharyngitis (7.5%), diarrhoea (3.3%), and nausea (3.0%). Drug-related hypoglycaemia did not occur with B1 1356 or PBO but in 3 patients receiving GLIM. Ten patients (3.7%) experienced serious AEs but none of these events were considered drug-related.

The addition of B1 1356 to MET in patients with T2DM inadequately controlled on MET alone achieved clinically relevant and statistically significant reductions in HbA1c. Combination treatment with B1 1356 1, 5, and 10 mg and MET was well tolerated and no case of hypoglycaemia was reported. The incidence of AEs was comparable with B1 1356 and PBO.
BI 1356, a Potent and Selective DPP-4 Inhibitor, Does Not Prolong the QT Interval when Given in Therapeutic and 20-fold Supratherapeutic Doses

A thorough QT study of BI 1356, a potent and selective dipeptidyl peptidase-4 inhibitor, was performed in adult healthy female and male subjects, using 5 mg (therapeutic dose) and 100 mg. The study was a randomised, single-dose, placebo-controlled, double-blind, four-way crossover study with open-label moxifloxacin (400 mg) as positive control. Triplicate 12-lead electrocardiograms (ECGs) of 10 seconds' duration were recorded for all subjects pre-dose and at various time points over a 24-h period after each treatment. The primary parameter was the subject-specific heart rate corrected QT interval (QTcI). Forty-four subjects were enrolled, 26 (59.1%) of whom were male. The mean age was 36.4 years (range 22 to 48 years). The maximum mean concentration after single oral administration was 7.05 nM (28.5% gCV) for 5 mg BI 1356, and 267 nM (66.6% gCV) for 100 mg BI 1356.

The upper limits of the one-sided 95% confidence intervals of the adjusted mean QTcI change from baseline (1-4 h) of BI 1356 compared with placebo were 0.5 ms (5 mg) and -0.9 ms (100 mg) with mean estimates of -1.1 and -2.5 ms, respectively. Over the 24 h observation period, the maximum upper limits of the one-sided 95% confidence intervals for the adjusted QTcI changes from baseline compared with placebo were below 2.5 ms for both doses and thus well below the non-inferiority margin of 10 ms. Assay sensitivity of the trial was shown by the largest estimated effect size of the QTcI difference between moxifloxacin and placebo being 10.5 ms with a lower limit of the two-sided 90% confidence interval of 8.1 ms.

There were no notable changes in heart rate or other ECG parameters, and overall the safety assessment yielded similar results for all treatments.

In summary, single dose administration of therapeutic (5 mg) and supratherapeutic (100 mg) doses of BI 1356 did not prolong the QT interval. The supratherapeutic dose resulted in maximum plasma concentrations that were about 38-fold higher than those obtained after the administration of the therapeutic dose of 5 mg, providing further support for the unique safety profile of BI 1356 within the class of DPP-4 inhibitors.
Claims

1. A DPP-4 inhibitor, which is
   of formula (I)
   \[
   R_1\begin{array}{c}\text{O} \\
   \text{N}
   \end{array}\begin{array}{c}\text{N} \\
   \text{N}
   \end{array}\begin{array}{c}\\
   \text{O}
   \end{array}\begin{array}{c}\\
   \text{R}_2
   \end{array}
   \]

   or of formula (II)
   \[
   R_1\begin{array}{c}\text{O} \\
   \text{N}
   \end{array}\begin{array}{c}\text{N} \\
   \text{N}
   \end{array}\begin{array}{c}\text{O} \\
   \text{CN}
   \end{array}\begin{array}{c}\text{R}_2
   \end{array}
   \]

   or of formula (III)
   \[
   R_1\begin{array}{c}\text{O} \\
   \text{N}
   \end{array}\begin{array}{c}\text{N} \\
   \text{N}
   \end{array}\begin{array}{c}\\
   \text{CN}
   \end{array}\begin{array}{c}\\
   \text{R}_2
   \end{array}
   \]

   or of formula (IV)
   \[
   R_1\begin{array}{c}\text{O} \\
   \text{N}
   \end{array}\begin{array}{c}\text{N} \\
   \text{N}
   \end{array}\begin{array}{c}\\
   \text{CN}
   \end{array}\begin{array}{c}\\
   \text{R}_2
   \end{array}
   \]

   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; for treating and/or preventing of metabolic diseases in paediatric patients.

2. The DPP-4 inhibitor according to claim 1 for treating and/or preventing of paediatric type 2 diabetes.

3. The DPP-4 inhibitor according to claim 1 or 2 for improving glycemic control (e.g. HbA1c and/or FPG levels) in paediatric patients with type 2 diabetes mellitus.

4. The DPP-4 inhibitor according to claim 1, 2 or 3 further for use in combination with metformin and/or insulin.

5. The DPP-4 inhibitor according to claim 1, 2, 3 or 4 for improving glycemic control in paediatric type 2 diabetes patients with inadequate glycemic control despite metformin therapy alone.

6. The DPP-4 inhibitor according to any one of claims 1-5 for improving glycemic control in paediatric type 2 diabetes patients with inadequate glycemic control despite metformin therapy alone, wherein said DPP-4 inhibitor is used in combination 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).

7. The DPP-4 inhibitor according to any one of claims 1-6 for improving glycemic control in paediatric type 2 diabetes patients with inadequate glycemic control despite metformin therapy alone, wherein said DPP-4 inhibitor is used as add-on to metformin.

8. The DPP-4 inhibitor according to any one of claims 1-5 for improving glycemic control in paediatric type 2 diabetes patients with inadequate glycemic control despite metformin therapy alone, wherein said DPP-4 inhibitor is used as replacement of metformin.
9. The DPP-4 inhibitor according to any one of claims 1-8 for use in paediatric type 2 diabetes patients, wherein said paediatric patients are adolescent patients, preferably 10 to 17 years of age or from 10 to less than 18 years of age.

10. The DPP-4 inhibitor according to any one of claims 1-9, wherein said DPP-4 inhibitor is administered to said patients orally in an amount of 1 mg per day.

11. The DPP-4 inhibitor according to any one of claims 1-9, wherein said DPP-4 inhibitor is administered to said patients orally in an amount of 5 mg per day.

12. The DPP-4 inhibitor according to any one of claims 1-11, wherein said DPP-4 inhibitor is administered to said patients orally once daily.

13. The DPP-4 inhibitor according to any one of the claims 1 to 12, wherein said patients are ineligible for metformin therapy or are in need of reduced-dose metformin therapy due to intolerability or contraindication against metformin, such as e.g. renally impaired patients.

14. The DPP-4 inhibitor according to any one of the claims 1 to 13, wherein said patients are such paediatric type 2 diabetes patients who are associated with obesity, and/or who are associated with insulin resistance or metabolic syndrome optionally with hypertension, acanthosis nigricans, dyslipidemia, polycystic ovarian disease, hyperandrogenism and/or non alcoholic fatty liver disease (NAFLD).

15. A DPP-4 inhibitor for oral therapeutic use in diabetic patients characterized in that < 10%, preferably ≤ 7%, of the administered oral dose is excreted via the kidneys.

16. The DPP-4 inhibitor according to claim 15 characterized in that it is primarily excreted unchanged via the bile.

17. The DPP-4 inhibitor according to any claim 15 or 16 characterized in that > 80%, preferably ≥ 90%, of the administered oral dose is excreted unchanged as parent drug.

18. The DPP-4 inhibitor according to any one of claims 15 to 17 characterized in that its main metabolite is pharmacologically inactive.
19. The DPP-4 inhibitor according to any one of claims 1 to 18, wherein said 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.
### INTERNATIONAL SEARCH REPORT

**International application No**
PCT/EP2010/051093

#### A. CLASSIFICATION OF SUBJECT MATTER


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 practical, search terms used)

EPO-Internal, EMBASE, WPI Data, CHEMABS Data

#### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO 2004/018468 A2 (BOEHRINGER INGELHEIM PHARMA [DE]; HIMMELSBACK FRANK [DE]; LANGKOPF ELK) 4 March 2004 (2004-03-04) claims 1, 17, 20 page 1 page 36, lines 10-12 page 38, lines 17-24 page 39, lines 14-17</td>
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<td>WO 2004/041820 A1 (BOEHRINGER INGELHEIM PHARMA [DE]; HIMMELSBACK FRANK [DE]; LANGKOPF ELK) 21 May 2004 (2004-05-21) page 38, lines 5-14; claims 5, 8 page 39, lines 4-30</td>
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*Further documents are listed if the continuation of Box C

**See patent family annex**

**Date of the actual completion of the international search**

27 April 2010

**Date of mailing of the international search report**

14/07/2010

**Name and mailing address of the ISA/Authorized officer**

European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040 Fax (+31-70) 340-3016

Haider, Ursula

Form PCT/ISA/210 (second sheet) (April 2005)
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<td>WO 2005/085246 Al (BOEHRINGER INGELHEIM INT [DE]; BOHERINGER INGELHEIM PHARMA GM [DE]; HI) 15 September 2005 (2005-09-15) cl aims 1, 6 page 11, lines 5-16 page 13, lines 2-11 page 14, lines 5-8</td>
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<td>SCHWARTZ M S ET AL: &quot;Type 2 diabetes mellitus in childhood: Obesity and insulin resistance&quot; JOURNAL OF THE AMERICAN OSTEOPATHIC ASSOCIATION 200809 US, vol. 108, no. 9, September 2008 (2008-09), pages 518-524, XP002579452 page 521, right-hand column, paragraphs 3,4 page 522, left-hand column, last paragraph - right-hand column, paragraph 1</td>
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<td>WO 2010/015664 A1 (BOEHRINGER INGELHEIM INT [DE]; DUGI KLAUS [DE]; GRAEFE-MODY EVA ULRIKE) 11 February 2010 (2010-02-11) claims 1,7,20,21 page 30, line 19 - page 31, line 18</td>
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INTERNATIONAL SEARCH REPORT

Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. [ ] Claims Nos.: because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see annex

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-14, 19(all partially)

   A DPP-4 inhibitor of formula (I) for use in the treatment/prevention of metabolic diseases in paediatric patients.

2. claims: 1-14(partially)

   A DPP-4 inhibitor of formula (II) for use in the treatment/prevention of metabolic diseases in paediatric patients.

3. claims: 1-14(partially)

   A DPP-4 inhibitor of formula (III) for use in the treatment/prevention of metabolic diseases in paediatric patients.

4. claims: 1-14(partially)

   A DPP-4 inhibitor of formula (IV) for use in the treatment/prevention of metabolic diseases in paediatric patients.

5. claims: 15-18(completely); 19(partially)

   A DPP-IV inhibitor for oral therapeutic use in the treatment of diabetes with pharmacokinetic properties as defined in claims 15-18, with the proviso that said DPP-IV inhibitors are not covered by formulas (I)-(IV).
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