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(54) **Title**: COMBINATION THERAPY

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

Combination therapy

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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