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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING AN SGLT2 INHIBITOR AND A PPAR- GAMMA AGONIST AND USES THEREOF

(57) Abstract: The invention relates to a pharmaceutical composition comprising an SGLT2 inhibitor and a PPARγ agonist which is suitable in the treatment or prevention of one or more conditions selected from type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance and hyperglycemia. In addition the present invention relates to methods for preventing or treating of metabolic disorders and related conditions.

PHARMACEUTICAL COMPOSITION COMPRISING AN SGLT2 INHIBITOR AND A PPAR- GAMMA AGONIST AND USES THEREOF

Technical Field of the Invention

The invention relates to a pharmaceutical composition comprising an SGLT2-inhibitor and a PPARγ agonist which is suitable in the treatment or prevention of one or more conditions selected from type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance, impaired fasting blood glucose and hyperglycemia inter alia.

Furthermore the invention relates to 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, 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 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;
- 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 restoring the functionality of pancreatic insulin secretion;
- for preventing, slowing, delaying or treating diseases or conditions attributed to an abnormal accumulation of ectopic fat;
- maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance,
- for preventing, slowing progression of, delaying, or treating new onset diabetes after transplantation (NODAT) and/or post-transplant metabolic syndrome (PTMS);
- for preventing, delaying, or reducing NODAT and/or PTMS associated complications including micro- and macrovascular diseases and events, graft rejection, infection, and death;
- for treating hyperuricemia and hyperuricemia associated conditions;
- for treating or preventing kidney stones;
- for treating hyponatremia;

in patients in need thereof characterized in that an SGLT2 inhibitor and a PPARγ agonist as defined hereinafter is administered in combination or alternation.

In addition the present invention relates to the use of an SGLT2 inhibitor for the manufacture of a medicament for use in a method as described hereinbefore and hereinafter.

In addition, the present invention relates to the use of a PPARγ agonist for the manufacture of a medicament for use in a method as described hereinbefore and hereinafter.

The invention also relates to a use of a pharmaceutical composition according to this invention for the manufacture of a medicament for use in a method as described hereinbefore and hereinafter.

Background of the Invention

Type 2 diabetes is an increasingly prevalent disease that due to a high frequency of complications leads to a significant reduction of life expectancy. Because of diabetes-associated microvascular complications, type 2 diabetes is currently the most frequent cause of adult-onset loss of vision, renal failure, and amputations in the industrialized world. In addition, the presence of type 2 diabetes is associated with a two to five fold increase in cardiovascular disease risk.

After long duration of disease, most patients with type 2 diabetes will eventually fail on oral therapy and become insulin dependent with the necessity for daily injections and multiple daily glucose measurements.

The UKPDS (United Kingdom Prospective Diabetes Study) demonstrated that intensive treatment with metformin, sulfonylureas or insulin resulted in only a limited improvement of glycemic control (difference in HbA1c ~0.9%). In addition, even in patients within the intensive treatment arm glycemic control deteriorated significantly over time and this was attributed to deterioration of β-cell function. Importantly, intensive treatment was not associated with a significant reduction in macrovascular complications, i.e. cardiovascular events. Therefore many patients with type 2 diabetes remain inadequately treated, partly because of limitations in long term efficacy, tolerability and dosing inconvenience of existing antihyperglycemic therapies.

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

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

Therefore, there is an unmet medical need for methods, medicaments and pharmaceutical compositions with a good efficacy with regard to glycemic control, with regard to disease-modifying properties and with regard to reduction of cardiovascular morbidity and mortality while at the same time showing an improved safety profile.

SGLT2 inhibitors inhibitors represent a novel class of agents that are being developed for the treatment or improvement in glycemic control in patients with type 2 diabetes. Glucopyranosyl-substituted benzene derivative are described in the prior art as SGLT2 inhibitors, for example in WO 01/27128, WO 03/099836, WO 2005/092877, WO 2006/034489, WO 2006/064033, WO 2006/117359, WO 2006/117360, WO 2007/025943, WO 2007/028814, WO 2007/031548, WO 2007/093610, WO 2007/128749, WO 2008/049923, WO 2008/055870, WO 2008/055940. The glucopyranosyl-substituted benzene derivatives are proposed as inducers of urinary sugar excretion and as medicaments in the treatment of diabetes.

Renal filtration and reuptake of glucose contributes, among other mechanisms, to the steady state plasma glucose concentration and can therefore serve as an antidiabetic target. Reuptake of filtered glucose across epithelial cells of the kidney proceeds via sodium-dependent glucose cotransporters (SGLTs) located in the brush-border membranes in the tubuli along the sodium gradient. There are at least 3 SGLT isoforms that differ in their expression pattern as well as in their physico-chemical properties. SGLT2 is exclusively expressed in the kidney, whereas SGLT1 is expressed additionally in other tissues like intestine, colon, skeletal and cardiac muscle. SGLT3 has been found to be a glucose sensor in interstitial cells of the intestine without any transport function. Potentially, other related, but not yet characterized genes, may contribute further to renal glucose reuptake. Under normoglycemia, glucose is completely reabsorbed by SGLTs in the kidney, whereas the reuptake capacity of the kidney is saturated at glucose concentrations higher than 10mM,

resulting in glucosuria ("diabetes mellitus"). This threshold concentration can be decreased by SGLT2-inhibition. It has been shown in experiments with the SGLT inhibitor phlorizin that SGLT-inhibition will partially inhibit the reuptake of glucose from the glomerular filtrate into the blood leading to a decrease in blood glucose concentrations and to glucosuria.

PPARγ agonists represent another class of agents that are being developed for the treatment or improvement in glycemic control in patients with type 2 diabetes.

Aim of the present invention

The aim of the present invention is to provide a pharmaceutical composition and method for preventing, slowing progression of, delaying or treating a metabolic disorder, in particular of type 2 diabetes mellitus.

A further aim of the present invention is to provide a pharmaceutical composition and method for improving glycemic control in a patient in need thereof, in particular in patients with type 2 diabetes mellitus.

Another aim of the present invention is to provide a pharmaceutical composition and method for improving glycemic control in a patient with insufficient glycemic control despite monotherapy with an antidiabetic drug.

Another aim of the present invention is to provide a pharmaceutical composition and method for preventing, slowing or delaying progression from impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or metabolic syndrome to type 2 diabetes mellitus.

Yet another aim of the present invention is to provide a pharmaceutical composition and method for preventing, slowing progression of, delaying or treating of a condition or disorder from the group consisting of complications of diabetes mellitus.

A further aim of the present invention is to provide a pharmaceutical composition and method for reducing body weight and/or body fat, or preventing or reducing an increase of body weight and/or body fat in a patient in need thereof.

Another aim of the present invention is to provide a new pharmaceutical composition with a high efficacy for the treatment of metabolic disorders, in particular of diabetes mellitus,

impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), and/or hyperglycemia, which has good to very good pharmacological and/or pharmacokinetic and/or physicochemical properties.

Further aims of the present invention become apparent to the one skilled in the art by description hereinbefore and in the following and by the examples.

Summary of the Invention

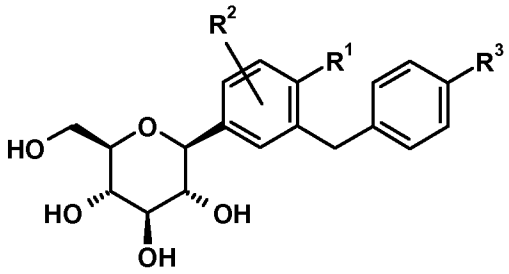
Within the scope of the present invention it has now been found that a pharmaceutical composition comprising a SGLT2 inhibitor and a PPARγ agonist as defined hereinafter can advantageously be used for preventing, slowing progression of, delaying or treating a metabolic disorder, in particular for improving glycemic control in patients, while preventing or reducing an increase of body weight and/or body fat. This opens up new therapeutic possibilities in the treatment and prevention of type 2 diabetes mellitus, overweight, obesity, complications of diabetes mellitus and of neighboring disease states.

Therefore, in a first aspect the present invention provides a pharmaceutical composition comprising

(a) an SGLT2 inhibitor, and

(b) a PPARγ agonist or a pharmaceutically acceptable salt thereof.

In one embodiment, the SGLT2 inhibitor is selected from the group consisting of dapagliflozin, canagliflozin, atigliflozin, remogliflozin, sergliflozin and glucopyranosyl-substituted benzene derivatives of the formula (I)



I

wherein R^1 denotes Cl, methyl or cyano; R^2 denotes H, methyl, methoxy or hydroxy and R^3 denotes ethyl, cyclopropyl, ethynyl, ethoxy, *(R)*-tetrahydrofuran-3-yloxy or *(S)*-tetrahydrofuran-3-yloxy; or a prodrug thereof.

In one embodiment, the PPARγ agonist is a thiazolidindione (TZD), or a pharmaceutically acceptable salt thereof, for example pioglitazone or rosiglitazone, or a pharmaceutically acceptable salt thereof.

In one embodiment, the composition is suitable for combined or simultaneous or sequential use of the SGLT2 inhibitor and the PPARγ agonist.

According to another aspect of the invention, there is provided a method for preventing, slowing the progression of, delaying or treating a metabolic disorder selected from the group consisting of type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), hyperglycemia, postprandial hyperglycemia, overweight, obesity, metabolic syndrome and gestational diabetes in a patient in need thereof characterized in that an SGLT2 inhibitor and a PPARγ agonist as defined hereinbefore and hereinafter are administered, for example in combination or alternation, to the patient.

According to another aspect of the invention, there is provided a method for improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c in a patient in need thereof characterized in that an SGLT2 inhibitor and a PPARγ agonist as defined hereinbefore and hereinafter are administered, for example in combination or alternation, to the patient.

The pharmaceutical composition according to this invention may also have valuable disease-modifying properties with respect to diseases or conditions related to impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or metabolic syndrome.

According to another aspect of the invention, there is provided a method for preventing, slowing, delaying or reversing progression from impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or from metabolic syndrome to type 2 diabetes mellitus in a patient in need thereof characterized in that an SGLT2 inhibitor and a PPARγ agonist as defined hereinbefore and hereinafter are administered, for example in combination or alternation, to the patient.

As by the use of a pharmaceutical composition according to this invention, an improvement of the glycemic control in patients in need thereof is obtainable, also those conditions and/or diseases related to or caused by an increased blood glucose level may be treated.

According to another aspect of the invention, there is provided a method for preventing, slowing the progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus such as cataracts and micro- and macrovascular diseases, such as nephropathy, retinopathy, neuropathy, tissue ischaemia, diabetic foot, arteriosclerosis, myocardial infarction, accute coronary syndrome, unstable angina pectoris, stable angina pectoris, stroke, peripheral arterial occlusive disease, cardiomyopathy, heart failure, heart rhythm disorders and vascular restenosis, in a patient in need thereof characterized in that an SGLT2 inhibitor and a PPARγ agonist as defined hereinbefore and hereinafter are administered, for example in combination or alternation, to the patient. In particular one or more aspects of diabetic nephropathy such as hyperperfusion, proteinuria and albuminuria may be treated, their progression slowed or their onset delayed or prevented. The term "tissue ischaemia" particularly comprises diabetic macroangiopathy, diabetic microangiopathy, impaired wound healing and diabetic ulcer. The terms "micro- and macrovascular diseases" and "micro- and macrovascular complications" are used interchangeably in this application.

Due to the activity of the SGLT2 inhibitor excessive blood glucose levels are not converted to insoluble storage forms, like fat, but excreted through the urine of the patient. In animal models using a SGLT2 inhibitor it can be seen that loss of fat accounts for the majority of the observed weight loss whereas no significant changes in body water or protein content are observed. Therefore, no gain in weight or even a reduction in body weight is the result. By contrast, PPARγ agonists, in particular thiazolidindiones (TZD) typically lead to weight gain and fat redistribution.

It has now been found that an increase of body weight resulting from the administration of a PPARγ agonist is prevented or reduced by the administration of a pharmaceutical composition according to this invention.

It has now also been surprisingly found that an increase of body fat resulting from the administration of a PPARγ agonist is prevented or reduced by the administration of a pharmaceutical composition according to this invention.

Accordingly, according to another aspect of the invention, there is provided a method for reducing body weight or preventing or reducing an increase in body weight or facilitating a reduction in body weight fat in a patient in need thereof characterized in that an SGLT2 inhibitor and a PPARγ agonist as defined hereinbefore and hereinafter are administered, for example in combination or alternation, to the patient.

Accordingly, according to another aspect of the invention, there is provided a method for reducing body fat or preventing or reducing an increase in body fat or facilitating a reduction in body fat in a patient in need thereof characterized in that an SGLT2 inhibitor and a PPARγ agonist as defined hereinbefore and hereinafter are administered, for example in combination or alternation, to the patient.

According to another aspect of the invention, there is provided any one of the methods below:

- 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, slowing progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus;
- 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 restoring the functionality of pancreatic insulin secretion;
- for preventing, slowing, delaying or treating diseases or conditions attributed to an abnormal accumulation of ectopic fat;
- maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance,
- for preventing, slowing progression of, delaying, or treating new onset diabetes after transplantation (NODAT) and/or post-transplant metabolic syndrome (PTMS);
- for preventing, delaying, or reducing NODAT and/or PTMS associated complications including micro- and macrovascular diseases and events, graft rejection, infection, and death;
- for treating hyperuricemia and hyperuricemia associated conditions;
- for treating or preventing kidney stones;

- for treating hyponatremia;
- for treating or preventing fluid retention and peripheral edema.

in patients in need thereof characterized in that an SGLT2 inhibitor and a PPARγ agonist as defined hereinafter is administered in combination or alternation, while reducing body weight and/or body fat or preventing or reducing an increase in body weight and/or body fat or facilitating a reduction in body weight and/or body fat in said patients.

The pharmacological effect of the SGLT2 inhibitor in the pharmaceutical composition according to this invention is independent of insulin. Therefore, an improvement of the glycemic control is possible without an additional strain on the pancreatic beta cells. By an administration of a pharmaceutical composition according to this invention a beta-cell degeneration and a decline of beta-cell functionality such as for example apoptosis or necrosis of pancreatic beta cells can be delayed or prevented. Furthermore, the functionality of pancreatic cells can be improved or restored, and the number and size of pancreatic beta cells increased. It may be shown that the differentiation status and hyperplasia of pancreatic beta-cells disturbed by hyperglycemia can be normalized by treatment with a pharmaceutical composition according to this invention.

According to another aspect of the invention, there is provided a method for 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 restoring the functionality of pancreatic insulin secretion in a patient in need thereof characterized in that an SGLT2 inhibitor and a PPARγ agonist as defined hereinbefore and hereinafter are administered, for example in combination or alternation, to the patient.

By the administration of a combination or pharmaceutical composition according to the present invention, an abnormal accumulation of ectopic fat, in particular of the liver, may be reduced or inhibited. Therefore, according to another aspect of the present invention, there is provided a method for preventing, slowing, delaying or treating diseases or conditions attributed to an abnormal accumulation of ectopic fat, in particular of the liver, in a patient in need thereof characterized in that an SGLT2 inhibitor and a PPARγ agonist as defined hereinbefore and hereinafter are administered, for example in combination or alternation, to the patient. Diseases or conditions which are attributed to an abnormal accumulation of liver fat are particularly selected from the group consisting of general fatty liver, non-alcoholic fatty

liver (NAFL), non-alcoholic steatohepatitis (NASH), hyperalimentation-induced fatty liver, diabetic fatty liver, alcoholic-induced fatty liver or toxic fatty liver.

As a result thereof, another aspect of the invention provides a method for maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance in a patient in need thereof characterized in that an SGLT2 inhibitor and a PPARγ agonist as defined hereinbefore and hereinafter are administered, for example in combination or alternation, to the patient.

According to another aspect of the invention, there is provided a method for preventing, slowing progression of, delaying, or treating new onset diabetes after transplantation (NODAT) and/or post-transplant metabolic syndrome (PTMS) in a patient in need thereof characterized in that an SGLT2 inhibitor and a PPARγ agonist as defined hereinbefore and hereinafter are administered, for example in combination or alternation, to the patient.

According to a further aspect of the invention, there is provided a method for preventing, delaying, or reducing NODAT and/or PTMS associated complications including micro- and macrovascular diseases and events, graft rejection, infection, and death in a patient in need thereof characterized in that an SGLT2 inhibitor and a PPARγ agonist as defined hereinbefore and hereinafter are administered, for example in combination or alternation, to the patient.

The pharmaceutical composition according to the invention is capable of facilitating the lowering of serum total urate levels in the patient. Therefore according to another aspect of the invention, there is provided a method for treating hyperuricemia and hyperuricemia-associated conditions, such as for example gout, hypertension and renal failure, in a patient in need thereof characterized in that an SGLT2 inhibitor and a PPARγ agonist as defined hereinbefore and hereinafter are administered, for example in combination or alternation, to the patient. The patient may be a diabetic or non-diabetic patient.

The administration of a pharmaceutical composition increases the urine excretion of glucose. This increase in osmotic excretion and water release and the lowering of urate levels are beneficial as a treatment or prevention for kidney stones. Therefore in a further aspect of the invention, there is provided a method for treating or preventing kidney stones in a patient in need thereof characterized in that an SGLT2 inhibitor and a PPARγ agonist as defined

hereinbefore and hereinafter are administered, for example in combination or alternation, to the patient.

According to a further aspect of the invention, there is provided a method for treating hyponatremia, water retention and water intoxication in a patient in need thereof characterized in that an SGLT2 inhibitor and a PPARγ agonist as defined hereinbefore and hereinafter are administered, for example in combination or alternation, to the patient. By the administration of the pharmaceutical composition according to this invention it may be possible to reverse the effects of hyponatremia, water retention and water intoxication by acting on the kidney to reverse water retention and electrolyte imbalances associated with these diseases and disorders.

According to another aspect of the invention there is provided the use of an SGLT2 inhibitor for the manufacture of a medicament for

- preventing, slowing the progression of, delaying or treating a metabolic disorder selected from the group consisting of type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), hyperglycemia, postprandial hyperglycemia, overweight, obesity, metabolic syndrome and gestational diabetes; or
- improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c; or
- preventing, slowing, delaying or reversing progression from impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or from metabolic syndrome to type 2 diabetes mellitus; or
- preventing, slowing the progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus such as cataracts and micro- and macrovascular diseases, such as nephropathy, retinopathy, neuropathy, tissue ischaemia, arteriosclerosis, myocardial infarction, stroke and peripheral arterial occlusive disease; or
- 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; or
- 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 restoring the functionality of pancreatic insulin secretion; or

- preventing, slowing, delaying or treating diseases or conditions attributed to an abnormal accumulation of ectopic fat; or
- maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance;
- preventing, slowing progression of, delaying, or treating new onset diabetes after transplantation (NODAT) and/or post-transplant metabolic syndrome (PTMS);
- preventing, delaying, or reducing NODAT and/or PTMS associated complications including micro- and macrovascular diseases and events, graft rejection, infection, and death;
- treating hyperuricemia and hyperuricemia associated conditions;
- treating or prevention kidney stones;
- treating hyponatremia;
- treating or preventing fluid retention and peripheral edema;

in a patient in need thereof characterized in that the SGLT2 inhibitor is administered, for example in combination or alternation, with a PPARγ agonist as defined hereinbefore and hereinafter.

According to another aspect of the invention, there is provided the use of a PPARγ agonist as defined hereinbefore and hereinafter for the manufacture of a medicament for

- preventing, slowing the progression of, delaying or treating a metabolic disorder selected from the group consisting of type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), hyperglycemia, postprandial hyperglycemia, overweight, obesity and metabolic syndrome; or
- improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c; or
- preventing, slowing, delaying or reversing progression from impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or from metabolic syndrome to type 2 diabetes mellitus; or
- preventing, slowing the progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus such as cataracts and micro- and macrovascular diseases, such as nephropathy, retinopathy, neuropathy, tissue ischaemia, arteriosclerosis, myocardial infarction, stroke and peripheral arterial occlusive disease; or
- 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; or

- 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 restoring the functionality of pancreatic insulin secretion; or
- preventing, slowing, delaying or treating diseases or conditions attributed to an abnormal accumulation of liver fat; or
- maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance;

in a patient in need thereof characterized in that the PPARγ agonist is administered, for example in combination or alternation, with an SGLT2 inhibitor and optionally a third antidiabetic agent as defined hereinbefore and hereinafter.

According to another aspect of the invention, there is provided the use of a pharmaceutical composition according to the present invention for the manufacture of a medicament for a therapeutic and preventive method as described hereinbefore and hereinafter.

Definitions

The term **"active ingredient"** of a pharmaceutical composition according to the present invention means the SGLT2 inhibitor and/or the PPARγ agonist according to the present invention.

The term **"body mass index"** or **"BMI"** of a human patient is defined as the weight in kilograms divided by the square of the height in meters, such that BMI has units of kg/m².

The term **"overweight"** is defined as the condition wherein the individual has a BMI greater than or 25 kg/m² and less than 30 kg/m². The terms "overweight" and "pre-obese" are used interchangeably.

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

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

The term **"abdominal obesity"** is usually defined as the condition wherein the waist circumference is > 40 inches or 102 cm in men, and is > 35 inches or 94 cm in women. With regard to a Japanese ethnicity or Japanese patients abdominal obesity may be defined as waist circumference ≥ 85 cm in men and ≥ 90 cm in women (see e.g. investigating committee for the diagnosis of metabolic syndrome in Japan).

The term **"euglycemia"** is defined as the condition in which a subject has a fasting blood glucose concentration within the normal range, greater than 70 mg/dL (3.89 mmol/L) and less than 100 mg/dL (5.6 mmol/L). The word "fasting" has the usual meaning as a medical term.

The term **"hyperglycemia"** is defined as the condition in which a subject has a fasting blood glucose concentration above the normal range, greater than 100 mg/dL (5.6 mmol/L). The word "fasting" has the usual meaning as a medical term.

The term **"hypoglycemia"** is defined as the condition in which a subject has a blood glucose concentration below the normal range, in particular below 70 mg/dL (3.89 mmol/L).

The term **"postprandial hyperglycemia"** is defined as the condition in which a subject has a 2 hour postprandial blood glucose or serum glucose concentration greater than 200 mg/dL (11.11 mmol/L).

The term **"impaired fasting blood glucose"** or **"IFG"** is defined as the condition in which a subject has a fasting blood glucose concentration or fasting serum glucose concentration in a range from 100 to 125 mg/dl (i.e. from 5.6 to 6.9 mmol/l), in particular greater than 110 mg/dL and less than 126 mg/dl (7.00 mmol/L). A subject with "normal fasting glucose" has a fasting glucose concentration smaller than 100 mg/dl, i.e. smaller than 5.6 mmol/l.

The term **"impaired glucose tolerance"** or **"IGT"** is defined as the condition in which a subject has a 2 hour postprandial blood glucose or serum glucose concentration greater than 140 mg/dl (7.78 mmol/L) and less than 200 mg/dL (11.11 mmol/L). The abnormal glucose tolerance, i.e. the 2 hour postprandial blood glucose or serum glucose concentration can be

measured as the blood sugar level in mg of glucose per dL of plasma 2 hours after taking 75 g of glucose after a fast. A subject with "normal glucose tolerance" has a 2 hour postprandial blood glucose or serum glucose concentration smaller than 140 mg/dl (7.78 mmol/L).

The term **"hyperinsulinemia"** is defined as the condition in which a subject with insulin resistance, with or without euglycemia, has fasting or postprandial serum or plasma insulin concentration elevated above that of normal, lean individuals without insulin resistance, having a waist-to-hip ratio < 1.0 (for men) or < 0.8 (for women).

The terms "insulin-sensitizing", "insulin resistance-improving" or "insulin resistance-lowering" are synonymous and used interchangeably.

The term **"insulin resistance"** is defined as a state in which circulating insulin levels in excess of the normal response to a glucose load are required to maintain the euglycemic state (Ford ES, *et al. JAMA.* (2002) **287**:356-9). A method of determining insulin resistance is the euglycaemic-hyperinsulinaemic clamp test. The ratio of insulin to glucose is determined within the scope of a combined insulin-glucose infusion technique. There is found to be insulin resistance if the glucose absorption is below the 25th percentile of the background population investigated (WHO definition). Rather less laborious than the clamp test are so called minimal models in which, during an intravenous glucose tolerance test, the insulin and glucose concentrations in the blood are measured at fixed time intervals and from these the insulin resistance is calculated. With this method, it is not possible to distinguish between hepatic and peripheral insulin resistance.

Furthermore, insulin resistance, the response of a patient with insulin resistance to therapy, insulin sensitivity and hyperinsulinemia may be quantified by assessing the "homeostasis model assessment to insulin resistance (HOMA-IR)" score, a reliable indicator of insulin resistance (Katsuki A, *et al.* Diabetes Care 2001; 24: 362-5). Further reference is made to methods for the determination of the HOMA-index for insulin sensitivity (*Matthews et al., Diabetologia 1985, 28: 412-19*), of the ratio of intact proinsulin to insulin (*Forst et al., Diabetes 2003, 52(Suppl.1): A459*) and to an euglycemic clamp study. In addition, plasma adiponectin levels can be monitored as a potential surrogate of insulin sensitivity. The estimate of insulin resistance by the homeostasis assessment model (HOMA)-IR score is calculated with the formula (Galvin P, *et al.* Diabet Med 1992;9:921-8):

HOMA-IR = [fasting serum insulin (µU/mL)] x [fasting plasma glucose(mmol/L)/22.5]

As a rule, other parameters are used in everyday clinical practice to assess insulin resistance. Preferably, the patient's triglyceride concentration is used, for example, as increased triglyceride levels correlate significantly with the presence of insulin resistance.

Patients with a predisposition for the development of IGT or IFG or type 2 diabetes are those having euglycemia with hyperinsulinemia and are by definition, insulin resistant. A typical patient with insulin resistance is usually overweight or obese. If insulin resistance can be detected, this is a particularly strong indication of the presence of pre-diabetes. Thus, it may be that in order to maintain glucose homoeostasis a person needs 2-3 times as much insulin as a healthy person, without this resulting in any clinical symptoms.

The methods to investigate the **function of pancreatic beta-cells** are similar to the above methods with regard to insulin sensitivity, hyperinsulinemia or insulin resistance: An improvement of beta-cell function can be measured for example by determining a HOMA-index for beta-cell function (*Matthews et al., Diabetologia 1985, 28: 412-19*), the ratio of intact proinsulin to insulin (*Forst et al., Diabetes 2003, 52(Suppl.1): A459*), the insulin/C-peptide secretion after an oral glucose tolerance test or a meal tolerance test, or by employing a hyperglycemic clamp study and/or minimal modeling after a frequently sampled intravenous glucose tolerance test (*Stumvoll et al., Eur J Clin Invest 2001, 31: 380-81*).

The term **"pre-diabetes"** is the condition wherein an individual is pre-disposed to the development of type 2 diabetes. Pre-diabetes extends the definition of impaired glucose tolerance to include individuals with a fasting blood glucose within the high normal range ≥ 100 mg/dL (J. B. Meigs, *et al.* Diabetes 2003; 52:1475-1484) and fasting hyperinsulinemia (elevated plasma insulin concentration). The scientific and medical basis for identifying pre-diabetes as a serious health threat is laid out in a Position Statement entitled "The Prevention or Delay of Type 2 Diabetes" issued jointly by the American Diabetes Association and the National Institute of Diabetes and Digestive and Kidney Diseases (Diabetes Care 2002; 25:742-749).

Individuals likely to have insulin resistance are those who have two or more of the following attributes: 1) overweight or obese, 2) high blood pressure, 3) hyperlipidemia, 4) one or more 1st degree relative with a diagnosis of IGT or IFG or type 2 diabetes. Insulin resistance can be confirmed in these individuals by calculating the HOMA-IR score. For the purpose of this invention, insulin resistance is defined as the clinical condition in which an individual has a

HOMA-IR score > 4.0 or a HOMA-IR score above the upper limit of normal as defined for the laboratory performing the glucose and insulin assays.

The term **"type 2 diabetes"** is defined as the condition in which a subject has a fasting blood glucose or serum glucose concentration greater than 125 mg/dL (6.94 mmol/L). The measurement of blood glucose values is a standard procedure in routine medical analysis. If a glucose tolerance test is carried out, the blood sugar level of a diabetic will be in excess of 200 mg of glucose per dL (11.1 mmol/l) of plasma 2 hours after 75 g of glucose have been taken on an empty stomach. In a glucose tolerance test 75 g of glucose are administered orally to the patient being tested after 10-12 hours of fasting and the blood sugar level is recorded immediately before taking the glucose and 1 and 2 hours after taking it. In a healthy subject, the blood sugar level before taking the glucose will be between 60 and 110 mg per dL of plasma, less than 200 mg per dL 1 hour after taking the glucose and less than 140 mg per dL after 2 hours. If after 2 hours the value is between 140 and 200 mg, this is regarded as abnormal glucose tolerance.

The term **"late stage type 2 diabetes mellitus"** includes patients with a secondary drug failure, indication for insulin therapy and progression to micro- and macrovascular complications e.g. diabetic nephropathy, or coronary heart disease (CHD).

The term **"HbA1c"** refers to the product of a non-enzymatic glycation of the haemoglobin B chain. Its determination is well known to one skilled in the art. In monitoring the treatment of diabetes mellitus the HbA1c value is of exceptional importance. As its production depends essentially on the blood sugar level and the life of the erythrocytes, the HbA1c in the sense of a "blood sugar memory" reflects the average blood sugar levels of the preceding 4-6 weeks. Diabetic patients whose HbA1c value is consistently well adjusted by intensive diabetes treatment (i.e. < 6.5 % of the total haemoglobin in the sample), are significantly better protected against diabetic microangiopathy. For example, metformin on its own achieves an average improvement in the HbA1c value in the diabetic of the order of 1.0 – 1.5 %. This reduction of the HbA1C value is not sufficient in all diabetics to achieve the desired target range of < 6.5 % and preferably < 6 % HbA1c.

The term **"insufficient glycemic control"** or "inadequate glycemic control" in the scope of the present invention means a condition wherein patients show HbA1c values above 6.5 %, in particular above 7.0 %, even more preferably above 7.5 %, especially above 8 %.

The **"metabolic syndrome"**, also called "syndrome X" (when used in the context of a metabolic disorder), also called the "dysmetabolic syndrome" is a syndrome complex with the cardinal feature being insulin resistance (Laaksonen DE, *et al. Am J Epidemiol* 2002;**156**:1070-7). According to the ATP III/NCEP guidelines (Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) *JAMA: Journal of the American Medical Association* (2001) **285**:2486-2497), diagnosis of the metabolic syndrome is made when three or more of the following risk factors are present:

1. Abdominal obesity, defined as waist circumference > 40 inches or 102 cm in men, and > 35 inches or 94 cm in women; or with regard to a Japanese ethnicity or Japanese patients defined as waist circumference ≥ 85 cm in men and ≥ 90 cm in women;
2. Triglycerides: ≥ 150 mg/dL
3. HDL-cholesterol < 40 mg/dL in men
4. Blood pressure ≥ 130/85 mm Hg (SBP ≥ 130 or DBP ≥ 85)
5. Fasting blood glucose ≥ 100 mg/dL

The NCEP definitions have been validated (Laaksonen DE, *et al. Am J Epidemiol.* (2002) **156**:1070-7). Triglycerides and HDL cholesterol in the blood can also be determined by standard methods in medical analysis and are described for example in Thomas L (Editor): "Labor und Diagnose", TH-Books Verlagsgesellschaft mbH, Frankfurt/Main, 2000.

According to a commonly used definition, **hypertension** is diagnosed if the systolic blood pressure (SBP) exceeds a value of 140 mm Hg and diastolic blood pressure (DBP) exceeds a value of 90 mm Hg. If a patient is suffering from manifest diabetes it is currently recommended that the systolic blood pressure be reduced to a level below 130 mm Hg and the diastolic blood pressure be lowered to below 80 mm Hg.

The definitions of **NODAT** (new onset diabetes after transplantation) and **PTMS** (post-transplant metabolic syndrome) follow closely that of the American Diabetes Association diagnostic criteria for type 2 diabetes, and that of the International Diabetes Federation (IDF) and the American Heart Association/National Heart, Lung, and Blood Institute, for the metabolic syndrome. NODAT and/or PTMS are associated with an increased risk of micro- and macrovascular disease and events, graft rejection, infection, and death. A number of predictors have been identified as potential risk factors related to NODAT and/or PTMS

including a higher age at transplant, male gender, the pre-transplant body mass index, pre-transplant diabetes, and immunosuppression.

The term **"gestational diabetes"** (diabetes of pregnancy) denotes a form of the diabetes which develops during pregnancy and usually ceases again immediately after the birth. Gestational diabetes is diagnosed by a screening test which is carried out between the 24th and 28th weeks of pregnancy. It is usually a simple test in which the blood sugar level is measured one hour after the administration of 50 g of glucose solution. If this 1 h level is above 140 mg/dl, gestational diabetes is suspected. Final confirmation may be obtained by a standard glucose tolerance test, for example with 75 g of glucose.

The term **"hyperuricemia"** denotes a condition of high serum total urate levels. In human blood, uric acid concentrations between 3.6 mg/dL (ca. 214 µmol/L) and 8.3 mg/dL (ca. 494 µmol/L) are considered normal by the American Medical Association. High serum total urate levels, or hyperuricemia, are often associated with several maladies. For example, high serum total urate levels can lead to a type of arthritis in the joints kown as gout. Gout is a condition created by a build up of monosodium urate or uric acid crystals on the articular cartilage of joints, tendons and surrounding tissues due to elevated concentrations of total urate levels in the blood stream. The build up of urate or uric acid on these tissues provokes an inflammatory reaction of these tissues. Saturation levels of uric acid in urine may result in kidney stone formation when the uric acid or urate crystallizes in the kidney. Additionally, high serum total urate levels are often associated with the so-called metabolic syndrome, including cardiovascular disease and hypertension.

The term **"hyponatremia"** denotes a condition of a positive balance of water with or without a deficit of sodium, which is recognized when the plasma sodium falls below the level of 135 mml/L. Hyponatremia is a condition which can occur in isolation in individuals that over-consume water; however, more often hyponatremia is a complication of medication or other underlying medical condition that leas to a diminished excretion of water. Hyponatremia may lead to water intoxication, which occurs when the normal tonicity of extracellular fluid falls below the safe limit, due to retention of excess water. Water intoxication is a potentially fatal disturbance in brain function. Typical symptoms of water intoxication include nausea, vomiting, headache and malaise.

The term **"SGLT2 inhibitor"** in the scope of the present invention relates to a compound, in particular to a glucopyranosyl-derivative, i.e. compound having a glucopyranosyl-moiety,

which shows an inhibitory effect on the sodium-glucose transporter 2 (SGLT2), in particular the human SGLT2. The inhibitory effect on hSGLT2 measured as IC50 is prerably below 1000 nM, even more preferably below 100 nM, most preferably below 50 nM. IC50 values of SGLT2 inhibitors are usually above 0.01 nM, or even equal to or above 0.1 nM. The inhibitory effect on hSGLT2 can be determined by methods known in the literature, in particular as described in the application WO 2005/092877 or WO 2007/093610 (pages 23/24), which are incorporated herein by reference in its entirety. The term "SGLT2 inhibitor" also comprises any pharmaceutically acceptable salts thereof, hydrates and solvates thereof, including the respective crystalline forms.

The terms **"treatment"** and "treating" comprise therapeutic treatment of patients having already developed said condition, in particular in manifest form. Therapeutic treatment may be symptomatic treatment in order to relieve the symptoms of the specific indication or causal treatment in order to reverse or partially reverse the conditions of the indication or to stop or slow down progression of the disease. Thus the compositions and methods of the present invention may be used for instance as therapeutic treatment over a period of time as well as for chronic therapy.

The terms **"prophylactically treating"**, "preventivally treating" and "preventing" are used interchangeably and comprise a treatment of patients at risk to develop a condition mentioned hereinbefore, thus reducing said risk.

Brief Description of the Figures

Figure 1 shows the body weight of animal after treatment with pharmaceutical compositions according to the present invention.

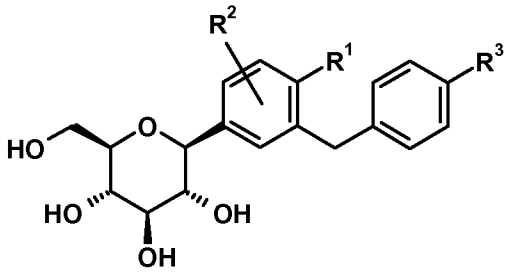
Figure 2 shows plasma insulin values of animal after treatment with pharmaceutical compositions according to the present invention.

Figure 3 shows the effect of pharmaceutical compositions according to the present invention on glycemic control in animals.

Detailed Description

The aspects according to the present invention, in particular the pharmaceutical compositions, methods and uses, refer to SGLT2 inhibitors and a PPARγ agonist as defined hereinbefore and hereinafter.

Preferably the SGLT2 inhibitor is selected from the group consisting of dapagliflozin, canagliflozin, atigliflozin, remogliflozin, sergliflozin and glucopyranosyl-substituted benzene derivatives of the formula (I)



I

wherein R^1 denotes Cl, methyl or cyano; R^2 denotes H, methyl, methoxy or hydroxy and R^3 denotes ethyl, cyclopropyl, ethynyl, ethoxy, *(R)*-tetrahydrofuran-3-yloxy or *(S)*-tetrahydrofuran-3-yloxy; or a prodrug of one of the beforementioned SGLT2 inhibitors.

Compounds of the formula (I) and methods of their synthesis are described for example in the following patent applications: WO 2005/092877, WO 2006/117360, WO 2006/117359, WO 2006/120208, WO 2006/064033, WO 2007/031548, WO 2007/093610, WO 2008/020011, WO 2008/055870.

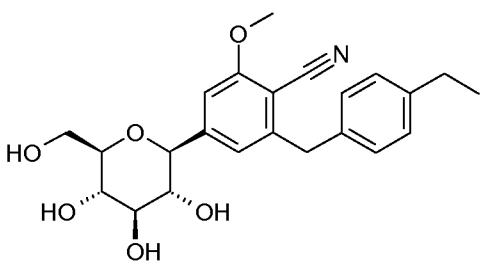
In the above glucopyranosyl-substituted benzene derivatives of the formula (I) the following definitions of the substituents are preferred.

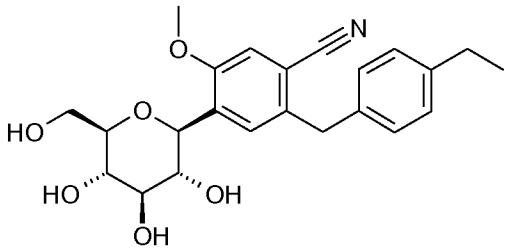
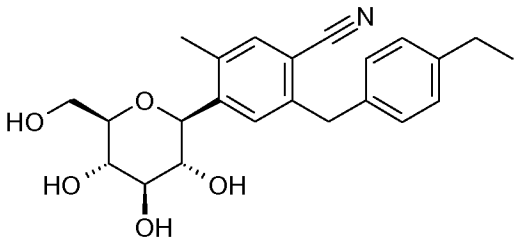
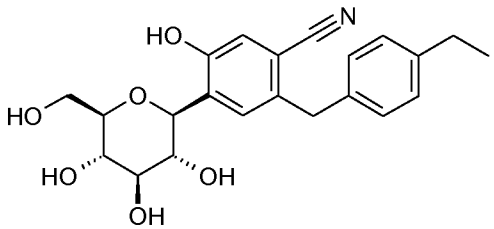
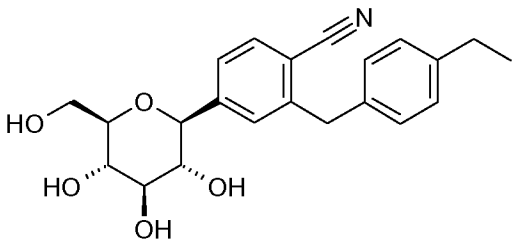
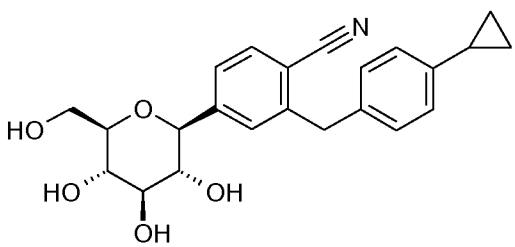
Preferably R^1 denotes chloro or cyano; in particular chloro.

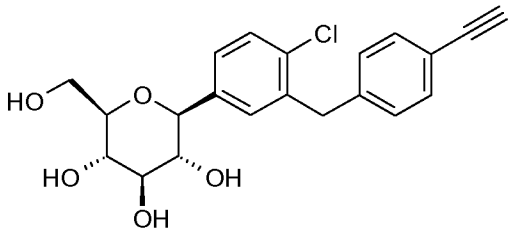
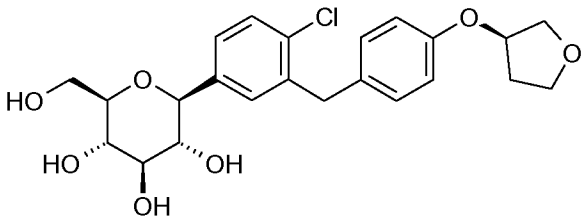
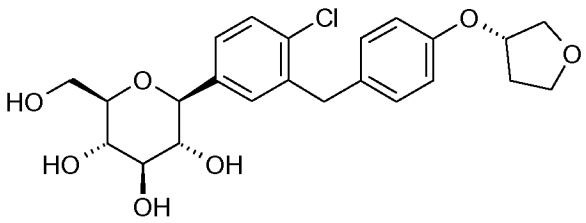
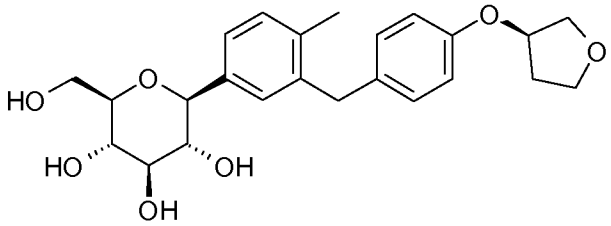
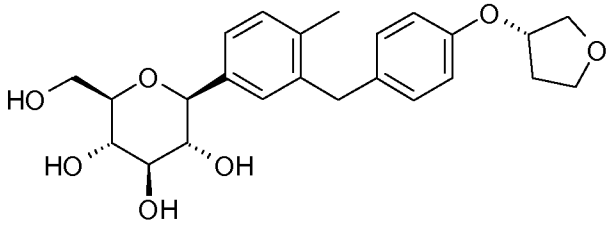
Preferably R^2 denotes H.

Preferably R^3 denotes ethyl, cyclopropyl, ethynyl, *(R)*-tetrahydrofuran-3-yloxy or *(S)*-tetrahydrofuran-3-yloxy. Even more preferably R^3 denotes cyclopropyl, ethynyl, *(R)*-tetrahydrofuran-3-yloxy or *(S)*-tetrahydrofuran-3-yloxy. Most preferably R^3 denotes ethynyl, *(R)*-tetrahydrofuran-3-yloxy or *(S)*-tetrahydrofuran-3-yloxy.

Preferred glucopyranosyl-substituted benzene derivatives of the formula (I) are selected from the group of compounds (I.1) to (I.11):

(I.1)	

	6-(4-ethylbenzyl)-4-(β-D-glucopyranos-1-yl)-2-methoxy-benzonitrile,
(I.2)	 2-(4-ethylbenzyl)-4-(β-D-glucopyranos-1-yl)-5-methoxy-benzonitrile,
(I.3)	 1-cyano-2-(4-ethylbenzyl)-4-(β-D-glucopyranos-1-yl)-5-methyl-benzene,
(I.4)	 2-(4-ethylbenzyl)-4-(β-D-glucopyranos-1-yl)-5-hydroxy-benzonitrile,
(I.5)	 2-(4-ethyl-benzyl)-4-(β-D-glucopyranos-1-yl)-benzonitrile,
(I.6)	 2-(4-cyclopropyl-benzyl)-4-(β -D-glucopyranos-1-yl)-benzonitrile,

(I.7)	 1-chloro-4-(β-D-glucopyranos-1-yl)-2-(4-ethynyl-benzyl)-benzene,
(I.8)	 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-(*(R)*-tetrahydrofuran-3-yloxy)-benzyl]-benzene,
(I.9)	 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-(*(S)*-tetrahydrofuran-3-yloxy)-benzyl]-benzene,
(I.10)	 1-methyl-2-[4-(*(R)*-tetrahydrofuran-3-yloxy)-benzyl]-4-(β-D-glucopyranos-1-yl)-benzene,
(I.11)	 1-methyl-2-[4-(*(S)*-tetrahydrofuran-3-yloxy)-benzyl]-4-(β-D-glucopyranos-1-

	yl)-benzene.

Even more preferred glucopyranosyl-substituted benzene derivatives of the formula (I) are selected from the compounds (I.6), (I.7), (I.8), (I.9) and (I.11).

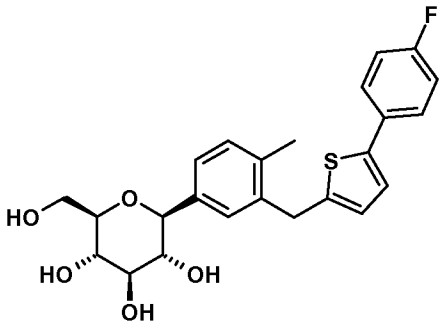
Therefore the group preferably consists of dapagliflozin, remogliflozin, the compound (I.6), the compound (I.7), the compound (I.8), the compound (I.9) and the compound (I.11).

Even more preferably the group consists of dapagliflozin and the compound (I.9).

According to this invention, it is to be understood that the definitions of the above listed glucopyranosyl-substituted benzene derivatives of the formula (I) also comprise their hydrates, solvates and polymorphic forms thereof, and prodrugs thereof. With regard to the preferred compound (I.7) an advantageous crystalline form is described in the international patent application WO 2007/028814 which hereby is incorporated herein in its entirety. With regard to the preferred compound (I.8), an advantageous crystalline form is described in the international patent application WO 2006/117360 which hereby is incorporated herein in its entirety. With regard to the preferred compound (I.9) an advantageous crystalline form is described in the international patent application WO 2006/117359 which hereby is incorporated herein in its entirety. With regard to the preferred compound (I.11) an advantageous crystalline form is described in the international patent application WO 2008/049923 which hereby is incorporated herein in its entirety. These crystalline forms possess good solubility properties which enable a good bioavailability of the SGLT2 inhibitor. Furthermore, the crystalline forms are physico-chemically stable and thus provide a good shelf-life stability of the pharmaceutical composition.

The term "dapagliflozin" as employed herein refers to dapagliflozin, including hydrates and solvates thereof, and crystalline forms thereof. The compound and methods of its synthesis are described in WO 03/099836 for example. Preferred hydrates, solvates and crystalline forms are described in the patent applications WO 2008/116179 and WO 2008/002824 for example.

The term "canagliflozin" as employed herein refers to canagliflozin, including hydrates and solvates thereof, and crystalline forms thereof and has the following structure:



The compound and methods of its synthesis are described in WO 2005/012326 and WO 2009/035969 for example. Preferred hydrates, solvates and crystalline forms are described in the patent applications WO 2008/069327 for example.

The term "atigliflozin" as employed herein refers to atigliflozin, including hydrates and solvates thereof, and crystalline forms thereof. The compound and methods of its synthesis are described in WO 2004/007517 for example.

The term "remogliflozin" as employed herein refers to remogliflozin and prodrugs of remogliflozin, in particular remogliflozin etabonate, including hydrates and solvates thereof, and crystalline forms thereof. Methods of its synthesis are described in the patent applications EP 1213296 and EP 1354888 for example.

The term "sergliflozin" as employed herein refers to sergliflozin and prodrugs of sergliflozin, in particular sergliflozin etabonate, including hydrates and solvates thereof, and crystalline forms thereof. Methods for its manufacture are described in the patent applications EP 1344780 and EP 1489089 for example.

For avoidance of any doubt, the disclosure of each of the foregoing documents cited above in connection with the specified SGLT2 inhibitors is specifically incorporated herein by reference in its entirety.

The aspects according to the present invention, in particular the pharmaceutical compositions, methods and uses, refer to a PPARγ agonist as defined hereinbefore and hereinafter, or prodrugs thereof, or pharmaceutically acceptable salts thereof.

A PPARγ agonist according to the present invention is for example a thiazolidindione. Examples of thiazolidindiones (TZD) are pioglitazone and rosiglitazone. TZD therapy is associated with significant weight gain and fat redistribution. In addition, TZD cause fluid

retention and are not indicated in patients with congestive heart failure. Long term treatment with TZD are further associated with an increased risk of bone fractures. The advantageous properties of a SGLT2 inhibitor can minimize side effects of the treatment with TZD. It has now been found that an increase of body weight resulting from the administration of a PPARγ agonist is prevented or reduced by the administration of a pharmaceutical composition according to this invention. It has also been surprisingly found that an increase of body fat resulting from the administration of a PPARγ agonist is prevented or reduced by the administration of a pharmaceutical composition according to this invention. Water retention may also be reduced or prevented by the administration of a pharmaceutical composition according to this invention.

The term "pioglitazone" as employed herein refers to pioglitazone, including its enantiomers, mixtures thereof and its racemate, or a pharmaceutically acceptable salt thereof such as the hydrochloride salt. Pioglitazone is for example disclosed in US Patents No. 4,687,777 and 5,965,584 incorporated herein by reference in their entireties.

The term "rosiglitazone" as employed herein refers to rosiglitazone, including its enantiomers, mixtures thereof and its racemate, or a pharmaceutically acceptable salt thereof such as the maleate salt. Rosiglitazone is for example disclosed in US Patents No. 5,002,953, 5,741,803, 6,288,095 and 7,358,366 incorporated herein by reference in their entireties.

The combination of an SGLT2 inhibitor and a PPARγ agonist according to this invention significantly improves the glycemic control, in particular in patients as described hereinafter, compared with a monotherapy using either a SGLT2 inhibitor or a PPARγ agonist. The improved glycemic control is determined as an increased lowering of blood glucose and an increased reduction of HbA1c. With monotherapy in a patient, in particular in patients as described hereinafter, the glycemic control can usually not be further improved significantly by an administration of the drug above a certain highest dose. In addition, a long term treatment using a highest dose may be unwanted in view of potential side effects. Therefore, a satisfying glycemic control cannot be achieved in all patients via a monotherapy using either the SLGT2 inhibitor or the PPARγ agonist. In such patients a progression of the diabetes mellitus may continue and complications associated with diabetes mellitus may occur, such as macrovascular complications. The pharmaceutical composition as well as the methods according to the present invention allow a reduction of the HbA1c value to a desired target range, for example < 7 % and preferably < 6.5 %, for a higher number of patients and

for a longer time of therapeutic treatment compared with a corresponding monotherapy or a therapy using only two of the combination partners.

In addition, the combination of an SGLT2 inhibitor and a PPARγ agonist according to this invention may allow a reduction in the dose of either the SGLT2 inhibitor or the PPARγ agonist. A dose reduction is beneficial for patients which otherwise would potentially suffer from side effects in a therapy using a higher dose of one or more of the active ingredients. Therefore, the pharmaceutical composition as well as the methods according to the present invention, show less side effects, thereby making the therapy more tolerable and improving the patients compliance with the treatment.

When this invention refers to patients requiring treatment or prevention, it relates primarily to treatment and prevention in humans, but the pharmaceutical composition may also be used accordingly in veterinary medicine in mammals. In the scope of this invention adult patients are preferably humans of the age of 18 years or older. Also in the scope of this invention, patients are adolescent humans, i.e. humans of age 10 to 17 years, preferably of age 13 to 17 years. It is assumed that in a adolescent population the administration of the pharmaceutical composition according to the invention a very good HbA1c lowering and a very good lowering of the fasting plasma glucose can be seen. In addition it is assumed that in an adolescent population, in particular in overweight and/or obese patients, a pronounced weight loss can be observed.

As described hereinbefore by the administration of the pharmaceutical composition according to this invention and in particular in view of the high SGLT2 inhibitory activity of the SGLT2 inhibitors therein, excessive blood glucose is excreted through the urine of the patient, so that no gain in weight or even a reduction in body weight may result. Therefore, a treatment or prophylaxis according to this invention is advantageously suitable in those patients in need of such treatment or prophylaxis who are diagnosed of one or more of the conditions selected from the group consisting of overweight and obesity, in particular class I obesity, class II obesity, class III obesity, visceral obesity and abdominal obesity. In addition a treatment or prophylaxis according to this invention is advantageously suitable in those patients in which a weight increase is contraindicated.

The pharmaceutical composition according to this invention and in particular the SGLT2 inhibitor therein exhibits a very good efficacy with regard to glycemic control, in particular in view of a reduction of fasting plasma glucose, postprandial plasma glucose and/or

glycosylated hemoglobin (HbA1c). By administering a pharmaceutical composition according to this invention, a reduction of HbA1c equal to or greater than preferably 1.0 %, more preferably equal to or greater than 2.0 %, even more preferably equal to or greater than 3.0 % can be achieved and the reduction is particularly in the range from 1.0 % to 3.0 %.

Furthermore, the method and/or use according to this invention is advantageously applicable in those patients who show one, two or more of the following conditions:

(a) a fasting blood glucose or serum glucose concentration greater than 100 mg/dL or 110 mg/dL, in particular greater than 125 mg/dL;

(b) a postprandial plasma glucose equal to or greater than 140 mg/dL;

(c) an HbA1c value equal to or greater than 6.5 %, in particular equal to or greater than 7.0 %, especially equal to or greater than 7.5 %, even more particularly equal to or greater than 8.0 %.

The present invention also discloses the use of the pharmaceutical composition for improving glycemic control in patients having type 2 diabetes or showing first signs of pre-diabetes. Thus, the invention also includes diabetes prevention. If therefore a pharmaceutical composition according to this invention is used to improve the glycemic control as soon as one of the above-mentioned signs of pre-diabetes is present, the onset of manifest type 2 diabetes mellitus can be delayed or prevented.

Furthermore, the pharmaceutical composition according to this invention is particularly suitable in the treatment of patients with insulin dependency, i.e. in patients who are treated or otherwise would be treated or need treatment with an insulin or a derivative of insulin or a substitute of insulin or a formulation comprising an insulin or a derivative or substitute thereof. These patients include patients with diabetes type 2 and patients with diabetes type 1.

Therefore, according to a preferred embodiment of the present invention, there is provided a method for improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c in a patient in need thereof who is diagnosed with impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG) with insulin resistance, with metabolic syndrome and/or with type 2 or type 1 diabetes mellitus characterized in that an SGLT2 inhibitor and a PPARγ agonist as defined hereinbefore and hereinafter are administered, for example in combination or alternation, to the patient.

According to another preferred embodiment of the present invention, there is provided a method for improving gycemic control in patients, in particular in adult patients, with type 2 diabetes mellitus as an adjunct to diet and exercise.

Therefore, the method and/or use according to this invention is advantageously applicable in those patients who show one, two or more of the following conditions:

(a) insufficient glycemic control with diet and exercise alone;

(b) insufficient glycemic control despite oral monotherapy with metformin, in particular despite oral monotherapy at a maximal recommended or tolerated dose of metformin;

(c) insufficient glycemic control despite oral monotherapy with the third antidiabetic agent, in particular despite oral monotherpy at a maximal recommended or tolerated dose of the third antidiabetic agent;

(d) insufficient glycemic control despite oral monotherapy with the SGLT2 inhibitor, in particular despite oral monotherpy at a maximal recommended or tolerated dose of the SGLT2 inhibitor;

(e) insufficient glycemic control despite oral monotherapy with the PPARγ agonist, in particular despite oral monotherpy at a maximal recommended or tolerated dose of the PPARγ agonist;

(f) insufficient glycemic control despite combination therapy with two agents selected from the group of the SGLT2 inhibitor and the PPARγ agonist;

(g) insufficient glycemic control despite oral combination therapy with the SGLT2 inhibitor and the third antidiabetic agent (for example metformin), in particular despite oral monotherpy at a maximal recommended or tolerated dose of at least one of the combination partners;

(h) insufficient glycemic control despite oral combinationtherapy with the PPARγ agonist, in particular despite oral monotherpy at a maximal recommended or tolerated dose of at least one of the combination partners.

The lowering of the blood glucose level by the administration of an SGLT2 inhibitor according to this invention is insulin-independent. Therefore, a pharmaceutical composition according to this invention is particularly suitable in the treatment of patients who are diagnosed having one or more of the following conditions

- insulin resistance,
- hyperinsulinemia,
- pre-diabetes,

- type 2 diabetes mellitus, particular having a late stage type 2 diabetes mellitus,
- type 1 diabetes mellitus.

Furthermore, a pharmaceutical composition according to this invention is particularly suitable in the treatment of patients who are diagnosed having one or more of the following conditions

(a) obesity (including class I, II and/or III obesity), visceral obesity and/or abdominal obesity,
(b) triglyceride blood level ≥ 150 mg/dL,
(c) HDL-cholesterol blood level < 40 mg/dL in female patients and < 50 mg/dL in male patients,
(d) a systolic blood pressure ≥ 130 mm Hg and a diastolic blood pressure ≥ 85 mm Hg,
(e) a fasting blood glucose level ≥ 100 mg/dL.

It is assumed that patients diagnosed with impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), with insulin resistance and/or with metabolic syndrome suffer from an increased risk of developing a cardiovascular disease, such as for example myocardial infarction, coronary heart disease, heart insufficiency, thromboembolic events. A glycemic control according to this invention may result in a reduction of the cardiovascular risks.

Furthermore, the pharmaceutical composition and the methods according to this invention are particularly suitable in the treatment of patients after organ transplantation, in particular those patients who are diagnosed having one or more of the following conditions

(a) a higher age, in particular above 50 years,
(b) male gender;
(c) overweight, obesity (including class I, II and/or III obesity), visceral obesity and/or abdominal obesity,
(d) pre-transplant diabetes,
(e) immunosuppression therapy.

Furthermore, the pharmaceutical composition and the methods according to this invention are particularly suitable in the treatment of patients who are diagnosed having one or more of the following conditions:

(a) hyponatremia, in particular chronical hyponatremia;
(b) water intoxication;
(c) water retention;
(d) plasma sodium concentration below 135 mmol/L.

The patient may be a diabetic or non-diabetic mammal, in particular human.

Furthermore, the pharmaceutical composition and the methods according to this invention are particularly suitable in the treatment of patients who are diagnosed having one or more of the following conditions:

(a) high serum uric acid levels, in particular greater than 6.0 mg/dL (357 µmol/L);
(b) a history of gouty arthritis, in particular recurrent gouty arthritis;
(c) kidney stones, in particular recurrent kidney stones;
(d) a high propensity for kidney stone formation.

A pharmaceutical composition according to this invention, in particular due to the SGLT2 inhibitor therein, exhibits a good safety profile. Therefore, a treatment or prophylaxis according to this invention is advantageously possible in those patients for which the mono-therapy with another antidiabetic drug, such as for example metformin, is contraindicated and/or who have an intolerance against such drugs at therapeutic doses. In particular, a treatment or prophylaxis according to this invention may be advantageously possible in those patients showing or having an increased risk for one or more of the following disorders: renal insufficiency or diseases, cardiac diseases, cardiac failure, hepatic diseases, pulmonal diseases, catabolytic states and/or danger of lactate acidosis, or female patients being pregnant or during lactation.

Furthermore, it can be found that the administration of a pharmaceutical composition according to this invention results in no risk or in a low risk of hypoglycemia. Therefore, a treatment or prophylaxis according to this invention is also advantageously possible in those patients showing or having an increased risk for hypoglycemia.

A pharmaceutical composition according to this invention is particularly suitable in the long term treatment or prophylaxis of the diseases and/or conditions as described hereinbefore and hereinafter, in particular in the long term glycemic control in patients with type 2 diabetes mellitus.

The term "long term" as used hereinbefore and hereinafter indicates a treatment of or administration in a patient within a period of time longer than 12 weeks, preferably longer than 25 weeks, even more preferably longer than 1 year.

Therefore, a particularly preferred embodiment of the present invention provides a method for therapy, preferably oral therapy, for improvement, especially long term improvement, of

glycemic control in patients with type 2 diabetes mellitus, especially in patients with late stage type 2 diabetes mellitus, in particular in patients additionally diagnosed of overweight, obesity (including class I, class II and/or class III obesity), visceral obesity and/or abdominal obesity.

The effects mentioned above are observed both, when the SGLT2 inhibitor and the the PPARγ agonist are administered in combination, for example simultaneously in one single or two separate formulations, and when they are administered in alternation, for example successively in two separate formulations.

It will be appreciated that the amount of the pharmaceutical composition according to this invention to be administered to the patient and required for use in treatment or prophylaxis according to the present invention will vary with the route of administration, the nature and severity of the condition for which treatment or prophylaxis is required, the age, weight and condition of the patient, concomitant medication and will be ultimately at the discretion of the attendant physician. In general, however, the SGLT2 inhibitor and the PPARγ agonist according to this invention are included in the pharmaceutical composition or dosage form in an amount sufficient that by their administration in combination and/or alternation the glycemic control in the patient to be treated is improved.

For the treatment of hyperuricemia or hyperuricemia associated conditions the SGLT2 inhibitor according to this invention is included in the pharmaceutical composition or dosage form in an amount sufficient that is sufficient to treat hyperuricemia without disturbing the patient's plasma glucose homeostasis, in particular without inducing hypoglycemia.

For the treatment or prevention of kidney stones the SGLT2 inhibitor according to this invention is included in the pharmaceutical composition or dosage form in an amount sufficient that is sufficient to treat or prevent kidney stones without disturbing the patient's plasma glucose homeostasis, in particular without inducing hypoglycemia.

For the treatment of hyponatremia and associated conditions the SGLT2 inhibitor according to this invention is included in the pharmaceutical composition or dosage form in an amount sufficient that is sufficient to treat hyponatremia or the associated conditions without disturbing the patient's plasma glucose homeostasis, in particular without inducing hypoglycemia.

In the following preferred ranges of the amount of the SGLT2 inhibitor and the PPARγ agonist to be employed in the pharmaceutical composition and the methods and uses according to this invention are described. These ranges refer to the amounts to be administered per day with respect to an adult patient, in particular to a human being, for example of approximately 70 kg body weight, and can be adapted accordingly with regard to an administration 2, 3, 4 or more times daily and with regard to other routes of administration and with regard to the age of the patient. The ranges of the dosage and amounts are calculated for the inidividual active moiety. Advantageously, the combination therapy according to the present invention utilizes lower dosages of the individual SGLT2 inhibitor and/or the PPARγ agonist used in monotherapy or used in conventional therapeutics, thus avoiding possible toxicity and adverse side effects incurred when those agents are used as monotherapies.

Within the scope of the present invention, the pharmaceutical composition is preferably administered orally. Other forms of administration are possible and described hereinafter. Preferably the one or more dosage forms comprising the SGLT2 inhibitor and the PPARγ agonist is oral or usually well known.

In general, the amount of the SGLT2 inhibitor in the pharmaceutical composition and methods according to this invention is preferably in the range from 1/5 to 1/1 of the amount usually recommended for a monotherapy using said SGLT2 inhibitor.

The preferred dosage range of the SGLT2 inhibitor is in the range from 0.5 mg to 200 mg, even more preferably from 1 to 100 mg, most preferably from 1 to 50 mg per day. The oral administration is preferred. Therefore, a pharmaceutical composition may comprise the hereinbefore mentioned amounts, in particular from 1 to 50 mg or 1 to 25 mg. Particular dosage strengths (e.g. per tablet or capsule) are for example 1, 2.5, 5, 7.5, 10, 12.5, 15, 20, 25 or 50 mg of the compound of the formula (I), in particular of the compound (I.9), or of dapagliflozin. The application of the active ingredient may occur up to three times a day, preferably one or two times a day.

A preferred dosage range of pioglitazone when administered orally is 5 to 50 mg per day. The preferred range of amounts in the pharmaceutical composition is 5 to 50 mg, 10 to 45 mg and 15 to 45 mg respectively. Examples are 15, 30 or 45 mg. Preferably the administration of said amounts is once or twice daily, in particular once daily. Pioglitazone

can be administered in the form as it is marketed for example under the trademark ACTOS™.

A preferred dosage range of rosiglitazone when administered orally is 1 mg to 10 mg per day. The preferred range of amounts in the pharmaceutical composition is 1 to 10 mg, 2 to 8 mg, 4 to 8 mg and 1 to 4 mg. Examples are 1, 2, 4 or 8 mg. Preferably the administration of said amounts is once or twice daily. Preferably the dose should not exceed 8 mg daily. Rosiglitazone can be administered in the form as it is marketed for example under the trademark AVANDIA™.

A preferred dosage range of a thiazolidindione (other than pioglitazone or rosiglitazone as described above) when administered orally is 2 to 100 mg per day. The preferred range of amounts in the pharmaceutical composition for an administration once, twice or three times daily is 2 to 100, 1 to 50 and 1 to 33 mg respectively.

The amount of the SGLT2 inhibitor and the PPARγ agonist in the pharmaceutical composition and in the methods and uses according to this invention correspond to the respective dosage ranges as provided hereinbefore. For example, preferred dosage ranges in a pharmaceutical composition and in methods and uses according to this invention are an amount of 1 to 50 mg (in particular 1 to 25 mg) of a SGLT2 inhibitor according to the formula (I), in particular of the compound (I.9), and an amount of 5 to 50 mg (in particular 10 to 45 mg) of pioglitazone. An oral administration once or twice daily is preferred.

For example, preferred dosages in a pharmaceutical composition and in methods and uses according to this invention are amounts of:

- 5 mg of compound (I.9) and 15 mg of pioglitazone,
- 5 mg of compound (I.9) and 30 mg of pioglitazone,
- 5 mg of compound (I.9) and 45 mg of pioglitazone,
- 10 mg of compound (I.9) and 15 mg of pioglitazone,
- 10 mg of compound (I.9) and 30 mg of pioglitazone,
- 10 mg of compound (I.9) and 45 mg of pioglitazone,
- 25 mg of compound (I.9) and 15 mg of pioglitazone,
- 25 mg of compound (I.9) and 30 mg of pioglitazone,
- 25 mg of compound (I.9) and 45 mg of pioglitazone,
- 50 mg of compound (I.9) and 15 mg of pioglitazone,
- 50 mg of compound (I.9) and 30 mg of pioglitazone,

- 50 mg of compound (I.9) and 45 mg of pioglitazone.

Particularly preferred dosages in a pharmaceutical composition and in methods and uses according to this invention are amounts of:

- 10 mg of compound (I.9) and 30 mg of pioglitazone,
- 25 mg of compound (I.9) and 45 mg of pioglitazone.

In the methods and uses according to the present invention the SGLT2 inhibitor and the PPARγ agonist are administered in combination or alternation. The term "administration in combination" means that the active ingredients are administered at the same time, i.e. simultaneously, or essentially at the same time. The term "administration in alternation" means that at first one or two active ingredients are administered and after a period of time the other two or one active ingredients are administered, i.e. at least two of the three active ingredients are administered sequentially. The period of time may be in the range from 30 min to 12 hours. The administration which is in combination or in alternation may be once, twice, three times or four times daily, preferably once or twice daily.

With regard to the administration of the SGLT2 inhibitor and the PPARγ agonist may be present in one single dosage form, for example in one tablet or capsule, or the two active ingredients may be present in a separate dosage form, for example in two different or identical dosage forms.

With regard to their administration in alternation, one or the two active ingredients are present in a separate dosage form, for example in two different or identical dosage forms.

Therefore, the pharmaceutical composition according to this invention may be present as single dosage forms which comprise the SGLT2 inhibitor and the PPARγ agonist.

According to another embodiment the pharmaceutical composition according to the invention is characterized in that the SGLT2 inhibitor and the PPARγ agonist are present each in a separate dosage form.

The case may arise in which one active ingredient has to be administered more often, for example twice per day, than the other active ingredients, which for example needs administration once daily. Therefore the term "administration in combination or alternation" also includes an administration scheme in which first all active ingredients are administered

in combination or alternation and after a period of time only one active ingredient is administered again or *vice versa*.

A pharmaceutical composition which is present as a separate or multiple dosage form, preferably as a kit of parts, is useful in combination therapy to flexibly suit the individual therapeutic needs of the patient.

According to a first embodiment a preferred kit of parts comprises

(a) a first containment containing a dosage form comprising the SGLT2 inhibitor and at least one pharmaceutically acceptable carrier, and

(b) a second containment containing a dosage form comprising the PPARγ agonist and at least one pharmaceutically acceptable carrier.

A further aspect of the present invention is a manufacture comprising the pharmaceutical composition being present as separate dosage forms according to the present invention and a label or package insert comprising instructions that the separate dosage forms are to be administered in combination or alternation.

According to a first embodiment a manufacture comprises (a) a pharmaceutical composition comprising a SGLT2 inhibitor according to the present invention and (b) a label or package insert which comprises instructions that the medicament may or is to be administered, for example in combination or alternation, with a medicament comprising a PPARγ agonist according to the present invention.

According to a second embodiment a manufacture comprises (a) a pharmaceutical composition comprising a PPARγ agonist according to the present invention and (b) a label or package insert which comprises instructions that the medicament may or is to be administered, for example in combination or alternation, with a medicament comprising a SGLT2 inhibitor according to the present invention.

The desired dose of the pharmaceutical composition according to this invention may conveniently be presented in a once daily or as divided dose administered at appropriate intervals, for example as two, three or more doses per day.

The pharmaceutical composition may be formulated for oral, rectal, nasal, topical (including buccal and sublingual), transdermal, vaginal or parenteral (including intramuscular, sub-

cutaneous and intravenous) administration in liquid or solid form or in a form suitable for administration by inhalation or insufflation. Oral administration is preferred. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active ingredient with one or more pharmaceutically acceptable carriers, like liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired formulation.

The pharmaceutical composition may be formulated in the form of tablets, granules, fine granules, powders, capsules, caplets, soft capsules, pills, oral solutions, syrups, dry syrups, chewable tablets, troches, effervescent tablets, drops, suspension, fast dissolving tablets, oral fast-dispersing tablets, etc..

The pharmaceutical composition and the dosage forms preferably comprises one or more pharmaceutical acceptable carriers. Preferred carriers must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Examples of pharmaceutically acceptable carriers are known to the one skilled in the art.

Pharmaceutical compositions suitable for oral administration may conveniently be presented as discrete units such as capsules, including soft gelatin capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution, a suspension or as an emulsion, for example as syrups, elixirs or self-emulsifying delivery systems (SEDDS). The active ingredients may also be presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), or preservatives.

The pharmaceutical composition according to the invention may also be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small

volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredients may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Pharmaceutical compositions suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art, and the suppositories may be conveniently formed by admixture of the active compound(s) with the softened or melted carrier(s) followed by chilling and shaping in moulds.

The pharmaceutical compositions and methods according to this invention show advantageous effects in the treatment and prevention of those diseases and conditions as described hereinbefore compared with pharmaceutical compositions and methods which comprise only one or two of the three active ingredients. Advantageous effects may be seen for example with respect to efficacy, dosage strength, dosage frequency, pharmacodynamic properties, pharmacokinetic properties, fewer adverse effects, convenience, compliance, etc..

Methods for the manufacture of SGLT2 inhibitors according to this invention and of prodrugs thereof are known to the one skilled in the art. Advantageously, the compounds according to this invention can be prepared using synthetic methods as described in the literature, including patent applications as cited hereinbefore. Preferred methods of manufacture are described in the WO 2006/120208 and WO 2007/031548. With regard to the preferred compound (I.9) an advantageous crystalline form is described in the international patent application WO 2006/117359 which hereby is incorporated herein in its entirety.

The active ingredients may be present in the form of a pharmaceutically acceptable salt. Pharmaceutically acceptable salts include, without being restricted thereto, such as salts of inorganic acid like hydrochloric acid, sulfuric acid and phosphoric acid; salts of organic carboxylic acid like oxalic acid, acetic acid, citric acid, malic acid, benzoic acid, maleic acid, fumaric acid, tartaric acid, succinic acid and glutamic acid and salts of organic sulfonic acid like methanesulfonic acid and p-toluenesulfonic acid. The salts can be formed by combining

the compound and an acid in the appropriate amount and ratio in a solvent and decomposer. They can be also obtained by the cation or anion exchange from the form of other salts.

The active ingredients or a pharmaceutically acceptable salt thereof may be present in the form of a solvate such as a hydrate or alcohol adduct.

Any of the above mentioned combinations and methods within the scope of the invention may be tested by animal models known in the art. In the following, *in vivo* experiments are described which are suitable to evaluate pharmacologically relevant properties of pharmaceutical compositions and methods according to this invention:

Pharmaceutical compositions and methods according to this invention can be tested in genetically and/or environmentally-induced hyperinsulinemic and/or diabetic animals like db/db mice, ob/ob mice, Zucker Fatty (fa/fa) rats or Zucker Diabetic Fatty (ZDF) rats, dietary-induced obese Wistar rats. In addition, they can be tested in animals with experimentally induced diabetes like HanWistar or Sprague Dawley rats pretreated with streptozotocin.

The effect on glycemic control of the combinations according to this invention can be tested after multiple dosing of the SGLT2 inhibitor and the PPARγ agonist alone and in combination by measuring fed blood glucose or HbA1c in the animal models described hereinbefore. The combinations according to the present invention significantly lower blood glucose further compared to each monotherapy. In addition, after multiple dosing of the SGLT2 inhibitor and the PPARγ agonist alone and in combination in the animal models described hereinbefore, the effect on glycemic control was determined by measuring glucose and/or HbA1c value in blood. The combinations according to this invention significantly further reduced glucose and/or HbA1c compared to each monotherapy.

A superior effect of the combination of a SGLT2 inhibitor and a PPARγ agonist according to the present invention on beta-cell regeneration and neogenesis can be determined after multiple dosing in the animal models described hereinbefore by measuring the increase in pancreatic insulin content, or by measuring increased beta-cell mass by morphometric analysis after immunhistochemical staining of pancreatic sections, or by measuring increased glucose-stimulated insulin secretion in isolated pancreatic islets.

Pharmacological Examples

Example 1:

The following example shows the beneficial effect of an SGLT2 inhibitor in combination with a PPARγ agonist in comparison to a PPARγ agonist treatment alone on body weight and total body fat content. The SGLT2 inhibitor is the glucopyranosyl-substituted benzene derivative described as compound (I.9) hereinabove and referred to as "Cpd. A" in the following. The PPARγ agonist is pioglitazone. All experimental procedures concerning the use of laboratory animals were carried out under a Home Office Certificate of Designation.

An animal model of obesity was used to study the effect of Cpd. A, Pioglitazone or the combination of Cpd. A with Pioglitazone on body weight and total body fat content. For this, female Wistar rats were made obese by exposure to a simplified cafeteria diet containing high fat chow, chocolate and ground peanuts for approximately 19 weeks.
Following the induction of obesity, rats were given vehicle (0.5% aqueous hydroxyethylcellulose) for 7 days and were then dosed orally once-daily with either vehicle, 10 mg/kg Cpd. A, 10 mg/kg Pioglitazone, or the combination of Cpd. A and Pioglitazone for 29 days. For the duration of the study rats were maintained on cafeteria diet. Body weight was monitored daily and the final body weight after 28 day treatment is given in Figure 1.

After 28 days of treatment, blood samples were collected from the tail vein (from fed animals) for analysis of insulin. Plasma insulin values were determined by using a Millipore Luminex RENDO 85K kit. Results are shown in Figure 2.

At the end of the study on Day 31 (24 hours after the last treatment on Day 30) all rats were terminated, the body exsanguinated and the following tissues removed: the caudate liver lobe, the pancreas, the kidneys. Body composition (body fat, protein and water) was determined using the FoodScan NIR (near infra-red) meat analyser (Foss UK). This machine has AOAC (Association of Official Analytical Chemists) approval as reference method for the analysis of moisture, fat and protein in meat. The carcasses were milled under liquid nitrogen and a portion of the milled carcass was analysed in the FoodScan Analyser. The results of the determination of body fat content are given in table 1.

In Figure 1, results are mean body weights (adjusted for differences between the body weights of the different treatment groups at baseline (Day 1)) ± SEM (calculated from the residuals of the statistical model), n = 10) after 28 day once-daily oral treatment with the

glucopyranosyl-substituted benzene derivative (Cpd. A), Pioglitazone or the combination of both Cpd. A and Pioglitazone at the indicated doses.
Body weight data were analyzed by unpaired t-test. P values versus vehicle control are indicated by symbols above the bars (*, $p<0.05$) The glucopyranosyl-substituted benzene derivative (Cpd. A) reduced the body weight significantly by 3.1% at 10 mg/kg. Pioglitazone significantly increased the body weight compared to vehicle-treated control animals by 6.8%. Combination of Cpd. A and Pioglitazone did not lead to a significant increase in body weight compared to control animals.

In Figure 2, results are mean plasma insulin levels ± SEM after 29 days of once-daily oral treatment with the glucopyranosyl-substituted benzene derivative (Cpd. A), Pioglitazone or the combination of both Cpd. A and Pioglitazone at the indicated doses.
Plasma insulin values were analyzed by unpaired t-test. P values versus vehicle control are indicated by symbols above the bars (*, $p<0.05$; **, $p<0.01$; ***, $p<0.001$). The glucopyranosyl-substituted benzene derivative reduced the plasma insulin levels significantly at 10 mg/kg. Pioglitazone significantly decreased plasma insulin levels significantly compared to vehicle-treated control animals. Combination of Cpd. A and Pioglitazone led to further significant reduction of plasma insulin levels compared to either treatment alone.

Table 1: Body fat reduction by the combination of Cpd. A with Pioglitazone compared to Pioglitazone alone

Group	Water (%)	Fat (%)	Protein (%)	Carcass weight (%)
Vehicle	0.0	0.0	0.0	0.0
Cpd. A 10 mg/kg po	-0.3	-4.5	-1.5	-3.5
Pioglitazone 10 mg/kg po	3.6	15.4	1.1	6.2
Pioglitazone 10 mg/kg + Cpd. A 10 mg/kg po	-0.2	1.5	-2.3	0.5

Results are the percentage reduction in each parameter when compared to control and presented along with the corresponding percentage reduction in carcass weight compared to the vehicle-treated control group. Body composition (body fat, protein and water) was determined using the FoodScan NIR (near infra-red) meat analyser (Foss UK).
Pioglitazone led to a significant increase of body fat content in comparison to vehicle-treated control animals. Combination of the glucopyranosyl-substituted benzene derivative (Cpd. A),

with Pioglitazone prevented the increase in body fat content observed with Pioglitazone-treatment alone.

Example 2:

The following example shows the beneficial effect on glycemic control of the combination of an SGLT2 inhibitor and a PPARγ agonist as compared to the respective monotherapies. The SGLT2 inhibitor is the glucopyranosyl-substituted benzene derivative described as compound (I.9) hereinabove and referred to as "Cpd. A" in the following. The PPARγ agonist is pioglitazone. All experimental protocols concerning the use of laboratory animals were reviewed by a federal Ethics Committee and approved by governmental authorities. The time course of blood glucose was followed over a treatment period of 2 weeks in male Zucker diabetic fatty rats (ZDF/Crl-Lepr^{fa}) with an age of 10 weeks at the start of the study. A pre-dose blood sample was obtained by tail bleed (day 0) and blood glucose was measured with a glucometer. From day 1 to day 15, the animals (n = 5 / group) received once daily oral administrations of either vehicle alone (0.5% aqueous hydroxyethylcellulose) or this vehicle containing either Cpd. A or pioglitazone or the combination of the Cpd. A with pioglitazone. Blood glucose was measured in tail blood 2 h after dosing in freely fed animals. The data are presented as mean ± S.E.M. Statistical comparison was conducted by repeated measures two-way ANOVA followed by Bonferroni post tests for group-wise comparisons. A p value < 0.05 was considered to show a statistically significant difference. The result is shown in Figure 3.

Cpd. A is Cpd. A described as compound (I.9) hereinabove at a dose of 1 mg/kg. Pioglitazone was dosed at 10 mg/kg. Combination Cpd. A + Pioglitazone is the combination of the compound (I.9) and pioglitazone at the same doses. P values versus control are indicated by asterisks and p values of the monotherapies versus the combination are indicated by crosses (one symbol, $p < 0.05$; two symbols, $p < 0.01$; three symbols, $p < 0.001$). After two weeks of once daily treatment, Cpd. A had reduced blood glucose by 37%, and pioglitazone by 48%. The combination had decreased blood glucose by 76%, and this reduction in blood glucose was statistically significant versus each monotherapy.

Example 3: Treatment of pre-diabetes

The efficacy of a pharmaceutical composition according to the invention in the treatment of pre-diabetes characterised by pathological fasting glucose and/or impaired glucose tolerance can be tested using clinical studies. In studies over a shorter period (e.g. 2-4 weeks) the success of the treatment is examined by determining the fasting glucose values and/or the glucose values after a meal or after a loading test (oral glucose tolerance test or food

tolerance test after a defined meal) after the end of the period of therapy for the study and comparing them with the values before the start of the study and/or with those of a placebo group. In addition, the fructosamine value can be determined before and after therapy and compared with the initial value and/or the placebo value. A significant drop in the fasting or non-fasting glucose levels demonstrates the efficacy of the treatment. In studies over a longer period (12 weeks or more) the success of the treatment is tested by determining the HbA1c value, by comparison with the initial value and/or with the value of the placebo group. A significant change in the HbA1c value compared with the initial value and/or the placebo value demonstrates the efficacy of the combination according to the invention for treating pre-diabetes.

Example 4: Preventing manifest type 2 diabetes

Treating patients with pathological fasting glucose and/or impaired glucose tolerance (pre-diabetes) is also in pursuit of the goal of preventing the transition to manifest type 2 diabetes. The efficacy of a treatment can be investigated in a comparative clinical study in which pre-diabetes patients are treated over a lengthy period (e.g. 1-5 years) with either a pharmaceutical composition according to this invention or with placebo or with a non-drug therapy or other medicaments. During and at the end of the therapy, by determining the fasting glucose and/or a loading test (e.g. oGTT), a check is made to determine how many patients exhibit manifest type 2 diabetes, i.e. a fasting glucose level of >125 mg/dl and/or a 2h value according to oGTT of >199 mg/dl. A significant reduction in the number of patients who exhibit manifest type 2 diabetes when treated with a combination according to this invention as compared to one of the other forms of treatment, demonstrates the efficacy in preventing a transition from pre-diabetes to manifest diabetes.

Example 5: Treatment of type 2 diabetes

Treating patients with type 2 diabetes with the pharmaceutical composition according to the invention, in addition to producing an acute improvement in the glucose metabolic situation, prevents a deterioration in the metabolic situation in the long term. This can be observed is patients are treated for a longer period, e.g. 3 months to 1 year or even 1 to 6 years, with the pharmaceutical composition according to the invention and are compared with patients who have been treated with other antidiabetic medicaments. There is evidence of therapeutic success compared with patients treated with other antidiabetic medicaments if no or only a slight increase in the fasting glucose and/or HbA1c value is observed. Further evidence of therapeutic success is obtained if a significantly smaller percentage of the patients treated with a pharmaceutical composition according to the invention, compared with patients who

have been treated with other medicaments, undergo a deterioration in the glucose metabolic position (e.g. an increase in the HbA1c value to >6.5% or >7%) to the point where treatment with an additional oral antidiabetic medicament or with insulin or with an insulin analogue is indicated.

Example 6: Treatment of insulin resistance

In clinical studies running for different lengths of time (e.g. 2 weeks to 12 months) the success of the treatment is checked using a hyperinsulinaemic euglycaemic glucose clamp study. A significant rise in the glucose infusion rate at the end of the study, compared with the initial value or compared with a placebo group, or a group given a different therapy, proves the efficacy of a pharmaceutical composition according to the invention in the treatment of insulin resistance.

Example 7: Treatment of hyperglycaemia

In clinical studies running for different lengths of time (e.g. 1 day to 24 months) the success of the treatment in patients with hyperglycaemia is checked by determining the fasting glucose or non-fasting glucose (e.g. after a meal or a loading test with oGTT or a defined meal). A significant fall in these glucose values during or at the end of the study, compared with the initial value or compared with a placebo group, or a group given a different therapy, proves the efficacy of a pharmaceutical composition according to the invention in the treatment of hyperglycaemia.

Example 8: Prevention of micro- or macrovascular complications

The treatment of type 2 diabetes or pre-diabetes patients with a pharmaceutical composition according to the invention prevents or reduces or reduces the risk of developing microvascular complications (e.g. diabetic neuropathy, diabetic retinopathy, diabetic nephropathy, diabetic foot, diabetic ulcer) or macrovascular complications (e.g. myocardial infarct, acute coronary syndrome, unstable angina pectoris, stable angina pectoris, stroke, peripheral arterial occlusive disease, cardiomyopathy, heart failure, heart rhythm disorders, vascular restenosis). Type 2 diabetes or patients with pre-diabetes are treated long-term, e.g. for 1-6 years, with a pharmaceutical composition according to the invention or a combination of active ingredients according to the invention and compared with patients who have been treated with other antidiabetic medicaments or with placebo. Evidence of the therapeutic success compared with patients who have been treated with other antidiabetic medicaments or with placebo can be found in the smaller number of single or multiple complications. In the case of macrovascular events, diabetic foot and/or diabetic ulcer, the

numbers are counted by anamnesis and various test methods. In the case of diabetic retinopathy the success of the treatment is determined by computer-controlled illumination and evaluation of the background to the eye or other ophthalmic methods. In the case of diabetic neuropathy, in addition to anamnesis and clinical examination, the nerve conduction rate can be measured using a calibrated tuning fork, for example. With regard to diabetic nephropathy the following parameters may be investigated before the start, during and at the end of the study: secretion of albumin, creatinine clearance, serum creatinin values, time taken for the serum creatinine values to double, time taken until dialysis becomes necessary.

Example 9: Treatment of Metabolic Syndrome

The efficacy of a pharmaceutical composition according to the invention can be tested in clinical studies with varying run times (e.g. 12 weeks to 6 years) by determining the fasting glucose or non-fasting glucose (e.g. after a meal or a loading test with oGTT or a defined meal) or the HbA1c value. A significant fall in these glucose values or HbA1c values during or at the end of the study, compared with the initial value or compared with a placebo group, or a group given a different therapy, proves the efficacy of an active ingredient or combination of active ingredients in the treatment of Metabolic Syndrome. Examples of this are a reduction in systolic and/or diastolic blood pressure, a lowering of the plasma triglycerides, a reduction in total or LDL cholesterol, an increase in HDL cholesterol or a reduction in weight, either compared with the starting value at the beginning of the study or in comparison with a group of patients treated with placebo or a different therapy.

Example 10a: Prevention of NODAT and/or PTMS, and NODAT/PTMS associated complications

Treatment of patients after organ transplantation with the pharmaceutical composition according to the invention prevents the development of NODAT and/or PTMS, and associated complications. The efficacy of the treatment can be investigated in a comparative clinical study in which patients before or immediately after transplantation are treated over a lengthy period (e.g. 1-5 years) with either a pharmaceutical composition according to this intervention or with a placebo or with a non-drug therapy or other medicaments. During and at the end of the therapy, the incidence of NODAT, PTMS, micro- and macrovascular complications, graft rejection, infection and death will be assessed. A significant reduction in the number of patients experiencing these complications demonstrates the efficacy in preventing development of NODAT, PTMS, and associated complications.

Example 10b: Treatment of NODAT and/or PTMS with prevention, delay or reduction of associated complications

Treatment of patients with NODAT and/or PTMS with the pharmaceutical composition according to the invention prevents, delays or reduces the development of NODAT/PTMS associated complications. The efficacy of the treatment can be investigated in a comparative clinical study in which patients with NODAT and/or PTMS are treated over a lengthy period (e.g. 1-5 years) with either a pharmaceutical composition according to this intervention or with a placebo or with a non-drug therapy or other medicaments. During and at the end of the therapy, the incidence of micro- and macrovascular complications, graft rejection, infection and death is assessed. A significant reduction in the number of patients experiencing these complications demonstrates the efficacy in preventing, delaying or reducing the development of NODAT and/or PTMS associated complications.

Example 11a: Treatment of gestational diabetes

In clinical studies running for a shorter period (e.g. 2-4 weeks) the success of the treatment is checked by determining the fasting glucose values and/or the glucose values after a meal or after a loading test (oral glucose tolerance test or food tolerance test after a defined meal) at the end of the therapeutic period of the study and comparing them with the values before the start of the study and/or with those of a placebo group. In addition, the fructosamine value can be determined before and after treatment and compared with the initial value and/or a placebo value. A significant fall in the fasting or non-fasting glucose levels demonstrates the pharmaceutical compositon according to the invention.

In longer-running studies (12 weeks or more) the success of the treatment is checked by determining the HbA1c value (compared with initial value and placebo group). A significant change in the HbA1c value compared with the starting value and/or placebo value demonstrates the efficacy of the pharmaceutical composition according to the invention in the treatment of gestational diabetes.

Example 11b: Treatment of women who have had gestational diabetes

Patients with gestational diabetes have a significantly increased risk of contracting manifest type 2 diabetes after the pregnancy. Therapy may be provided with the objective of preventing the transition to manifest type 2. For this purpose, women with a history of gestational diabetes are treated either with a pharmaceutical composition according to the invention or with placebo or with a non-drug therapy or with other medicaments, over a lengthy period (e.g. 1-4 years). During and at the end of the treatment a check is carried out by determining the fasting glucose and/or by a loading test (e.g. oGTT) to see how many

patients have developed manifest type 2 diabetes (fasting glucose level >125 mg/dl and/or 2h value after oGTT >199 mg/dl). A significant reduction in the number of patients who develop manifest type 2 diabetes when treated with a pharmaceutical composition according to the invention compared with a different type of therapy, is proof of the efficacy of a pharmaceutical composition in preventing manifest diabetes in women with a history of gestational diabetes.

Example 12: Treatment of hyperuricemia

Patients with elevated levels of uric acid above the normal range (above 8.3 mg/dL or 494 µmol/L) or patients with a history of gout or gouty arthritis with a uric acid level greater than 6.0 mg/dL or 357 µmol/L have a significant risk of future episodes of gout or gouty arthritis as well as having an increased risk of cardiovascular disease. Therapy may be provided with the objective of lowering serum levels of uric acid as a means of preventing future episodes or flare-ups of gout or gouty arthritis. Additionally, lowering serum uric acid levels may reduce the risk of cardiovascular disease. For this purpose patients with an elevated uric acid level or a history of gout or gouty arthritis are treated either with a pharmaceutical composition according to the invention or with placebo or with a non-drug therapy or with other medicaments, over a lengthy period (e.g. 6 months to 4 years). During and at the end of the treatment a check is carried out by determining the serum uric acid level and the number of episodes of gout or gouty arthritis occurences. A reduction in uric acid below 6.0 mg/dL and/or fewer episodes of gout or gouty arthritis occurrence when treated with a pharmaceutical composition according to the invention compared with a different type of therapy, is proof of the efficacy of a pharmaceutical composition in preventing episodic gout or gouty arthritis or treating hyperuricemia.

Example 13: Treatment of hyponatremia

Patients with hyponatremia and water intoxication whether due to an increase in water resorption or an increase in water intake, are at risk of central nervous system abnormalities and possibly death. Therapy may be provided with the objective of increasing the amount of free water to be excreted in the renal filtrate without disturbing sodium balance with the objective of increasing the overall sodium concentration of the interstitial fluids. For this purpose, patients with a history of hyponatremia are treated either with a pharmaceutical composition according to the invention or with placebo or with a non-drug therapy or with other medicaments, over a short period (e.g. 3 to 6 months), with periodic assessment of serum sodium levels. An increase in sodium levels into the normal range reported during this time period when treated with a pharmaceutical composition according to the invention

compared with a different type of therapy, is proof of the efficacy of a pharmaceutical composition in treating hyponatremia.

Example 14: Treatment/ prevention of kidney stones

Patients with a history of kidney stones, particularly calcium, mixed calcium, and uric acid stones frequently have a history of hyperuricemia. These renal stones may relate to small urate crystals forming a nidus in the renal filtrate upon which further crystalization of urate or other crystalizing substances in the solute can induce renal stone formation. These stones are not related to renal stones caused by certain kidney infections (such as staghorn – type stones). Therapy may be provided with the objective of increasing the neutral solutes (for example glucose) and free water content of the renal filtrate, making it difficult for a urate nidus to form, despite a possible increase in the absolute amounts of urate in the renal filtrate. These neutral solutes and free water will also reduce the formation of stones other than uric acid stones. For this purpose patients with a history of kidney stones particularly calcium, mixed calcium, and uric acid stones are treated either with a pharmaceutical composition according to the invention or with placebo or with a non-drug therapy or with other medicaments, over a lengthy period (e.g. 6 months to 4 years). A reduction in the number of kidney stones stones particularly calcium, mixed calcium, and uric acid stones reported during this time period when treated with a pharmaceutical composition according to the invention compared with a different type of therapy, is proof of the efficacy of a pharmaceutical composition in preventing kidney stones particularly calcium, mixed calcium, and uric acid stones.

Examples of Formulations

The following examples of formulations, which may be obtained analogously to methods known in the art, serve to illustrate the present invention more fully without restricting it to the contents of these examples. The term "active ingredient" denotes one or more compounds according to the invention, i.e. denotes an SGLT2 inhibitor or a PPARγ agonist according to this invention or a combination of two of said active ingredients.

Example 1: Dry ampoule containing 75 mg of active ingredient per 10 ml

Composition:

Active ingredient	75.0 mg
Mannitol	50.0 mg
water for injections	ad 10.0 ml

Preparation:

Active ingredient and mannitol are dissolved in water. After packaging the solution is freeze-dried. To produce the solution ready for use, the product is dissolved in water for injections.

Example 2: Dry ampoule containing 35 mg of active ingredient per 2 ml

Composition:

Active ingredient	35.0 mg
Mannitol	100.0 mg
water for injections	ad 2.0 ml

Preparation:

Active ingredient and mannitol are dissolved in water. After packaging, the solution is freeze-dried. To produce the solution ready for use, the product is dissolved in water for injections.

Example 3: Tablet containing 50 mg of active ingredient

Composition:

(1) Active ingredient	50.0 mg
(2) Mannitol	98.0 mg
(3) Maize starch	50.0 mg
(4) Polyvinylpyrrolidone	15.0 mg
(5) Magnesium stearate	2.0 mg
	215.0 mg

Preparation:

(1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granulated material. From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side.

Diameter of the tablets: 9 mm.

Example 4: Tablet containing 350 mg of active ingredient

Preparation:

(1) Active ingredient	350.0 mg
(2) Mannitol	136.0 mg
(3) Maize starch	80.0 mg
(4) Polyvinylpyrrolidone	30.0 mg
(5) Magnesium stearate	4.0 mg

600.0 mg

(1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granulated material. From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side.
Diameter of the tablets: 12 mm.

Example 5: Tablet containing 850 mg of active ingredient

Preparation:

(1) Active ingredient	850.0 mg
(2) Mannitol	300.0 mg
(3) Maize starch	200.0 mg
(4) Polyvinylpyrrolidone	70.0 mg
(5) Magnesium stearate	10.0 mg
	1430.0 mg

(1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granulated material. From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side.
Diameter of the tablets: 12 mm.

Example 6: Capsules containing 50 mg of active ingredient

Composition:

(1) Active ingredient	50.0 mg
(2) Dried maize starch	58.0 mg
(3) Mannitol	50.0 mg
(4) Magnesium stearate	2.0 mg
	160.0 mg

Preparation:
(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing. This powder mixture is packed into size 3 hard gelatin capsules in a capsule filling machine.

Example 7: Capsules containing 350 mg of active ingredient

Composition:

(1) Active ingredient	350.0 mg
(2) Dried maize starch	46.0 mg
(3) Mannitol	30.0 mg
(4) Magnesium stearate	4.0 mg
	430.0 mg

Preparation:

(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing. This powder mixture is packed into size 0 hard gelatin capsules in a capsule filling machine.

Example 8: Tablets containing 2.5mg, 5mg, 10mg, 25mg, 50mg of active substance

Active substance	2.5 mg mg/per tablet	5 mg mg/per tablet	10 mg mg/per tablet	25 mg mg/per tablet	50 mg mg/per tablet
Wet granulation					
active substance	2.5000	5.000	10.00	25.00	50.00
Lactose Monohydrate	40.6250	81.250	162.50	113.00	226.00
Microcrystalline Cellulose	12.5000	25.000	50.00	40.00	80.00
Hydroxypropyl Cellulose	1.8750	3.750	7.50	6.00	12.00
Croscarmellose Sodium	1.2500	2.500	5.00	4.00	8.00
Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.
Dry Adds					
Microcrystalline Cellulose	3.1250	6.250	12.50	10.00	20.00
Colloidal silicon dioxide	0.3125	0.625	1.25	1.00	2.00
Magnesium stearate	0.3125	0.625	1.25	1.00	2.00
Total core	62.5000	125.000	250.00	200.00	400.00
Film Coating					
Film coating pre-mix	2.5000	4.000	7.00	6.00	9.00
Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.
Total	**65.000**	**129.000**	**257.00**	**206.00**	**409.00**

The active ingredient is for example compound (I.9) as described hereinabove.

The tablet is for example prepared as follows:

Active substance granulate

The active substance, e.g. the compound (I.9), preferably in the crystalline form (I.9X), Lactose Monohydrate, Croscarmellose sodium, Hydroxypropylcellulose and Cellulose microcristalline are screened and subsequently pre-mixed in an appropriate high-shear mixer.

The pre-mix is moistened with purified water and granulated using an appropriate high-shear mixer. The granulate is dried in a fluid bed dryer. Subsequently, the granulate is screened through a suitable sieve.

Final blend

Pre-screened silicia, colloidal anhydrous and cellulose microcristalline are added to the granulate and blended in an appropriate free-fall blender.

Pre-screened magnesium stearate is added to the blend and subsequently final blending is performed in an appropriate free-fall blender.

Tablet cores

The final blend is compressed into tablet cores using a standard rotary tablet press.

Film-coating suspension

An aqueous suspension of opadry yellow 02B38190 (dye suspension) is dispersed within in purified water.

Film-coated tablets

The tablet cores are coated with the film-coating suspension in a drum coater to produce film-coated tablets.

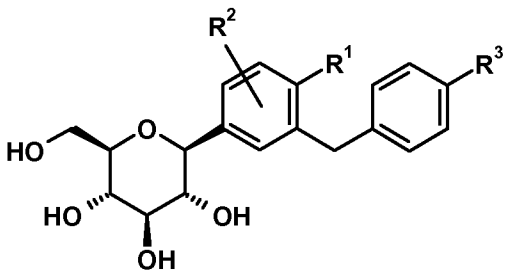
Patent Claims:

1. A pharmaceutical composition comprising
(a) an SGLT2 inhibitor, and
(b) a PPARγ agonist.

2. The pharmaceutical composition according to claim 1, wherein said PPARγ agonist is a thiazolidindione, or a pharmaceutically acceptable salt thereof.

3. The pharmaceutical composition according to claim 1 or 2, wherein said thiazolidindione is pioglitazone or rosiglitazone, or a pharmaceutically acceptable salt thereof.

4. The pharmaceutical composition according to any one of claims 1 to 3, wherein the SGLT2 inhibitor is selected from the group consisting of dapagliflozin, canagliflozin, atigliflozin, remogliflozin, sergliflozin and glucopyranosyl-substituted benzene derivatives of the formula (I)



I

wherein R^1 denotes Cl, methyl or cyano; R^2 denotes H, methyl, methoxy or hydroxy and R^3 denotes ethyl, cyclopropyl, ethynyl, ethoxy, *(R)*-tetrahydrofuran-3-yloxy or *(S)*-tetrahydrofuran-3-yloxy; or a prodrug thereof.

5. The pharmaceutical composition according to any one of claims 1 to 4, wherein the composition is suitable for combined or simultaneous or sequential use of the SGLT2 inhibitor and the PPARγ agonist.

6. Method for preventing, slowing the progression of, delaying or treating a metabolic disorder selected from the group consisting of type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance, impaired fasting blood glucose, hyperglycemia,

postprandial hyperglycemia, overweight, obesity, metabolic syndrome, gestational diabetes, new onset diabetes after transplantation (NODAT) and complications associated therewith, and post-transplant metabolic syndrome (PTMS) and complications associated therewith in a patient in need thereof characterized in that an SGLT2 inhibitor and a PPARγ agonist according to any one of claims 1 to 4 are administered in combination or alternation to the patient.

7. Method for improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c in a patient in need thereof characterized in that an SGLT2 inhibitor and a PPARγ agonist according to any one of claims 1 to 4 are administered in combination or alternation to the patient.

8. Method 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 in a patient in need thereof characterized in that an SGLT2 inhibitor and a PPARγ agonist according to any one of claims 1 to 4 are administered in combination or alternation to the patient.

9. Method for preventing, slowing the progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus such as cataracts and micro- and macrovascular diseases, such as nephropathy, retinopathy, neuropathy, tissue ischaemia, diabetic foot, arteriosclerosis, myocardial infarction, accute coronary syndrome, unstable angina pectoris, stable angina pectoris, stroke, peripheral arterial occlusive disease, cardiomyopathy, heart failure, heart rhythm disorders and vascular restenosis, in a patient in need thereof characterized in that an SGLT2 inhibitor and a PPARγ agonist according to any one of claims 1 to 4 are administered in combination or alternation to the patient.

10. Method for reducing body weight and/or body fat or preventing or reducing an increase in body weight and/or body fat or facilitating a reduction in body weight and/or body fat in a patient in need thereof characterized in that an SGLT2 inhibitor and a PPARγ agonist according to any one of claims 1 to 4 are administered in combination or alternation to the patient.

11. Method for 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 restoring the functionality of pancreatic insulin secretion in a patient in need thereof characterized in that an SGLT2 inhibitor and a PPARγ agonist according to any one of claims 1 to 4 are administered in combination or alternation to the patient.

12. Method for preventing, slowing, delaying or treating diseases or conditions attributed to an abnormal accumulation of ectopic fat in a patient in need thereof characterized in that an SGLT2 inhibitor and a PPARγ agonist according to any one of claims 1 to 4 are administered in combination or alternation to the patient.

13. Method for maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance in a patient in need thereof characterized in that an SGLT2 inhibitor and a PPARγ agonist according to any one of claims 1 to 4 are administered in combination or alternation to the patient.

14. Method for treating and preventing hyperuricemia and hyperuricemia associated conditions, kidney stones and hyponatremia in a patient in need thereof characterized in that an SGLT2 inhibitor and a PPARγ agonist according to any one of claims 1 to 4 are administered in combination or alternation to the patient.

15. Method according to any one of the claims 6, 7, 8, 9, 10, 11, 12, 13 or 14 wherein the patient:

(1) is an individual diagnosed of one or more of the conditions selected from the group consisting of overweight, obesity, visceral obesity and abdominal obesity; or

(2) is an individual who shows one, two or more of the following conditions:

(a) a fasting blood glucose or serum glucose concentration greater than 110 mg/dL, in particular greater than 125 mg/dL;

(b) a postprandial plasma glucose equal to or greater than 140 mg/dL;

(c) an HbA1c value equal to or greater than 6.5 %, in particular equal to or greater than 7.0 %; or

(3) is an individual wherein one, two, three or more of the following conditions are present:

(a) obesity, visceral obesity and/or abdominal obesity,

(b) triglyceride blood level ≥ 150 mg/dL,

(c) HDL-cholesterol blood level < 40 mg/dL in female patients and < 50 mg/dL in male patients,

(d) a systolic blood pressure ≥ 130 mm Hg and a diastolic blood pressure ≥ 85 mm Hg,

(e) a fasting blood glucose level ≥ 100 mg/dL; or

(4) has insufficient glycemic control despite diet and exercise or despite monotherapy with either the SGLT2 inhibitor or the PPARγ agonist.

Figure 1

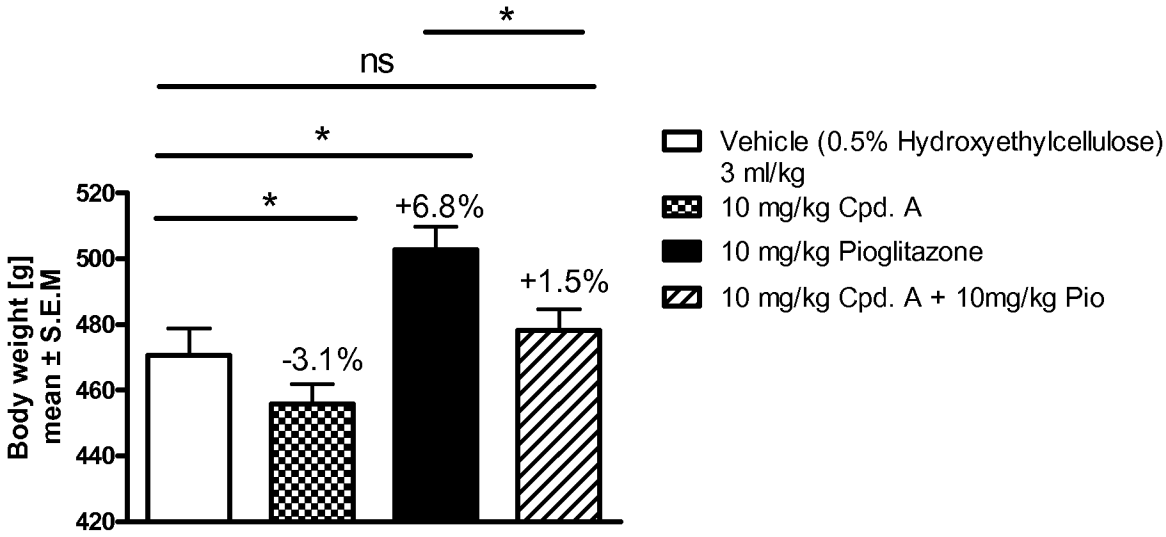

*
ns
*
*
+6.8%
+1.5%
-3.1%
520
500
480
460
440
420
Body weight [g]
mean ± S.E.M
Vehicle (0.5% Hydroxyethylcellulose)
3 ml/kg
10 mg/kg Cpd. A
10 mg/kg Pioglitazone
10 mg/kg Cpd. A + 10mg/kg Pio

Figure 2

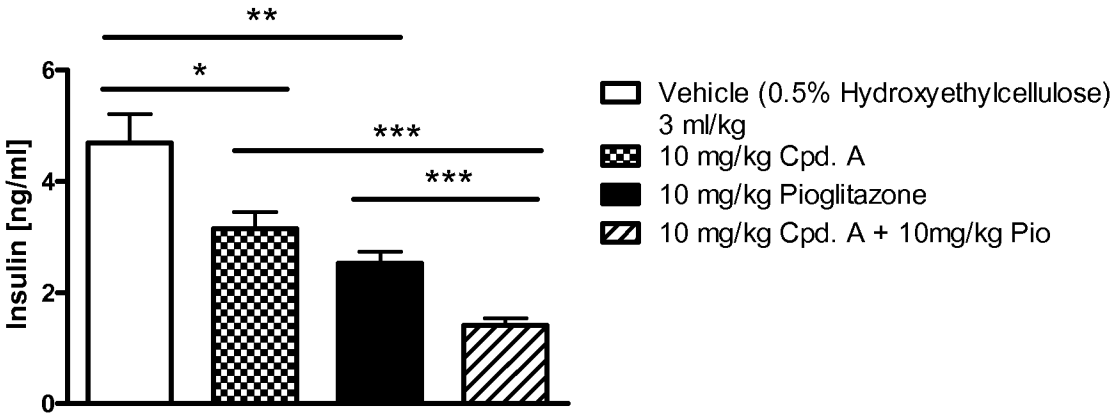
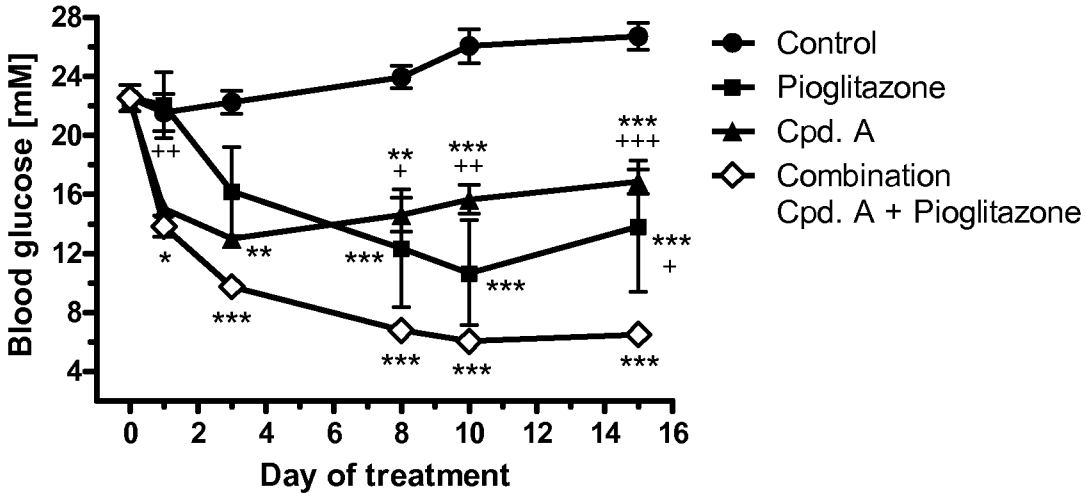

**
*
***
***
Insulin [ng/ml]
0
2
4
6
Vehicle (0.5% Hydroxyethylcellulose) 3 ml/kg
10 mg/kg Cpd. A
10 mg/kg Pioglitazone
10 mg/kg Cpd. A + 10mg/kg Pio

Figure 3


Blood glucose [mM]
28
24
20
16
12
8
4
0
2
4
6
8
10
12
14
16
Day of treatment
Control
Pioglitazone
Cpd. A
Combination
Cpd. A + Pioglitazone

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/054734

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4439 A61K31/70 A61K45/06 A61P3/10
ADD.

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2010/138535 A1 (SQUIBB BRISTOL MYERS CO [US]; ASTRAZENECA UK LTD [GB]; STRUMPH PAUL [U) 2 December 2010 (2010-12-02) claims 1,4,6,8,9 page 62, paragraph 00157 page 60, paragraph 00146 page 69; table I	1-8,10, 13
X,P	WO 2010/092125 A1 (BOEHRINGER INGELHEIM INT [DE]; EICKELMANN PETER [DE]; MARK MICHAEL [DE) 19 August 2010 (2010-08-19) claims 1-11,13	1-10,13

-/--

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 August 2011	12/08/2011

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

3

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

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/116179 A1 (BRISTOL MYERS SQUIBB [US]; BINDRA DILBIR S [US]; DALI MANDAR V [US]; P) 25 September 2008 (2008-09-25) claims 1,16,17,20 page 30, paragraph 0080 - paragraph 0083 paragraph [00145]	1-10,13
X	WO 03/099836 A1 (SQUIBB BRISTOL MYERS CO [US]; ELLSWORTH BRUCE [US]; WASHBURN WILLIAM N) 4 December 2003 (2003-12-04) claims 1,4,5,7,14,16	1-10,13
X	WO 2004/007517 A1 (AVENTIS PHARMA GMBH [DE]) 22 January 2004 (2004-01-22) claims 1,12-14 page 22, line 9 - line 11 page 32, line 8	1-7,10
Y	ISAJI MASAYUKI: "Sodium-glucose cotransporter inhibitors for diabetes", CURRENT OPINION IN INVESTIGATIONAL DRUGS, PHARMAPRESS, US, vol. 8, no. 4, 1 April 2007 (2007-04-01), pages 285-292, XP009087223, ISSN: 1472-4472 page 290, left-hand column, Conclusion	1-9,11, 13,15
X	LI T ET AL: "LACK OF PHARMACOKINETIC INTERACTION BETWEEN DAPAGLIFLOZIN AND PIOGLITAZONE IN HEALTHY", JOURNAL OF CLINICAL PHARMACOLOGY, LIPPINCOTT CO, HAGERSTOWN, MD, US, vol. 49, no. 9, 1 January 2009 (2009-01-01), page 1093, XP009136670, ISSN: 0091-2700	1-5
Y	abstract	1-9,11, 13,15
X	ZHANG L ET AL: "Dapagliflozin treatment in patients with different stages of type 2 diabetes mellitus: effects on glycaemic control and body weight", DIABETES, OBESITY AND METABOLISM, BLACKWELL SCIENCE, OXFORD, GB, vol. 12, no. 6, 4 March 2010 (2010-03-04), pages 510-516, XP002593698, ISSN: 1462-8902 page 511, right-hand column, paragraph 2 510, Results	1-8,10, 13,15

3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2011/054734

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.:

10(completely); 1-5, 15(partially)

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.:

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 6-9, 11, 13(completely); 1-5, 15(partially)

   Pharmaceutical composition comprising an SGLT2 inhibitor and a PPAR-gamma agonist and the use thereof for the treatment of diabetes and its complications

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2. claims: 10(completely); 1-5, 15(partially)

   Pharmaceutical composition comprising an SGLT2 inhibitor and a PPAR-gamma agonist and the use thereof for reducing body weight and/or body fat

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3. claims: 12(completely); 1-5, 15(partially)

   Pharmaceutical composition comprising an SGLT2 inhibitor and a PPAR-gamma agonist and the use thereof for the treatment of diseases or conditions attributed to an abnormal accumulation of ectopic fat

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4. claims: 14(completely); 1-5, 15(partially)

   Pharmaceutical composition comprising an SGLT2 inhibitor and a PPAR-gamma agonist and the use thereof for the treatment of hyperuricemia, kidney stones and hyponatremia

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2011/054734

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010138535 A1	02-12-2010	NONE	
WO 2010092125 A1	19-08-2010	AR 075421 A1	30-03-2011
		US 2011046076 A1	24-02-2011
		UY 32441 A	30-09-2010
WO 2008116179 A1	25-09-2008	AR 065809 A1	01-07-2009
		AU 2008228714 A1	25-09-2008
		CA 2681526 A1	25-09-2008
		CN 101686988 A	31-03-2010
		EA 200901277 A1	26-02-2010
		EP 2139494 A1	06-01-2010
		JP 2010522244 A	01-07-2010
		KR 20090123964 A	02-12-2009
		PE 01852009 A1	28-02-2009
		US 2008234366 A1	25-09-2008
		US 2011064801 A1	17-03-2011
WO 03099836 A1	04-12-2003	AR 040032 A1	09-03-2005
		AT 353334 T	15-02-2007
		AU 2003237886 A1	12-12-2003
		BR 0311323 A	15-03-2005
		CA 2486539 A1	04-12-2003
		CN 1653075 A	10-08-2005
		CN 101092409 A	26-12-2007
		CN 101628905 A	20-01-2010
		DE 60311649 T2	22-11-2007
		DK 1506211 T3	10-04-2007
		EP 1506211 A1	16-02-2005
		ES 2280759 T3	16-09-2007
		HK 1068214 A1	24-08-2007
		HR 20041084 A2	30-06-2005
		IS 7529 A	16-11-2004
		JP 2005531588 A	20-10-2005
		JP 2009275050 A	26-11-2009
		KR 20050004161 A	12-01-2005
		MX 249731 B	01-10-2007
		NO 329107 B1	23-08-2010
		NZ 536605 A	31-05-2007
		PE 07602004 A1	20-11-2004
		PT 1506211 E	30-04-2007
		RS P99204 A	15-12-2006
		RU 2337916 C2	10-11-2008
		TW 200404813 A	01-04-2004
		UA 77306 C2	15-03-2005
		US 2002137903 A1	26-09-2002
WO 03099836 A1		ZA 200409295 A	22-02-2006
WO 2004007517 A1	22-01-2004	AR 040474 A1	06-04-2005
		AT 414095 T	15-11-2008
		AT 479697 T	15-09-2010
		AT 477266 T	15-08-2010
		AT 477265 T	15-08-2010
		AU 2003246620 A1	02-02-2004
		BR 0312513 A	12-04-2005
		CA 2493391 A1	22-01-2004
		CN 1668628 A	14-09-2005

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2011/054734

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		CN 101240000 A	13-08-2008
		DE 10231370 A1	05-02-2004
		DK 1523488 T3	16-03-2009
		EC SP055531 A	10-03-2005
		EP 1523488 A1	20-04-2005
		EP 1964844 A1	03-09-2008
		EP 1967523 A1	10-09-2008
		EP 1964845 A1	03-09-2008
		ES 2316818 T3	16-04-2009
		HK 1080482 A1	02-01-2009
		HR 20050014 A2	30-04-2006
		JP 4511927 B2	28-07-2010
		JP 2005536497 A	02-12-2005
		KR 20050021452 A	07-03-2005
		MA 27366 A1	01-06-2005
		MX PA05000044 A	08-04-2005
		OA 12880 A	15-09-2006
		PA 8577101 A1	07-02-2004
		PE 06552004 A1	15-11-2004
		PT 1523488 E	30-01-2009
		RS P115004 A	05-02-2007
		RU 2317300 C2	20-02-2008
		SI 1523488 T1	30-04-2009
		UA 78823 C2	25-04-2007
		US 2006293252 A1	28-12-2006
		US 2004138143 A1	15-07-2004
		UY 27891 A1	31-12-2003
		ZA 200409779 A	28-06-2006