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(54) Title: COMBINATION THERAPY

(57) Abstract: Provided herein is a method for the treatment or prevention of a disease or disorder, the method comprising administering a PDE4 inhibitor and a GLP1 receptor agonist to a subject, wherein the disease or disorder is selected from: an inflammatory disease, an autoimmune disease, fibrosis, a neurodegenerative disease, a musculoskeletal disorder, a metabolic disease or disorder, alcoholic liver disease (ALD), cardiovascular disease and a gastrointestinal disorder.

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COMBINATION THERAPY

[0001] The present invention relates to a PDE4 inhibitor for use in the treatment or prevention of a disease or disorder, said use comprising co-administration of the PDE4 inhibitor with a GLP1 receptor agonist. More particularly, the invention relates to the use of a PDE4 inhibitor and a GLP1 receptor agonist in the treatment of diseases and disorders including inflammatory disease, autoimmune disease, fibrosis, neurodegenerative disease, musculoskeletal disorders, metabolic diseases or disorders, alcoholic liver disease (ALD), cardiovascular disease and gastrointestinal disorders.

BACKGROUND

[0002] Obesity is a chronic disease characterized by the abnormal or excessive accumulation of body fat. According to data from the World Health Organization (WHO), more than 1 billion people in the world are obese, including 650 million adults, 340 million adolescents, and 39 million children, which will cause about 167 million people to become ill by 2025 (Yang et al., Healthcare 2022, 10(9), 1616). Obesity is commonly associated with many other disorders, including type 2 diabetes, metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), cardiovascular diseases, and certain cancers such as hepatocellular carcinoma, breast cancer and pancreatic ductal adenocarcinoma. Obesity and related diseases are often also associated with low grade inflammation, both systemic and in the gastrointestinal tract, causing impaired gut barrier function. The prevalence of obesity-related conditions, such as diabetes and NAFLD have been steadily increasing over the past few decades. According to the WHO, about 422 million people worldwide have diabetes and 1.5 million deaths are directly attributed to diabetes each year. Global prevalence of NAFLD is estimated to be at least 24%, and the disease is anticipated to become the leading reason for liver transplantation.

[0003] Accordingly, there remains an urgent need for new therapies for diseases and disorders including metabolic disorders such as obesity, diabetes and NAFLD/NASH.

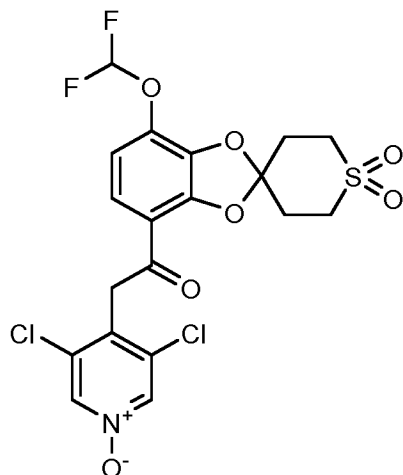
[0004] Phosphodiesterases (PDEs) constitute a superfamily of enzymes catalysing the hydrolysis of the intracellular secondary messengers cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate that play key roles in mediating biological responses generated by a variety of extracellular signals. Eleven families of PDE enzymes have been identified, with the PDE4 family constituting 4 subtypes (A-D) and more than 20 isoforms (Houslay MD, et al., "Keynote review: phosphodiesterase-4 as a therapeutic target", Drug Discov Today; 2005, 10(22):1503-1519 2005). PDEs represent the only cellular pathway for the degradation of cyclic nucleotides, which emphasizes their critical role in the regulation of the intracellular levels of these secondary messengers and, consequently,

various functional responses of cells (Dastidar SG et al., "Therapeutic benefit of PDE4 inhibitors in inflammatory diseases". *Curr Opin Investig. Drugs*. 2007;8(5):364-372). PDE4 is a cAMP-specific PDE expressed by immune and inflammatory cells, including T-lymphocytes, neutrophils, eosinophils, monocytes, dendritic cells, and macrophages (Spina et al., "PDE4 inhibitors: current status"; *Br. J. Pharmacol*. 2008;155(3):308-315). In these cells, PDE4 is the predominant PDE form, and PDE4 inhibitors increase cAMP levels. High intracellular cAMP levels down-regulate inflammatory activity and up-regulate anti-inflammatory activity resulting in, for example, decreased proliferation and cytokine production, whereas low cAMP concentrations have the opposite effect. Accordingly, inhibition of PDE4 up-regulates anti-inflammatory cytokines, for example IL-10, and down-regulates inflammatory cytokines, for example one or more of TNF- α , IFN- γ , IL-5, IL-8, IL-13, IL-17, IL-22 and/or IL-23 (Samrao A et al., *Arch Dermatol* 2012;148(8):890-897; and Li H et al., "Phosphodiesterase-4 Inhibitors for the Treatment of Inflammatory Diseases, *Front. Pharmacol* 2018;9:1048)

[0005] PDE4 inhibitors demonstrate potent effects in inflammatory diseases, neurological disorders (e.g. cognitive impairment, depression, psychosis, schizophrenia and Alzheimer's disease), cancer, metabolic disease, alcohol use disorders (e.g. ALD) and dermatological conditions (Paes et al., "The Molecular Biology of Phosphodiesterase 4 Enzymes as Pharmacological Targets: An Interplay of Isoforms, Conformational States, and Inhibitors"; *Pharmacol Rev*. 2021;73(3):1016-1049; Richter et al., "PDE4 as a target for cognition enhancement", *Expert Opin Ther Targets*. 2013 Sep;17(9):1011-27; Li et al., supra; and Lugnier et al., "Cyclic nucleotide phosphodiesterases: New targets in the metabolic syndrome?" *Pharmacol Ther*. 2020; Grigsby et al., "Preclinical and clinical evidence for suppression of alcohol intake by apremilast" *J Clin Invest* 2023; 133(6):e159103; Rodriguez et al., "PDE4 inhibition as a therapeutic target for alcoholic liver disease: from bedside to bench" *Hepatology* 2019; 70(6):1958-1971).

[0006] Several PDE4-specific inhibitors are in late stages of clinical development or have recently been marketed. For example, the oral PDE4 inhibitor roflumilast (Daxas[®]/Daliresp[®]) is approved in the United States and Europe to reduce the risk of exacerbation in patients with chronic obstructive pulmonary disease and chronic bronchitis (Roflumilast Summary of Product Characteristics). The oral PDE4 inhibitor apremilast (Otezla[®]) is approved in the United States and Europe for multiple indications including psoriatic arthritis and psoriasis (Apremilast Summary of Product Characteristics) and it has been studied for atopic dermatitis and other chronic inflammatory diseases (Samrao A et al., *Arch Dermatol*. 2012;148(8):890-897).

[0007] Orismilast, 2-(3,5-dichloro-1-oxidopyridin-1-ium-4-yl)-1-[7-(difluoromethoxy)-1',1'-dioxospiro[1,3-benzodioxole-2,4'-thiane]-4-yl]ethanone, is a potent and selective PDE4 inhibitor of the formula:



- 5 **[0008]** Orismilast is disclosed in WO 2011/160632 and is a selective PDE4 inhibitor and is a potent inhibitor of PDE4B and PDE4D subtype splice variants *in vitro*. When tested *in vitro* Orismilast inhibited production of tumour necrosis factor α (TNF α), INF γ , IL13 and IL4 in human whole blood, and additionally IL5, IL22 and IL23 in human peripheral mononuclear cells (PMBCs).. *In vivo*, 10 and 30 mg/kg doses of orismilast significantly reduced ear
- 10 thickness and inflammation markers in a murine model of chronic oxazolone-induced ear skin inflammation (Silverberg JI et al., Pharmacology of orismilast, a potent and selective PDE4 inhibitor. J Eur Acad Dermatol Venereol. 2023;37(4):721-729).

[0009] The present invention has been devised with these issues in mind.

BRIEF SUMMARY OF THE DISCLOSURE

- 15 **[0010]** According to a first aspect of the invention there is provided a method for the treatment or prevention of a disease or disorder, the method comprising administering a PDE4 inhibitor and a GLP1 receptor agonist.

- [0011]** In some embodiments, the disease or disorder is selected from: an inflammatory disease, an autoimmune disease, fibrosis, a neurodegenerative disease, a musculoskeletal
- 20 disorder, a metabolic disease or disorder, alcoholic liver disease (ALD), cardiovascular disease and a gastrointestinal disease or disorder.

- [0012]** In some embodiment the disease or disorder is a metabolic disease or disorder. The metabolic disease or disorder may be selected from: obesity, hyperlipidaemia, diabetes (including pre-diabetes), diabetes-associated cardiac dysfunction, metabolic syndrome, non-
- 25 alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD).

[0013] In some embodiments the disease or disorder is an inflammatory disease, for example an inflammatory pulmonary, dermatological or neurological disease or inflammatory myopathy (e.g. polymyositis).

[0014] In some embodiments, the disease or disorder is a musculoskeletal disorder, such as muscular dystrophy (e.g. Duchenne muscular dystrophy), sarcopenia, or sporadic inclusion body myositis.

[0015] In some embodiments the disease or disorder is fibrosis, such as hepatic fibrosis, renal fibrosis, biliary fibrosis, pancreatic fibrosis, or idiopathic pulmonary fibrosis.

[0016] In some embodiments the disease or disorder is an autoimmune disease, such as ulcerative colitis, Crohn's disease, primary sclerosing cholangitis or primary biliary cholangitis.

[0017] In some embodiments the disease or disorder is alcoholic liver disease (ALD).

[0018] In some embodiments the disease or disorder is cardiovascular disease.

[0019] In some embodiments the disease or disorder is a neurodegenerative disease, such as dementia, Alzheimer's disease, amyotrophic lateral sclerosis, Huntingdon's disease, neurodegeneration or Parkinson's disease.

[0020] In some embodiments the disease or disorder is a gastrointestinal disorder, such as short bowel syndrome, inflammatory bowel disease, coeliac disease or intestinal toxicity.

[0021] In some embodiments, the disease or disorder is one which is ameliorated by elevated cAMP levels.

[0022] In some embodiments the PDE4 inhibitor and the GLP1 receptor agonist are administered for a treatment period which is at least 4 weeks, optionally at least 8 weeks.

[0023] It may be that the PDE4 inhibitor and the GLP1 receptor agonist are administered simultaneously, separately or sequentially.

[0024] In some embodiments, the PDE4 inhibitor, or the pharmaceutically acceptable solvate thereof, is administered to the subject at a total daily dose of no more than 500 mg, no more than 250 mg, no more than 120 mg, no more than 80 mg, no more than 60 mg or no more than 40 mg.

[0025] In some embodiments, the PDE4 inhibitor is administered to the subject at a unit dose of from 0.01 mg to 250 mg, optionally from 1 to 100 mg or from 5 to 70 mg, e.g. 10, 15, 20, 30 or 40 mg.

[0026] The PDE4 inhibitor may be administered to the subject once daily or twice daily.

[0027] In some embodiments the PDE4 inhibitor is administered to the subject orally.

[0028] In some embodiments the PDE4 inhibitor is administered to the subject in the form of a modified release formulation.

[0029] In some embodiments the GLP1 receptor agonist is administered at a unit dose of
5 from about 0.5 µg to about 500 mg, from about 1 µg to about 200 mg, from about 5 µg to about 100 mg, from about 10 µg to about 50 mg, from about 100 µg to about 10 mg, or from about 0.5 mg to about 4 mg.

[0030] In some embodiments the GLP1 receptor agonist is administered to the subject once or twice daily. The total daily dose of the GLP1R agonist may be from about 1 µg to
10 about 100 mg.

[0031] In some embodiments, the GLP1 receptor agonist is administered to the subject once weekly or twice weekly. The total weekly dose of the GLP1 receptor agonist may be from about 0.05 mg to about 100 mg.

[0032] In some embodiments the GLP1 receptor agonist is administered to the subject orally or subcutaneously. In some embodiments, both the PDE4 inhibitor and the GLP1R agonist are administered to the subject orally.
15

[0033] In some embodiments both the PDE4 inhibitor and the GLP1R agonist are administered to the subject once or twice daily.

[0034] In some embodiments, the PDE4 inhibitor is selected from difamilast, crisaborole, apremilast, roflumilast, ibudilast, drotaverine (e.g. drotaverine hydrochloride), orismilast, mufemilast, tanimilast (tranimilast), ensifentrine, zatolmilast, BI-1015550, TQC-3721, ME-3183, PF-07038124 or a pharmaceutically acceptable salt, solvate or hydrate thereof.
20

[0035] In some embodiments the PDE4 inhibitor is orismilast, or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[0036] In certain embodiments in any of the dosage regimens disclosed wherein the orismilast is administered to the subject in the form of a modified release formulation comprising the orismilast. In certain embodiments the modified release formulation releases a mean amount of about 10% to about 70% of the orismilast after 45 minutes and more than about 70% after 180 minutes. In certain embodiments the modified release formulation
25 releases a mean amount of from about 11 % to about 65 % of the orismilast after 45 minutes and more than 75% of the orismilast after 180 minutes. In certain embodiments the modified release formulation releases a mean amount of from about 35 % to about 65 % of the orismilast after 45 minutes and more than 70% of the orismilast after 180 minutes. In certain
30 embodiments the modified release formulation releases a mean amount of from about 35 %

to about 55 % of the PDE4 inhibitor after 45 minutes and more than about 80% of the orismilast after 180 minutes. In each case above dissolution is determined using Ph. Eur. 2.9.3 Apparatus II, with a dissolution medium of 900 ml 0.5% sodium dodecyl sulfate in 0.1N HCl, a paddle speed of 75 rpm, and the dissolution medium at 37 ± 0.5 °C.

5 **[0037]** In some embodiments, the method comprises administering the orismilast to the subject, wherein:

(Ai) an initial orismilast dose is administered to the subject once per day for an initial time period followed by;

10 (Aii) an interim orismilast dose administered to the subject twice per day for an interim time period followed by;

(Aiii) a maintenance orismilast dose administered to the subject twice per day;

wherein:

15 (a) the initial orismilast dose and the interim orismilast dose are independently selected from 10 mg to 30 mg orismilast, provided that the interim orismilast dose is greater than or equal to the initial orismilast dose;

(b) the initial time period is two to eight weeks;

(c) the interim time period is one to eight weeks; and

20 (d) the maintenance orismilast dose is greater than the interim orismilast dose when the subject has a body mass that is greater than or equal to a threshold body mass, wherein the threshold body mass is at least 90 kg.

[0038] In some embodiments, the method is for treating or preventing a disease or disorder in a subject with a body mass that is greater than or equal to a threshold body mass. In such embodiments, the method comprises administering orismilast to the subject, wherein:

25 (Bi) an initial orismilast dose is administered to the subject once per day for a preliminary time period followed by;

(Bii) a interim orismilast dose administered to the subject twice per day for an interim time period followed by;

30 (Biii) a maintenance orismilast dose administered to the subject twice per day, wherein the maintenance orismilast dose is greater than the interim orismilast dose;

wherein:

- (a) the initial orismilast dose and the interim orismilast doses are independently selected from 10 mg to 30 mg orismilast, provided that the interim orismilast dose is greater than or equal to the initial orismilast dose;
- (b) the preliminary time period is up to eight weeks;
- 5 (c) the interim time period is one week to eight weeks; and
- (d) the threshold body mass is at least 90 kg.

[0039] In some embodiments, the GLP1 receptor agonist is exenatide (including exenatide extended release), lixisenatide, beinaglutide, dulaglutide, liraglutide, semaglutide, albiglutide, efpeglenatide, PEG-lonexatide or tirzepatide, or a pharmaceutically acceptable salt, solvate
10 or hydrate thereof. In some embodiments the GLP1 receptor agonist is suitable for oral administration. In some embodiments the GLP1 receptor agonist is semaglutide.

[0040] In some embodiments, the GLP1 receptor agonist is comprised within a combination product. For example, the GLP1 receptor agonist may be co-formulated with at least one (e.g. one, two or more) further therapeutic agent. In some embodiments, the
15 GLP1 receptor agonist comprises or is a combination of semaglutide and cagrilintide.

[0041] In some embodiments the PDE4 inhibitor is orismilast, or a pharmaceutically acceptable salt, solvate or hydrate thereof, and the GLP1 receptor agonist is suitable for oral administration, optionally wherein the GLP1 receptor agonist is semaglutide or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[0042] In some embodiments the method results in a reduction in body weight, a reduction in body fat mass, a reduction in BMI, a reduction in liver fat, a reduction in a level of alanine transaminase (ALT) and/or aspartate aminotransferase (AST), improved glycaemic control (e.g. increased time within normal levels (Time in Range (TIR))), a reduction in fasting plasma glucose (FPG), a reduction in 2-hour post-load plasma glucose, an increase in insulin
25 sensitivity, a reduction in appetite, a reduction in liver fibrosis, a reduction in a level of HbA1c, a reduction in fasting blood levels of triglycerides, a reduction in fasting blood levels of cholesterol, a reduction in fasting blood levels of insulin, a reduction in fasting blood levels of LDL, a reduction in waist circumference, a reduction in cholesterol ratio and/or a reduction in insulin resistance.

[0043] In some embodiments, the method results in a reduction in body weight of at least 1 %. In some embodiments, the method results in an average reduction in body weight of at least 0.1% per week over the treatment period.

[0044] The subject may be a human or an animal. Preferably the subject is a human.

[0045] According to a second aspect of the invention there is provided a PDE4 inhibitor for use in the treatment or prevention of an inflammatory disease, an autoimmune disease, fibrosis, a neurodegenerative disease, a musculoskeletal disorder, a metabolic disease or disorder, alcoholic liver disease (ALD), cardiovascular disease or a gastrointestinal disorder, said use comprising co-administration of the PDE4 inhibitor with a GLP1 receptor agonist.

[0046] According to a third aspect of the invention there is provided a GLP1 receptor agonist for use in the treatment or prevention of an inflammatory disease, an autoimmune disease, fibrosis, a neurodegenerative disease, a musculoskeletal disorder, a metabolic disease or disorder, alcoholic liver disease (ALD), cardiovascular disease or a gastrointestinal disorder, said use comprising co-administration of the GLP1 receptor agonist with a PDE4 inhibitor.

[0047] According to a fourth aspect of the invention, there is provided the use of a PDE4 inhibitor in the manufacture of a medicament for the treatment or prevention of an inflammatory disease, an autoimmune disease, fibrosis, a neurodegenerative disease, a musculoskeletal disorder, a metabolic disease or disorder, alcoholic liver disease (ALD), cardiovascular disease or a gastrointestinal disorder in a subject in need thereof by co-administration with a GLP1 receptor agonist.

[0048] According to a fifth aspect of the invention there is provided the use of a GLP1 receptor agonist in the manufacture of a medicament for the treatment or prevention of an inflammatory disease, an autoimmune disease, fibrosis, a neurodegenerative disease, a musculoskeletal disorder, a metabolic disease or disorder, alcoholic liver disease (ALD), cardiovascular disease or a gastrointestinal disorder in a subject in need thereof by co-administration with a PDE4 inhibitor.

[0049] According to a sixth aspect of the invention, there is provided a combination comprising a PDE4 inhibitor and a GLP1 receptor agonist.

[0050] According to seventh aspect of the invention, there is provided pharmaceutical composition comprising the combination of the sixth aspect.

[0051] In a further aspect, the invention provides a kit comprising the combination of the sixth aspect, or the composition of the seventh aspect, and instructions for use.

[0052] In a further aspect, the invention provides a product comprising a PDE4 inhibitor and a GLP1 receptor agonist for simultaneous, separate or sequential use in the treatment or prevention of an inflammatory disease, an autoimmune disease, fibrosis, a neurodegenerative disease, a musculoskeletal disorder, a metabolic disease or disorder, alcoholic liver disease (ALD), cardiovascular disease or a gastrointestinal disorder.

[0053] It will be appreciated that any of the disclosures, aspects and embodiments described herein may be combined in any combination, unless otherwise stated.

BRIEF DESCRIPTION OF THE DRAWINGS

[0054] Embodiments of the invention will now be described by way of example and with reference to the accompanying drawings, in which:

Figure 1 (landscape) shows the X-ray powder diffraction pattern for orismilast crystalline Form E measured using CuK α radiation $\lambda = 1.5418 \text{ \AA}$. The x-axis shows the 2θ values and the y-axis the intensity (counts).

Figure 2 shows a DSC trace for two different batches of orismilast crystalline Form E measured with a heating rate of 2 to 10 °C/minute (two measurements per batch). The x-axis shows temperature and the y-axis heat flow (W/g). Each trace shows the melting onset temperature and the enthalpy change for each sample of the Form E.

Figure 3 shows the *in-vitro* dissolution profile for 10 mg and 30 mg orismilast modified release tablets measured using the Standard Dissolution Assay defined in the description herein. The x-axis shows time and the y-axis the % orismilast released into the dissolution medium.

Figure 4 shows the impact of orismilast (Ori), semaglutide (Sema), and the combination thereof on insulin secretion in Rin-m cells. (A) Orismilast and Semaglutide's effect alone on insulin secretion with semaglutide. Statistical significance of respective condition compared to control. (B) Semaglutide's impact on insulin secretion has an estimated EC₅₀ of 26 nM. (C) and (D) Combination of 100 nM (C) and 1000 nM orismilast (D) with increasing concentrations of semaglutide. The table below each graph shows the percent increase in insulin levels of orismilast and semaglutide alone, the combination of both, and the resulting additive effect of orismilast. Statistical significance of effect of respective combination compared to effect of semaglutide concentration tested in combination (e.g. 0.04 nM Semaglutide + 1000 nM Orismilast versus 0.04 nM Semaglutide) **** $p < 0.0001$, *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

Figure 5. shows an illustration of a randomised (1:1:1:1), parallel-group, single-centre clinical trial investigating body weight management effects of open-label once-weekly semaglutide with- or without double-blind, placebo-controlled orismilast in 80 people living with obesity. V1, screening visit; V2, randomisation visit; V3, first up-titration visit, V4, second up-titration visit; V5, end-of-treatment visit; V6, follow-up visit. QD, Once daily; BID, Twice daily; QW, Once weekly.

DETAILED DESCRIPTION

Definitions

[0055] Unless otherwise stated, the following terms used in the specification and claims have the following meanings set out below.

5 [0056] The terms “treating” or “treatment” refers to any indicia of success in the treatment or amelioration of a disease, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the pathology or condition more tolerable to the subject; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving the physical or mental well-being of the subject.

[0057] When a compound or salt, solvate or hydrate described in this specification is administered to treat a disorder, a “therapeutically effective amount” is an amount sufficient to reduce or completely alleviate symptoms or other detrimental effects of the disorder; cure the disorder; reverse, completely stop, or slow the progress of the disorder; or reduce the risk of the disorder getting worse.

[0058] The term “pharmaceutically acceptable salt” refers to salts that retain the biological effectiveness and properties of the compounds described herein, and which are not biologically or otherwise undesirable. Pharmaceutically acceptable salts of compound (I) are well known to skilled persons in the art. It may be that a reference to a salt of compound (I) herein may refer to a pharmaceutically acceptable salt of compound (I). The invention covers all crystalline modifications, polymorphic forms and mixtures thereof. In some embodiments, the treatment comprises administration of the polymorphic form E of orismilast.

[0059] The term “solvate” is intended to indicate a species formed by interaction between a compound, e.g. a compound of formula (I), and a solvent, e.g. alcohol, glycerol or water, wherein said species are in a solid form. When water is the solvent, said species is referred to as a “hydrate”.

[0060] The phrase “phosphodiesterase” as used herein refers to one or more of the phosphodiesterases (PDEs), PDE4, PDE7 and PDE8 being selective for cAMP. PDE4 is the most important modulator of cAMP. PDE4 is cAMP-specific and the dominant PDE in inflammatory cells. PDE4 enzymes are encoded by four genes (PDE4A, PDE4B, PDE4C and PDE4D), each of which is capable of producing a number of isoforms through mRNA splicing and the use of different promoters. Each PDE4 isoform within a particular PDE4 sub-family comprises a common core region, consisting of the catalytic unit and the C-

terminal portion, and is defined by its unique N-terminal region. The PDE4 isoforms are further classified as long, short or super-short, depending on the presence or absence (or truncation) of two highly conserved sequences: Upstream Conserved Region 1 (UCR1) and Upstream Conserved Region 2 (UCR2). “Long” isoforms comprise both UCR1 and UCR2;
5 “short” isoforms lack UCR1 and “super-short” isoforms lack UCR1 and have a truncated UCR2.

[0061] The phrase “PDE inhibitor” as used herein refers to a substance which inhibits PDE.

[0062] The term “GLP1 receptor agonist” refers to a substance which is an agonist of the
10 GLP-1 receptor. The GLP 1 receptor agonist may be an analogue of glucagon-like peptide-1 (GLP-1). GLP1 receptor agonists are also referred to as “incretin mimetics”. The GLP1 receptor agonist may agonise the receptor of GLP-1 only. In some embodiments, the GLP1 receptor agonist is a co-agonist, i.e. it agonises the receptor of GLP-1 and a further receptor (e.g. GIP). The term “GLP1 receptor agonists” encompasses all types of substances which
15 act as agonists of the GLP-1 receptor, including chemical compounds, peptides or other biologics, fusion proteins, combination products, and derivatives, variants and analogues thereof (e.g. pegylated derivatives).

[0063] Reference to a “subject” herein means a human or animal subject. Preferably the subject is warm-blooded mammal. More preferably the subject is a human.

[0064] The term “particle size distribution” of a powder refers to a value that defines the
20 relative amounts of particles present, sorted according to size. The D(50) and D(90) values indicate that 50% and 90% of the particles measured are less than or equal to the size stated. For example a D(50) = 6 µm means that 50% of the particles are less than or equal to 6µm. A D(90) of ≤ 10 µm mean that 90% of the particles have a particle size of less than or
25 equal to 10 µm. Particle size may be measured using conventional methods such as laser diffraction technique.

[0065] The term “immediate release” refers to a pharmaceutical composition or formulation which does not significantly delay release of the active ingredient following oral
administration. Generally immediate release refers to compositions or formulations wherein
30 ≥85% of the active ingredient is released within 30 minutes when placed in a aqueous dissolution medium.

[0066] The term “modified release” refers to a pharmaceutical formulation or composition where the rate and/or site of release of the active ingredient are different from that of an immediate release dosage form administered orally. The modified release composition may

be a delayed release composition wherein release of the active is delayed for a period or time following oral administration.

[0067] Unless stated otherwise, reference herein to a “% by weight of the compound of formula (I), or a pharmaceutically acceptable salt, solvate or hydrate thereof” is intended to refer to the amount of the non-salt form of the compound. For example, reference to a composition comprising “5 % by weight of orismilast or a pharmaceutically acceptable salt, solvate or hydrate thereof” refers to a composition comprising 5% by weight of the compound in the non-salt form. Accordingly, where such a composition comprises a pharmaceutically acceptable salt the compound, the absolute amount of the salt in the composition will be higher than 5 % by weight in view of the salt counter ion that will also be present in the composition.

[0068] Reference to “about” in the context of a numerical is intended to encompass the value +/- 10%. For example, about 20% includes the range of from 18% to 22%.

[0069] Throughout the description and claims of this specification, the words “comprise” and “contain” and variations of them mean “including but not limited to”, and they are not intended to (and do not) exclude other moieties, additives, components, integers or steps. Throughout the description and claims of this specification, the singular encompasses the plural unless the context otherwise requires. In particular, where the indefinite article is used, the specification is to be understood as contemplating plurality as well as singularity, unless the context requires otherwise.

[0070] Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein unless incompatible therewith. All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive. The invention is not restricted to the details of any foregoing embodiments. The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

[0071] The reader's attention is directed to all papers and documents which are filed concurrently with or previous to this specification in connection with this application and which are open to public inspection with this specification, and the contents of all such papers and documents are incorporated herein by reference.

Compounds

PDE4 inhibitors

[0072] The present invention relates to the therapeutic use of a PDE4 inhibitor, or a pharmaceutically acceptable salt, hydrate or solvate thereof.

- 5 **[0073]** In embodiments, the PDE4 inhibitor is selected from difamilast, crisaborole, apremilast, roflumilast, ibudilast, drotaverine (e.g. drotaverine hydrochloride), orismilast, mufemilast, tanimilast (tranmilast), ensifentrine, zatolmilast, BI-1015550, TQC-3721, ME-3183, PF-07038124 or a pharmaceutically acceptable salt, solvate or hydrate thereof.

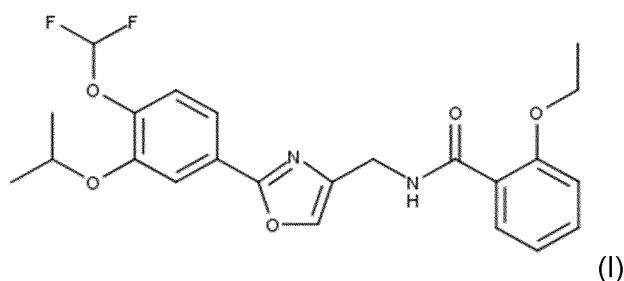
- 10 **[0074]** In embodiments, the PDE4 inhibitor is selected from difamilast, crisaborole, apremilast, roflumilast, ibudilast, drotaverine (e.g. drotaverine hydrochloride), and orismilast, or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[0075] In some embodiments, the PDE4 is selective for PDE4B and/or PDE4D.

[0076] In some embodiments the PDE4 inhibitor is orismilast, or a pharmaceutically acceptable salt, solvate or hydrate thereof.

15 Difamilast

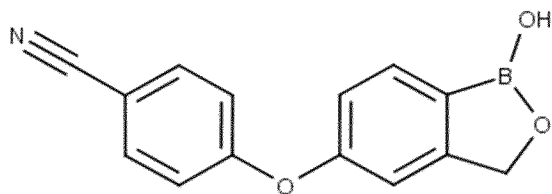
[0077] In some embodiments the PDE4 inhibitor is Difamilast. Difamilast (also referred to as OPA-15406 or MM36) is a selective PDE4 inhibitor with the chemical name N-[[2-[4-(Difluoromethoxy)-3-[(propan-2-yl)oxy]phenyl]-1,3-oxazol-4-yl]methyl]-2-ethoxybenzamide, having the structure as shown in Formula (I) below:



[0078] Difamilast and methods for synthesizing the compound are disclosed in WO 2007058338, JP 2008308496, WO 2014034958, WO 2017115780, WO 2019194211, JP 2021059538 and JP 2022088524.

Crisaborole

- 25 **[0079]** In some embodiments the PDE4 inhibitor is Crisaborole. The chemical name for Crisaborole (also referred to as AN-2728 or PF-06930164) is 4-(1-Hydroxy-1,3-dihydro-2,1-benzoxaborol-5-yloxy)benzonitrile, having the structure as shown in Formula (II) below:

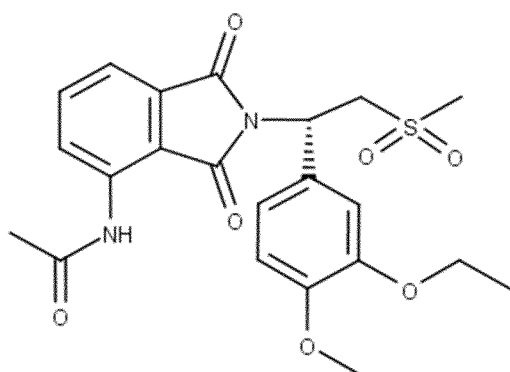


(II)

[0080] Crisaborole and methods for synthesizing the compound are disclosed in WO 2006089067 and WO 2007095638.

Apremilast

- 5 [0081] In some embodiments the PDE4 inhibitor is Apremilast. The chemical name for Apremilast is (+)-N-[2-[1(S)-(3-Ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide having the structure as shown in Formula (III) below:

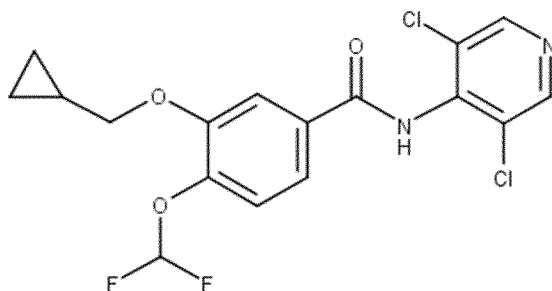


(III)

- 10 [0082] Apremilast and methods for synthesizing the compound are disclosed in WO 2003080049, WO 2006065814 and WO 2009120167.

Roflumilast

[0083] In some embodiments the PDE4 inhibitor is roflumilast. The chemical name for Roflumilast is 3-(Cyclopropylmethoxy)-N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)benzamide, having the structure as shown in Formula (IV) below: (IV)

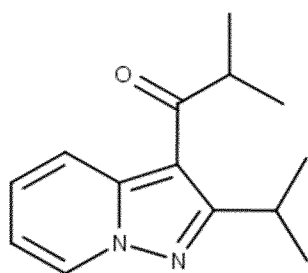


(IV)

[0084] Roflumilast and methods for synthesizing the compound are disclosed in WO 1995001338, WO 2002038155 and WO 2003070279.

Ibudilast

[0085] In some embodiments the PDE4 inhibitor is Ibudilast. The chemical name for Ibudilast is 1-(2-Isopropylpyrazolo[1,5-a]pyridin-3-yl)-2-methylpropan-1-one, having the structure as shown in Formula (V) below:

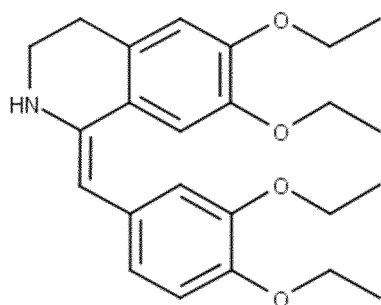


(V)

[0086] Ibudilast and methods for synthesizing the compound are disclosed in US 3850941.

Drotaverine

[0087] In some embodiments the PDE4 inhibitor is Drotaverine. The chemical name for Drotaverine is 1-(3,4-Diethoxybenzylidene)-6,7-diethoxy-3,4-dihydroisoquinoline, having the structure as shown in Formula (VI) below:

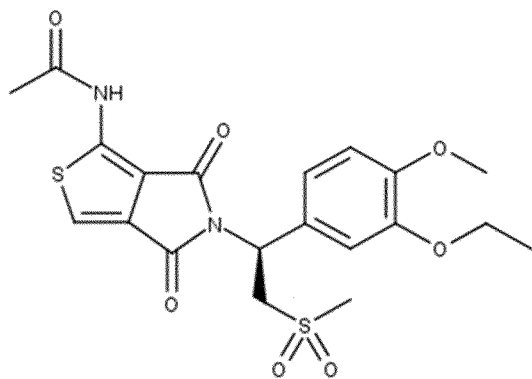


(VI)

[0088] Preferably, the Drotaverine is in the form of a hydrochloride salt. Drotaverine and methods for synthesizing the compound are disclosed in RU2561489C2, EP 2156835 and WO 2012159964.

Mufemilast

[0089] In some embodiments the PDE4 inhibitor is mufemilast. The chemical name for mufemilast (also referred to as Hemay-005) is N-[5-[(1S)-1-(3-Ethoxy-4-methoxyphenyl)-2-(methanesulfonyl)ethyl]-4,6-dioxo-5,6-dihydro-4H-thieno[3,4-c]pyrrol-1-yl]acetamide, having the structure as shown in Formula VII below:

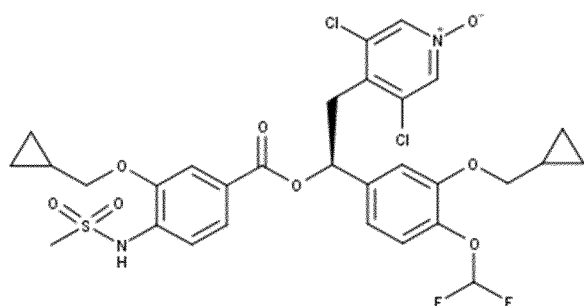


(VII)

Mufemilast and methods for synthesising the compound are disclosed in WO2010/130224 and US2018/0354967.

Tanimilast (tranimilast)

- 5 **[0090]** In some embodiments the PDE4 inhibitor is tanimilast. The chemical name for tanimilast (also known as 0984EU6E2F or CHF-6001) is (-)-(1S)-1-[3-(Cyclopropylmethoxy)-4-(difluoromethoxy)phenyl]-2-(3,5-dichloro-1-oxidopyridin-4-yl)ethyl 3-(cyclopropylmethoxy)-4-[(methylsulfonyl)amino]benzoate, having the structure as shown in Formula VIII below:

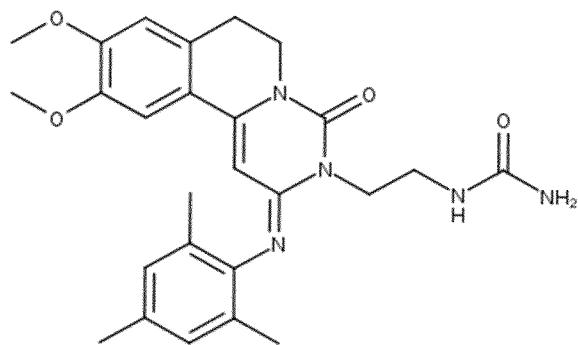


(VIII)

- 10 Tanimilast and methods for synthesising the compound are disclosed in WO 2012016845 and US8440834B2.

Ensifentrine

- [0091]** In some embodiments the PDE4 inhibitor is ensifentrine. The chemical name for ensifentrine (also known as 3E3D8T1GIX, RPL-554, VMX-554 or VRP-554) is N-[2-[9,10-Dimethoxy-2-(2,4,6-trimethylphenylimino)-4-oxo-3,4,6,7-tetrahydro-2H-pyrimido[6,1-a]isoquinolin-3-yl]ethyl]urea, having the structure as shown in Formula IX below:
- 15

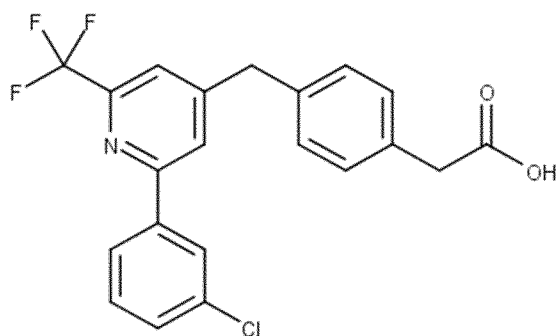


(IX)

Ensifentrine and methods for synthesising the compound are disclosed in WO2000058308.

Zatolmilast

[0092] In some embodiments the PDE4 inhibitor is Zatolmilast. The chemical name for zatolmilast (also known as BPN-14770 or G786V328X6) is (4-[[2-(3-Chlorophenyl)-6-(trifluoromethyl)pyridin-4-yl]methyl]phenyl)acetic acid, having the structure as shown in Formula X below:

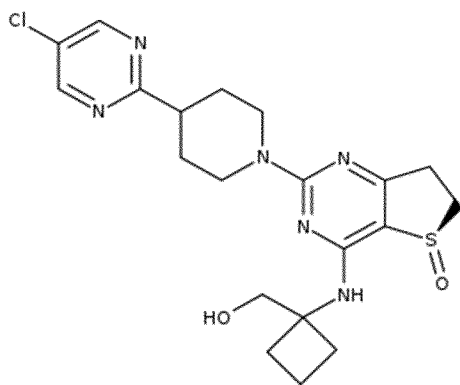


(X)

Zatolmilast and methods for synthesising the compound are disclosed in WO2014066659.

10 BI-1015550

[0093] In some embodiments the PDE4 inhibitor is BI-1015550. The chemical name for BI-1015550 is (5R)-2-[4-(5-Chloropyrimidin-2-yl)piperidin-1-yl]-4-[[1-(hydroxymethyl)cyclobutyl]amino]-6,7-dihydro-5H-5lambda4-thieno[3,2-d]pyrimidin-5-one having the structure as shown in Formula XI below:

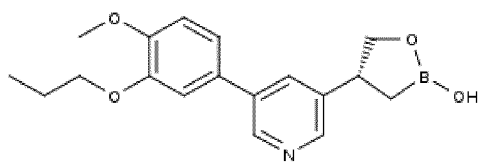


(XI)

BI-1015550 and methods for synthesising the compound are disclosed in WO2013026797.

PF-07038124

[0094] In some embodiments the PDE4 inhibitor is PF-07038124. The chemical name for PF-07038124 is (4R)-4-[5-(4-Methoxy-3-propoxyphenyl)pyridin-3-yl]-1,2-oxaborolan-2-ol, having the structure as shown in Formula XII below:

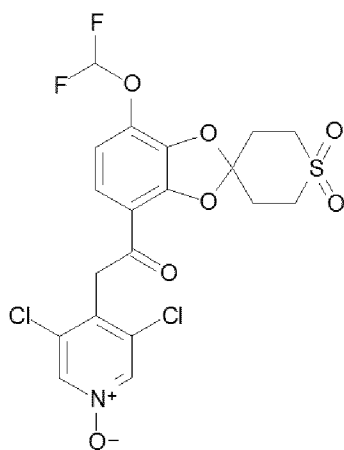


(XII)

PF-07038124 and methods for synthesising the compound are disclosed in WO2020070651.

Orismilast

- 10 **[0095]** In some embodiments the PDE4 inhibitor is orismilast. The chemical name for orismilast is 2-(3,5-Dichloro-1-oxido-pyridine-4-yl)-1-(7-difluoro-methoxy-2',3',5',6'-tetrahydro-spiro[1,3-benzodioxole-2, 4'-(4H)-thiopyran-1',1'-dioxide]-4-yl)ethanone, having the structure as shown in Formula (XIII) below:



(XIII)

The Chem Abstracts name for orismilast is ethanone, 2-(3,5-dichloro-1-oxido-4-pyridinyl)-1-[7-(difluoromethoxy)-2',3',5',6'-tetrahydro-1',1'-dioxidospiro[1,3-benzodioxole-2,4'-[4H]thiopyran]-4-yl]; CAS Number 1353546-86-7.

[0096] Orismilast and methods for synthesizing the compound are disclosed in WO 2011/160632, WO 2015/197534, WO 2017/103058, and WO 2018/234299

[0097] In certain embodiments the orismilast may be administered to the subject as a solid, which may be amorphous, crystalline or semi-crystalline. In some embodiments the orismilast is crystalline. In preferred embodiments the orismilast is in the form of polymorphic Form E. Polymorphic Form E of orismilast ("Form E") is described in WO 2018/234299.

[0098] In some embodiments the orismilast is Form E characterised by a powder X-ray diffraction pattern with at least one 2θ peak selected from 8.0, 8.6, 11.8, 14.1, 15.0, 16.0, 16.8, 18.1, 18.5, 20.0, 21.4, 23.4, 25.6 and $29.7^\circ \pm 0.2^\circ$, when measured using a $\text{CuK}\alpha$ radiation ($\lambda = 1.5418 \text{ \AA}$).

[0099] In some embodiments the orismilast is Form E characterised by a powder X-ray diffraction pattern with two 2θ peaks selected from 8.0, 8.6, 11.8, 14.1, 15.0, 16.0, 16.8, 18.1, 18.5, 20.0, 21.4, 23.4, 25.6 and $29.7^\circ \pm 0.2^\circ$, when measured using a $\text{CuK}\alpha$ radiation ($\lambda = 1.5418 \text{ \AA}$).

[00100] In some embodiments the orismilast is Form E characterised by a powder X-ray diffraction pattern with five 2θ peaks selected from 8.0, 8.6, 11.8, 14.1, 15.0, 16.0, 16.8, 18.1, 18.5, 20.0, 21.4, 23.4, 25.6 and $29.7^\circ \pm 0.2^\circ$, when measured using a $\text{CuK}\alpha$ radiation ($\lambda = 1.5418 \text{ \AA}$).

[00101] In some embodiments the orismilast is Form E characterised by a powder X-ray diffraction pattern with 2θ peaks at 15.0, 16.0, 18.1, 18.5, 21.4 and $23.4^\circ \pm 0.2^\circ$, when measured using a $\text{CuK}\alpha$ radiation ($\lambda = 1.5418 \text{ \AA}$).

[00102] In some embodiments the orismilast is Form E characterised by a powder X-ray diffraction pattern with 2θ peaks at 8.0, 11.8, 15.0, 16.0, 16.8, 18.1, 18.5, 23.4, 25.6 and $29.7^\circ \pm 0.2^\circ$, when measured using a $\text{CuK}\alpha$ radiation ($\lambda = 1.5418 \text{ \AA}$).

[00103] In some embodiments the orismilast is Form E characterised by a powder X-ray diffraction pattern with 2θ peaks at 8.0, 8.6, 11.8, 14.1, 15.0, 16.0, 16.8, 18.1, 18.5, 21.4, 23.4, 25.6 and $29.7^\circ \pm 0.2^\circ$, when measured using a $\text{CuK}\alpha$ radiation ($\lambda = 1.5418 \text{ \AA}$).

[00104] In some embodiments the orismilast is Form E characterised by a powder X-ray diffraction pattern with at least 10 of the 2θ peaks shown in Table X, when measured using a $\text{CuK}\alpha$ radiation ($\lambda = 1.5418 \text{ \AA}$).

[00105] In some embodiments the orismilast is Form E characterised by a powder X-ray diffraction pattern with the 2θ peaks shown in Table X, when measured using a CuK α radiation ($\lambda = 1.5418 \text{ \AA}$).

Table X

Peak Position ($2\theta \pm 0.2^\circ$)	Peak Position ($2\theta \pm 0.2^\circ$)
5.9	21.9
8.0	22.0
8.6	22.3
8.7	22.9
9.8	23.1
11.8	23.4
12.1	23.6
14.1	23.9
14.4	24.1
15.0	24.4
15.2	24.7
16.0	25.6
16.4	25.8
16.6	26.2
16.8	26.3
17.0	26.6
17.3	27.3
17.7	27.8
18.1	28.1
18.5	28.3
19.3	28.6
19.7	29.2
19.9	29.5
20.0	29.7
20.2	30.0
20.3	30.5
21.4	31.5
21.5	31.7
21.6	

5

[00106] In some embodiments the orismilast is Form E characterised by a powder X-ray diffraction pattern substantially as shown in Figure 1, when measured using a CuK α radiation ($\lambda = 1.5418 \text{ \AA}$).

[00107] In certain embodiments Form E is characterised as having a melting endotherm with an onset temperature of about 210 °C to about 213 °C (e.g. about 211.6 °C) when measured by Differential Scanning Calorimetry (DSC) with a heating rate of 2 to 10 °C/minute in a sealed aluminium pan with a pierced lid under a nitrogen atmosphere. In

5 certain embodiments the Form E has a melting enthalpy change of about 80 to 90 J/g when measured under the DSC conditions above. In certain embodiments the Form E has DSC curve substantially as shown in Figure 2.

[00108] Form E may be obtained by crystallisation from a suitable solvent for example one or more solvents selected from ethanol, isopropanol, dimethylsulfoxide, acetonitrile and
10 acetone. In some embodiments the solvent is acetone or ethanol. Crystallisation of Form E may be obtained by, for example dissolving orismilast in the hot solvent (e.g. at 50 °C) to form a solution and allowing the resulting solution to cool to room temperature.

[00109] Orismilast is a selective and efficient inhibitor of PDE4. It has been found that orismilast is a selective inhibitor of PDE4D and PDE4B. In some embodiments orismilast is
15 a selective inhibitor of PDE4B1, PDE4B2, PDE4B3, PDE4D1, PDE4D2, PDE4D3, PDE4D4, PDE4D5 and/or PDE4D7. In some embodiments orismilast is a selective inhibitor of PDE4B2, PDE4B3, PDE4D2, PDE4D3, PDE4D4, PDE4D5 and/or PDE4D7. In some embodiments orismilast is a selective inhibitor of PDE4B2, PDE4B3, PDE4D5 and PDE4D7. In some embodiments orismilast is a selective inhibitor of PDE4B3, PDE4D5 and PDE4D7.
20 In particular, it has been found that orismilast is a selective inhibitor of the PDE4 isoforms PDE4D3 and PDE4B2.

GLP1 receptor agonists

[00110] In some embodiments, the GLP1 receptor agonist is or comprises an amino acid sequence according to SEQ ID NO. 1:

25 Xaa₁ Xaa₂ Xaa₃, Gly Thr Xaa₄ Xaa₅ Xaa₆ Xaa₇ Xaa₈

Ser Lys Gln Xaa₉, Glu Glu Glu Ala Val Arg Leu

Xaa₁₀ Xaa₁₁ Xaa₁₂ Xaa₁₃ Leu Lys Asn Gly Gly Xaa₁₄

Ser Ser Gly Ala Xaa₁₅ Xaa₁₆ Xaa₁₇ Xaa₁₈ -Z (SEQ ID NO. 1)

wherein Xaa₁ is His, Arg or Tyr; Xaa₂ is Ser, Gly, Ala or Thr; Xaa₃ is Asp or Glu; Xaa₄ is Phe,
30 Tyr or naphthalanine; Xaa₅ is Thr or Ser; Xaa₆ is Ser or Thr; Xaa₇ is Asp or Glu; Xaa₈ is Leu, Ile, Val, pentylglycine or Met; Xaa₉ is Leu, Ile, pentylglycine, Val or Met; Xaa₁₀ is Phe, Tyr or naphthalanine; Xaa₁₁ is Ile, Val, Leu, pentylglycine, tert-butylglycine or Met; Xaa₁₂ is Glu or Asp; Xaa₁₃ is Trp, Phe, Tyr, or naphthylalanine; Xaa₁₄ Xaa₁₅ Xaa₁₆ and Xaa₁₇ are independently Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine, N-

alkylpentylglycine or N-alkylalanine; Xaa₁₈ is Ser, Thr or Tyr; and Z is -OH or -NH₂; or a pharmaceutically acceptable salt thereof.

[00111] In some embodiments, the GLP1 receptor agonist is or comprises a polypeptide of Formula A (below);

5 H₂N-W-COOH (A)

wherein W is an amino acid sequence selected from the group consisting of

His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-

Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-

Arg-Gly (SEQ ID NO: 2) and

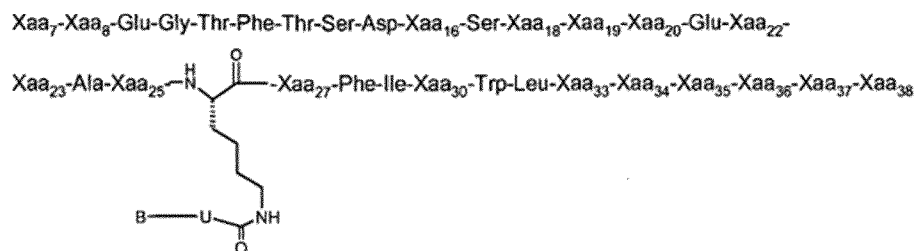
10 His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-

Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly- Arg (SEQ ID NO: 3);

and the pharmaceutically-acceptable salts thereof wherein the derivative has a pI of about 4.0 or less, or a pI of about 7.0 or greater and which derivative when processed in a mammal

15 results in a polypeptide derivative having an insulinotropic activity.

[00112] In some embodiments, the GLP1 receptor agonist is or comprises an amino acid sequence of SEQ ID NO. 4 (below):

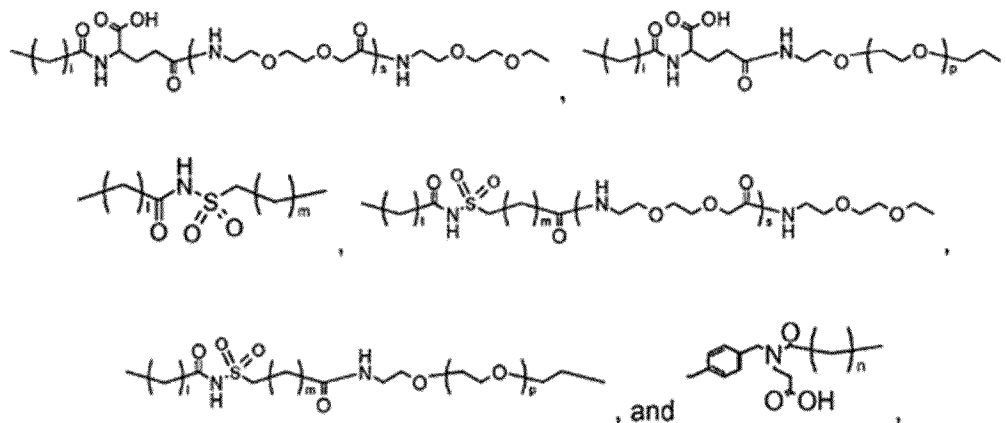


(SEQ ID NO. 4)

wherein

20 Xaa₇ is L-histidine; Xaa₈ is Aib; Xaa₁₆ is Val; Xaa₁₈ is Ser; Xaa₁₉ is Tyr; Xaa₂₀ is Leu; Xaa₂₂ is Gly or Aib; Xaa₂₃ is Gln; Xaa₂₅ is Ala; Xaa₂₇ is Glu; Xaa₃₀ is Ala; Xaa₃₃ is Val; Xaa₃₄ is Arg; Xaa₃₅ is Gly; Xaa₃₆ is Arg; Xaa₃₇ is Gly; Xaa₃₈ is absent; and

where U is a spacer selected from



where n is 12, 13, 14, 15, 16, 17, or 18,

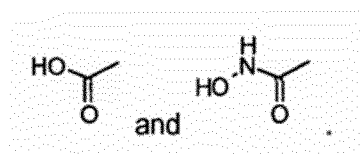
l is 12, 13, 14, 15, 16, 17, or 18,

m is 0, 1, 2, 3, 4, 5, or 6,

5 s is 0, 1, 2, or 3,

p is 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23; and

where B is an acidic group selected from



10 [00113] In some embodiments, the GLP1 receptor agonist is or comprises SEQ ID NO. 5 (below):

[00114] YX₁EGTFTSDYSIX₂LDKIAQKAX₃VQWLIAGGPSSGAPPP; (SEQ ID NO. 5)

wherein

X₁ is 2-Aminoisobutyric acid (Aib);

X₂ is 2-Aminoisobutyric acid (Aib);

15 K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)_a-CO-(CH₂)_b-CO₂H wherein a is 1 to 2 and b is 10 to 20;

X₃ is Phe or 1-Nal;

20 and the C-terminal amino acid is optionally amidated as a C-terminal primary amide, or a pharmaceutically acceptable salt thereof.

[00115] In some embodiments, the GLP1 receptor agonist is selected from one of the agents disclosed in Table 1:

Table 1: GLP1 receptor agonists, approved and under development

Generic Name(s)	Code name(s)	Chemical name or description	Synthesis/ structure described in
ecnoglutide	XW-003	L-Histidyl-L-valyl-L-alpha-glutamylglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-alpha-aspartyl-L-valyl-L-seryl-L-seryl-L-tyrosyl-L-leucyl-L-alpha-glutamyl-L-alpha-glutamyl-L-glutamyl-L-alanyl-L-alanyl-L-arginyl-L-alpha-glutamyl-L-phenylalanyl-L-isoleucyl-N6-[17-[[N-(17-carboxyheptadecanoyl)-L-gamma-glutamyl]amino]-10-oxo-3,6,12,15-tetraoxa-9-azaheptadecanan-1-oyl]-L-lysyl-L-tryptophyl-L-leucyl-L-valyl-L-arginylglycyl-L-arginylglycine HVEGTFSTSDVSSYLEEQAAREFI-N6-[17-[[N-(17-carboxyheptadecanoyl)-L-gamma-E]amino]-10-oxo-3,6,12,15-tetraoxa-9-azaheptadecanan-1-oyl]-KWLVRGRG	WO2019201333 CN110386975
mazdutide	IBI-362 LY-3305677 MB76Z4IBZ 5 OXM-3	L-Histidyl-2-methylalanyl-L-glutamylglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-alpha-aspartyl-L-tyrosyl-L-seryl-L-lysyl-L-tyrosyl-L-leucyl-L-aspartyl-L-alpha-glutamyl-L-lysyl-L-lysyl-L-alanyl-N6-[17-[[N-(19-carboxynonadecanoyl)-L-gamma-glutamyl]amino]-10-oxo-3,6,12,15-tetraoxa-9-azaheptadecanan-1-oyl]-L-lysyl-L-alpha-glutamyl-L-phenylalanyl-L-valyl-L-alpha-glutamyl-L-tryptophyl-L-leucyl-L-leucyl-L-alpha-glutamylglycylglycyl-L-prolyl-L-seryl-L-serylglycinamide	US2016368960 WO2021252829
	PB-119	23 kD Polyethylene glycolated (pegylated) derivative of exendin-4 variant PB-105 (39Cys-exendin-4) through a ppMAL linker	CN 104277103 WO 2017114425
Efpeglenatide; langlenatide LAPS-CA- exendin 4	3M1V5Z227 0 HM-11260C SAR- 439977	Long acting exenatide analog formed by conjugating the exendin-4 analog CA exendin-4 and the constant region of human immunoglobulin fragment (Fc) IgG4 via a flexible non-peptidyl linker	WO 2017052321

cotadutide	G-933 MEDI-0382	N2-(L-Histidyl-L-seryl-L-glutaminyglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-alpha-aspartyl)-N6-(N-palmitoyl-L-gamma-glutamyl)-L-lysyl-L-seryl-L-alpha-glutamyl-L-tyrosyl-L-leucyl-L-alpha-aspartyl-L-seryl-L-alpha-glutamyl-L-arginyl-L-alanyl-L-arginyl-L-alpha-aspartyl-L-phenylalanyl-L-valyl-L-alanyl-L-tryptophyl-L-leucyl-L-alpha-glutamyl-L-alanylglycylglycine	WO 2014091316
Diabegone; supaglutide	GLP-1/hlgG2 GLP-1/hlgG2-Fc	Fc fusion protein comprising the human glucagon-like peptide 1 (GLP-1) fused to human IgG2 Fc fragment; expressed in CHO cells	WO 2007012188
	BI-456906	N2-[1-(L-Histidylamino)cyclobutane-1-carbonyl]-L-glutaminyglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-alpha-aspartyl-L-tyrosyl-L-seryl-L-lysyl-L-tyrosyl-L-leucyl-L-alpha-aspartyl-L-alpha-glutamyl-L-arginyl-L-alanyl-L-alanyl-L-lysyl-L-alpha-aspartyl-L-phenylalanyl-L-isoleucyl-N6-[N-(17-carboxyheptadecanoyl)-L-alpha-glutamylglycyl-L-serylglycyl-L-serylglycylglycyl]-L-lysyl-L-tryptophyl-L-leucyl-L-alpha-glutamyl-L-seryl-L-alaninamide	WO 2021214220
retatrutide	LY-3437943 NOP2Y096 GV	L-Tyrosyl-2-methylalanyl-L-glutaminyglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-aspartyl-L-tyrosyl-L-seryl-L-isoleucyl-2-methyl-L-leucyl-L-leucyl-L-aspartyl-L-lysyl-N6-[[2-[2-[[N-(19-carboxynonadecanoyl)-L-gamma-glutamyl]amino]ethoxy]ethoxy]acetyl]-L-lysyl-L-alanyl-L-glutaminy-2-methylalanyl-L-alanyl-L-phenylalanyl-L-isoleucyl-L-glutamyl-L-tyrosyl-L-leucyl-L-leucyl-L-glutamylglycylglycyl-L-prolyl-L-seryl-L-serylglycyl-L-alanyl-L-prolyl-L-prolyl-L-prolyl-L-serinamide	WO 2019125938
	TG-103 TJ-103	Fc fusion protein consisting of recombinant humanized long-acting glucagon-like peptide-1 (hGLP-1) fused to a hybrid Fc (hyFc)	CN 110204617
orforglipron	LY-3502970 OWL-833	3-[(1S,2S)-1-(5-[(4S)-2,2-Dimethyloxan-4-yl]-2-[(4S)-2-(4-fluoro-3,5-dimethylphenyl)-3-[3-(4-fluoro-1-methyl-1H-indazol-5-yl)-2-oxo-2,3-dihydro-1H-imidazol-1-yl]-4-methyl-2,4,6,7-tetrahydro-5H-pyrazolo[4,3-c]pyridine-5-carbonyl]-	WO 2018056453

		1H-indol-1-yl)-2-methylcyclopropyl]-1,2,4-oxadiazol-5(2H)-one	
danuglipron	DN9IUI24G P PF- 06882961	2-[(4-[6-[(4-Cyano-2-fluorophenyl)methoxy]pyridin-2-yl]piperidin-1-yl)methyl]-1-[[[(2S)-oxetan-2-yl]methyl]-1H-benzimidazole-6-carboxylic acid	WO 2018109607
	NLY-001 NLY-01	Long-acting PEGylated form of exenatide	WO 2017112889 US 2021353710
	HM-15211	Long-acting GLP-1/GIP/Glucagon triple agonist consisting of a fusion protein comprising a 40-mer polypeptide consisting of fragments of activating glucagon-like peptide-1 (GLP-1), glucagon (GCG) and glucose-dependent insulinotropic polypeptide (GIP) receptors; comprising an unnatural amino acid (aminoisobutyric acid) at position 2 and loop forming amino acids at positions 16 and 20; fused via a polyethylene glycol (PEG) linker to an IgG Fc domain	WO 2017116205
pemvidutide	ALT-801 SP-1373 VPD-107	L-Histidyl-2-methylalanyl-L-glutaminyglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-alpha-aspartyl-L-tyrosyl-L-seryl-L-lysyl-L-tyrosyl-L-leucyl-L-alpha-aspartyl-L-alpha-glutamyl-N6-[[[(2S,3S,4S,5R,6R)-6-(17-carboxyheptadecyloxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl]carbonyl]-L-lysyl-L-alanyl-L-alanyl-L-lysyl-L-alpha-glutamyl-L-phenylalanyl-L-isoleucyl-L-glutamyl-L-tryptophyl-L-leucyl-L-leucyl-L-glutamyl-L-threoninamide C-5.16-N-6.20-cyclic peptide	WO 2019136158
	TT-OAD-2 TTP-273	N-[(3S,8S)-3-[4-[(3,4-Dichlorophenyl)methoxy]phenyl]-7-[(1S)-1-phenylpropyl]-2,3,6,7,8,9-hexahydro[1,4]dioxino[2,3-g]isoquinoline-8-carbonyl]-4-(2,3-dimethylpyridin-4-yl)-L-phenylalanine bis(hydrogen chloride)	WO 2010114824
efinopegdutide	DR6P1M58 PO HM-12525A JNJ-5111 JNJ- 64565111	Fusion protein consisting of glucagon-like peptide-1 (GLP-1) analogue fused to an Fc portion dimer of IgG4 and conjugated by a 10 kDa polyethylene glycol (PEG) linker	WO 2021235915

	LAPS-GLP-1/GCG LAPS-GLP/GCG LAPS-OXM MK-6024		
	PT-302 PT-320 SR Exanatide	Injectable sustained release Exenatide using the SmartDepot technology	WO 2008117927 WO 2018075901 WO 2021020885
pegapamodutide	LY-2944876 OPK-88003 TT-401 WG4ID2U7 FT	L-Histidyl-2-methylalanyl-L-glutaminyglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-alpha-aspartyl-L-tyrosyl-L-seryl-L-lysyl-L-tyrosyl-L-leucyl-L-alpha-aspartyl-L-seryl-L-lysyl-L-lysyl-L-alanyl-L-glutaminy-L-alpha-glutamyl-L-phenylalanyl-L-valyl-L-glutaminy-L-tryptophyl-L-leucyl-L-leucyl-L-asparaginy-2-methylalanyglycyl-L-arginyl-L-asparaginy-L-arginyl-L-asparaginy-L-asparaginy-L-isoleucyl-L-alanyl-S-[1-[3-[[3-(methoxy)polyethyleneglycol]propyl]amino]-3-oxopropyl]-2,5-dioxopyrrolidin-3-yl]-L-cysteinyl-S-[1-[3-[[3-(methoxy)polyethyleneglycol]propyl]amino]-3-oxopropyl]-2,5-dioxopyrrolidin-3-yl]-L-cysteinamide (linear PEG chain containing n=450 units)	US 2011152182
	XW-004	Co-formulation of ecnoglutide with an oral absorption enhancer (compound T2026)	CN 112062690 CN 112661663 WO 2021238088 CN 113735733
dapiglutide	ZP-7570	N6-[N-(17-Carboxyheptadecanoyl)-L-gamma-glutamyl]-N2-(L-histidyl-2-methylalanyl-L-glutaminyglycyl-L-seryl-L-phenylalanyl-L-threonyl-L-seryl-L-glutamyl-L-leucyl-L-alanyl-L-threonyl-L-isoleucyl-L-leucyl-L-aspartyl)-L-lysyl-L-glutaminy-L-alanyl-L-alanyl-L-arginyl-L-aspartyl-L-phenylalanyl-L-isoleucyl-L-alanyl-L-tryptophyl-L-leucyl-L-isoleucyl-L-glutaminy-L-histidyl-L-lysyl-L-isoleucyl-L-threonyl-L-aspartic acid	WO 2018104561 WO 2022175410 WO 2023031380
	MOD-6031	N-[[[2-[[3-[(Polyethyleneglycol)sulfanyl]-2,5-dioxopyrrolidin-1-yl]propanoyl]amino]-7-sulfo-9H-fluoren-9-yl]methoxy]carbonyl]-L-histidyl-L-seryl-L-glutaminyglycyl-L-threonyl-L-phenylalanyl-L-	WO 2012167251

		threonyl-L-seryl-L-alpha-aspartyl-L-tyrosyl-L-seryl-L-lysyl-L-tyrosyl-L-leucyl-L-alpha-aspartyl-L-seryl-L-arginyl-L-arginyl-L-alanyl-L-glutamyl-L-alpha-aspartyl-L-phenylalanyl-L-valyl-L-glutamyl-L-tryptophyl-L-leucyl-L-methionyl-L-asparagyl-L-threonyl-L-lysyl-L-arginyl-L-asparagyl-L-arginyl-L-asparagyl-L-asparagyl-L-isooleucyl-L-alanine (linear PEG chain of a molecular mass of about 30000 dalton)	
	PB-1023 PF-1801	Recombinant GLP-1 analogue fused to an elastin-like peptide (ELP) biopolymer	WO 2013003449 WO 2014081849
cagrilintide/sema glutide	Cagrisema NN-9388	Fixed-dose combination of semaglutide and cagrilintide	
	Icosema Insulin 287/semagl utide LAlsema NN-1535 NNC0148- 0287sema	Fixed-dose combination of semaglutide and insulin 287	
	Uni-E4		
	RGT-001- 075 RGT-075 RGT001- 075		
	GZR-18		
	AMG-133		
	NN-9389 NNC0480- 0389/sema glutide	Fixed-dose combination of NNC0480-0389 and semaglutide	
	PF- 07081532		
vurolenatide (USAN)	GLP-1- XTEN GT0UZY3R PJ	Recombinant fusion protein comprising exenatide and XTEN recombinant polypeptide	

	NB-1001 NM-002 XTEN-GLP-1		
	MK-8521		
	AZD-0186		
	GSBR-1290		
Amycretin			
	HS-20094		
	XW-014		
	VK-2735		
	LY-3493269		
	DD-01		
	SCO-094 TAK-094		
	NN-1177 NN-9277 NNC9204-1177		
albenatide		Synthetic exendin 4 conjugated to recombinant human albumin through a N6-[1-(2,5-Dioxo-3-sulfanylpiperidin-1-yl)-3,12-dioxo-7,10-dioxo-4,13-diazaheptadecan-17-yl]-L-lysine linker bound to cysteine-34 of albumin	
tirzepatide	LY-3298176	L-Tyrosyl-2-methylalanyl-L-alpha-glutamylglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-alpha-aspartyl-L-tyrosyl-L-seryl-L-isoleucyl-2-methylalanyl-L-leucyl-L-alpha-aspartyl-L-lysyl-L-isoleucyl-L-alanyl-L-glutamyl-N6-[17-[[N-(19-carboxynonadecanoyl)-L-alpha-glutamyl]amino]-10-oxo-3,6,12,15-tetraoxa-9-azaheptadecan-1-oyl]-L-lysyl-L-alanyl-L-phenylalanyl-L-valyl-L-glutamyl-L-tryptophyl-L-leucyl-L-isoleucyl-L-alanyl-L-prolyl-L-seryl-L-serylglycyl-L-alanyl-L-prolyl-L-prolyl-L-prolyl-L-serinamide	WO 2016111971
PEG-loxanatide polyethylene glycol loxanatide	PEX-168	L-Histidyl-D-alanyl-L-alpha-glutamylglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-alpha-aspartyl-L-leucyl-L-seryl-L-lysyl-L-glutamyl-L-norleucyl-L-alpha-glutamyl-L-alpha-	WO 2012155780

		glutamyl-L-alpha-glutamyl-L-alanyl-L-valyl-L-arginyl-L-leucyl-L-phenylalanyl-L-isoleucyl-L-alpha-glutamyl-L-tryptophyl-L-leucyl-L-lysyl-L-glutamylglycylglycyl-L-prolyl-L-seryl-L-serylglycyl-L-alanyl-L-prolyl-L-prolyl-L-prolyl-S-[1-[3-[2-[N2,N6-bis[[2-[2-methoxy(polyethylenglycol)ethoxy]ethoxy]carbonyl]lysyl]amino]ethyl]amino]-3-oxopropyl]-2,5-dioxopyrrolidin-3-yl]-L-cysteinamide (linear PEG chain of a molecular mass of about 40.000 dalton)	
semaglutide	EX-9924 NN-9535 NN-9536 NN-9924 NN-9928 NN-9931 NN-9932 NNC-0113-0217 OG-217GT OG-217SC	Recombinant long-acting analogue of human glucagon like-1 peptide, comprising a 2-Aminoisobutyric acid (X) at position 2 and a large fatty acid chain attached at lysine residue; expressed in <i>Saccharomyces cerevisiae</i> L-Histidyl-2-methylalanyl-L-glutamyl-glycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-aspartyl-L-valyl-L-seryl-L-seryl-L-tyrosyl-L-leucyl-L-glutamyl-glycyl-L-glutamyl-L-alanyl-L-alanyl-N6-[17-[N-(17-carboxyheptadecanoyl)-L-gamma-glutamylamino]-10-oxo-3,6,12,15-tetraoxa-9-azaheptadecanoyl]-L-lysyl-L-glutamyl-L-phenylalanyl-L-isoleucyl-L-alanyl-L-tryptophyl-L-leucyl-L-valyl-L-arginyl-glycyl-L-arginyl-glycine H-2-methyl-AEGTFTSDVSSYLEGQAA-N6-[17-[N-(17-carboxyheptadecanoyl)-L-gamma-glutamylamino]-10-oxo-3,6,12,15-tetraoxa-9-azaheptadecanoyl]-KEFIWLVRGRG	WO2006/097537 WO 2012080471
lixisenatide/ Insulin glargine	AVE-0010/Lantus HOE901/AVE0010 Lixisenatide/Lantus	Combination product containing lixisenatide and insulin glargine	WO 1998008871 WO2011147980A1
Beinaglutide; benaglutide	rhGLP-1(7-36)	L-histidyl-L-alanyl-L-glutamylglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-aspartyl-L-valyl-L-seryl-L-seryl-L-tyrosyl-L-leucyl-L-glutamylglycyl-L-glutamyl-L-alanyl-L-alanyl-L-lysyl-L-glutamyl-L-phenylalanyl-L-isoleucyl-L-alanyl-L-tryptophyl-L-leucyl-L-valyl-L-lysylglycyl-L-arginyl-OH Human glucagon-like peptide-1 (7-36)-peptide	WO 1993025579

insulin degludec/liraglutide	NN-9068	Fixed dose combination of insulin degludec and liraglutide	WO 1998008871 WO 2010043566
dulaglutide	GLP-1-Fc LY-2189265	Dimeric fusion protein comprising dipeptidyl peptidase-IV (DPP-IV)-protected human glucagon-like peptide 1 (GLP-1; aa 7-37) analog linked via a synthetic 16-amino acid linker to a modified human IgG4 Fc fragment containing F234A and L235A mutations	WO 2009009562
albiglutide	GSK-716155 PGC GLP-1	Recombinant fusion protein created by fusing the gene encoding human albumin to the gene encoding GLP-1	WO 2006111169 WO 2007028394
lixisenatide	AVE-0010 ZP-10 ZP-10A	H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser-Lys-Lys-Lys-Lys-Lys-Lys-NH ₂ Des-36-proline-exendine-4 (Heloderma suspectum)-(1-39)-peptidylpenta-L-lysyl-L-lysineamide	WO 1998008871 WO2011147980A1
liraglutide	4-P-004 LATIN T1D NN-2211 NN-8022 NN-9211 NN2211 NNC-90-1170	[Nepsilon-[(Nalpha-Hexadecanoyl)-gamma-L-Glu]-L-Lys26,L-Arg34]-GLP-1(7-37) L-Histidyl-L-alanyl-L-glutamyl-glycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-aspartyl-L-valyl-L-seryl-L-seryl-L-tyrosyl-L-leucyl-L-glutamyl-glycyl-L-glutamyl-L-alanyl-L-alanyl-Nepsilon-(N2-hexadecanoyl-gamma-L-glutamyl)-L-lysyl-L-glutamyl-L-phenylalanyl-L-isoleucyl-L-alanyl-L-tryptophyl-L-leucyl-L-valyl-L-arginyl-glycyl-L-arginyl-glycine	1998008871 and WO 2010043566
Exenatide; exendin-4	AC-2993 AC-2993 LAR DA-3091 Ex-4 FT-228 LY-2148568 ORMD-0901	L-Histidyl-glycyl-L-glutamyl-glycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-aspartyl-L-leucyl-L-seryl-L-lysyl-L-glutamyl-L-methionyl-L-glutamyl-L-glutamyl-L-glutamyl-L-alanyl-L-valyl-L-arginyl-L-leucyl-L-phenylalanyl-L-isoleucyl-L-glutamyl-L-tryptophyl-L-leucyl-L-lysyl-L-asparaginyl-glycyl-glycyl-L-prolyl-L-seryl-L-seryl-glycyl-L-alanyl-L-prolyl-L-prolyl-L-prolyl-L-serinamide	WO 1998005351

[00116] In some embodiments, the GLP1 receptor agonist is exenatide (including exenatide extended release), lixisenatide, beinaglutide, dulaglutide, liraglutide, semaglutide, albiglutide,

PEG-lonexatide or tirzepatide, or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[00117] In some embodiments the GLP1 receptor agonist is suitable for oral administration.

[00118] In some embodiments, the GLP1 receptor agonist is exenatide or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[00119] In some embodiments, the GLP1 receptor agonist is lixisenatide or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[00120] In some embodiments, the GLP1 receptor agonist is beinaglutide or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[00121] In some embodiments, the GLP1 receptor agonist is dulaglutide or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[00122] In some embodiments, the GLP1 receptor agonist is liraglutide or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[00123] In some embodiments, the GLP1 receptor agonist is albiglutide or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[00124] In some embodiments, the GLP1 receptor agonist is PEG-lonexatide or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[00125] In some embodiments, the GLP1 receptor agonist is tirzepatide, or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[00126] In some embodiments the GLP1 receptor agonist is semaglutide or a pharmaceutically acceptable salt, solvate or hydrate thereof. In some embodiments the semaglutide is provided as an oral formulation. In some embodiments the semaglutide is provided as a formulation for subcutaneous administration.

[00127] In some embodiments, the GLP1 receptor agonist is comprised within a combination product. For example, the GLP1 receptor agonist may be co-formulated with at least one (e.g. one, two or more) further therapeutic agent.

[00128] In some embodiments, the GLP1 receptor agonist comprises or is a combination of semaglutide, or a pharmaceutically acceptable salt, solvate or hydrate thereof, and cagrilintide, or a pharmaceutically acceptable salt, solvate or hydrate thereof.

[00129] In some embodiments, the combination of the PDE4 inhibitor and the GLP1 receptor agonist is selected from the combinations listed in Table T below:

Table T

Combination	PDE4 inhibitor (or a pharmaceutically acceptable salt, solvate or hydrate thereof).	GLP1 receptor agonist (or a pharmaceutically acceptable salt, solvate or hydrate thereof).
1	orismilast	exenatide
2	orismilast	lixisenatide
3	orismilast	beinaglutide
4	orismilast	dulaglutide
5	orismilast	liraglutide
6	orismilast	albiglutide
7	orismilast	PEG-Ionexatide
8	orismilast	tirzepatide
9	orismilast	semaglutide
10	apremilast	exenatide
11	apremilast	lixisenatide
12	apremilast	beinaglutide
13	apremilast	dulaglutide
14	apremilast	liraglutide
15	apremilast	albiglutide
16	apremilast	PEG-Ionexatide
17	apremilast	tirzepatide
18	apremilast	semaglutide
19	roflumilast	exenatide
20	roflumilast	lixisenatide
22	roflumilast	beinaglutide
23	roflumilast	dulaglutide
24	roflumilast	liraglutide
25	roflumilast	albiglutide
26	roflumilast	PEG-Ionexatide

27	roflumilast	tirzepatide
28	roflumilast	semaglutide
29	difamilast	exenatide
30	difamilast	lixisenatide
31	difamilast	beinaglutide
32	difamilast	dulaglutide
33	difamilast	liraglutide
34	difamilast	albiglutide
35	difamilast	PEG-Ionexatide
36	difamilast	tirzepatide
37	difamilast	semaglutide
38	crisaborole	exenatide
39	crisaborole	lixisenatide
40	crisaborole	beinaglutide
41	crisaborole	dulaglutide
42	crisaborole	liraglutide
43	crisaborole	albiglutide
44	crisaborole	PEG-Ionexatide
45	crisaborole	tirzepatide
46	crisaborole	semaglutide
47	ibudilast	exenatide
48	lbudilast	lixisenatide
49	lbudilast	beinaglutide
50	lbudilast	dulaglutide
51	lbudilast	liraglutide
52	lbudilast	albiglutide
53	lbudilast	PEG-Ionexatide
54	lbudilast	tirzepatide
55	lbudilast	semaglutide

56	drotaverine	exenatide
57	drotaverine	lixisenatide
58	drotaverine	beinaglutide
59	drotaverine	dulaglutide
60	drotaverine	liraglutide
61	drotaverine	albiglutide
62	drotaverine	PEG-lonexatide
63	drotaverine	tirzepatide
64	drotaverine	semaglutide
65	tanimilast	exenatide
66	Tanimilast	lixisenatide
67	Tanimilast	beinaglutide
68	Tanimilast	dulaglutide
69	Tanimilast	liraglutide
70	Tanimilast	albiglutide
71	Tanimilast	PEG-lonexatide
72	Tanimilast	tirzepatide
73	tanimilast	semaglutide
74	ensifentrine	exenatide
75	ensifentrine	lixisenatide
76	ensifentrine	beinaglutide
77	ensifentrine	dulaglutide
78	ensifentrine	liraglutide
79	ensifentrine	albiglutide
80	ensifentrine	PEG-lonexatide
81	ensifentrine	tirzepatide
82	ensifentrine	semaglutide
83	zatolmilast	exenatide
84	zatolmilast	lixisenatide

85	zatolmilast	beinaglutide
86	zatolmilast	dulaglutide
87	zatolmilast	liraglutide
88	zatolmilast	albiglutide
89	zatolmilast	PEG-lonexatide
90	zatolmilast	tirzepatide
91	zatolmilast	semaglutide

In a preferred embodiment the PDE4 inhibitor is orismilast or a pharmaceutically acceptable salt, hydrate or solvate thereof and optionally the GLP1 receptor agonist is semaglutide or a pharmaceutically acceptable salt, hydrate or solvate thereof.

5 Pharmaceutical Compositions

[00130] The PDE4 inhibitor (e.g. orismilast) and/or the GLP1 receptor agonist may be comprised within a pharmaceutical composition. The PDE4 inhibitor and the GLP1 receptor agonist may be comprised within the same pharmaceutical composition. In some embodiments, the PDE4 inhibitor may be comprised within a separate pharmaceutical composition to the GLP1 receptor agonist.

[00131] Thus, the present invention also provides a first pharmaceutical composition comprising a PDE4 inhibitor (e.g. orismilast) for use any of the methods described herein. The present invention further provides a second pharmaceutical composition comprising a GLP1 receptor agonist for use in any of the methods described herein. Also provided is a third pharmaceutical composition comprising a PDE4 inhibitor and a GLP1 receptor agonist for use any of the methods described herein.

[00132] Pharmaceutical compositions of the invention may optionally further comprise one or more viscosity modifying agents, carriers (e.g. mannitol, lactose, microcrystalline cellulose or trehalose), emulsifiers, surfactants, humectants, oils, waxes, polymers, preservatives, pH modifying agents (for example a suitable acid or base, for example an organic acid or organic amine base), buffers, stabilizers, electrolytes antioxidants (for example, butylated hydroxyanisol or butylated hydroxytoluene), crystallisation inhibitors (for example a cellulose derivative such as hydroxypropylmethyl cellulose or polyvinylpyrrolidone), colorants, fragrances and taste-masking agents. Such excipients are well-known, for example as listed in the Handbook of Pharmaceutical Excipients, 10th Edition, Sheskey *et al.*

[00133] In some embodiments the PDE4 inhibitor (e.g. orismilast) is present in the first pharmaceutical composition in an amount of from about 0.01 to 50% by weight of the composition. Thus it may be that the PDE4 inhibitor (e.g. orismilast), is present in the solid composition in an amount of about 0.05 to 40%, from 0.1 to 30%, from 0.2 to 20%, from 0.3 to 15%, from 0.4 to 12%, from 0.5 to 11%, from 1 to 10%, from 1.5 to 9.5%, from 2 to 9%, from 2.5 to 8.5%, from 3 to 8%, from 3.5 to 7.5%, from 4 to 7%, from 4.5 to 6.5%, or from about 5 to 6%, e.g. about 5.5%, wherein the % are by weight based on the weight of the composition.

[00134] In some embodiments the GLP1 receptor agonist is present in the second pharmaceutical composition in an amount of from about 0.01 to 50% by weight of the composition. Thus it may be that the GLP1 receptor agonist, is present in the solid composition in an amount of from about 0.01 to 70%, from 0.02 to 60%, from 0.03 to 50%, from 0.05 to 40%, from 0.1 to 30%, from 0.2 to 20%, from 0.3 to 15%, from 0.4 to 12%, from 0.5 to 11%, from 1 to 10%, from 1.5 to 9.5%, from 2 to 9%, from 2.5 to 8.5%, from 3 to 8%, from 3.5 to 7.5%, from 4 to 7%, from 4.5 to 6.5%, or from about 5 to 6%, e.g. about 5.5%, wherein the % are by weight based on the weight of the composition.

Pharmaceutical compositions for oral administration

[00135] In some embodiments any of the pharmaceutical compositions described herein may be suitable for oral administration. Suitably the pharmaceutical composition is a solid pharmaceutical composition, preferably a solid pharmaceutical composition suitably for oral administration. The pharmaceutical composition may be in the form of discrete units such as capsules, sachets, tablets, lozenges or granules, each containing a predetermined amount of the PDE4 inhibitor. The discrete units may contain the composition in the form of a powder or granules, a solution or a suspension in aqueous or non-aqueous liquid, such as ethanol or glycerol, or in the form of an oil-in-water emulsion or a water-in-oil emulsion. Such oils may be edible oils, such as e.g. cottonseed oil, sesame oil, coconut oil or peanut oil. Suitable dispersing or suspending agents for aqueous suspensions include synthetic or natural gums such as tragacanth, alginate, acacia, dextran, sodium carboxymethylcellulose, gelatin, methylcellulose, hydroxypropyl methylcellulose, hydroxypropylcellulose, carbomers and polyvinylpyrrolidone. The formulation may also be administered in the form of a bolus, electuary or paste.

[00136] Powders may be prepared using well-known methods, for example by milling, blending, micro-precipitation, lyophilisation or spray drying, or spray-freeze drying a solution comprising the active agent (i.e. the PDE4 inhibitor (e.g. orismilast) and/or the GLP1 receptor agonist).

[00137] The amount of PDE4 inhibitor (e.g. orismilast) in an oral dosage form (e.g. tablet, capsule, sachet or lozenge) may range from about 0.01 to about 1000 mg, from about 0.1 mg to about 500 mg, from about 1 mg to about 250 mg or from about 5 mg to about 100 mg. The amount of PDE4 inhibitor may for example range from 0.1 mg to 80 mg, from 0.5 mg to 60 mg, from 0.8 mg to 50 mg, from 1 mg to 40 mg, from 5 mg to 40 mg, from 10 mg to 40 mg, from 15 mg to 35 mg, from 20 to 30 mg, from 25 mg to 30 mg, from 5 mg to 30 mg or from 10 mg to 30 mg. In some embodiments, the amount of PDE4 inhibitor in each oral dosage form (e.g. tablet, capsule, sachet or lozenge) is 1 mg, 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg or 100 mg.

[00138] The amount of GLP1 receptor agonist in an oral dosage form (e.g. a tablet, capsule, sachet or lozenge) may range from about 0.01 to about 1000 mg, from about 0.1 mg to about 500 mg, from about 1 mg to about 250 mg or from about 5 mg to about 100 mg. The amount of GLP1 receptor agonist may for example range from 0.1 mg to 80 mg, from 0.5 mg to 60 mg, from 0.8 mg to 50 mg, from 1 mg to 40 mg, from 5 mg to 40 mg, from 10 mg to 40 mg, from 15 mg to 35 mg, from 20 to 30 mg, from 25 mg to 30 mg, from 5 mg to 30 mg, from 10 mg to 30 mg or from 12 to 15 mg. In some embodiments, the amount of GLP1 receptor agonist, in each oral dosage form (e.g. tablet, capsule, sachet or lozenge) is 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg or 100 mg.

[00139] In some embodiments, an oral dosage form comprises a therapeutically effective amount of a PDE4 inhibitor (e.g. orismilast) and a therapeutically effective amount of a GLP1 receptor agonist. In some embodiments, the oral dosage form comprises from 0.01 mg to 1000 mg of the PDE4 inhibitor and from 0.01 mg to 1000 mg of the GLP1 receptor agonist, e.g. from 0.5 mg to 500 mg of the PDE4 inhibitor and from 0.5 mg to 500 mg of the GLP1 receptor agonist. For example the oral dosage form may comprise:

- from 0.1 to 80 mg of the PDE4 inhibitor and from 0.1 to 80 mg of the GLP1 receptor agonist;
- from 1 to 60 mg of the PDE4 inhibitor and from 0.5 to 60 mg of the GLP1 receptor agonist;
- from 10 to 40 mg of the PDE4 inhibitor and from 1 to 40 mg of the GLP1 receptor agonist.

In some of these embodiments, the PDE4 inhibitor may be orismilast. In some of these embodiments, the GLP1 receptor agonist is semaglutide. In some of these embodiments, the PDE4 inhibitor is orismilast and the GLP1 receptor agonist is semaglutide.

[00140] In certain embodiments particles comprising the PDE4 inhibitor (e.g. orismilast) and/or the GLP1 receptor agonist may be prepared by precipitation, lyophilisation or spray

drying, or spray-freeze drying a solution comprising the PDE4 inhibitor, and/or the GLP1 receptor agonist, and a suitable carrier to provide powder particles comprising the PDE4 inhibitor, and/or the GLP1 receptor agonist, and the carrier as composite particles. Suitable carriers include inert carriers such as starch, sugars (e.g. mannitol, lactose, microcrystalline cellulose or trehalose).

[00141] In some embodiments the PDE4 inhibitor (e.g. orismilast) and/or the GLP1 receptor agonist is present in the composition as a micronised powder, for example a micronised crystalline powder (e.g. micronised crystalline form E of orismilast). Thus it may be that the particle size distribution of the PDE4 inhibitor and/or the GLP1 receptor agonist in the composition has a $D(50) \leq 25 \mu\text{m}$, for example $D(50) \leq 20 \mu\text{m}$, $D(50) \leq 10 \mu\text{m}$, $D(50) \leq 5 \mu\text{m}$, or $D(50) \leq 3 \mu\text{m}$. In some embodiments the particle size distribution of the PDE4 inhibitor and/or the GLP1 receptor agonist in the composition has a $D(90) \leq 10 \mu\text{m}$. In some embodiments the particle size distribution of the PDE4 inhibitor and/or the GLP1 receptor agonist in the composition has a $D(50)$ of about $1 \mu\text{m}$ to about $6 \mu\text{m}$.

[00142] Powders comprising a PDE4 inhibitor (e.g. orismilast) and/or a GLP1 receptor agonist, as described herein, may be dissolved or suspended in a suitable solvent (preferably water) prior to administration, e.g. application of a spray or gel. Alternatively, a powder or granule comprising the PDE4 inhibitor (e.g. orismilast) and/or the GLP1 receptor agonist may be sprinkled onto food or into a liquid prior to administration.

[00143] A tablet may be made by compressing or moulding the composition, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable tableting machine, the formulation in a free-flowing form such as a powder or granules, optionally mixed by a binder, such as e.g. lactose, glucose, starch, gelatine, acacia gum, tragacanth gum, sodium alginate, carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, polyethylene glycol, waxes or the like; a lubricant such as sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride or the like; a disintegrating agent such as starch, methylcellulose, agar, bentonite, croscarmellose sodium, sodium starch glycollate, crospovidone or the like or a dispersing agent, such as polysorbate 80.

[00144] Moulded tablets may be made by moulding. Suitable techniques for moulding tablets are well-known in the art. For example, in a suitable machine, a mixture of the powdered active ingredient and suitable carrier may be moistened with an inert liquid diluent. In some embodiments, moulded tablets may be made by dispersing a water-soluble excipient with the powdered PDE4 inhibitor (e.g. orismilast) and/or GLP1 agonist in a suitable solvent such as water, alcohol or organic solvents (e.g. acetone, hydrocarbons).

Alternatively, moulded tablets may be made using thermoplastic polymers (e.g. polyethyleneoxide or polyvinyl caprolactam-polyvinylacetate-polyethylene glycol copolymers), without an inert liquid diluent.

[00145] A process for producing a tablet comprising a GLP1 receptor agonist is described in WO2021043803.

[00146] Representative examples of oral pharmaceutical compositions comprising orismilast are shown in Table 2.

Table 2

	1: hard capsule	2: modified release tablet	3: soft capsule	4: blend, hard capsule	5: gastro-resistant capsule
core ingredients	orismilast	orismilast	orismilast	orismilast	orismilast
		Lactose monohydrate	Triglyceride, medium chain	Microcrystalline cellulose	Microcrystalline cellulose
		Hypromellose	Lecithin	Lactose monohydrate	Lactose monohydrate
		Silica, colloidal anhydrous	Hard fat	Hypromellose	Coscarmellose sodium
		Magnesium stearate	Silica, colloidal anhydrous	Silica, colloidal anhydrous	Silica, colloidal anhydrous
				Magnesium stearate	Magnesium stearate
shell/coating	Gelatin	Macrogol	Gelatin	Gelatin	Hypromellose
	Ferric oxide red	PVA	Glycerol	Ferric oxide red	Hypromellose acetate succinate
	Titanium dioxide	Titanium dioxide	Ferric oxide red	Titanium dioxide	Titanium dioxide
		Talc	Water, purified		

		Ferric oxide yellow			
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Modified release compositions

[00147] In some embodiments, the orismilast is comprised within a modified release composition formulation, for example a modified release composition for oral administration.

5 Thus it may be that the orismilast may be comprised within a modified release tablet composition for oral administration. The use of modified release compositions may control the release of the therapeutic agent and thus control absorption of orismilast from gastrointestinal tract. It has previously been described by the Applicant (in a PCT application published as WO2020/148271) that beneficial effects with respect to improved tolerability
10 towards gastrointestinal adverse events and maintained systemic exposure can be achieved by formulating orismilast in a modified release tablet formulation, wherein the in-vitro release is fast in comparison to convention delayed or extended release oral release profiles but not yet as fast as for an immediate release tablet where major tolerability issues were seen.

[00148] It will be appreciated that the rate of dissolution of a modified release composition
15 will be determined by several factors e.g. the composition excipients and nature of the composition, the particle sizes of the components used in the composition, particularly the particle size of the orismilast, and the use of coatings or capsules to modulate release of orismilast from the composition. The dissolution target area in Figure 1 of WO2020/0148271 illustrates suitable dissolution profiles for modified release compositions comprising
20 orismilast are suitably determined *in-vitro* using Ph. Eur. 2.9.3 Apparatus II, with a dissolution medium of 900 ml 0.5% sodium dodecyl sulfate in 0.1N HCl, a paddle speed of 75 rpm, and the dissolution medium at 37 ± 0.5 °C, referred herein as “the Standard Dissolution Assay”.

[00149] In some embodiments the orismilast is formulated as a modified release formulation
25 described in WO2020/0148271, which is incorporated herein by reference thereto.

[00150] Other modified release compositions comprising orismilast are also contemplated. For example the orismilast may be dispersed, dissolved or conjugated (e.g. complexed) with a polymer matrix. The polymer matrix may be hydrophobic or hydrophilic, but is preferably hydrophilic. In some embodiments the composition comprises orismilast and a polymeric
30 matrix, wherein the polymer is one or more polymers selected from hydroxypropyl methylcellulose, methyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, sodium carboxymethyl cellulose a polyethylene oxide, polyethylene glycols; polyethyleneoxide and polypropyleneoxide block-co-polymers (e.g. poloxamers), cellulose acetate phthalate,

hydroxypropylmethyl cellulose phthalate, polyvinylpyrrolidone (PVP), copolymers of PVP and vinyl acetate, a poly (ethylene-vinyl acetate), polyvinyl alcohol, sugar alcohols (e.g. xylitol or sorbitol) and a biodegradable polymer (e.g. a poly(lactide-co-glycolide)).

[00151] Orismilast may also be dissolved, dispersed or conjugated with one or more protein-based polymers, such as collagen, albumin, gelatin, and polysaccharides, such as agarose, alginate, carrageenan, hyaluronic acid (HA), dextran, chitosan, galactomannan, guar gum; carob gum; gum arabic; sterculia gum, agar or a cyclodextrin.

[00152] In some embodiments the polymer matrix is present in the composition in an amount of from 10 to 40% by weight of the composition, for example from 15 to 30% by weight of the composition. The modified release composition comprising orismilast may further comprise one or more fillers, binders, or glidants. Such additional excipients are well known to the skilled person.

[00153] In some embodiments the orismilast is dissolved or dispersed within the polymer matrix by melt extrusion. Alternatively the orismilast may be dispersed or dissolved in the polymer matrix by blending the excipients followed by wet or dry granulation and/or pressing composition into a suitable dosage form such as a tablet. The orismilast may also be dispersed or dissolved in a gel matrix, for example a hydrogel system comprising a gel-forming polymer.

[00154] The modified release composition comprising orismilast may also be prepared as a nanoparticulate composition. For example nanoparticles comprising orismilast and a biodegradable polymer such as a poly(lactide-co-glycolide) or orismilast conjugated with a suitable polymer carrier.

[00155] In some embodiments the composition comprising orismilast is a solid dispersion wherein the orismilast is present in a matrix (typically a polymer matrix) in an amorphous form. Examples of amorphous solid dispersions are disclosed in Jain S et al. Solubility and dissolution enhancement strategies: Current understanding and recent trends. Drug Dev. Ind. Pharm. 2015;41:875–887. Solid dispersions may be prepared using known methods, for example hot melt extrusion.

[00156] Modified release of orismilast may also be achieved through the use of coatings on a core composition (e.g. a tablet core) comprising the orismilast, or wherein orismilast is present in a coating applied to a suitable substrate (e.g. and inert core such as a sugar or polymeric core) to provide layer containing orismilast on the core. Suitable coatings which could provide modified release of orismilast include, for example, modified celluloses, polymethacrylates, polyvinylpyrrolidone, polyvinyl acetate phthalate, zein and/or shellac or natural gum, such as, for example, carrageenan. For example, a coating comprising a

water-soluble polymers, such as, for example, low-viscosity hydroxypropylmethyl cellulose, hydroxypropyl cellulose or a PVA polymer.

[00157] Also contemplated are coatings applied to a core composition comprising orismilast, for example a core comprising orismilast and a polymer matrix as described herein. The coating may be any of the coatings described herein and acts to further modulate release of the orismilast from the composition. In certain embodiments the composition comprises a core comprising orismilast wherein the core is coated with a coating comprising orismilast. In this embodiment orismilast is released from both the coating and the core.

[00158] Modified release compositions comprising orismilast may also be formulated as a lipid-based composition, for example as a liposome, emulsion or micro emulsion, a self-emulsifying drug delivery system, a nano-emulsion, a lipid-drug conjugate, solid-lipid nanoparticles or solid lipid microparticles. Accordingly the composition may, for example, be a self-emulsifying drug delivery (SEDD) composition, a self-microemulsifying drug delivery (SMEDD) composition or a self-nanoemulsifying drug delivery (SNEDD) composition. The lipid may be, for example, mono-, di- or triglycerides (e.g. a medium chain triglyceride) a lipid emulsifiers, for example, phosphatidylcholine, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), hydrogenated soy phosphatidylcholine (HSPC), 1-myristoyl-2-stearoyl-sn-glycero-3-phosphocholine (MSPC), 1-hexadecenyl-2-oleoyl-sn-glycero-3-phosphocholine (HOPC), 1,2-dipalmitoyl-sn-glycero-3-phosphatidylglycerol (DPPG), 1,2-distearoyl-sn-glycero-3-phosphatidylglycerol (DSPG), represents 1,2-dimyristoyl-sn-glycero-3-phosphatidylglycerol (DMPG), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[amino (polyethylene glycol)-2000] (DSPE-PEG2000), 1,2-dimyristoyl-sn-glycero-3-phosphoethanolamine (DMPE), 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), unsaturated polyglycolized glycerides (e.g. oleoyl macrogolglycerides or linoleoyl macrogolglycerides), sorbitan esters (e.g. sorbitan monooleate, sorbitan monostearate, sorbitan monolaurate or sorbitan monopalmitate), polyoxyethylene sorbitan esters (e.g. Polysorbate 20, polysorbate 40, polysorbate 60, and polysorbate 80), polyoxyl castor oil derivatives (e.g. polyoxyl 35 castor oil or polyoxyl 40 hydrogenated castor oil), polyoxyethylene polyoxypropylene block copolymers (e.g. poloxamer 188 or poloxamer 407), saturated polyglycolized glycerides (e.g. lauroyl macrogolglycerides or stearoyl macrogolglycerides), PEGylated caprylic/capric glycerides (e.g. caprylocaproyl macrogolglycerides) or vitamin E derivatives (e.g. D-tocopheryl polyethylene glycol succinate). The lipid formulations may further comprise one or more surfactant and/or co-solvent. Lipid drug delivery systems are described in Examples, of emulsifiers in Rahim MA et al, Recent Advancements in Stimuli Responsive Drug Delivery Platforms for Active and Passive Cancer Targeting. Cancers (Basel). 2021 Feb 7;13(4):670;

and Yingchoncharoen et al., Lipid-Based Drug Delivery Systems in Cancer Therapy: What Is Available and What Is Yet to Come. Pharmacol Rev. 2016 Jul;68(3):701-87.

[00159] Also contemplated are osmotic-release drug delivery systems comprising a composition comprising orismilast and an osmotic agent surrounded by a semipermeable membrane capsule containing a small orifice. In use water is drawn is drawn through the semipermeable membrane by the osmotic agent, and the osmotic agent becomes hydrated and swells, forcing the drug out through the orifice in the capsule.

[00160] In some embodiments the modified release formulation releases less than 40% of the orismilast after 12 minutes. In some embodiments the modified release formulation releases less than 20% of the orismilast after 12 minutes. In some embodiments the modified release composition releases less than 40% of the orismilast after 30 minutes. In some embodiments the modified release composition releases less than 35 % of the orismilast after 30 minutes. In some embodiments the modified release composition releases from about 20 % to about 40 % of the orismilast after 30 minutes. In some embodiments the modified release composition releases from about 25 % to about 35 % of the orismilast after 30 minutes. In some embodiments the modified release composition releases from about 25 % to about 50% of the orismilast after 30 minutes. In some embodiments the modified release composition releases from about 25 % to about 45 % of the orismilast after 30 minutes. In some embodiments the modified release composition releases from about 24 % to about 36% of the orismilast after 30 minutes. In some embodiments the modified release composition releases from about 11 % to about 65 % of the orismilast after 45 minutes. In some embodiments the modified release composition releases from about 25 % to about 60 % of the orismilast after 45 minutes. In some embodiments the modified release composition releases from about 35 % to about 55% of the orismilast after 45 minutes. In some embodiments the modified release composition releases from about 30 % to about 45 % of the orismilast after 45 minutes. In some embodiments the modified release composition releases from about 30 % to about 46 % of the orismilast after 45 minutes. In some embodiments the modified release composition releases from about 40 % to about 65 % of the orismilast after 60 minutes. In some embodiments the modified release composition releases from about 40 % to about 55 % of the orismilast after 60 minutes. In some embodiments the modified release composition releases more than about 60 % of the orismilast after 60 minutes. In some embodiments the modified release composition releases more than about 40 % of the orismilast after 60 minutes. In some embodiments the modified release composition releases more than about 60 % of the orismilast after 60 minutes. In some embodiments the modified release composition releases from about 35 % to about 65 % of the orismilast after 60 minutes. In

some embodiments the modified release composition releases from about 35 % to about 50 % of the orismilast after 60 minutes. In some embodiments the modified release composition releases from about 40 % to about 50 % of the orismilast after 60 minutes. In some embodiments the modified release composition releases from about 35 % to about 53 % of the orismilast after 60 minutes. In some embodiments the modified release composition releases from about 50 % to about 75% of the orismilast after 90 minutes. In some embodiments the modified release composition releases from about 50 % to about 60 % of the orismilast after 90 minutes. In some embodiments the modified release composition releases from about 44 % to about 66 % of the orismilast after 90 minutes. In some embodiments the modified release composition releases from about 60 % to about 80 % of the orismilast after 120 minutes. In some embodiments the modified release composition releases from about 65 % to about 80 % of the orismilast after 120 minutes. In some embodiments the modified release composition releases from about 60 % to about 70 % of the orismilast after 120 minutes. In some embodiments the modified release composition releases from about 52 % to about 78 % of the orismilast after 120 minutes. In some embodiments the modified release composition releases more than about 70 % of the orismilast after 180 minutes. In some embodiments the modified release composition releases more than about 80 % of the orismilast after 180 minutes. In some embodiments the modified release composition releases from about 66 % to about 100 % of the orismilast after 180 minutes. In some embodiments the modified release composition releases from about 70 % to about 100 % of the orismilast after 180 minutes. In some embodiments the modified release composition releases from about 80 % to about 100 % of the orismilast after 180 minutes. In some embodiments the modified release composition releases from about 85 % to about 100 % of the orismilast after 180 minutes. In some embodiments the modified release composition releases from about 90 % to about 100 % of the orismilast after 180 minutes. In some embodiments the modified release composition releases from about 95 % to about 100 % of the orismilast after 180 minutes.

[00161] In certain embodiments the modified release composition releases from about 11 % to about 65 % of the orismilast after 45 minutes and more than 80% of the orismilast after 180 minutes. In certain embodiments the modified release composition releases from about 25 % to about 65 % of the orismilast after 45 minutes and at least 75 % of the orismilast after 180 minutes. In certain embodiments the modified release composition releases from about 30 % to about 50 % of the orismilast after 45 minutes and at least 75 % of the orismilast after 180 minutes. In some embodiments the modified release composition releases from about 30 % to about 55 % of the orismilast after 45 minutes and at least 80 % of the orismilast after 180 minutes.

[00162] In some embodiments the modified release composition releases from about 30 % to about 46 % of the orismilast after 45 minutes and at least 80 % of the orismilast after 180 minutes. In certain embodiments the modified release composition releases from about 30 % to about 50 % of the orismilast after 45 minutes and about 80 % to about 100 % of the orismilast after 180 minutes. In some embodiments the modified release composition releases from about 30 % to about 55 % of the orismilast after 45 minutes, from about 44 % to about 66 % after 90 minutes and at least 80 % of the orismilast after 180 minutes.

[00163] In some embodiments the modified release composition releases about 50 % of the orismilast between about 60 and 100 minutes. In some embodiments the modified release composition releases about 80 % of the orismilast between about 120 and 180 minutes. In some embodiments the modified release composition releases less than 40 % of the orismilast after 30 minutes; 50 % of the orismilast is released between 60 and 100 minutes; and 80 % of the orismilast is released between 115 and 180 minutes. In some embodiments the modified release composition releases from about 30 % to about 46 % of the orismilast after 45 minutes; about 52% to about 78 % of the orismilast after 120 minutes and at least about 80 % of the orismilast after 180 minutes.

[00164] In any of the embodiments in the four paragraphs above the modified release composition releases, for example, less than 40% of the orismilast after 30 minutes, for example, less than about 30% after 30 minutes. In any of the embodiments in the four paragraphs above the modified release composition releases, for example, less than 20% of the orismilast after 12 minutes.

[00165] In each case in the paragraphs above and as described elsewhere, the release of orismilast refers to the release *in-vitro* as measured using the "Standard Dissolution Assay" defined herein.

[00166] In the paragraph above reference to "release of the orismilast" from a composition refers to the % by weight of the compound of orismilast initially present in the modified release composition that is released into a dissolution medium at the specified time point as measured using the Standard Dissolution Assay. The amount of the orismilast present in the dissolution medium may be determined by reversed phase, isocratic HPLC using a C18 column and UV detection at 272 nm. Suitably the % release values of the compound of orismilast is a mean value obtained by measuring the release profile of more than one sample of the modified release composition, thereby reducing the effects of inter- or intra-batch variability. The mean release % may be obtained by measuring the release from, for example 6, 12 or 24 samples of the modified-release composition.

[00167] The modified release composition may, for example, be any of the modified release compositions described herein which provides a release profile described herein.

[00168] In some embodiments the composition comprising orismilast has an *in-vitro* release profile which is similar to the release profile shown in Figure 3 measured using the Standard
 5 Dissolution Assay. Reference to a “similar” release profile means a release profile that would be considered to be similar from a regulatory perspective, for example as set out in FDA Dissolution Testing of Immediate Release Solid Oral Dosage Forms. Guidance for Industry August 1997, available online:

<https://www.fda.gov/downloads/drugs/guidances/ucm070237.pdf>; or EMA Guideline on the
 10 Investigation of Bioequivalence 2010, available online:
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf.

[00169] Accordingly in some embodiments the composition comprising orismilast has an *in-vitro* release profile that has a similarity factor f_2 of between 50 and 100 compared to the
 15 release profile in Figure 3, wherein:

$$f_2 = 50 \cdot \log \left\{ 100 \cdot \left[1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \right\}$$

wherein R is the one of the reference compositions comprising orismilast in Figure 3, T is the similar composition, n is a number of time points and R_t and T_t are the mean percentages of the released drug from the (R) and (T) products, respectively, at the t time
 20 point, $1 \leq t \leq n$, and the log is $\log_{10}$.

[00170] Suitably the following conditions are applied to the f_2 value in accordance with the FDA guidelines above:

- (1) the dissolution measurements are made under the same conditions for both products;
- (2) a minimum of three-time points (time zero excluded) is considered for both products;
- 25 (3) the time points at which the dissolutions are measured are the same for both products;
- (4) at least 12 individual dosage units are used for both products;
- (5) not more than one mean percentage value is higher than 85% for any of the products;

(6) the coefficient of variation (CV) of either product should be less than 20% at the first (non-zero) time point and less than 10% at the following time points.

[00171] In some embodiments the composition comprising orismilast has an *in-vitro* release profile that has a difference factor f_1 of between 0 and 15 compared to the release profile in figure 3, wherein

$$f_1 = \{ [\sum_{t=1}^n |R_t - T_t|] / [\sum_{t=1}^n R_t] \} \cdot 100$$

[00172] The difference factor is a sum of the absolute values for the differences between the (T) product and (R) products relative to the sum of the mean percentage of the released drug from the (R) product.

[00173] In some embodiments the composition comprising orismilast has an *in-vitro* release profile corresponding to the release profile shown in Table C in Example 1, wherein the % orismilast released at each time point corresponds to $\pm 20\%$ of the value shown in Table C for the 30 mg composition measured using the Standard Dissolution Assay. By way of illustration, at 45 minutes the 30 mg tablet had released 39% of the orismilast at 45 minutes. Accordingly, in this embodiment the composition comprising orismilast releases $\pm 20\%$ of that value at 45 minutes, i.e. from 31.2% to 46.8% of the orismilast is released at 45 minutes. The same $\pm 20\%$ values apply to the other time points shown in Table C.

[00174] In some embodiments the modified release composition comprises orismilast and a pharmaceutically acceptable hydrophilic matrix former (e.g. HPMC). In some embodiments the modified release composition comprises orismilast; a pharmaceutically acceptable hydrophilic matrix former (e.g. HPMC); and a filler (e.g. lactose monohydrate). In some embodiments the modified release composition comprises orismilast; and 15 %w/w to 30 %w/w of a pharmaceutically acceptable hydrophilic matrix former (e.g. HPMC). In some embodiments the modified release composition comprises a compound of the orismilast; and 15 %w/w to 25 %w/w of HPMC.

[00175] In some embodiments the modified release composition comprises orismilast; and 15 %w/w to 20 %w/w of HPMC.

[00176] In some embodiments, the modified release composition comprises a core comprising

- (i) orismilast;
- (ii) one or more of a pharmaceutically acceptable hydrophilic matrix former;

(iii) optionally, one or more pharmaceutically acceptable excipients selected from the group consisting of fillers, glidants and lubricants; and

(iv) optionally a pharmaceutically acceptable coating system on the core.

[00177] In some embodiments the hydrophilic matrix former in the modified release

5 composition comprises hydroxypropyl methylcellulose or hydroxypropylcellulose, or mixtures thereof.

[00178] In some embodiments the one or more pharmaceutically acceptable excipients present in the modified release composition comprises a filler, selected from lactose monohydrate and microcrystalline cellulose, and mixtures thereof. In some embodiments

10 the fillers are present in a concentration from about 30 % to about 78% w/w of lactose monohydrate and from 0 % to about 40 % w/w of microcrystalline cellulose, based on the weight of the core. In some embodiments the filler is lactose monohydrate. In some embodiments the filler is lactose monohydrate and is present in a concentration from about 30 % to about 78 %w/w based on the weight of the core. Thus it may be that the lactose

15 monohydrate is present in a concentration of about 71 % w/w based on the weight of the core. Reference herein to a “% w/w based on the weight of the core” refers to the % by weight of a component of the core prior to the application of a coating system.

[00179] In some embodiments the modified release composition comprises a coating on the core. For example a PVA-based coating system.

20 **[00180]** In some embodiments the modified release composition comprises a core comprising

(i) orismilast;

(ii) a hydrophilic matrix former, wherein the hydrophilic matrix former is present in a concentration of from about 15 %w/w to about 25 %w/w hydroxypropyl methylcellulose

25 based on the weight of the core;

(iii) from about 30 %w/w to about 78 %w/w lactose monohydrate based on the weight of the core; and

(iv) optionally one or more pharmaceutically acceptable excipients selected from the group consisting of glidants and lubricants;

30 optionally wherein the composition further comprises a pharmaceutically acceptable coating system on the core.

[00181] In some embodiments the modified release composition comprises a core comprising orismilast, about 0.5 %w/w colloidal silicon dioxide, about 1.0 %w/w magnesium

stearate based on the weight of the core; and optionally a PVA-based coating system on the core.

[00182] In some embodiments the modified release composition comprises a core comprising orismilast, about 17.5 %w/w HPMC, about 71.0 %w/w lactose monohydrate, about 0.5 %w/w colloidal silicon dioxide, and about 1.0 %w/w magnesium stearate based on the weight of the core; and optionally a PVA-based coating system on the core.

[00183] In some embodiments the orismilast is present in the modified release composition in an amount of from about 1 %w/w to about 40 %w/w. In some embodiments the orismilast is present in the modified release composition in an amount of about 1 %w/w to about 30 %w/w. In some embodiments the orismilast is present in the modified release composition in an amount of from about 1 %w/w to about 20 %w/w. In some embodiments the orismilast is present in the modified release composition in an amount of from about 2 %w/w to about 15% w/w. In some embodiments the orismilast is present in the modified release composition in an amount of from about 2 %w/w to about 5 %w/w. In some embodiments the orismilast is present in the modified release composition in an amount of from about 8 %w/w to about 12 %w/w.

[00184] In some embodiments the orismilast is present in the modified release composition in an amount of from about 5 mg to about 60 mg; about 10 mg to about 50 mg. For example about 10 mg, or about 30 mg.

[00185] In some embodiments, the orismilast is evenly distributed in the pharmaceutical composition,. In some embodiments the orismilast in the pharmaceutical composition is micronized. In some embodiments, the orismilast in the pharmaceutical composition is crystalline. In some embodiments, the orismilast present in the pharmaceutical composition is crystalline and micronized.

[00186] In some embodiments the pharmaceutical composition comprises polymorphic form E of orismilast. In some embodiments, the polymorphic form E of orismilast is micronized. In some embodiments, the polymorphic form E of the orismilast is crystalline and micronized.

[00187] The hydrophilic matrix former may be hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose (HPC), or mixtures thereof. For example, the hydrophilic matrix former could be hydroxypropyl methylcellulose, and mixtures thereof. The hydrophilic matrix former may be present at various concentrations and combinations from about 10 %w/w to about 30 %w/w HPMC. In some embodiments the hydrophilic matrix former is present in an amount of from about 15 %w/w to about 25 %w/w HPMC. In some embodiments the hydrophilic matrix former is present in an amount of from about 15 %w/w to about 20 %w/w

HPMC. In some embodiments the hydrophilic matrix former is present in an amount of 17.5 %w/w HPMC.

[00188] In some embodiments the hydrophilic matrix former in the modified release composition comprises hydroxypropyl methylcellulose (HPMC). In some embodiments the hydrophilic matrix former in the modified release composition consists of HPMC. In some embodiments the HPMC has a viscosity of from 30 to 150 mPa.s. In some embodiments the HPMC has a viscosity of from 35 to 130 mPa.s. In some embodiments the HPMC has a viscosity of from 40 to 60 mPa.s. In some embodiments the HPMC has a viscosity of from 80 to 120 mPa.s. Reference herein to the viscosity of HPMC refers to the viscosity of a 2% (w/w) solution of the HPMC in water at 20°C in accordance with United States Pharmacopoeia (USP XXIII).

[00189] In some embodiments the hydrophilic matrix former in the modified release composition comprises HPMC with a methoxyl substitution of from about 5% to about 35%. In some embodiments the HPMC has a methoxyl substitution of from about 15% to about 30%. In some embodiments the HPMC has a methoxyl substitution of from about 19% to about 24%. In some embodiments the HPMC has a methoxyl substitution of from about 25% to about 35%. In some embodiments the HPMC has a methoxyl substitution of from about 28% to about 30%. In some embodiments the HPMC has a methoxyl substitution of from about 22% to about 24%.

[00190] In some embodiments the hydrophilic matrix former in the modified release composition comprises HPMC with a hydroxypropyl substitution of from about 4% to about 15%. In some embodiments the hydrophilic matrix former in the modified release composition comprises HPMC with a hydroxypropyl substitution of from about 4% to about 12%. In some embodiments the hydrophilic matrix former in the modified release composition comprises HPMC with a hydroxypropyl substitution of from about 7% to about 12%. In some embodiments the hydrophilic matrix former in the modified release composition comprises HPMC with a hydroxypropyl substitution of from about 7.5% to about 9.5%.

[00191] In some embodiments the hydrophilic matrix former in the modified release composition comprises HPMC with a methoxyl substitution of from about 19% to about 24%; and a hydroxypropyl substitution of from about 4% to about 12%.

[00192] In some embodiments the hydrophilic matrix former in the modified release composition comprises HPMC with a methoxyl substitution of from about 19% to about 24%; and a hydroxypropyl substitution of from about 7% to about 12%.

[00193] In some embodiments the hydrophilic matrix former in the modified release composition comprises HPMC with a methoxyl substitution of from about 28% to about 30%; and a hydroxypropyl substitution of from about 7% to about 12%.

[00194] In some embodiments the hydrophilic matrix former in the modified release composition comprises HPMC with a methoxyl substitution of from about 22% to about 24%; and a hydroxypropyl substitution of from about 7.5% to about 9.5%.

[00195] Suitably in any of the six paragraphs above the HPMC has a viscosity of from 80 to 120 mPa.s. Reference herein to the viscosity of HPMC refers to the viscosity of a 2% (w/w) solution of the HPMC in water at 20°C in accordance with United States Pharmacopoeia (USP XXIII).

[00196] In some embodiments the hydroxypropyl methylcellulose is Hypromellose 2910, Hypromellose 2208, Methocel K100 or mixtures thereof.

[00197] Suitably the hydrophilic matrix former is present in a concentration from about 10 %w/w to about 30 %w/w hydroxypropyl methylcellulose based on the weight of the core.

Thus it may be that the hydrophilic matrix former is present in a concentration from about 15 %w/w to about 25 %w/w hydroxypropyl methylcellulose based on the weight of the core. For example, wherein the hydrophilic matrix former is present in a concentration of 17.5 %w/w hydroxypropyl methylcellulose based on the weight of the core. The hydroxypropyl methylcellulose may be, for example, any of the grades of hydroxypropyl methylcellulose disclosed herein (e.g. Hypromellose 2910, Hypromellose 2208, Methocel K100 or mixtures thereof).

[00198] In some embodiments the modified release composition comprises one or more fillers and/or binders. The term "filler" as used herein may also function as a binder. The filler or binder may be selected from lactose monohydrate, lactose hydrous or anhydrous, microcrystalline cellulose, mannitol, isomalt, and mixtures thereof. For example, the filler could be lactose monohydrate. The filler may be present at various concentrations from about 30 %w/w to about 78 %w/w. For example, the filler may comprise about from about 30 %w/w to about 78 %w/w of lactose monohydrate and from about 0 to about 40 %w/w of microcrystalline cellulose. For example, the filler could be lactose monohydrate in an amount of about 71 %w/w.

[00199] In some embodiment the modified release composition (e.g. modified release tablet composition) comprises one or more glidants. The term "glidant" as used herein includes colloidal silicon dioxide, talc, etc. For example, the glidant could be colloidal silicon dioxide. The glidant may be present at various concentrations from about 0.1 %w/w to about 2 %w/w, for example from about 0.2 %w/w to about 1 %w/w, e.g. about 0.5 %w/w.

[00200] In some embodiment the modified release composition (e.g. modified release tablet composition) further comprises one or more lubricants. The term "lubricant" as used herein includes magnesium stearate, sodium stearyl fumarate, talc, etc. For example, the lubricant may be magnesium stearate. The lubricant may be present at various concentrations from about 0.1 %w/w to about 2 %w/w, for example from about 0.5 %w/w to about 1.5 %w/w, e.g. about 1.0 %w/w.

[00201] The %w/w of the components comprising the modified release compositions (e.g. modified release tablet compositions, (e.g. those comprising the orismilast, the hydrophilic matrix former, the filler, glidant and/or lubricant)) refer to the %w/w prior to adding the optional coating to the composition (e.g. onto the core comprising orismilast and the other excipients). Thus as will be realised by the skilled person, in those embodiments where the modified release compositions (e.g. tablets) are coated, the %w/w of each component in the coated composition based on the total weight of the coated composition will be lower than the %w/w based on the uncoated composition due to the additional weight of the coating.

[00202] In some embodiments the modified release composition comprises a film coating on the cores. A suitable coating may be a PVA-based coating system. The term "coating system", as used herein includes HPMC-based coating systems, PVA-based coating systems (polyvinyl alcohol), PVA-PEG based coating systems (polyethylene glycol) or ethylcellulose based functional barrier membrane coating systems. For example, the coating system could be the PVA-based coating system. For example, the coating system could be Opadry ® II. For example the coating system could be present in an amount from about 3% to about 5 % weight gain of the core composition, for example a 4 % weight gain of the core.

[00203] In some embodiments the composition comprising orismilast is a core composition comprising Core 1, Core 2 or Core 3 selected from Table A or Core 4, Core 5 or Core 6 selected from Table B:

Table A

Component	% w/w of the core		
	Core 1	Core 2	Core 3
orismilast	2.5-4.5%	5.5-7.7%	9-11%
Lactose monohydrate	70-85%	69-80%	66-76%
HPMC	12-23%	12-23%	12-23%
Anhydrous colloidal silica	0.01-1.5%	0.01-1.5%	0.01-1.5%
Magnesium stearate	0.01-2.0%	0.01-2.0%	0.01-2.0%

wherein the core is coated with a water-soluble film coating in an amount to provide about 3% to 5% weight gain of the core.

Table B

Component	Amount		
	Core 4	Core 5	Core 6
orismilast	10 mg	20 mg	30 mg
Lactose monohydrate	233 mg	223 mg	213 mg
HPMC	52.5 mg	52.5 mg	52.5 mg
Anhydrous colloidal silica	1.5 mg	1.5 mg	1.5 mg
Magnesium stearate	3.0 mg	3.0 mg	3.0 mg
Core weight	300 mg	300 mg	300 mg
Water-soluble film coating	12 mg	12 mg	12 mg
Coated core weight	312 mg	312 mg	312 mg

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[00204] Suitably the film coating on the cores in Table A and Table B is a PVA-based coating. Preferably the film coating comprises polyvinyl alcohol (Ph. Eur. 1961), macrogol (Ph. Eur. 1444), titanium dioxide (Ph. Eur. 0150), talc (Ph. Eur. 0438) and optionally a colorant. For example the film coating may be Opadry® II.

10 **[00205]** Suitably the lactose monohydrate in the compositions described herein, including those in Tables A and B complies with European Pharmacopeia (Ph. Eur.) 0187. Suitably the anhydrous colloidal silica in the compositions described herein, including those in Tables A and B complies with Ph. Eur. 0434. Suitably the magnesium stearate in the compositions described herein, including those in Tables A and B complies with Ph. Eur. 0229. Suitably
15 the hydroxymethyl cellulose (HPMC, Hypromellose) in the compositions described herein, including those in Tables A and B complies with Ph. Eur. 0348.

[00206] Suitably the HPMC in Tables A and B comprises HPMC with a methoxyl substitution of from about 22% to about 24%; and a hydroxypropyl substitution of from about 7.5% to about 9.5%. Suitably the HPMC has a viscosity of from 80 to 120 mPa.s. Reference
20 herein to the viscosity of HPMC refers to the viscosity of a 2% (w/w) solution of the HPMC in

water at 20°C in accordance with United States Pharmacopoeia (USP XXIII). For example the HPMC is Methocel™ K100 or mixtures thereof

[00207] The modified release compositions comprising a hydrophilic matrix such as HPMC described herein, including the compositions in Table A and Table B may be prepared may be prepared using well-known methods. For example by blending and sieving steps of the orismilast and excipients followed by direct compression, or roller compaction followed by compression. The water-soluble coating is then applied to the cores using, for example, a spray coater.

[00208] In preferred embodiments the modified release composition comprising orismilast described herein is a modified release tablet comprising orismilast.

[00209] In some embodiments, the particle size distribution of the orismilast present in the pharmaceutical composition (e.g. tablet composition) may be $D(50) \leq 25 \mu\text{m}$, for example $D(50) \leq 20 \mu\text{m}$, $D(50) \leq 10 \mu\text{m}$, $D(50) \leq 5 \mu\text{m}$, $D(50) \leq 3 \mu\text{m}$ and/or $D(90) \leq 10 \mu\text{m}$. For example in the compositions in Table A and Table B the orismilast particle size distribution may be $D(9) \leq 10 \mu\text{m}$ and a $D(50) < 1$ to $6 \mu\text{m}$.

[00210] In some embodiments the pharmaceutical composition comprising orismilast is formulated as a unit dosage form, for example a tablet or capsule. The amount of orismilast in each unit dosage (e.g. tablet) may range from about 1 mg to about 40 mg, from about 5 mg to about 35 mg, from 5 mg to 30 mg, from 10 mg to 30 mg, or from 10 to 20 mg. In some embodiments, the amount of orismilast in each unit dosage form (e.g. tablet) may be from about 10 to about 30 mg. In some embodiments, the amount of orismilast in each unit dosage form (e.g. tablet) is 1 mg, 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg or 40 mg. In some embodiments, the amount of orismilast in each unit dosage form (e.g. tablet) is 10 mg. In some embodiments, the amount of orismilast in each unit dosage form (e.g. tablet) is 20 mg. In some embodiments, the amount of orismilast in each unit dosage form (e.g. tablet) is 30 mg. In some embodiments, the amount of orismilast in each unit dosage form (e.g. tablet) is 40 mg.

[00211] In some embodiments, orismilast is comprised within a granulated blend composition. A granulated blend composition may comprise:

- orismilast; and
- one or more of a pharmaceutically acceptable hydrophilic matrix former;
- one or more pharmaceutically acceptable excipients selected from the group consisting of fillers, binders, glidants and lubricants; and
- a hard capsule shell material.

[00212] The hydrophilic matrix former could be hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose (HPC), or mixtures thereof. The hydrophilic matrix former could be present at various concentrations and combinations from about 10 %w/w to about 20 %w/w HPMC.

5 [00213] The fillers/binders could be selected from lactose monohydrate, lactose hydrous or microcrystalline cellulose, and mixtures thereof. The fillers/binders could be present at various concentrations from about 20 %w/w to about 75 %w/w of lactose monohydrate and from 0 to about 50%w/w of microcrystalline cellulose. The glidant could be colloidal silicon dioxide, which could be present at various concentrations from about 0.1 %w/w to about 2
10 %w/w.

[00214] The lubricant could be magnesium stearate, which could be present at various concentrations from about 0.1 %w/w to about 2 %w/w.

[00215] In some embodiments the orismilast is present in the granulated blend composition in an amount of from about 1 %w/w to about 40 %w/w, for example about 1 %w/w to about
15 30 %w/w, from about 1 %w/w to about 20 %w/w, or from about 2 %w/w to about 15% w/w.

[00216] The blend composition could be dispensed in a hard capsule. Capsule shell material for hard capsules could be made of several materials such as gelatin (pig, bovine, fish etc), hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol, starch and pullulan could be applied.

20 [00217] In some embodiments the granulated blend composition is formulated as a unit dosage form (e.g. a capsule composition). The amount of orismilast in each unit dose form may range from about 1 mg to about 40 mg, or from about 5 mg to about 30 mg. The amount of the compound may for example range from 10 mg to 30mg. In some
25 embodiments, the amount of the compound in unit dosage form comprising the granulated blend composition may be from about 10 mg to about 30 mg. In some embodiments, the amount of orismilast in each unit dosage form is 1 mg, 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg or 40 mg.

[00218] The granulated blend composition can be prepared using known could consist of blending and sieving steps of the drug substance and excipients followed by granulation,
30 e.g. roller compaction, and encapsulation.

Formulations for parenteral administration

[00219] Formulations of the present invention comprising a PDE4 inhibitor (e.g. orismilast) and/or a GLP1 receptor agonist suitable for parenteral (e.g. intravenous, intramuscular or subcutaneous) administration may be in the form of granules, powder or a concentrated

liquid (e.g. a solution or suspension) which can be reconstituted or diluted prior to use by the addition of a liquid, such as an aqueous liquid (e.g. water or saline) to form an essentially clear, stable liquid comprising the formulation dissolved in solution. The reconstituted or diluted solution also forms part of the present invention. In some embodiments, a GLP1
5 receptor agonist (e.g. semaglutide) may be formulated for parenteral (e.g. subcutaneous) administration, for example in solution.

Products and kits

[00220] The invention further provides a product comprising a PDE4 inhibitor and a GLP1 receptor agonist for simultaneous, separate or sequential use in the treatment or prevention
10 of the diseases or disorders described herein.

[00221] In some embodiments, the PDE4 inhibitor and the GLP1 receptor agonist are provided separately. For example, the product may comprise one or more containers comprising the PDE4 inhibitor, and one or more further containers comprising the GLP1 receptor agonist.

15 [00222] In some embodiments, the PDE4 inhibitor and the GLP1 receptor agonist are provided in a single composition or formulation. For example, the product may comprise tablets, granules, powder, liquid (e.g. a solution, suspension or gel) comprising both the PDE4 inhibitor and the GLP1 receptor agonist.

[00223] Thus, the invention provides a combination comprising a PDE4 inhibitor and a
20 GLP1 receptor agonist. The combination may be comprised within a pharmaceutical composition. Also provided is a kit comprising the combination or the pharmaceutical composition, and instructions for use.

Treatment

[00224] The glucagon-like peptide 1 receptor (GLP-1R) is a class B G protein-coupled
25 receptor which mediates the effects of GLP-1, an incretin hormone. GLP-1R exerts metabolic effects including the release of insulin and suppression of appetite. GLP-1R-stimulated pathways in pancreatic beta cells act to increase cAMP levels. A rapid increase in cAMP is accompanied by activation of exchange protein activated by cAMP-2 (Epac2) and protein kinase A (PKA), which have a range of effects including potentiation of insulin
30 secretion, reduced glucagon secretion, and weight loss via satiety induction that results in increased insulin sensitivity. GLP-1R agonists work to stimulate insulin secretion in a glucose-dependent manner, carrying a low risk of hypoglycaemia, and have therefore emerged as a safe and effective treatments for diabetes (Marzook et al., Front. Endocrinol., 2021, Sec. Gut Endocrinology, Volume 12).

[00225] Insulin resistance in the liver and adipose tissue has been regarded as a crucial driver of NASH morbidity and mortality. Since GLP-1 analogues have been shown to improve glycaemic control, lower weight and activate liver enzymes in diabetes patients, GLP1 receptor agonists may also be effective in the treatment of other metabolic diseases such as obesity, NAFLD and NASH (Li et al., Front Endocrinol, 2021; 12: 721198).

[00226] GLP-1 not only regulates blood glucose levels, but is also closely associated with various pathophysiological processes, such as inflammation. GLP1 receptor agonists, such as liraglutide, show beneficial effects on inflammation-related diseases (Que et al., Journal of Inflammation volume 16, Article number: 13 (2019)). Consistent evidence from in vitro studies and preclinical models has suggested that GLP1 receptor agonists have anti-inflammatory properties and may modulate the immune-system. For example, it has been demonstrated that administration of GLP1 receptor agonists to animals and humans with diabetes or obesity is associated with a reduction in local or systemic inflammation, independently of changes in glycaemic state and body weight (Bendotti et al., Pharmacological Research, Volume 182, August 2022, 106320). In patients with inflammatory bowel disease (IBD) and type 2 diabetes, a lower risk of adverse clinical events has been observed amongst patients treated with GLP-1 based therapies compared with treatment with other antidiabetics. These findings suggest that treatment with GLP-1 based therapies may improve the disease course of IBD (Villumsen et al., EClinicalMedicine 37 (2021) 100979).

[00227] GLP1 receptor agonists are also reported to have broader pharmacological effects including neuro-protection, and reduced lipotoxicity. An overview of the roles of GLP-1 and GLP1 receptor agonists in a range of diseases including autoimmune disease, cardiovascular disease (CVD), diabetic kidney disease (DKD), diabetic foot ulcer (DFU) and Alzheimer's disease (AD) is provided by Shao et al., Pharmacology and Therapeutics, Volume 239, November 2022, 108270.

[00228] Recent studies have shown that insulin resistance (IR) occurs in the brain of Alzheimer's Disease (AD) patients with significantly decreased expression of the insulin receptor, concomitant with the disease progression, indicating that the defects in insulin signalling are associated with AD pathogenesis. Evidence has also shown that AD is impacted by GLP-1 analogues through mechanisms including insulin resistance, inflammatory cytokines and oxidative stress. Studies have further suggested that most GLP-1 analogues can cross the blood-brain barrier and exert physiological influences directly on the human brain. GLP-1 analogues may also modulate the neuronal and immune systems via systemic effects. In addition, mice overexpressing GLP-1R in the hippocampus have shown an increase in neurite growth and improvement in spatial learning abilities (Li et al.,

Front Endocrinol, 2021; 12: 721198). It has been suggested that the anti-inflammatory and neuroprotection effects of GLP-1 might be exerted through inhibiting NF- κ B and MAPKs signalling pathways (Chen et al., Appl Microbiol Biotechnol (2018) 102:7565–75.) GLP1 receptor agonists may therefore be effective in the treatment of inflammatory and neurodegenerative conditions, such as AD.

[00229] Clinical data has also indicated that GLP1 receptor agonists reduce blood pressure in diabetic patients (Holman et al., N Engl J Med (2017) 377:1228–39), indicating their utility in the treatment of cardiovascular diseases.

[00230] Emerging data has also proposed GLP1 receptor agonists as potential treatments for intestinal diseases, including inflammatory bowel diseases, short-bowel syndrome, intestinal toxicities and coeliac disease. Possible beneficial mechanisms for these diseases include the influence of GLP1 on gastric emptying, its anti-inflammatory properties and its intestinotrophic effect (Hunt et al., Biomedicines 2021, 9(4), 383).

[00231] There is also increasing evidence that GLP1 receptor agonists have beneficial skeletal effects, including bone quality and strength (Mabilleau et al., Journal of Endocrinology, vol. 236, issue 1).

[00232] Recent evidence suggests that PDE4 plays an essential role in glucose and fat metabolism. The cAMP-degrading phosphodiesterase 4 (PDE4) enzyme, in particular PDE4D, has been implicated in the regulation of glucagon-like peptide-1 (GLP-1), an incretin hormone with glucose-lowering properties. The PDE4 inhibitor Rolipram was found to enhance glucose-induced GLP-1 release from GLUTag cells (Ong et al., Br J Pharmacol. 2009 Jun; 157(4): 633–644). It was also observed that the PDE4 inhibitor Roflumilast elevates GLP-1 levels and prevented disease progression in diabetic mice (Vollert et al. Diabetologia, 2012, 55:2779-2788). It has further been shown that roflumilast improves glucose homoeostasis in treatment-naïve type 2 diabetes patients (Wouters et al., The Journal of Clinical Endocrinology & Metabolism, Volume 97, Issue 9, 1 September 2012, Pages E1720–E1725). More recently it has been found that apremilast improves insulin resistance in psoriasis patients (Morita et al., J Dermatol. 2022 Apr; 49(4): e125–e126).

[00233] Without being bound by theory, it is believed that PDE4 inhibition may potentiate the effects of GLP-1 receptor stimulation by further increasing cAMP levels ultimately leading to an increased insulin secretion and improved glycaemic control. The PDE4 inhibitor orismilast may be particularly effective at potentiating the effects of GLP-1R agonism due to its high potency and selectivity for PDE4B/D isoforms (Silverberg et al., Journal of the European Academy of Dermatology and Venereology, 2023; 37:721-729).

[00234] Administration of a PDE4 inhibitor, or a pharmaceutically acceptable salt, solvate or hydrate thereof, and a GLP1 receptor agonist, is therefore expected to be beneficial in a wide range of diseases and disorders, including inflammatory diseases, autoimmune diseases, fibrosis, neurodegenerative diseases, musculoskeletal disorders, metabolic diseases or disorders, alcoholic liver disease (ALD), cardiovascular disease and a gastrointestinal disorders.

[00235] In some embodiment the disease or disorder is a metabolic disease or disorder, for example excessive weight, obesity and related diseases and disorders, all forms of diabetes (including hyperglycaemia, type 1 diabetes, type 2 diabetes, pre-diabetes, gestational diabetes, MODY (maturity onset diabetes of the young), latent autoimmune diabetes impaired glucose tolerance, diabetes-associated disorders (including diabetes-associated cardiac dysfunction and neuropathy, including peripheral neuropathy, nephropathy, or retinopathy), metabolic syndrome, non-alcoholic steatohepatitis (NASH) or non-alcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated steatotic liver disease (MASLD) or metabolic dysfunction-associated steatohepatitis (MASH).

[00236] In some embodiments the disease or disorder is an inflammatory disease, for example an inflammatory pulmonary, dermatological or neurological disease or inflammatory myopathy.

[00237] In some embodiments the inflammatory disease is asthma, allergy, allergic rhinitis, allergic airway inflammation, atopic dermatitis (AD), chronic obstructive pulmonary disease (COPD), respiratory syncytial virus (RSV) infection, inflammatory bowel disease, multiple sclerosis, arthritis, psoriasis, eosinophilic esophagitis, eosinophilic pneumonia, eosinophilic psoriasis, hypereosinophilic syndrome, graft-versus-host disease, uveitis, cardiovascular disease, pain, multiple sclerosis, lupus, vasculitis, chronic idiopathic urticaria and Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss Syndrome), or polymyositis.

[00238] In some embodiments, the disease or disorder is a musculoskeletal disorder, such as muscle atrophy, muscular dystrophy (e.g. Duchenne muscular dystrophy), sarcopenia, or sporadic inclusion body myositis. In such embodiments, the administration of the PDE4 inhibitor and the GLP1 receptor agonist may result in one or more of: a slowing of disease progression, improved motor control and/or sensory function, greater ease of movement, and prevention of or a reduction in the rate of muscle atrophy.

[00239] In some embodiments the disease or disorder is fibrosis, such as hepatic fibrosis, renal fibrosis, biliary fibrosis, pancreatic fibrosis, or idiopathic pulmonary fibrosis. In such embodiments, the administration of the PDE4 inhibitor and the GLP1 receptor agonist may

result in one or more of: a reduction in/reversal of fibrosis, a reduction in or prevention of the progression of fibrosis, and improved organ (liver, kidney, pancreas and/or lung) function.

[00240] In some embodiments the disease or disorder is an autoimmune disease, such as multiple sclerosis, immune rejection, graft versus host disease, uveitis, optic neuropathies, optic neuritis, transverse myelitis, inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, myasthenia gravis, Graves disease, ulcerative colitis, Crohn's disease, primary sclerosing cholangitis or primary biliary cholangitis.

[00241] In some embodiments wherein the disease or disorder is an autoimmune disease, the administration of the PDE4 inhibitor and the GLP1 receptor agonist may result in one or more of: a reduction in pain, a reduction in inflammation, improved liver function, improved vision, a reduction in or prevention of immune rejection, a slowing or prevention of disease progression, and improved motor control and/or sensory function.

[00242] In some embodiments the disease or disorder is a neurodegenerative disease, such as dementia, Alzheimer's disease, amyotrophic lateral sclerosis, Huntingdon's disease, neurodegeneration or Parkinson's disease.

[00243] In some embodiments wherein the disease or disorder is a neurodegenerative disease, the treatment with the PDE4 inhibitor and the GLP1 receptor agonist results in one or more of an improvement in, or a prevention or reduction in the loss of: cognitive function, memory, speech, comprehension, motor control.

[00244] In some embodiments the disease or disorder is a gastrointestinal disorder, such as short bowel syndrome, inflammatory bowel disease (IBD), coeliac disease or intestinal toxicity. In such embodiments, the treatment with the PDE4 inhibitor and the GLP1 receptor agonist may result in one or more of: improved nutrition, a reduction or elimination of diarrhoea, constipation, nausea and/or vomiting, weight gain, and increased energy levels.

[00245] In some embodiments the disease or disorder is alcoholic liver disease (ALD). ALD is a term used to describe a range of conditions of the liver resulting from overconsumption of alcohol, including fatty liver disease (steatosis), alcoholic hepatitis, inflammation of the liver, and liver fibrosis or cirrhosis. In such embodiments, the treatment with the PDE4 inhibitor and the GLP1 receptor agonist results in one or more of: a reduction in liver fat levels, improved liver function, a change (e.g. an increase) in serum albumin, reduced inflammation of the liver, and the prevention of, reduction in or reversal of fibrosis.

[00246] In some embodiments, administration of PDE4 inhibitor, or a pharmaceutically acceptable salt, solvate or hydrate thereof, and a GLP1 receptor agonist may be used to treat or prevent diseases or disorders ameliorated by elevated cAMP levels.

Obesity

5 [00247] In some embodiments, the PDE4 inhibitor, or a pharmaceutically acceptable salt, solvate or hydrate thereof, and the GLP1 receptor agonist, may be used to treat or prevent obesity, or diseases or disorders associated therewith. Diseases or disorders associated with obesity include type 2 diabetes, coronary heart disease, certain cancers (e.g. breast cancer, colorectal cancer), stroke, high blood pressure, high blood cholesterol, high blood
10 low-density lipoprotein (LDL) cholesterol, high blood triglycerides, dyslipidemia, gallbladder disease and gallstones, NAFLD (non-alcoholic fatty liver disease) and NASH (non-alcoholic steatohepatitis), metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH), osteoarthritis, gout, breathing problems such as sleep apnea and asthma, insulin resistance and diabetes mellitus.

15 [00248] Obesity is defined as abnormal or excessive fat accumulation that presents a risk to health. For many adult humans, a body mass index (BMI) of 25 to 29.9 is considered to be overweight, a BMI of 30 to 39.9 is considered obese, and a BMI of 40 or more is considered severely obese. However, it has been observed that ethnic differences affect how much extra weight different people can carry before it affects their health. For example, people of
20 Asian descent are more likely to have health risks at a lower BMI.

[00249] Thus, in some embodiments, the subject has a BMI of 27.5 or more, a BMI of 30 or more, a BMI of 35 or more, or BMI of 40 or more, prior to treatment.

[00250] In some embodiments, the subject has a BMI of at least 27 and one or more of: diabetes, high blood pressure, obstructive sleep apnea, abnormal levels of fats in the blood,
25 or a history of heart attack, stroke or blood vessel disorders.

[00251] In some embodiments, the subject has a weight of at least 90 kg, at least 100 kg, at least 110 kg, at least 120 kg, at least 130 kg, at least 140 kg or at least 150 kg.

[00252] In some embodiment, the subject has a waist circumference of at least 70 cm, at least 75 cm, at least 80 cm, at least 85 cm or at least 90 cm for women or at 90 cm, at least
30 94 cm, at least 96 cm, or at least 100 cm for men.

[00253] In some embodiments, the administration of the PDE4 inhibitor and the GLP1 receptor agonist results in a reduction in one or more of: (i) body weight; (ii) body fat mass; (iii) BMI; (iv) appetite or food intake (v) fasting blood levels of glucose; (vi) fasting blood levels of insulin; (vii) insulin resistance; (viii) fasting blood levels of triglycerides (ix) fasting

blood levels of cholesterol; (x) fasting blood levels of low-density lipoprotein (LDL) cholesterol; (xi) waist circumference; (xii) cholesterol ratio; (xiii) level of one or more inflammation biomarkers (such as those described herein) in a suitable sample taken from the subject.

5 **[00254]** In some embodiments the administration of the PDE4 inhibitor and the GLP1 receptor agonist results in a reduction in body weight of the subject. The treatment may result in a reduction in body weight of at least 0.5%, at least 1%, at least 1.5%, at least 2%, at least 2.5%, at least 3%, at least 3.5%, at least 4%, at least 4.5%, at least 5%, at least 5.5%, at least 6%, at least 6.5%, at least 7%, at least 7.5%, at least 7.5%, at least 8%, at
10 least 8.5%, at least 9%, at least 9.5%, at least 10%, at least 12 %, at least 15%, at least 18%, at least 20%, at least 22%, at least 25%, or at least 30%. In some embodiments, treatment may result in a reduction in body weight of no more than 50%, no more than 40%, no more than 30%, no more than 25%, no more than 20%, no more than 15% or no more than 10%. In some embodiments the treatment may result in a reduction in body weight of
15 more than 1%, 2%, more than 5%, more than 7%, more than 10% or more than 15%. In some embodiments, treatment results in a reduction in body weight of at least 5%, at least 10% or at least 15%, suitably at least 5%.

[00255] In some embodiments the treatment results in an average (i.e. mean) reduction in body weight of a subject of at least 0.1% per week over the treatment period. In some
20 embodiments, the treatment results in an average reduction in body weight of at least 0.15%, at least 0.2%, at least 0.25%, at least 0.3%, at least 0.35%, at least 0.4%, at least 0.45% or at least 0.5% per week over the treatment period. It will be appreciated that the rate of weight loss over the treatment period may be non-linear.

[00256] In some embodiments, the subject has a BMI of 30 or more, prior to treatment. In
25 such embodiments, the treatment may result in a reduction in body weight of at least 5%, at least 8%, or at least 10%. It may be that treatment is discontinued if the weight loss of the subject is at least 5%, or at least 10%.

[00257] In some embodiments, the administration of the PDE4 inhibitor and the GLP1 receptor agonist results in a reduction in waist circumference of the subject. The reduction
30 may be at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 12%, at least 15%, or at least 20%, over a treatment period.

[00258] In some embodiments, the subject is receiving concomitant treatment with at least one additional therapeutic agent for metabolic syndrome, obesity, dyslipidemia, diabetes
35 and/or hypertension. It may be that there is a change in the concomitant treatment as a

result of the treatment with inhibitor and the GLP1 receptor agonist. For example, the treatment with the at least one additional therapeutic agent may be reduced (in terms of dosage and/or frequency) or terminated.

[00259] In some embodiments, the treatment results in a reduction in the cholesterol ratio.

5 Total cholesterol comprises three types of cholesterol: High-density lipoprotein (HDL); low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL). The subject's cholesterol ratio can be calculated by dividing the total cholesterol level by the HDL level. A healthy cholesterol ratio is considered to be 5 or below.

[00260] In some embodiments, the subject has a baseline cholesterol ratio of more than 5,

10 more than 6 or more than 7. In some embodiments, the administration of the PDE4 inhibitor and the GLP1 receptor agonist results in a reduction in the cholesterol ratio of the subject to 5 or less.

[00261] In some embodiments, treatment results in a reduction in the level of one or more inflammation biomarkers in a suitable sample taken from the subject. For example, a

15 sample may be a plasma, serum or faecal sample. Suitably a serum sample may be used. In some embodiments the inflammation biomarkers are selected from C-reactive protein (CRP) (e.g. high sensitivity CRP, hs-CRP), IL-6, TNF- α , and resistin, for example from C-reactive protein (CRP) (e.g. high sensitivity CRP, hs-CRP), IL-6 and TNF- α . In certain embodiments treatment results in reduction in the level of one or more of C-reactive protein
20 (CRP) (e.g. high sensitivity CRP, hs-CRP), IL-6 and TNF- α .

[00262] Elevated serum levels of inflammation markers, such as C-reactive protein (CRP)

(e.g. high sensitivity CRP, hs-CRP), IL-6, TNF- α , and resistin are commonly found in patients with obesity. Thus, in some embodiments, the subject has an elevated serum level of C-reactive protein (CRP), IL-6, TNF- α , and/or resistin. The treatment with the PDE4

25 inhibitor and the GLP1 receptor agonist may result in a reduction in the serum level of CRP, IL-6, TNF- α , and/or resistin.

[00263] In some embodiments, levels of one or more inflammation markers such as those described herein are reduced by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% from baseline. For example, levels may be reduced by 5, 6, 7, 8, 9, 10, 11, 12, 13,

30 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49 or 50% or more.

Diabetes

[00264] In some embodiments the PDE4 inhibitor, or a pharmaceutically acceptable salt, solvate or hydrate thereof, and the GLP1 receptor agonist, may be used to treat or prevent

diabetes, or diseases or disorders associated therewith. Diabetes includes hyperglycaemia, type 1 diabetes, type 2 diabetes, pre-diabetes, gestational diabetes, MODY (maturity onset diabetes of the young) and impaired glucose tolerance. Diabetes-associated disorders include diabetes associated cardiac dysfunction and neuropathy, including peripheral neuropathy; nephropathy; or retinopathy or pre-diabetes. In some embodiments, the diabetes is Type I diabetes, Type 2 diabetes, or pre-diabetes.

[00265] A fasting glucose test (FGT) can be used to help diagnose diabetes or pre-diabetes. Fasting plasma glucose (FPG) levels are determined by taking a blood sample from participants who have fasted for at least 8 hours. The World Health Organisations defines the following fasting glucose test results:

Normal: from 3.9 mmol/l to 5.6 mmol/l (from 70 mg/dl to 100 mg/dl)

Impaired fasting glucose (a form of pre-diabetes): from 5.6 to 6.9 mmol/l (from 100 mg/dl to 125 mg/dl)

Diabetic: 7.0 mmol/l and above (126 mg/dl and above) on two separate tests.

In some embodiments, the subject has a baseline FPG level (i.e. prior to treatment) of at least 5.6 mmol/l, at least 6.0 mmol/l, at least 6.5 mmol/l, or at least 7.0 mmol/l. The treatment with the PDE4 inhibitor and the GLP1 receptor agonist may result in a reduction in the level of FPG, e.g. to below 7.0 mmol/l or to below 5.6 mmol/l.

[00266] Diabetes may also be diagnosed if a subject has: (1) symptoms (e.g. polyuria, polydipsia and unexplained weight loss for Type 1) plus:

a random venous plasma glucose concentration of ≥ 11.1 mmol/l or

a fasting plasma glucose concentration of ≥ 7.0 mmol/l (whole blood ≥ 6.1 mmol/l) or

two hour plasma glucose concentration of ≥ 11.1 mmol/l two hours after 75g anhydrous glucose in an oral glucose tolerance test (OGTT).

[00267] Haemoglobin A1c (HbA1c) testing may also be used to help diagnose diabetes. The HbA1c diagnostic threshold for diabetes is ≥ 48 mmol/L ($\geq 6.5\%$). A normal HbA1c level is considered to be below 39 mmol/L (below 5.7%). HbA1c testing is not recommended for diagnosis of diabetes in all cases (e.g. in children and patients suspected of having Type I diabetes).

[00268] In some embodiments, the treatment with the PDE4 inhibitor and the GLP1 receptor agonist results in a reduction in the level of HbA1c.

[00269] In some embodiments, the subject has a baseline HbA1c level (i.e. prior to treatment) of from 39 to 47 mmol/L (from 5.7% to 6.4%). It may be that the treatment results in a reduction in the HbA1c level to below 39 mmol/L (below 5.7%), i.e. normoglycaemia.

[00270] In some embodiments, the subject has a baseline HbA1c level (i.e. prior to treatment) of from 48 to 53 mmol/L (from 6.5% to 7%). It may be that the treatment results in a reduction in the HbA1c level to below 48 mmol/L (below 6.5%).

[00271] In some embodiments, the subject has a baseline HbA1c level (i.e. prior to treatment) of above 53 mmol/L (above 7%). It may be that the treatment results in a reduction in the HbA1c level to 53 mmol/L or below (7% or below).

[00272] In some embodiments, the treatment with the PDE4 inhibitor and the GLP1 receptor agonist results in one or more of: improved glycaemic control; a reduction in fasting plasma glucose (FPG); a reduction in 2-hour post-load plasma glucose; an increase in insulin sensitivity, a reduction in appetite; a reduction in a level of HbA1c; a reduction in insulin resistance; improved beta-cell function, decreased beta-cell apoptosis, increased beta-cell mass and/or improved glucose sensitivity to beta-cells.

[00273] Time in Range (TIR) is a metric of glycaemic control, which can be measured by a continuous glucose monitoring (CGM) device. Improved glycaemic control may therefore be expressed as an increase in the time per day within a target glucose range. TIR may be expressed as a percentage, as the number of hours and minutes per day, or both. For example, the target range may be 3.9-10.0 mmol/L. For subjects with type I or Type II diabetes, a target time in range may be more than 70%, or more than 16 hours, 48 minutes.

[00274] Thus, in some embodiment, treatment with the PDE4 inhibitor and the GLP1 receptor agonist results in an increase in TIR. It may be that, prior to treatment, the TIR of the subject is 70% or below (or 16 hours, 48 minutes or below). As a result of the treatment, the TIR may be above 70%, or above 16 hours, 48 minutes. In some embodiments, the TIR is increased by at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 8% or at least 10%.

Metabolic syndrome

[00275] In some embodiments the disease or disorder is metabolic syndrome. "Metabolic syndrome" is a term used to describe a cluster of common abnormalities which may include insulin resistance, impaired glucose tolerance, abdominal obesity, reduced high-density lipoprotein (HDL)-cholesterol levels, elevated triglycerides, and hypertension. There are various different definitions of metabolic syndrome.

[00276] In some embodiments, metabolic syndrome is diagnosed in a subject who has a combination of diabetes, hypertension and obesity. Hypertension is defined as blood pressure that is at least 140/90 mm Hg. It may be that treatment with the PDE4 inhibitor and the GLP1 receptor agonist results in a reduction to blood pressure to below 140/90 mm Hg, or below 130/85 mmHg.

[00277] In some embodiments, metabolic syndrome is diagnosed in a subject if three or more of the following five criteria are met: waist circumference over 40 inches (102 cm) (men) or 35 inches (89 cm) (women); blood pressure over 130/85 mmHg; fasting triglyceride (TG) level over 150 mg/dl or 1.7 mmol/L; fasting high-density lipoprotein (HDL) cholesterol level less than 40 mg/dl (1.04 mmol/L) (men) or 50 mg/dl (1.3 mmol/L)(women); and fasting blood glucose over 100 mg/dl (5.6 mmol/L). It may be that treatment results in 2, 1 or none of these criteria being met.

[00278] In some embodiments, the treatment with the PDE4 inhibitor and the GLP1 receptor agonist results in one or more of: improved glycaemic control (e.g. increased time within normal levels (Time in Range (TIR))); a reduction in fasting plasma glucose (FPG); a reduction in 2-hour post-load plasma glucose; an increase in insulin sensitivity, a reduction in appetite; a reduction in a level of HbA1c; a reduction in insulin resistance; a reduction in body weight; a reduction in body fat mass; a reduction in BMI; a reduction in appetite; and a reduction in blood pressure.

NAFLD or NASH

[00279] In some embodiments the disease or disorder is non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH). NAFLD is a term used for a range of conditions caused by a build-up of fat in the liver. NAFLD is linked to high calorie intake and an impaired glucose metabolism: 60-75% of patients with diabetes have NAFLD.

[00280] NAFLD develops in 4 main stages:

1. simple fatty liver (steatosis) – a largely harmless build-up of fat in the liver cells;
2. non-alcoholic steatohepatitis (NASH) – a more serious form of NAFLD, where the liver has become inflamed;
3. fibrosis – where persistent inflammation causes scar tissue around the liver and nearby blood vessels, but the liver is still able to function normally;
4. cirrhosis – the most severe stage, usually occurring after years of inflammation, where the liver shrinks and becomes scarred and lumpy; this damage is permanent and can lead to liver failure and liver cancer.

The subject may have stage 1, 2, 3 or 4 NAFLD.

[00281] NASH is usually may be diagnosed by liver tests included in blood test panels.

Such liver tests include alanine aminotransaminase (ALT) or aspartate aminotransaminase (AST). When further evaluation shows no apparent reason for liver disease (such as medications, viral hepatitis, or excessive use of alcohol) and when x-rays or other imaging studies of the liver reveal the presence of fat, NASH is suspected. A definitive diagnosis of NASH and the dismissal of a diagnosis of simple fatty liver may require a liver biopsy.

[00282] In some embodiments, the treatment with the PDE4 inhibitor and the GLP1 receptor agonist results in a reduction in one or more of: body weight; body fat; liver fat; a level of serum alanine transaminase (ALT) and/or serum aspartate transaminase (AST); fibrosis in the liver; and insulin resistance.

[00283] In a further aspect, the invention provides a method of reducing one or more of the following in a subject in need thereof:

A. body weight; body fat mass; BMI; appetite or food intake; fasting blood levels of triglycerides; fasting blood levels of cholesterol; fasting blood levels of low-density lipoprotein (LDL) cholesterol; waist circumference; cholesterol ratio; or

B. blood glucose; fasting plasma glucose (FPG); fasting blood levels of insulin; insulin resistance; 2-hour post-load plasma glucose; a level of HbA1c; beta-cell apoptosis; or

C. serum levels of CRP (e.g. hs-CRP), IL-6, TNF- α , and/or resistin; or

D. blood pressure; or

E. liver fat; a level of serum alanine transaminase (ALT); a level of serum aspartate transaminase (AST); liver fibrosis;

wherein the method comprises administering a PDE4 inhibitor and a GLP1 receptor agonist to the subject.

Administration, dosages and dosage regimens

[00284] Administration of the PDE4 inhibitor (e.g. orismilast), or a pharmaceutically acceptable salt, solvate or hydrate thereof, and the GLP1 receptor agonist may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ orismilast within a therapeutically effective dosage range described hereinbefore and the GLP1 receptor agonist within its approved dosage range.

[00285] Herein, where the term "combination" is used it is to be understood that this refers to simultaneous, separate or sequential administration. In one aspect of the invention

“combination” refers to simultaneous administration. In another aspect of the invention “combination” refers to separate administration. In a further aspect of the invention “combination” refers to sequential administration. Where the administration is sequential or separate, the delay in administering the second component should not be such as to lose the beneficial effect of the combination.

[00286] In some embodiments the PDE4 inhibitor is administered at a suitable time interval before or after the GLP1 receptor agonist. For example, the PDE4 inhibitor may be administered at least 30 minutes, 45 minutes or 1 hour before the GLP1 receptor agonist. Also contemplated are embodiments where the GLP1 receptor agonist is administered before the PDE4 inhibitor. In these embodiments the PDE4 inhibitor may be orismilast and the GLP1 receptor agonist may be semaglutide.

[00287] Thus, in some embodiments, the PDE4 inhibitor (e.g. orismilast) and the GLP-1R agonist are administered simultaneously. In some embodiments the PDE4 inhibitor (e.g. orismilast) and the GLP-1R agonist are administered separately. In some embodiments the PDE4 inhibitor (e.g. orismilast) and the GLP-1R agonist are administered sequentially.

[00288] In some embodiments in which a combination treatment is used, the amount of orismilast and the amount of the GLP1 receptor agonist are, when combined, therapeutically effective to treat a targeted disorder in the patient. In this context, the combined amounts are “therapeutically effective amount” if they are, when combined, sufficient to reduce or completely alleviate symptoms or other detrimental effects of the disorder; cure the disorder; reverse, completely stop, or slow the progress of the disorder; or reduce the risk of the disorder getting worse. Typically, such amounts may be determined by one skilled in the art by, for example, starting with the dosage range described in this specification for orismilast, or a pharmaceutically acceptable salt, solvate or hydrate thereof present in the formulation of the invention and an approved or otherwise published dosage range(s) of the GLP1 receptor agonist.

[00289] The dosage and dosing regimen of the formulations of the invention will depend upon a number of factors that may readily be determined by a physician, for example the severity of the disease or condition, the responsiveness to initial treatment, the mode of administration and the particular disease or condition being treated.

[00290] Suitable modes of administration may include oral, intranasal, parenteral (e.g. intravenous, intramuscular, intra-arterial, subcutaneous or intradermal), topical, inhalation (intraorally or intranasally), or a combination thereof. One or more doses may be delivered to the subject via multiple modes of administration.

[00291] In some embodiments, the PDE4 inhibitor is administered orally. In some embodiments, the GLP1 receptor agonist is administered orally or subcutaneously. In some embodiments both the PDE4 inhibitor and the GLP1 Receptor agonist are administered orally.

5 [00292] The total daily dose of the PDE4 inhibitor (e.g. orismilast) administered to the subject may comprise one or more unit doses. The total daily dose may be no more than 500 mg, no more than 250 mg, no more than 200 mg, no more than 150 mg, no more than 120 mg, no more than 100 mg, no more than 80 mg, no more than 60 mg, no more than 40 mg, no more than 20 mg or no more than 10 mg of the PDE4 inhibitor. In some
10 embodiments, the treatment comprises administering a total daily dose of at least 0.5 mg, at least 1 mg, at least 5 mg, at least 10 mg, at least 20 mg, at least 30 mg, at least 40 mg, at least 50 mg, at least 60 mg, at least 80 mg, at least 100 mg, at least 120 mg, at least 140 mg, at least 160 mg, at least 180 mg, or at least 200 mg of the PDE4 inhibitor.

[00293] In some embodiments the total daily dose administered is from about 0.1 to about
15 250 mg, from about 0.5 to about 200 mg, from about 1 to about 180 mg, from about 5 mg to about 150 mg, from about 10 to about 120 mg, from about 20 to about 110 mg, from about 30 to about 100 mg, from about 40 to about 90 mg, from about 50 to about 80 mg, or from about 60 to about 70 mg of the PDE4 inhibitor.

[00294] In some embodiments, the treatment comprises administering a unit dose of the
20 PDE4 inhibitor of from about 0.01 mg to about 250 mg, from about 0.05 mg to about 200 mg, from about 0.1 mg to about 150 mg, from about 1 mg to about 100 mg, from about 5 mg to about 70 mg, from about 8 mg to about 65 mg, from about 10 mg to about 60 mg, from about 15 mg to about 50 mg, from about 20 mg to about 45 mg, or from about 30 to about 40 mg. In some embodiments, the treatment comprises administering a unit dose of from about 1
25 mg to about 50 mg, from about 5 mg to about 40 mg, or from about 10 mg to about 30 mg.

[00295] In some embodiments, the treatment comprises administering a unit dose of the PDE4 inhibitor of about 0.01 mg. In some embodiments, the treatment comprises administering a unit dose of about 0.1 mg. In some embodiments, the treatment comprises administering a unit dose of about 0.5 mg. In some embodiments, the treatment comprises
30 administering a unit dose of about 1 mg. In some embodiments, the treatment comprises administering a unit dose of about 5 mg. In some embodiments, the treatment comprises administering a unit dose of about 10 mg. In some embodiments, the treatment comprises administering a unit dose of about 20 mg. In some embodiments, the treatment comprises administering a unit dose of about 30 mg. In some embodiments, the treatment comprises
35 administering a unit dose of about 40 mg. In some embodiments, the treatment comprises

administering a unit dose of about 50 mg. In some embodiments, the treatment comprises administering a unit dose of about 60 mg. In some embodiments, the treatment comprises administering a unit dose of about 70 mg. In some embodiments, the treatment comprises administering a unit dose of about 80 mg. In some embodiments, the treatment comprises administering a unit dose of about 100 mg. In some embodiments, the treatment comprises administering a unit dose of about 120 mg. In some embodiments, the treatment comprises administering a unit dose of about 150 mg. In some embodiments, the treatment comprises administering a unit dose of about 200 mg.

[00296] In some embodiments, the treatment comprises administering a unit dose of the PDE4 inhibitor of no more than 100 mg/kg, no more than no more than 80 mg/kg, no more than 60 mg/kg, no more than 50 mg/kg, no more than 40 mg/kg, no more than 30 mg/kg, no more than 20 mg/kg, no more than 10 mg/kg, no more than 5 mg/kg, no more than 1 mg/kg, no more than 0.5 mg/kg, no more than 0.1 mg/kg, or no more than 0.05 mg/kg.

[00297] The PDE4 inhibitor (e.g. orismilast) may be administered from one to four times daily, for example from two to three times daily. In some embodiments the PDE4 inhibitor is administered once daily. In some embodiments the PDE4 inhibitor is administered twice daily.

[00298] Accordingly, in some embodiments the PDE4 inhibitor (e.g. orismilast) is administered in a dose of 5 mg once per day. In some embodiments the PDE4 inhibitor is administered in a dose of 10 mg once per day. In some embodiments the PDE4 inhibitor is administered in a dose of 20 mg once per day. In some embodiments PDE4 inhibitor is administered in a dose of 30 mg once per day. In some embodiments the PDE4 inhibitor is administered in a dose of 40 mg once per day. In some embodiments the PDE4 inhibitor is administered in a dose of 50 mg once per day. In some embodiments the PDE4 inhibitor is administered in a dose of 60 mg once per day. In some embodiments the PDE4 inhibitor is administered in a dose of 70 mg once per day. In some embodiments the PDE4 inhibitor is administered in a dose of 80 mg once per day. In some embodiments the PDE4 inhibitor is administered in a dose of 90 mg once per day. In some embodiments the PDE4 inhibitor is administered in a dose of 100 mg once per day.

[00299] In some embodiments the PDE4 inhibitor is administered in a dose of 5 mg twice per day. In some embodiments the PDE4 inhibitor is administered in a dose of 10 mg twice per day. In some embodiments the PDE4 inhibitor is administered in a dose of 20 mg twice per day. In some embodiments the PDE4 inhibitor is administered in a dose of 30 mg twice per day. In some embodiments the PDE4 inhibitor is administered in a dose of 40 mg twice

per day. In some embodiments the PDE4 inhibitor is administered in a dose of 50 mg twice per day.

[00300] In some embodiments the PDE4 inhibitor (e.g. orismilast) is administered in a dose of 10mg twice per day. Optionally the orismilast is in the form of an oral modified release formulation. Thus it may be that the orismilast is in the form of a modified release tablet.

[00301] In some embodiments the PDE4 inhibitor (e.g. orismilast) is administered in a dose of 20mg twice per day. Optionally the orismilast is in the form of an oral modified release formulation. Thus it may be that the orismilast is in the form of a modified release tablet.

[00302] In some embodiments the PDE4 inhibitor (e.g. orismilast) is administered in a dose of 30mg twice per day. Optionally the orismilast is in the form of an oral modified release formulation. Thus it may be that the orismilast is in the form of a modified release tablet.

[00303] The total daily dose of the GLP1 receptor agonist administered to the subject may comprise one or more unit doses. It will be appreciated that the dose and the dosing regimen will depend on the GLP1 receptor agonist being administered, and the mode of administration (e.g. oral or subcutaneous).

[00304] In some embodiments the GLP1 receptor agonist is administered from one to four times daily, for example from two to three times daily. In some embodiments the GLP1 receptor agonist is administered once daily. In some embodiments the GLP1 receptor agonist is administered twice daily. In some embodiments the GLP1 receptor agonist is administered once or twice weekly. Suitably the GLP1 receptor agonist is administered once weekly.

[00305] A total daily dose of the GLP1 receptor agonist may be no more than about 100 mg, no more than about 100 mg, no more than about 50 mg, no more than about 40 mg, no more than about 30 mg, no more than about 20 mg, no more than about 15 mg, no more than about 10 mg, no more than about 8 mg, no more than about 7 mg, no more than about 5 mg, no more than about 4 mg, no more than about 3 mg, no more than about 2 mg, no more than about 1 mg, no more than about 0.75 mg, no more than about 0.5 mg, no more than about 0.25 mg, no more than about 0.2 mg, no more than about 0.15 mg or no more than about 0.1 mg. In some embodiments the total daily dose of the GLP1 receptor agonist is no more than about 1 µg to about 200 µg, from about 2 µg to about 100 µg, from about 5 µg to about 50 µg, from about 10 µg to about 30 µg or from about 15 µg to about 20 µg.

[00306] In some embodiments, the treatment comprises administering a total daily dose of from about 1 µg to about 100 mg, from about 5 µg to about 50 mg, from about 10 µg to

about 10 mg, from about 50 µg to about 5 mg, from about 100 µg to about 1 mg or from about 200 µg to about 0.5 mg of the GLP1 receptor agonist.

[00307] In some embodiments a total weekly dose of the GLP1 receptor agonist may be from about 0.05 mg to about 100 mg, from about 0.1 mg to about 80 mg, from about 0.25 to about 60 mg, from about 0.5 mg to about 50 mg, from about 0.75 to about 40 mg, from about 1 mg to about 30 mg, from about 2 mg to about 20 mg, from about 3 mg to about 15 mg, from about 4 mg to about 12 mg, from about 5 mg to about 10 mg, or from about 6 mg to about 8 mg.

[00308] In some embodiments, the treatment comprises administering a unit dose of the GLP1 receptor agonist of from about 0.5 µg to about 500 mg, from about 1 µg to about 200 mg, from about 5 µg to about 100 mg, from about 10 µg to about 50 mg, from about 50 µg to about 20 mg, from about 100 µg to about 10 mg, from about 250 µg to about 5 mg, from about 0.5 mg to about 4 mg, from about 0.75 mg to about 3 mg, or from about 1 mg to about 2 mg.

[00309] In some embodiments, particularly where the GLP1 receptor agonist is administered subcutaneously, the GLP1 receptor agonist is administered in a total weekly dose of from about 0.1 mg to about 2.5 mg, for example, from about 0.2 mg to about 2 mg, from about 0.25 mg to about 1.5 mg, from about 0.25 mg to about 1 mg or from about 0.5 mg to about 1 mg, for example, 0.1, 0.2, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, or 2.5 mg, such as 0.25, 0.5 or 1 mg. Suitably administration is in a total weekly dose of 1 mg. In certain embodiments administration is once weekly. In these embodiments the GLP1 receptor agonist may be semaglutide.

[00310] In some embodiments, particularly where the GLP1 receptor agonist is administered orally, the GLP1 receptor agonist is administered in a total daily dose of from about 0.25 mg to about 50mg, for example, from about 1 mg to about 50 mg, for example, from about 1 mg to about 25 mg, from about 1 mg to about 14 mg, from about 1 mg to about 7 mg, from about 1 mg to about 3 mg, from about 3 mg to about 50 mg, from about 3 mg to about 25 mg, from about 3 mg to about 14 mg, from about 3 mg to about 7 mg, from about 7 mg to about 50 mg, from about 7 mg to about 25 mg, from about 7 mg to about 14 mg, from about 14 mg to about 50 mg or from about 14 mg to about 25 mg. Total daily dose may be for example, 0.25 mg, 0.5 mg, 1 mg, 1.25 mg, 1.5 mg, 1.75 mg, 2mg, 2.25 mg, 2.5 mg, 2.75 mg, 3 mg, 3.5 mg, 4 mg, 4.5 mg, 5 mg, 5.5mg, 6 mg, 6.5 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg or 50 mg. In some embodiments the total daily dose is less than about 14 mg, or less than about 7 mg or less than about 3 mg. Suitably the total daily dose is 1 mg.

Total daily dose may be administered in one or more unit doses as described herein. For example, a total daily dose of 1 mg may be administered in a unit dose of 1 mg once daily or in a unit dose of 0.5 mg administered twice daily. Suitably the total daily dose is administered in a unit dose once daily. In these embodiments the GLP1 receptor agonist may be semaglutide.

[00311] In some embodiments where the GLP1 receptor agonist is administered orally, the GLP1 receptor agonist (e.g. semaglutide) is administered in the morning (typically on an empty stomach).

[00312] In some embodiments where both the PDE4 inhibitor and the GLP1 receptor agonist are administered orally, the PDE 4 inhibitor is administered once daily in the morning or twice daily in the morning and evening as described herein and the GLP1 receptor agonist is administered in the morning as described herein. In these embodiments the PDE4 inhibitor may be orismilast and the GLP1 receptor agonist may be semaglutide.

[00313] In some embodiments, in particular where the PDE4 inhibitor is administered orally and the GLP1 receptor agonist is administered parenterally (e.g. subcutaneously), the weight ratio of the total daily dose of PDE4 inhibitor to the total weekly dose of GLP1 receptor agonist is at least about 20:1, 30:1, 40:1, 50:1, 60:1, 70:1, 80:1 or 90:1. The ratio may be for example from about 20:1 to about 90:1 or more, from about 30:1 to about 90:1 or more, from about 40:1 to about 90:1 or more, from about 50:1 to about 90:1 or more, from about 60:1 to about 90:1 or more, or from about 70:1 to 90:1 or more. In some embodiments the ratio is about 20:1, 30:1, 40:1, 50:1, 60:1, 70:1, 80:1 90:1 or more. For example, the ratio may be about 40:1 or 60:1 such as 60:1. For example, PDE4 inhibitor (e.g. orismilast) may be administered orally in a total daily dose of 60 mg and GLP1 receptor (e.g. semaglutide) may be administered subcutaneously in a total weekly dose of 1 mg. In these embodiments the PDE inhibitor may be orismilast and/or the GLP1 receptor agonist may be semaglutide.

[00314]

[00315] In some embodiments, in particular where both agents are administered orally, the weight ratio of the total daily dose of PDE4 inhibitor to the total daily dose of GLP1 receptor agonist is at least about 5:1, 10:1, 20:1, 30:1, 40:1, 50:1, 60:1, 70:1, 80:1 or 90:1. The ratio may be, for example, from about 10:1 to about 90:1 or more, from about 20:1 to 90:1 or more, from about 30:1 to about 90:1 or more, from about 40:1 to about 90:1 or more, from about 50:1 to about 90:1 or more, from about 60:1 to about 90:1 or more, or from about 70:1 to 90:1 or more. In some embodiments the ratio is about 10:1, 20:1, 30:1, 40:1, 50:1, 60:1, 70:1, 80:1, 90:1 or more. For example, the ratio may be about 20:1, 40:1 or 60:1 such as

60:1. In these embodiments the PDE inhibitor may be orismilast and/or the GLP1 receptor agonist may be semaglutide.

[00316] The treatment with the PDE4 inhibitor (e.g. orismilast) and the GLP1 receptor agonist may be administered to the subject over a number of consecutive days or weeks. In some embodiments the treatment is administered over a period of at least 10 days, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 6 weeks, at least 8 weeks, at least 10 weeks, at least 12 weeks, at least 16 weeks, at least 20 weeks, or at least 6 months. In some embodiments, the treatment is administered for no more than 12 months, no more than 10 months, no more than 9 months, no more than 8 months, no more than 6 months, no more than 24 weeks, no more than 20 weeks, no more than 16 weeks, no more than 12 weeks or no more than 10 weeks. For example, the treatment may be administered for a period of from 10 days to 20 weeks, from 14 days to 16 weeks, from 21 days to 14 weeks, from 4 to 12 weeks, from 5 to 10 weeks or from 6 to 8 weeks. In some embodiments, the treatment administered to the subject for up to 4, 6, 10, 16 or 20 weeks. Alternatively, it may be that the treatment is administered for a longer period of time, for example, for maintenance e.g. to maintain a desired body weight, to maintain glycaemic control. Thus, in some embodiments the treatment is administered for a period of time of from 6 months to 5 years, from 12 months to 4 years, from 15 months to 3 years, or from 18 to 24 months. It will be appreciated that the dosing period will be determined by the type and severity of the disease being treated. It may be that treatment is continued until a parameter of the subject is below a predetermined threshold, such as a threshold as disclosed above. For example, treatment may be continued until the treatment is no longer indicated.

[00317] In one embodiment, the dose of the PDE4 inhibitor (e.g. orismilast) of administered is increased over the first two weeks of treatment. Suitably, the dose is increased from 10 mg twice daily to 30 mg twice daily over the period of two weeks. In some embodiments the compound is administered in an initial total daily dose of about 5 mg to 20 mg and the total daily dose is increased over a period of 1 or 2 weeks. For example the initial daily dose may be 5 mg to 20 mg and this is increased to a daily dose of 50 to 100 mg over a period of 1 or 2 weeks. In some embodiments in an initial total daily dose of about 5 mg to 20 mg and the total daily dose is increased over a period of 1 or 2 weeks to a total daily dose of about 60 to 80 mg per day. In these embodiments the daily dose may be administered as a single daily dose of the compound. However, suitably the total daily dose is administered as a divided dose administered at regular intervals. For example the total daily dose may be administered as substantially equal divided doses 2 to 4 times per day. Suitably the total daily dose is administered as a substantially equal divided dose 2 times per day. In some embodiments the compound is administered for the first two weeks of treatment substantially

as described in the “Dose Titration Scheme” in Table 7. In some embodiments the compound is administered substantially as described in Table 11.

[00318] In some embodiments the dose of the PDE4 inhibitor administered is increased over the first 8 weeks of treatment. For example, the compound may be administered at an initial total daily dose of about 20 mg and increased to a total daily dose of about 60 mg over 8 weeks. In some embodiments dose is increased at the end of 4 weeks and also at the end of 8 weeks from start of treatment. For example, total daily dose may be increased from 20 mg to 40 mg at the end of 4 weeks from start of treatment and/or total daily dose may be increased from 40 mg to 60 mg at the end of 8 weeks. In some embodiments the total daily dose is administered as a single daily dose of the compound. In some embodiments the total daily dose is administered as a divided dose administered at regular intervals. For example the total daily dose may be administered as substantially equal divided doses 2 to 4 times per day. Suitably the total daily dose is administered as a substantially equal divided dose 2 times per day. In some embodiments the daily dose may be administered as a single daily dose for weeks 1-4 and as a substantially equally divided twice daily dose for weeks 5-8. In some embodiments, dose may be increased from 20 mg once daily to 30 mg twice daily over the period of 8 weeks. For example, the compound may be administered at 20 mg once daily for weeks 1-4, at 20 mg twice daily for weeks 5-8 and at 30 mg twice daily thereafter. In some embodiments the compound is administered substantially as described in the schematic in Figure 5 (described in Example 6). In these embodiments the PDE4 inhibitor may be orismilast.

[00319] In some embodiments the dose (e.g. total daily or total weekly dose) of the GLP1 receptor agonist (e.g. semaglutide) is increased over the first 8 weeks of treatment. For example, the dose may be increased at the end of 4 weeks and also at the end of 8 weeks from start of treatment. In some embodiments the increase in dose at the end of 4 weeks from start of treatment is at least 50%, 75% or 100% and/or the increase in dose at the end of 8 weeks from start of treatment is at least 50%, 75% or 100%. For example, the dose may be doubled at the end of 4 weeks from start of treatment and/or the dose may be doubled at the end of 8 weeks from start of treatment. In some embodiments, particularly where the compound (e.g. semaglutide) is administered subcutaneously, the compound may be administered at an initial total weekly dose of 0.25 mg and increased to a total weekly dose of 1.0 mg over 8 weeks. For example, total weekly dose may be increased from 0.25 mg to 0.5 mg at the end of 4 weeks from start of treatment and/or total weekly dose may be increased from 0.5 mg to about 1.0 mg at the end of 8 weeks. In some embodiments the total weekly dose is administered as a single weekly dose of the compound. In some embodiments the total weekly dose is administered as a divided dose administered at

regular intervals, for example as substantially equal divided doses 2 times per week.

Suitably the total weekly dose is administered as a single weekly dose of the compound. In some embodiments the compound is administered substantially as described in the

schematic in Figure 5 (described in Example 6). In some embodiments, particularly where

the compound (e.g. semaglutide) is administered orally, the compound may be administered at an initial total daily dose described anywhere herein, for example, an initial total daily dose of 0.25 mg, 0.5 mg, 1.0 mg, 1.5mg or 2.0 mg. In some embodiments dose is increased to a total daily dose described anywhere herein over 8 weeks, for example, 1.0 mg, 2.0 mg, 3.0 mg, 4.0 mg, 5.0 mg, 6.0 mg or 7.0 mg. In some embodiments, the total daily dose is

increased from 0.25 mg to a total daily dose of 1.0 mg over 8 weeks. For example, total daily dose may be increased from 0.25 mg to 0.5 mg at the end of 4 weeks from start of treatment and/or total daily dose may be increased from 0.5 mg to about 1.0 mg at the end of 8 weeks.

In some embodiments the total daily dose is administered as a single daily dose of the

compound. In some embodiments the total daily dose is administered as a divided dose

administered at regular intervals. For example the total daily dose may be administered as substantially equal divided doses 2 to 4 times per day, such as 2 times per day. Suitably the total daily dose is administered as a single daily dose. In these embodiments the GLP1 receptor agonist may be semaglutide.

[00320] In some embodiments the PDE4 inhibitor orismilast is administered at 20 mg

once daily for weeks 1-4, at 20 mg twice daily for weeks 5-8 and at 30 mg twice daily thereafter and the GLP1 receptor agonist semaglutide is administered subcutaneously at a total weekly dose of 0.25 mg once weekly for weeks 1-4, of 0.5 mg once weekly for weeks 5-8 and of 1.0 mg once weekly thereafter.

[00321] It will be appreciated that the dose and/or the dosage regime of the PDE4 inhibitor

and the GLP1 receptor agonist may be selected by the skilled person depending on a number of factors such as, but not limited to, the severity of the disease, the age of the subject and/or the presence of any underlying conditions.

[00322] One of the key challenges for an effective oral PDE4 therapy has been the narrow therapeutic window. Most of the programs investigating PDE4 inhibitors failed because of

safety issues, and there are currently only two approved oral PDE4 inhibitors available, roflumilast and apremilast. However, both of these therapies have tolerability issues

affecting, primarily but not exclusively, the gastrointestinal (GI) tract, characterized by nausea and diarrhoea. These undesired GI effects were consistently observed from the beginning of treatment, and this led to the titration of those drugs if an attempt to reduce or

mitigate undesirable side effects. As such, the PDE4 inhibitor may be administered according to a dosage regime which is designed to minimize side effects.

[00323] In some embodiments wherein the PDE4 inhibitor is orismilast, the method comprises administering the orismilast to the subject, wherein:

(Ai) an initial orismilast dose is administered to the subject once per day for an initial time period followed by;

5 (Aii) an interim orismilast dose administered to the subject twice per day for an interim time period followed by;

(Aiii) a maintenance orismilast dose administered to the subject twice per day;

wherein:

(a) the initial orismilast dose and the interim orismilast dose are independently selected
10 from 10 mg to 30 mg orismilast, provided that the interim orismilast dose is greater than or equal to the initial orismilast dose;

(b) the initial time period is two to eight weeks;

(c) the interim time period is one to eight weeks; and

(d) the maintenance orismilast dose is greater than the interim orismilast dose when
15 the subject has a body mass that is greater than or equal to a threshold body mass, wherein the threshold body mass is at least 90 kg.

[00324] In certain embodiments the initial time period is two weeks to six weeks. In certain
embodiments the initial time period is two weeks, four weeks or six weeks. In certain
embodiments the initial time period is two weeks. In certain embodiments the initial time
20 period is four weeks.

[00325] In certain embodiments the interim time period in (Aii) is two weeks, four weeks or
six weeks. In certain embodiments the interim time period in (Aii) is two weeks. In certain
embodiments the interim time period in (Aii) is four weeks. In certain embodiments the
interim time period in (Aii) is six weeks. In certain embodiments the interim time period in
25 (Aii) is eight weeks.

[00326] In certain embodiments both the initial and the interim time period are four weeks.

[00327] Analysis of clinical data has shown that most of the adverse events associated with
orismilast treatment (e.g. diarrhoea, nausea, headache, dizziness or vomiting) had an onset
during the initial four weeks of treatment and very few of these events had an onset after
30 eight weeks of treatment. Accordingly, in certain embodiments the total duration of the initial
time period and the interim time period is from four weeks to eight weeks. In certain
embodiments the total duration of the initial time period and the interim time period is four
weeks. In certain embodiments the total duration of the initial time period and the interim

time period is five weeks. In certain embodiments the total duration of the initial time period and the interim time period is six weeks. In certain embodiments the total duration of the initial time period and the interim time period is seven weeks. In certain embodiments the total duration of the initial time period and the interim time period is eight weeks.

5 **[00328]** Analysis of the clinical data also found that the efficacy of the 20 mg orismilast administered twice a day was comparable to the efficacy of 30 mg orismilast administered twice per day in the first 8 weeks of treatment for the treatment of moderate to severe plaque psoriasis. Accordingly, the dose titration during the initial and interim time periods are expected to provide therapeutic effects whilst also minimising undesirable side effects during
10 the initial period of treatment, particularly in the first 4 to 8 weeks of treatment.

[00329] In certain embodiments the maintenance orismilast dose in (Aiii) is the same as the interim orismilast dose when the subject has a body mass which is less than the threshold body mass.

[00330] In certain embodiments the maintenance orismilast dose in (Aiii) is up to 40 mg
15 orismilast when the subject has a body mass which is greater than or equal to the threshold body mass, provided the maintenance orismilast dose is greater than the interim orismilast dose. For example, it may be that the maintenance orismilast dose is 30 mg to 40 mg orismilast.

[00331] In certain embodiments the maintenance orismilast dose in (Aiii) is 30 mg orismilast
20 when the subject has a body mass which is greater than or equal to the threshold body mass and the interim orismilast dose is less than 30 mg. For example, the interim orismilast dose is 10 mg to 25 mg orismilast. In certain embodiments the maintenance orismilast dose is 30 mg orismilast and the interim orismilast dose is 10 mg orismilast. In certain embodiments the maintenance orismilast dose is 30 mg orismilast and the interim orismilast dose is 20 mg
25 orismilast.

[00332] Analysis of clinical trial data has also identified that administration of orismilast according to the dosage regimens described herein provide improved tolerability and/or treatment efficacy compared to administering orismilast in a twice daily dosage regimen. In particular, it has been found that patients which have a body mass greater than or equal to
30 the threshold body mass show improved tolerability and/or treatment response to orismilast when the maintenance orismilast dose is higher than the interim orismilast dose.

[00333] In some embodiments the method is for treating or preventing a disease or disorder in a subject with a body mass that is greater than or equal to a threshold body mass. In such embodiments, the method comprises administering the orismilast to the subject,
35 wherein:

(Bi) an initial orismilast dose is administered to the subject once per day for a preliminary time period followed by;

(Bii) an interim orismilast dose administered to the subject twice per day for an interim time period followed by;

- 5 (Biii) a maintenance orismilast dose administered to the subject twice per day, wherein the maintenance orismilast dose is greater than the interim orismilast dose;

wherein:

- (a) the initial orismilast dose and the interim orismilast doses are independently selected from 10 mg to 30 mg orismilast, provided that the interim orismilast dose is greater than or
10 equal to the initial orismilast dose;
- (b) the preliminary time period is up to eight weeks;
- (c) the interim time period is one week to eight weeks; and
- (d) the threshold body mass is at least 90 kg.

[00334] In certain embodiments the preliminary time period in (Bi) is one day to eight weeks.

- 15 In certain embodiments the preliminary time period in (Bi) is two days to eight weeks. In certain embodiments the preliminary time period in (Bi) is four days to eight weeks. In certain embodiments the preliminary time period in (Bi) is five days to eight weeks. In certain embodiments the preliminary time period in (Bi) is six days to eight weeks. In certain
20 embodiments the preliminary time period in (Bi) is one week to eight weeks. In certain embodiments the preliminary time period in (Bi) is one week to six weeks. In certain embodiments the preliminary time period in (Bi) is one week to four weeks. In certain embodiments the preliminary time period in (Bi) is one week to two weeks. In certain
25 embodiments the preliminary time period in (Bi) is two days to eight weeks. In certain embodiments the preliminary time period in (Bi) is one day. In certain embodiments the preliminary time period in (Bi) is two days. In certain embodiments the preliminary time period in (Bi) is three days. In certain embodiments the preliminary time period in (Bi) is four
30 days. In certain embodiments the preliminary time period in (Bi) is five days. In certain embodiments the preliminary time period in (Bi) is six days. In certain embodiments the preliminary time period in (Bi) is one week, two weeks, three weeks or four weeks. In certain
embodiments the preliminary time period in (Bi) is one week. In certain embodiments the preliminary time period in (Bi) is two weeks. In certain embodiments the preliminary time period in (Bi) is three weeks. In certain embodiments the preliminary time period in (Bi) is four weeks.

[00335] In certain embodiments the interim time period in (Bii) is two weeks, four weeks or six weeks. In certain embodiments the interim time period in (Bii) is two weeks. In certain embodiments the interim time period in (Bii) is four weeks. In certain embodiments the interim time period in (Bii) is six weeks. In certain embodiments the interim time period in (Bii) is eight weeks.

[00336] In certain embodiments both the preliminary and the interim time periods are four weeks.

[00337] As discussed above, most of the adverse events associated with orismilast have an onset in the first four to eight weeks of orismilast administration. In certain embodiments the total duration of the preliminary time period and the interim time period is from four weeks to eight weeks. In certain embodiments the total duration of the preliminary time period and the interim time period is four weeks. In certain embodiments the total duration of the preliminary time period and the interim time period is five weeks. In certain embodiments the total duration of the preliminary time period and the interim time period is six weeks. In certain embodiments the total duration of the preliminary time period and the interim time period is seven weeks. In certain embodiments the total duration of the preliminary time period and the interim time period is eight weeks.

[00338] In certain embodiments the maintenance orismilast dose in (Biii) is up to 40 mg orismilast, provided the maintenance orismilast dose is greater than the interim orismilast dose. For example it may be that the maintenance orismilast dose is 30 mg to 40 mg orismilast.

[00339] In certain embodiments the maintenance orismilast dose in (Biii) is 30 mg orismilast and the interim orismilast dose is less than 30 mg. For example, the interim orismilast dose is 10 mg to 25 mg orismilast. In certain embodiments the maintenance orismilast dose is 30 mg orismilast and the interim orismilast dose is 10 mg orismilast. In certain embodiments the maintenance orismilast dose is 30 mg orismilast and the interim orismilast dose is 20 mg orismilast.

[00340] In certain embodiments the initial dose in B(i) is 20 mg orismilast, the interim dose in B(ii) is 20 mg orismilast and the maintenance dose in B(iii) is 30 mg orismilast.

[00341] In certain embodiments in any of the dosage regimens disclosed herein the initial orismilast dose is administered to the subject in the evening.

[00342] In certain embodiments in any of the dosage regimens disclosed herein when the orismilast is administered twice per day (e.g. in the interim orismilast doses and the maintenance orismilast doses) the doses are suitably administered about 12 hours apart.

Suitably one dose is administered in the morning and one dose is administered in the evening.

[00343] In certain embodiments the orismilast is administered to the subject without any restriction on the intake of food or drink by the subject. However, gastrointestinal side effects may be further minimised by avoiding large meals and/or fatty foods prior to administering the orismilast. Accordingly, in some embodiments in any of the dosage regimens disclosed herein the orismilast is administered to the subject in a fasted state. For example, the orismilast is administered at least 4 hours after a meal. Suitably administering in a fasted state also requires the subject to fast for two hours after administration of the orismilast. In certain embodiments in any of the dosage regimens disclosed herein orismilast is administered to the subject in a fed state. For example the orismilast is administered to the subject in a time period of 30 minutes prior to a meal and 1 hour after a meal. In certain embodiments the orismilast is administered to the subject in a time period of 30 minutes prior to a meal and 1 hour after a meal, wherein the meal is a low fat meal (less than 50% of the total calorific value of the meal is from fat). In certain embodiments the orismilast is administered to the subject in a time period of 30 minutes prior to a meal and 1 hour after a meal, wherein the meal is a low calorie meal (less than about 1000 calories). In certain embodiments the orismilast is administered to the subject in a time period of 30 minutes prior to a meal and 1 hour after a meal, wherein the meal is a low-fat, low calorie meal. In certain embodiments in any of the dosage regimens disclosed herein orismilast is administered to the subject without restriction of food or drink intake.

[00344] In certain embodiments in any of the dosage regimens disclosed herein the initial orismilast dose and the interim orismilast dose are the same. In certain embodiments the initial orismilast dose and the interim orismilast dose are both 20 mg orismilast.

[00345] In certain embodiments in any of the dosage regimens disclosed herein the interim orismilast dose is greater than the initial orismilast dose. In certain embodiments the interim orismilast dose is 20 mg orismilast and the interim orismilast dose is greater than the initial orismilast dose. For example, the initial orismilast dose is 10 mg and the interim orismilast dose is 20 mg.

[00346] In certain embodiments in any of the dosage regimens disclosed herein the threshold body mass is 90 kg

[00347] In certain embodiments in any of the dosage regimens disclosed herein the threshold body mass is 95 kg.

[00348] In certain embodiments in any of the dosage regimens disclosed herein the threshold body mass is 100 kg.

[00349] In certain embodiments in any of the dosage regimens disclosed herein the threshold body mass is 105 kg.

[00350] In certain embodiments in any of the dosage regimens disclosed herein the maintenance orismilast dose is administered to the subject twice per day for the remainder
 5 of the treatment period. Accordingly, in certain embodiments the maintenance orismilast dose is administered to the subject twice per day for at least one week, at least two weeks, at least three weeks, at least four weeks, at least eight weeks, at least one month, at least two months, at least three months, at least four months, at least six months, at least nine months, at least one year, at least 18 months, at least 2 years.

10 Embodiments

1. A method for the treatment or prevention of a disease or disorder, the method comprising administering a PDE4 inhibitor and a GLP1 receptor agonist to a subject, wherein the disease or disorder is selected from: an inflammatory disease, an autoimmune disease, fibrosis, a neurodegenerative disease, a musculoskeletal
 15 disorder, a metabolic disease or disorder, alcoholic liver disease (ALD), cardiovascular disease and a gastrointestinal disease or disorder.
2. The method according to embodiment 1, wherein the metabolic disease or disorder is selected from: obesity, hyperlipidaemia, diabetes (including pre-diabetes), diabetes-associated cardiac dysfunction, metabolic syndrome, non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD).
 20
3. The method according to embodiment 1, wherein the inflammatory disease is an inflammatory pulmonary, dermatological or neurological disease or inflammatory myopathy (e.g. polymyositis).
 25
4. The method according to embodiment 3, wherein the inflammatory disease is asthma, allergy, allergic rhinitis, allergic airway inflammation, atopic dermatitis (AD), chronic obstructive pulmonary disease (COPD), respiratory syncytial virus (RSV)
 30 infection, inflammatory bowel disease, multiple sclerosis, arthritis, psoriasis, eosinophilic esophagitis, eosinophilic pneumonia, eosinophilic psoriasis, hypereosinophilic syndrome, graft-versus-host disease, uveitis, cardiovascular disease, pain, multiple sclerosis, lupus, vasculitis, chronic idiopathic urticaria and Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss Syndrome), or
 35 polymyositis.

5. The method according to embodiment 1, wherein the musculoskeletal disorder is muscular dystrophy (e.g. Duchenne muscular dystrophy), sarcopenia, or sporadic inclusion body myositis.
- 5 6. The method according to embodiment 1, wherein the fibrosis is hepatic fibrosis, renal fibrosis, biliary fibrosis, pancreatic fibrosis, or idiopathic pulmonary fibrosis.
7. The method according to embodiment 1, wherein the autoimmune disease is multiple sclerosis, immune rejection, graft versus host disease, uveitis, optic neuropathies,
10 optic neuritis, transverse myelitis, inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, myasthenia gravis, Graves disease, ulcerative colitis, Crohn's disease, primary sclerosing cholangitis or primary biliary cholangitis. .
- 15 8. The method according to embodiment 1, wherein the neurodegenerative disease is dementia, Alzheimer's disease, amyotrophic lateral sclerosis, Huntingdon's disease, neurodegeneration or Parkinson's disease.
9. The method according to embodiment 1, wherein the gastrointestinal disorder is
20 inflammatory bowel disease, short bowel syndrome, coeliac disease or intestinal toxicity.
10. The method according to embodiment 1, wherein the disease or disorder is alcoholic liver disease (ALD) or cardiovascular disease.
- 25 11. The method according to any of embodiments 1 to 10, wherein the disease or disorder is one which is ameliorated by elevated cAMP levels.
12. The method according to any preceding embodiment, wherein the PDE4 inhibitor and
30 the GLP1 receptor agonist are administered for a treatment period which is at least 4 weeks, optionally at least 8 weeks.
13. The method according to any preceding embodiment, wherein the PDE4 inhibitor and the GLP1 receptor agonist are administered simultaneously, separately or sequentially.
- 35 14. The method according to any preceding embodiment, wherein the PDE4 inhibitor, or the pharmaceutically acceptable solvate thereof, is administered to the subject at a

total daily dose of no more than 500 mg, optionally no more than 250 mg, optionally no more than 120 mg, optionally no more than 80 mg, no more than 60 mg no more than 40 mg, no more than 20 mg or no more than 10 mg.

- 5 15. The method according to any preceding claim, wherein the PDE4 inhibitor is administered to the subject once daily or twice daily.
16. The method according to any preceding embodiment, wherein the PDE4 inhibitor is administered to the subject at a unit dose of from 0.01 mg to 250 mg, from 1 to 100
10 mg, from 5 to 70 mg, or from 10 to 60 mg, e.g. 5, 10, 15, 20, 30 or 40 mg.
17. The method according to any preceding embodiment, wherein the PDE4 inhibitor is administered to the subject orally.
- 15 18. The method according to any preceding embodiment, wherein the PDE4 inhibitor is administered to the subject in the form of a modified release formulation.
19. The method according to any preceding embodiment, wherein the PDE4 inhibitor is selected from difamilast, crisaborole, apremilast, roflumilast, ibudilast, drotaverine (e.g.
20 drotaverine hydrochloride), orismilast, mufemilast, tanimilast (tranimilast), ensifentrine, zatolmilast, BI-1015550, TQC-3721, ME-3183, PF-07038124 or a pharmaceutically acceptable salt, solvate or hydrate thereof.
20. The method according to embodiment 19, wherein the PDE4 inhibitor is orismilast, or
25 a pharmaceutically acceptable salt, solvate or hydrate thereof.
21. The method of embodiment 20, wherein the orismilast is administered to the subject in the form of a modified release formulation comprising the orismilast.
- 30 22. The method of embodiment 21, wherein the modified release formulation releases a mean amount of about 10% to about 70% of the orismilast after 45 minutes and more than about 70% after 180 minutes, optionally wherein the modified release formulation releases a mean amount of from about 11 % to about 65 % of the orismilast after 45 minutes and more than 75% of the orismilast after 180 minutes, further optionally
35 wherein the modified release formulation releases a mean amount of from about 35 % to about 65 % of the orismilast after 45 minutes and more than 70% of the orismilast after 180 minutes, further optionally wherein the modified release formulation releases

a mean amount of from about 35 % to about 55 % of the PDE4 inhibitor after 45 minutes and more than about 80% of the orismilast after 180 minutes. In each case above dissolution is determined using Ph. Eur. 2.9.3 Apparatus II, with a dissolution medium of 900 ml 0.5% sodium dodecyl sulfate in 0.1N HCl, a paddle speed of 75 rpm, and the dissolution medium at 37 ± 0.5 °C.

23. The method according to any one of embodiments 20-22, wherein the method comprises administering the orismilast to the subject, wherein:

(Ai) an initial orismilast dose is administered to the subject once per day for an initial time period followed by;

(Aii) an interim orismilast dose administered to the subject twice per day for an interim time period followed by;

(Aiii) a maintenance orismilast dose administered to the subject twice per day;

wherein:

(a) the initial orismilast dose and the interim orismilast dose are independently selected from 10 mg to 30 mg orismilast, provided that the interim orismilast dose is greater than or equal to the initial orismilast dose;

(b) the initial time period is two to eight weeks;

(c) the interim time period is one to eight weeks; and

(d) the maintenance orismilast dose is greater than the interim orismilast dose when the subject has a body mass that is greater than or equal to a threshold body mass, wherein the threshold body mass is at least 90 kg.

24. The method according to any preceding embodiment, wherein the GLP1R agonist is administered to the subject once or twice daily, optionally wherein the total daily dose of the GLP1R agonist is from about 1 µg to about 100 mg.

25. The method according to any preceding embodiment, wherein the GLP1R agonist is administered to the subject once or twice weekly, optionally wherein the total weekly dose of the GLP1R agonist is from about 0.05 mg to about 100 mg.

26. The method according to any preceding embodiment, wherein the GLP1R agonist is administered at a unit dose of from about 0.5 µg to about 500 mg, from about 1 µg to about 200 mg, from about 5 µg to about 100 mg, from about 10 µg to about 50 mg, from about 100 µg to about 10 mg, or from about 0.5 mg to about 4 mg.

27. The method according to any preceding embodiment, wherein the GLP1R agonist is administered to the subject orally or subcutaneously.
28. The method according to any preceding embodiment, wherein both the PDE4 inhibitor and the GLP1R agonist are administered to the subject orally, optionally wherein both the PDE4 inhibitor and the GLP1R agonist are administered to the subject once or twice daily.
29. The method according to any preceding embodiment, wherein the GLP1 receptor agonist is exenatide (including exenatide extended release), lixisenatide, beinaglutide, dulaglutide, liraglutide, semaglutide, albiglutide, efpeglenatide, PEG-Ionexatide or tirzepatide, or a pharmaceutically acceptable salt, solvate or hydrate thereof.
30. The method according to embodiment 29, wherein the GLP1 receptor agonist is semaglutide.
31. The method of any preceding embodiment, wherein the GLP1 receptor agonist is comprised within a combination product.
32. The method according to any preceding embodiment, the PDE4 inhibitor is orismilast, or a pharmaceutically acceptable salt, solvate or hydrate thereof, and the GLP1 receptor agonist is suitable for oral administration, optionally wherein the GLP1 receptor agonist is semaglutide or a pharmaceutically acceptable salt, solvate or hydrate thereof.
33. The method according to any preceding embodiment, wherein the method results in one or more of:
- A. a reduction in body weight, a reduction in body fat mass, a reduction in BMI, improved glycaemic control (e.g. increased time within normal levels (Time in Range (TIR))), a reduction in fasting plasma glucose (FPG), a reduction in 2-hour post-load plasma glucose, an increase in insulin sensitivity, a reduction in appetite or food intake, a reduction in a level of HbA1c, a reduction in fasting blood levels of triglycerides, a reduction in fasting blood levels of cholesterol, a reduction in fasting blood levels of insulin, a reduction in fasting blood levels of LDL, a reduction in waist circumference, a reduction in cholesterol ratio, a reduction in insulin resistance, a reduction in serum levels of CRP, IL-6, TNF- α , and/or resistin, improved beta-cell function, decreased beta-cell apoptosis,

increased beta-cell mass, improved glucose sensitivity to beta-cells, a reduction in blood pressure;

B. a reduction in liver fat, a reduction in a level of alanine transaminase (ALT) and/or aspartate aminotransferase (AST), a reduction in liver fibrosis,

C. improved nutrition (e.g. improved absorption of nutrients from the gut), a reduction or elimination of diarrhoea, constipation, nausea and/or vomiting, weight gain, and increased energy levels, improved liver function, a change (e.g. an increase) in serum albumin, reduced inflammation of the liver;

D. an improvement in, or a prevention or reduction in the rate of loss of: cognitive function, memory, speech, comprehension and/or motor control;

E. a reduction in pain, a reduction in inflammation, a reduction in/reversal of fibrosis, a reduction in or prevention of the progression of fibrosis, improved organ (e.g. kidney, liver, pancreas, lung) function, improved vision, a reduction in or prevention of immune rejection, a slowing or prevention of disease progression, and improved motor control and/or sensory function, greater ease of movement, and prevention of or reduction in the rate of muscle atrophy.

34. The method according to any preceding embodiment, wherein the method results in an reduction in body weight of at least 1 %.

35. The method according to any preceding embodiment, wherein the method results in an average reduction in body weight of at least 0.1% per week over the treatment period.

36. The method according to any preceding embodiment, wherein the subject is human.

37. A PDE4 inhibitor for use in the treatment or prevention of an inflammatory disease, an autoimmune disease, fibrosis, a neurodegenerative disease, a musculoskeletal disorder, a metabolic disease or disorder, alcoholic liver disease (ALD), cardiovascular disease or a gastrointestinal disorder, said use comprising co-administration of the PDE4 inhibitor with a GLP1 receptor agonist.

38. A GLP1 receptor agonist for use in the treatment or prevention of an inflammatory disease, an autoimmune disease, fibrosis, a neurodegenerative disease, a musculoskeletal disorder, a metabolic disease or disorder, alcoholic liver disease (ALD), cardiovascular disease or a gastrointestinal disorder, said use comprising co-administration of the GLP1 receptor agonist with a PDE4 inhibitor.
39. Use of a PDE4 inhibitor in the manufacture of a medicament for the treatment or prevention of an inflammatory disease, an autoimmune disease, fibrosis, a neurodegenerative disease, a musculoskeletal disorder, a metabolic disease or disorder, alcoholic liver disease (ALD), cardiovascular disease or a gastrointestinal disorder in a subject in need thereof by co-administration with a GLP1 receptor agonist.
40. Use of a GLP1 receptor agonist in the manufacture of a medicament for the treatment or prevention of an inflammatory disease, an autoimmune disease, fibrosis, a neurodegenerative disease, a musculoskeletal disorder, a metabolic disease or disorder, alcoholic liver disease (ALD), cardiovascular disease or a gastrointestinal disorder in a subject in need thereof by co-administration with a PDE4 inhibitor.
41. A combination comprising a PDE4 inhibitor and a GLP1 receptor agonist.
42. A pharmaceutical composition comprising the combination of embodiment 41.
43. A kit comprising the combination of embodiment 41, or the composition of embodiment 42, and instructions for use.
44. A product comprising a PDE4 inhibitor and a GLP1 receptor agonist for simultaneous, separate or sequential use in the treatment or prevention of an inflammatory disease, an autoimmune disease, fibrosis, a neurodegenerative disease, a musculoskeletal disorder, a metabolic disease or disorder, alcoholic liver disease (ALD), cardiovascular disease or a gastrointestinal disorder.

EXAMPLES

[00351] The invention is further illustrated by the following examples.

Example 1: Oral Modified Release Tablet Formulations

[00352] 10 mg and 30 mg orismilast and placebo oral modified release tablets according to Table 3 were prepared:

Table 3

Name of Components	Quantity per tablet			Function	Reference to Quality Standard(s)
	10 mg	30 mg	Placebo		
Drug Substance					
Orismilast ^{note 1}					
Excipients	10 mg	30 mg	-	Drug substance	
Lactose monohydrate					
Hypromellose ^{note 3}					
Silica, colloidal anhydrous	233 mg	213 mg	243 mg	Filler	Ph. Eur.
Magnesium stearate	52.5 mg	52.5 mg	52.5 mg	Matrix former	Ph. Eur.
	1.5 mg	1.5 mg	1.5 mg	Glidant	Ph. Eur.
	3.0 mg	3.0 mg	3.0 mg	Lubricant	Ph. Eur.
Tablet core weight	300 mg	300 mg	300 mg	-	-
Film coating					
Opadry [®] II ^{note 3}					
	12 mg	12 mg	12 mg	Film coating system	
Coated tablet weight	312 mg	312 mg	312 mg	-	-

5 Note 1: The orismilast was used as milled crystalline Form E with a D50 particle size distribution of 1 to 6 µm.

Note 2: The Hypromellose was Methocel[™] K100 Premium LV DC2; 2% viscosity in water at 20 °C 80-120 mPa.s; methoxyl content 22-24%, and hydroxypropyl content 7.5 to 9.5%

Note 3: Contain polyvinyl alcohol (Ph. Eur. 1961), macrogol (Ph. Eur. 1444), titanium dioxide (Ph. Eur. 0150), talc(Ph. Eur. 0438) and ferric oxide, yellow (NF).

10 [00353] The tablets were prepared by blending together the excipients and the orismilast and compressing into tablets using a rotary press to provide tablet cores. The tablet cores were then coated with the PVA based coating (Opadry II).

[00354] The mean dissolution profile for the 10 mg and 30 mg modified release tablets was measured using the Standard Dissolution Assay described in the description and gave the results shown in Table 4, wherein the % values refer to the % of orismilast in the dissolution medium at each time point:

5 **Table 4: *in-vitro* dissolution profile**

Time (min)	6	12	20	30	45	60	90	120	180	210
10mg	7%	15%	22%	28%	36%	42%	54%	64%	81%	97%
30mg	7%	14%	23%	31%	39%	46%	56%	66%	82%	99%

The dissolution profile is shown in Figure 3.

Characteristics of orismilast

[00355] The orismilast used in the modified release tablet formulations was orismilast crystalline Form E. The powder X-ray diffraction pattern (XRPD) for Form E is shown in Figure 1. The XRPD was obtained using an X'pert PRO MPD diffractometer from PANalytical configured with transmission geometry and equipped with a PIXcel detector. A continuous 2θ scan range of $3-45^\circ$ was used with a $\text{CuK}\alpha$ radiation $\lambda = 1.5418 \text{ \AA}$ source and a generator power of 40 mA and 45 kV. A 2θ step size of $0.0070^\circ/\text{step}$ with a step time of 148.92 s was used. Samples were gently flattened onto a well in a 96-well plate for transmission measurements. The well plate was moved forward and backward in the x direction and all experiments were performed at room temperature. The 2θ peak values of the XRPD for orismilast Form E are shown in Table C:

Table C:

Peak Position ($2\theta \pm 0.2^\circ$)	Relative Intensity (%)	Peak Position ($2\theta \pm 0.2^\circ$)	Relative Intensity (%)
5.9	4.1	21.9	6.6
8.0	18.0	22.0	8.0
8.6	8.6	22.3	18.9
8.7	5.0	22.9	11.9
9.8	3.2	23.1	9.6
11.8	11.4	23.4	39.5
12.1	3.5	23.6	19.3
14.1	11.9	23.9	12.2

14.4	5.8	24.1	11.8
15.0	24.1	24.4	16.5
15.2	3.3	24.7	9.4
16.0	73.5	25.6	19.6
16.4	22.5	25.8	19.4
16.6	13.0	26.2	11.0
16.8	28.5	26.3	11.5
17.0	8.1	26.6	9.0
17.3	15.4	27.3	17.7
17.7	8.1	27.8	12.8
18.1	100.0	28.1	13.7
18.5	31.6	28.3	12.2
19.3	5.1	28.6	9.8
19.7	25.1	29.2	9.4
19.9	16.8	29.5	19.2
20.0	28.1	29.7	27.8
20.2	25.0	30.0	14.1
20.3	16.1	30.5	14.3
21.4	34.2	31.5	5.8
21.5	32.6	31.7	5.2
21.6	11.2		

[00356] The Form E was also characterised using DSC using a TA instrument Q20 systems. A few mg of sample was gently charged into and weighed in Al pans. A lid with pre-made pin-hole was adapted and crimped onto the pan. Both modulated temperature profiles and traditional temperature profiles were used with varying heating rates of 2 - 10 °C/min. The DSC traces for two batches (mean of two measurements) of orismilast is shown in Figure 2. The Form E exhibited melting endotherms with onset temperatures of 211.6 °C and 211.7 °C and enthalpy changes of 83 J/g and 85 J/g. No glass transition was observed in the modulated DSC of the two samples, indicating the Form E was crystalline with no detectable amorphous material present.

Example 2: Oral orismilast in hidradenitis suppurativa (HS), a clinical investigator initiated study

[00357] The 10 mg and 30 mg orismilast tablet used in the clinical trial described in this example are modified release tablets described in Table 5.

Table 5

	Quantity per tablet		
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Name of Components	10 mg	30 mg	Placebo	Function	Reference to Quality
Drug Substance					
Compound of formula (I) (orismilast)	10 mg	30 mg	-	Drug substance	
Excipients					
Lactose monohydrate					
Hypromellose	233 mg	213 mg	243 mg	Filler	Ph. Eur. 0187
Silica, colloidal anhydrous	52.5 mg	52.5 mg	52.5 mg	Matrix former	Ph. Eur. 0348
	1.5 mg	1.5 mg	1.5 mg	Glidant	Ph. Eur. 0434
Magnesium stearate	3.0 mg	3.0 mg	3.0 mg	Lubricant	Ph. Eur. 0229
Tablet core weight	300 mg	300 mg	300 mg	-	-
Film coating					
Opadry® II Note 1	12 mg	12 mg	12 mg	Film coating	
Coated tablet weight	312 mg	312 mg	312 mg	-	-

Note 1: Contain polyvinyl alcohol (Ph. Eur. 1961), macrogol (Ph. Eur. 1444), titanium dioxide (Ph. Eur. 0150), talc(Ph. Eur. 0438) and ferric oxide, yellow (NF).

Objectives and endpoints

[00358] Primary endpoint:

- 5 • Percent change from Baseline in AN (abscesses and nodules) count at Week 16.

[00359] Secondary endpoints:

- Change from Baseline in abscess, nodule, and draining fistula counts at Week 16.
- Change from Baseline in IHS4 value at Week 16.
- Change from Baseline in Patient's Global Assessment of Skin Pain (NRS) at Week 16.
- Change from Baseline in HiS-QoL Total Score at Week 16

[00360] Safety endpoints:

- Occurrence of treatment emergent adverse events (AEs).
- Change in clinical laboratory parameters (haematology and biochemistry).
- Change in vital signs.
- 5 • Change in weight.

[00361] Investigator assessed endpoints:

- Patients achieving HiSCR at Week 16.
- Patients achieving HiSCR 75 at Week 16.
- Patients achieving HiSCR 90 at Week 16.
- 10 • Patients achieving HS-PGA score of 0 or 1 at Week 16.
- At least 50, 75, 90, or 100 percent reduction in total abscess and inflammatory nodule count over time.
- Change from baseline in high-sensitivity C-Reactive Protein (hs-CRP) over time.
- HiSCR over time.
- 15 • Change from baseline in IHS4 value over time.
- Change in IHS4 category over time.
- HS-PGA score of 0 or 1 over time.

Use of rescue treatment (max 2 during active treatment, as needed during the follow-up).

[00362] Patients assessed endpoints:

- 20 • At least 30% reduction from baseline in Patient's Global Assessment of Skin Pain at Week 16 (NRS30).
- Patient Global Assessment score over time
- Patients with flares at each visit and patients with at least one flare during treatment assessed at Week 16 (Flares defined as an at least 25% increase in AN counts with a
- 25 minimum increase of 2 relative to Baseline).
- Change from Baseline in DLQI Score at Week 16.
- Change from Baseline in pruritus NRS over time.
- Change from Baseline in discharge NRS over time.

- At least 30% reduction from Baseline in Patient's Global Assessment of Skin Pain over time (NRS30).
 - Change from baseline in HiSQOL Total Score over time.
 - Change from baseline in Fatigue, DLQI, WPAI, McGill Pain, HADS, and EQ-5D.
- 5 • Duration of remission after the end of IMP.

Abbreviations: DLQI= Dermatology Life Quality Index; EQ-5D= European Quality of life - 5 Dimensions; HADS= Hospital Anxiety and Depression Scale; HiSCR= Hidradenitis Suppurativa Clinical Response; HiSQOL= Hidradenitis Suppurativa Quality of Life; HS= Hidradenitis Suppurativa; Hs-CRP= High sensitivity C-Reactive Protein; HS-PGA= Physician
 10 Global Assessment; IHS4= International Hidradenitis Suppurativa Severity Score System; IMP= investigational medicinal product; NRS= numerical rating scale; WPAI= Work productivity and activity impairment.

Overall trial design

[00363] This is a phase 2, single-centre, prospective, open-label, single-arm, exploratory
 15 clinical trial assessing the efficacy and safety of orismilast in patients with mild, moderate, or severe HS as defined by the IHS4 scores: A score of 3 or less signifies mild, a score of 4-10 signifies moderate and a score of 11 or higher signifies severe disease.

[00364] After signing the informed consent, and if all eligibility criteria are met, patients
 20 will be graded and assigned to a severity group. All groups will receive the same intervention.

[00365] Eligible patients will receive treatment with orismilast tablets twice daily for 16 weeks. The treatment dose will be according to a predefined titration scheme and adapted to the observed tolerance of each patient.

[00366] 24 adult patients (men and women) will be included; 8 with mild, 8 with moderate,
 25 and 8 with severe HS.

[00367] The patients will enter into a 10-visit trial, including the screening and End-of-Study visit, 6 of which will be on-site visits, and 4 of which will be telephone consultations. The maximum duration of the trial, considering the screening phase of up to 4 weeks and a follow up phase of 14 weeks, is 34 weeks.

[00368] For each patient the duration of the trial will consist of 3 phases:

- Screening phase (up to 4 weeks duration)
- Treatment phase (16 weeks)

- Follow up (14 weeks)

An End of Study visit will be scheduled 14 weeks after last orismilast administration.

[00369] In addition to the standard site visit conducted at the trial site, this trial introduces telephone consultations (TC). These TCs will be conducted through a mandatory telephone call with the aim to reduce the burden of frequent site visits while ensuring close safety monitoring of patients.

[00370] The standard site visits are conducted at Screening, Baseline, Week 2, 8, 16 (End of Treatment) and 14 weeks after last IMP administration (End of Study). At each standard site visit the (sub)investigator will administer IMP including return and compliance check, as applicable.

[00371] The TCs are conducted at Week 1, 4, 12, and Follow-up (42 days after last drug administration). The patient will be contacted by the (sub)investigator who will collect assessments.

Individual phases

[00372] Screening phase: Prior to the performance of any trial related procedure, signed informed consent must be obtained from the patient. The screening phase will consist of 1 screening visit (Visit 1).

[00373] Treatment phase: The treatment phase will consist of an initial 2 weeks titration with progressive increase in dose from 10 mg BID to 30 mg BID (Week 0 [Visit 2], Week 1 [Visit 3; Telephone consultation], and Week 2 [Visit 4]) ("BID" means *bis in die*, i.e. twice per day).

[00374] At Week 2 (Visit 4) the investigator and patient will decide if further up-titration to reach 40 mg BID should be initiated. If further up-titration is initiated, the patient will increase the morning dose to 40 mg and maintain the evening dose at 30 mg during the next 2 days. At day 3 after the Week 2 visit, the dose will be increased to 40 mg BID and this dose will be maintained until the end of the treatment period (Week 16). During this part of the treatment phase, the patient will have a telephone consultation at Week 4 (Visit 5) and Week 12 (Visit 7) and will be required to return to the trial site at Week 8 (Visit 6) and Week 16 (Visit 8 [End of Treatment]).

[00375] Assessment of treatment efficacy will be undertaken using:

1. Investigator assessments:

- a. Counts of abscess, inflammatory nodule, and draining fistula at each on site visit day.

b. International Hidradenitis Suppurativa Severity Score System (IHS4) at each on site visit day.

c. Physician's Global Assessment of disease severity (HS-PGA) at each on site visit day.

5 2. Patient assessments

a. Patients' Global Assessment of disease severity at Screening, Baseline, Week 2 (Visit 4), Week 8 (Visit 6), Week 12 (Visit 7), Week 16 (EoT, Visit 8), FU (Visit 9), and EoS (Visit 10).

10 b. Completion of questionnaires covering skin related quality of life DLQI at Screening, Baseline, Week 2 (Visit 4), Week 8 (Visit 6), Week 12 (Visit 7), Week 16 (EoT), FU, and EoS.

c. Completion of questionnaires covering HS specific quality of life (HiSQOL) at Screening, Baseline, Week 2 (Visit 4), Week 8 (Visit 6), Week 12 (Visit 7), Week 16 (EoT), FU, and EoS.

15 d. Completion of questionnaire covering skin pain (Patient's Global Assessment of Skin Pain) at each visit day.

e. Completion of questionnaire covering impact on work productivity (WPAI), anxiety and depression (HADS), fatigue (MFI-20), quality of life (EQ-5D), and McGill Pain questionnaire at Baseline, Week 16 (EoT), and EoS.

20 **[00376]** Safety and tolerability will be assessed by AE recording, vital signs (blood pressure, heart rate, body temperature), physical examination, ECG, and clinical laboratory (blood and urine).

[00377] Biomarker assessment comprising

25 - thermography of selected regions to assess temperature as a surrogate measure of inflammation and explore the methods utility as a biophysical biomarker.

- ultrasound before and after treatment to evaluate target lesion identified clinically at baseline, and carefully described (location) and photographed to facilitate later recognition.

- inflammatory biomarkers (CRP and neutrophilocyte/lymphocyte ratio)

30 - skin biopsy before and after treatment to assess inflammatory markers (cytokines)

- skin microbiome collected by simple skin swab.

[00378] In the case of early withdrawal from treatment before the Week 16 (Visit 8), the assessments scheduled for Visit 8 should be done at the end of treatment. Early withdrawal assessments should be performed as soon as possible.

Follow up phase: At Week 16, patients will roll-over to a no treatment observational period of up to Week 30. Conventional therapy will be started at the discretion of the patient. A follow up visit (TC) is scheduled 6 weeks after last IMP administration (Visit 9) and the End of Study visit (Visit 10) is scheduled 14 weeks after last IMP administration. For serious adverse events (SAEs), follow-up should continue until final outcome. In the case of early withdrawal from follow up before the End of Study visit (Visit 10) the assessments scheduled for Visit 10 should be done as soon as possible.

[00379] End of Trial Definition: The end of the trial is defined as the date of the last patient's last visit.

[00380] Trial Population: Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted. Adult male and female patients with mild to severe HS will be included in the trial if they fulfil all the inclusion criteria and do not present with any of the exclusion criteria.

Inclusion criteria:

- Male or female adult patients, 18 years of age or older.
- Have mild to severe HS for at least 1 year prior to the baseline visit, as determined by the investigator through participant interview and/or review of the medical history.
- Have HS lesions in at least 2 distinct anatomic area (right/left axillary, inguinal, inframammary, abdominal, perineal).
- Has a total inflammatory lesions (AN) count of greater than or equal to 2.
- Total draining fistula count of less than or equal to 30.
- A stable analgesic dose for 2 weeks prior to baseline.
- Women of childbearing potential (WOCBP) must be ready and able to use highly effective methods of birth control per ICH M3 that result in a low failure rate of less than 1% per year when used consistently and correctly, for the duration of the trial and 16 weeks after last administration. A list of contraception methods meeting these criteria is provided in the patient information.
- Signed and dated written informed consent in accordance with GCP and local legislation prior to the start of any screening procedures.

Exclusion criteria:

1. Presence of active skin lesions other than HS that could interfere with the assessment of HS.
2. Receipt of prescription topical therapies for HS within 7 days prior to the baseline visit (Visit 2).
- 5 3. Receipt of systemic therapies for HS, within 28 days prior to the baseline visit.
4. Any oral antibiotic within 28 days prior to baseline visit.
5. Receipt of a live vaccine within 14 days prior to screening.
6. Biologic use for indications other than HS within a minimum of 30 days or 5 half-lives of the drug, whichever is longer, prior to baseline.
- 10 7. Treatment with any investigational drug of chemical or biologic nature within a minimum of 30 days or 5 half-lives of the drug, whichever is longer, prior to baseline.
8. Patients who are immunosuppressed, or are taking medication that could have an immunosuppressive effect.
9. Women who are pregnant, nursing, or who plan to become pregnant while in the trial. Women who stop nursing before the study drug administration do not need to be excluded from participating.
- 15 10. Active systemic infection and/or fever – or clinical signs of local infection (stinging, increased soreness, burning sensation, erythematous perilesional halo or other signs of infection) - during the last 2 weeks prior to first drug administration.
- 20 11. History of allergy/hypersensitivity to the systemically administered trial medication agent or its excipients.
12. Patient with a transplanted organ (with exception of a corneal transplant > 12 weeks prior to screening) or who have ever received stem cell therapy (e.g., Remestemcel-L).
13. Any documented active or suspected malignancy or history of malignancy within 5 years prior to the screening visit, except appropriately treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix.
- 25 14. Relevant chronic or acute infections (exception: common cold), as determined by the investigator, including human immunodeficiency virus (HIV) or viral hepatitis. A patient can be re-screened if the patient was treated and is cured from the acute infection.
- 30 a. In case of a positive hepatitis C antibody test, a positive reflex testing for Hepatitis C RNA PCR is considered positive.

15. Major surgery (major according to the investigator) performed within 12 weeks prior to first study drug administration or planned during the study (e.g. hip replacement, aneurysm removal, stomach ligation).

16. Severe, progressive, or uncontrolled hepatic disease, defined as >3-fold Upper Limit of Normal (ULN) elevation in AST or ALT or alkaline phosphatase, and >2-fold ULN elevation in alkaline phosphatase.

17. Evidence of a current or previous disease, medical condition (including chronic alcohol or drug abuse or any condition) other than HS, surgical procedure, psychiatric or social problems, medical examination finding (including vital signs and ECG), or laboratory value at the screening outside the reference range that in the opinion of the investigator is clinically significant and would compromise the safety of the patient or compromise the quality of the data, make the study participant unreliable to adhere to the protocol, comply with all study visits/procedures or to complete the trial.

18. Planned use of laser or other hair removal procedures over HS-affected areas during the trial period.

19. Planned HS surgery during the trial period.

20. Any condition for which the use of any prohibited medication (see Table 16) is indicated.

Treatments administered

Table 6 shows an example of an medicinal product that may be investigated using the trial:

Table 6: Identification of investigational medicinal product

Study Treatment Name:	Orismilast modified release tablet
Dosage formulation:	Tablet
Unit dose strength(s)/Dosage level(s):	10 mg 30 mg
Active ingredient name	Orismilast (compound of formula (I))
Excipients	See Table 2
Route of Administration	oral

Study Treatment Name:	Orismilast modified release tablet
Dosing instructions:	Twice daily, morning and evening There should be at least 8 hours between the 2 administrations
Packaging and Labelling	Orismilast will be provided in alu-alu blister packaging with 10 tablets each

[00381] Patients will be instructed to take tablets of IMP at home two times daily. One dose in the morning and one dose in the evening, starting from Day 1 onwards according to the dose titration scheme, Table 7.

- 5 **[00382]** Patients will be provided with treatment instructions containing further guidance and precautions to follow when taking the IMP.

[00383] During the first 2 weeks there will be a progressive increase in dose until Week 2 (Visit 4) when the patient will be at 30 mg BID. At this visit the investigator and patient will decide if further up-titration to reach 40 mg BID should be initiated. If further up-titration is initiated, the patient will increase the morning dose to 40 mg and maintain the evening dose at 30 mg during the next 2 days. At day 3 after the Week 2 visit, the dose will be increased to 40 mg BID and this dose will be maintained until the end of the treatment period (Week 16).

[00384] In case of uncertainties or start of adverse events (AEs), the patient will primarily have telephonic access to a study-nurse. Should the patient wish to do so, or develop symptoms of AEs, the patient can discuss with the investigator the decrease of the daily dose to the last well tolerated dose. If this new dose is well tolerated, a new increase in the dose is left at the discretion of the patient and investigator.

Table 7: Dose titration scheme

Day	D1	D1	D2	D2	D3	D3	D4	D4
	AM	PM	AM	PM	AM	PM	AM	PM
Dose, mg	10	10	10+10	10	10+10	10+10	10+10	10+10

Day	D5 AM	D5 PM	D6 AM	D6 PM	D7 AM	D7 PM	From D8 to W2 visit AM/PM	W2 visit+1 & W2 visit + 2	From W2 visit + 3 until EoT
Dose, mg	30	10+10	30	10+10	30	30	30 / 2	30+10/ 30	30+10 / 30+10

EOT = End of Treatment

[00385] Prohibited medications: Restricted medications are not allowed while the patient is on trial treatment and prior to visit 2 for durations as specified below, Table 8. Patients are allowed restricted medication in the follow-up period after the last treatment.

5 **Table 8: Prohibited treatments/medications**

Medication	Washout period prior to Visit 2 (baseline)
Topical antibacterial agents for HS	1 week
Topical corticosteroids for HS	1 week
Systemic antibiotics ¹	4 weeks
Systemic corticosteroids	4 weeks
Biologics	12 weeks
Other systemic immunomodulatory agents	4 weeks
Live vaccines	6 weeks
Opioid analgesics ²	2 weeks
Non-opioid analgesics ³	1 week
Spirolactone ⁴	1 week
Metformin ⁴	1 week
Topical cannabis oil ⁵	1 week
Tricyclic antidepressants (e.g., nortriptyline, amitriptyline, imipramine, desipramine)	4 weeks
Type 1C antiarrhythmics (e.g. propafenone, flecainide, encainide)	4 weeks

¹ Systemic antibiotics can be used for indications other than HS and for a duration of less than or equal to 28 days during the entire course of the trial. (until last treatment)

² Opiate analgesics restricted for HS and non-HS indications.

³ Non-opioid analgesics for HS allowed for as needed use. Analgesics for indications other than HS only as needed.

⁴ Restricted if used for HS. If used for non-HS indication, dose should be stable over 3 months prior to V2.

⁵ Restricted if used for HS/ over affected areas. Other alternative therapies for HS are restricted, unless permitted after discussion with PI and trial team.

[00386] Efficacy assessments: Assessment of treatment efficacy will be undertaken using:

Investigator assessments:

- Counts of abscess, inflammatory nodule, and draining fistula. The lesions are defined in a Pan-European consensus paper (Daxhelet *et al.*, Dermatology. 2020;236(5):431-438). A nodule is defined as a palpable lesion, with a solid content, round rather than pointed, diameter >10 mm; usually deep seated, not raised; painful (spontaneously or on palpation) or not; inflammatory or not. An abscess is defined as a palpable lesion, with liquid content (pus), fluctuant, soft on palpation, diameter >10 mm, usually deep seated; acute, very painful phenomenon. A fistula is defined as one or several long, permeable channels connecting 2 (or more) suppurative cavities and/or skin openings, draining or not.
- 10 • Hidradenitis Suppurativa Clinical Response (HiSCR): A treatment target based on correlation between the changes in lesion counts and PROM (pain and HRQoL). Hidradenitis Suppurativa Clinical Response (HiSCR; a $\geq 50\%$ reduction from baseline in abscess and inflammatory nodule count and no increase in abscess or draining fistula counts) (Kimball *et al.*, Ann Intern Med. 2012 Dec 18;157(12):846-55; Kimball *et al.*, J Eur Acad Dermatol Venereol. 2016 Jun;30(6):989-94). Subsequently modified for further differentiation: HiSCR75; a $\geq 75\%$ reduction from baseline in abscess and inflammatory nodule count and no increase in abscess or draining fistula counts) and HiSCR-90; a $\geq 90\%$ reduction from baseline in abscess and inflammatory nodule count and no increase in abscess or draining fistula counts)
- 20 • International Hidradenitis Suppurativa Severity Score System (IHS4): A validated international clinimetric scale (Zouboulis *et al.*, Br J Dermatol. 2017 Nov;177(5):1401-1409). The score is based on a count of inflamed lesions. The resulting IHS4 score is arrived at by the number of nodules (multiplied by 1) plus the number of abscesses (multiplied by 2) plus the number of draining tunnels (multiplied by 4). A total score of 3 or less signifies mild, 4-10 signifies moderate and 11 or higher signifies severe disease.
- 25 • Physician's Global Assessment of disease severity (HS-PGA): The six-point hidradenitis suppurativa Physician Global Assessment (PGA) ranges from clear to very severe (Kimball *et al.*, Ann Intern Med. 2012 Dec 18;157(12):846-55). It is used in clinical trials to measure clinical improvement in inflammatory nodules, abscesses, and draining fistulae. The six stages are;
 - Clear: No inflammatory or non-inflammatory nodules.
 - Minimal: Only the presence of non-inflammatory nodules.
 - Mild: Less than 5 inflammatory nodules or 1 abscess or draining fistula and no inflammatory nodules.
- 30

Moderate: Less than 5 inflammatory nodules, or 1 abscess or draining fistula and 1 or more inflammatory nodules, or 2-5 abscesses or draining fistulas and less than 10 inflammatory nodules.

Severe: 2-5 abscesses or draining fistulas and 10 or more inflammatory nodules.

5 Very severe: More than 5 abscesses or draining fistulas.

Patient assessments:

- Patients' Global Assessment of disease severity using an anchored (0=no disease, 10=worst imaginable disease severity) 0-10 Numerical Rating Scale (NRS).
- Completion of questionnaire covering skin pain Patient's Global Assessment of Skin Pain (0=no pain, 10=worst imaginable pain) 0-10 Numerical Rating Scale (NRS).

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In addition, patients will complete the following questionnaires:

- Completion of questionnaires covering HS specific quality of life (HiSQOL).
- Completion of questionnaires covering skin related quality of life DLQI.
- Completion of questionnaires covering quality of life EQ-5D.
- Completion of questionnaire covering pain McGill Pain questionnaire.
- Completion of questionnaire covering impact on work productivity (WPAI).
- Completion of questionnaire covering fatigue (MFI-20)
- Completion of questionnaire covering anxiety and depression (HADS).
- The Hidradenitis Suppurativa Quality of Life (HiSQOL): The HiSQOL is based on the work of the Hidradenitis Suppurativa cORe outcomes set International Collaboration (HISTORIC). HiSQOL has been developed and validated systematically and is a 17-item questionnaire that contains HS specific items such as drainage and odor in addition to more general skin specific items. HiSQOL is a HS-specific questionnaire designed to evaluate HRQOL in clinical trials (Thorlacius *et al.*, Skin Appendage Disord. 2019 Jun;5(4):221-229; Kirby *et al.*, Br_J Dermatol. 2020 Aug;183(2):340-348). It has a recall-period of 7 days and consists of 17 items divided into three domains: Four symptom questions, five psychosocial questions, and eight activities adaptation questions. For each item a score between 0 and 4 is given, with a higher score representing a greater adverse impact on HRQOL. The scores are summated for all items (maximum score: 68)¹. Correlation with DLQI was 0.9, demonstrating very strong convergent validity.

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- Dermatology Life Quality Index (DLQI): A questionnaire of 10 questions concerning the patients' perception of the impact of skin diseases on different aspects of their health-related quality of life over the last week. Each question is scored on a four-point scale (0-3) resulting in a range of 0-30 points (0=Disease has no impact on quality of life, 30= Disease has maximum impact on quality of life). A validated scale first introduced by Finlay and Khan, Clin. Exp. Dermatol., 19 (1994), pp.210-216).
- European quality of life - 5 Dimensions on a 5-level scale (EQ-5D-5L): An EQ-5D is a standardized instrument for measuring generic health status in terms of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension receives a value of 1-5 leaving 55 55) different health states. The score is combined with an overall patient rating of health from 0 -100 where 0 is worst imaginable health and 100 is best imaginable health. The scale was further developed from the original EQ-5D by Herdman *et al.*, Qual Life Res. 2011 Dec;20(10):1727-36).
- McGill Pain questionnaire: This can be used to evaluate the sensation, strength and change over time of experienced pain. It can monitor pain over time or determine the effectiveness of intervention (Melzack, Pain: September 1975, Volume 1, Issue 3, p277-299).
- Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP): A questionnaire describing work impairment due to a specific disease. Outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity (Reilly *et al.*, Pharmacoeconomics. 1993 Nov;4(5):353-65).
- Anxiety and depression (HADS): A questionnaire comprising seven questions for anxiety and seven questions for depression. Each question is connected to four answers retrieving 0-3 points. For each condition, 0-7 points corresponds to normal case; 8-10 to borderline abnormal; and 11-21 to abnormal case (Zigmond and Snaith, Acta Psychiatrica Scandinavica (1983), 67(6): 361-370).
- Multidimensional Fatigue Inventory 20 (MFI-20): The MFI-20 was invented by Smets *et al.*, J Psychosom Res 1995; 39: 315–25. It consists of 20 items describing five subscales of fatigue: General Fatigue (GF), Physical Fatigue (PF), Reduced Motivation (RM), Reduced Activity (RA), and Mental Fatigue (MF). For each of the items the respondent must specify the extent to which the particular statements relate to him/her on a five-point scale, ranging from Yes, that is true to No, that is not true.

[00387] Biomarkers: Samples for biomarker research will be collected from all patients. The following biomarkers will be evaluated to explore possible differences in patients with mild,

moderate, or severe HS and to evaluate their association with the observed clinical responses to orismilast:

- Thermography of selected region.
- Ultrasound of target lesion.
- 5 • CRP (plasma).
- Neutrophilocyte/lymphocyte ratio (plasma).
- Inflammatory markers (cytokines) in skin (biopsies before and after treatment). Skin biopsies will be obtained as a standard 4mm punch biopsy at day 0 and week 16. Samples will be stored for analyses (to be performed after the last visit of the last patient) in the
- 10 biobank of Zeeland University Hospital, Roskilde and destroyed after analysis.
- Skin microbiome before and after treatment by simple skin swab.

Efficacy analyses

Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint, percent change in AN count from baseline to Week 16, will be

15 analysed for the full analysis set and the per protocol set.

AN count at each visit and for each severity group will be summarised. Change and percent change from baseline to Week 16 will also be included. For the Week 16 visit both observed data and completed data (with missing data imputed using LOCF imputation) will be presented.

20 The primary endpoint, percent change in AN count at Week 16, will be compared pair wise between severity groups using t-test supplemented by non-parametric Mann-Whitney U Test.

For the total sample the null hypothesis of no change from Baseline to week 16, $H_0: \mu = 0$, will be tested using a one-sample t-test. The 95% confidence interval for the percentage

25 change will be estimated

Analysis of Secondary Efficacy Endpoints

All secondary efficacy endpoints will be analysed for the full analysis set.

Abscess, nodule, and draining fistula counts, IHS4, patients global assessment pain (NRS) and HiSQOL Total Score will be tabulated for each visit. The change from baseline to Week

30 16 will be included also.

The change from Baseline in abscess, nodule, and draining fistula counts, IHS4, patients global assessment pain (NRS), and HiSQOL Total Score to Week 16, will be compared pair wise between severity groups using t-test supplemented by non-parametric Mann-Whitney U Test.

- 5 For the total sample the null hypothesis of no change from Baseline to week 16, $H_0: \mu = 0$, will be tested using a one-sample t-test. The 95% confidence interval for the percentage change will be estimated.

Analysis of Other Endpoints assessed by the investigator and by patients

- 10 All other endpoints will be summarized for the full analysis set. Tabulations of data may be supplemented by graphic displays. In general, no formal significance tests will be applied.

Patients achieving HiSCR at Week 16, patients achieving HiSCR75 at Week 16, and patients achieving HiSCR90 at Week 16

- 15 The number and percentage of patients who achieve each of these endpoints will be tabulated for each severity group. In addition, the number and percentage of patients who achieve HiSCR will be tabulated for each severity group at each visit.

For the total sample the null hypothesis of no response to treatment at week 16, $H_0: p = 0$, will be tested using a binominal test. The 95% confidence interval for the percentage of patients achieving HiSCR will be estimated using the binominal distribution.

Investigators global assessment of disease severity (HS-PGA)

- 20 The number and percentage of patients who achieve 'treatment success' according to HS-PGA (score 0 or 1) will be tabulated at each visit for each severity group.

Patients with at least 50%, 75%, 90%, or 100% reduction from baseline in total abscess and nodule count (AN count) over time.

- 25 The number and percentage of subjects who achieve these end points will be tabulated at each visit for each severity group.

Change from baseline in High-Sensitivity C-Reactive Protein (hs-CRP) will be summarized for each severity group at each visit.

Patient's global assessment of disease severity and HiSQOL Total Score and change from Baseline will be summarized at each visit and for each severity group.

- 30 IHS4 score and change from baseline will be summarized at each visit and for each severity group.

Change in IHS4 category over time.

The IHS4 category (mild, moderate, severe) will be tabulated for each visit. The change in

category will for each visit be summarized for each severity group as proportion of patients changing status as worsening, no change and improving severity category.

Patients with at least 30% reduction from baseline in Patient's Global Assessment of Skin Pain over time. The number and percentage of subjects who achieve this end point will be tabulated at each visit for each severity group.

Change from baseline in pruritus and discharge as assessed by NRS will be summarized for each severity group at each visit.

European Quality of life - 5 Dimensions (EQ-5D)

Each of the 5 dimensions 'mobility', 'self-care', 'usual activities', 'pain/discomfort', and 'anxiety/depression', the index score, will be summarized at each visit and for each severity group.

Dermatology Life Quality Index (DLQI)

The total DLQI score and change in DLQI will be summarized at each visit and for each severity group.

Hospitality Anxiety and Depression Scale (HADS)

The total HADS score and change in HADS score will be summarized for each severity group at Baseline and Week 16.

WPAI, McGill Pain, and Fatigue assessed by MFI-20

The total score will be summarized for each severity group at Baseline and Week 16. The change from Baseline to Week 16 will be summarized also.

Duration of remission

The remission period is the time between EoT and relapse date, relapse date being defined as the earliest date where the patient would have lost at least 50% of the benefit he got during the treatment phase assessed by % change in AN count.

For those patients who experience a reduction in AN count from baseline to EoT the median remission time will be estimated using a Kaplan-Meier survival analysis.

Patients with flares

A flare is determined as an at least 25% increase in AN counts with a minimum increase of 2 relative to Baseline.

The proportion of patients with flares will be tabulated at each visit for each severity group.

In addition, the proportion of patients who experienced at least one flare during treatment period from baseline to week 16 will be tabulated for each severity group.

Summary of Results

The trial is ongoing. The observed effect of the treatment on the weight of the subjects is shown in Table 9.

Table 9

Subject	Baseline BMI	Baseline weight	Max dose (mg BID)	Tolerated dose	Treatment duration (weeks)	Weekly weight change (kg)	Weight change (kg)	Weekly % change
1	33	100.6	40	40 mg BID	16	-0.075	-1.2	-0.1
2	25	72.5	40	NI	16	-0.41875	-6.7	-0.6
3	60	165.9	30	NI	4	-0.1	-0.4	-0.1
4	20	66.9	40	NI	2	-1.35	-2.7	-2
7	45	144.7	40	20 mg BID	16	-0.95625	-15.3	-0.7
10	26	67	10	10 mg daily	16	0	0	0
13	38.4	127.5	40	10-20 mg BID	16	-0.2125	-3.4	-0.2
14	34.9	126.1	40	30 + 20 mg	14	-0.171429	+2.4	+0.1
16	41.1	124.1	40	30 mg BID	16	-0.8875	-14.2	-0.7
17	32.6	90.8	?	?	16	-0.3	-4.8	-0.3
18	33.6	86.1	40	10 mg BID	8	-0.2375	-1.9	-0.3
19	23.27	84.1	30	10 mg BID	16	-0.175	-2.8	-0.2
20	35.43	99.5	30	10 + 20 mg	8	-0.1875	+1.5	+0.2

5 Orismilast modified release tablet formulations used in the clinical trials described in Examples 3 and 6

[00388] The following orismilast modified release tablet formulations were used in the clinical trials described in Examples 3 and 6 herein

Component	Amount		
	10 mg MR tablet	20 mg MR tablet	30 mg MR tablet
Orismilast ¹	10 mg	20 mg	30 mg
Lactose monohydrate ²	233 mg	223 mg	213 mg
HPMC ³	52.5 mg	52.5 mg	52.5 mg
Anhydrous colloidal silica ⁴	1.5 mg	1.5 mg	1.5 mg
Magnesium stearate ⁵	3.0 mg	3.0 mg	3.0 mg

Core weight	300 mg	300 mg	300 mg
Opadry® II 6	12 mg	12 mg	12 mg
Coated core weight	312 mg	312 mg	312 mg

Note 1: The orismilast was used as milled crystalline Form E with a D50 particle size distribution of <1 to 6 µm and a D(90) ≤ 10 µm

Note 2: Ph. Eur. 0187

- 5 Note 3: Hypromellose: Methocel™ K100 Premium LV DC2; 2% viscosity in water at 20 °C 80-120 mPa.s; methoxyl content 22-24%, and hydroxypropyl content 7.5 to 9.5%

Note 4: Ph. Eur. 0434

Note 5: Ph. Eur. 0229

- 10 Note 6: Contain polyvinyl alcohol (Ph. Eur. 1961), macrogol (Ph. Eur. 1444), titanium dioxide (Ph. Eur. 0150), talc(Ph. Eur. 0438) and ferric oxide, yellow (NF).

Example 3: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 2b Dose-Ranging Study to Evaluate the Efficacy and Safety of Orismilast in Adults with Moderate-to-Severe Plaque-Type Psoriasis.

- 15 **[00389]** The following phase 2b clinical trial was carried out:

Primary objective:

To evaluate the efficacy and safety of a modified-release orismilast tablet versus placebo in adults with moderate-to-severe plaque-type psoriasis.

Primary endpoint:

- 20 • Percentage change in Psoriasis Activity and Severity Index (PASI) score from Baseline at Week 16.

Key secondary endpoints

- 25 • Patients achieving 75% reduction in PASI (PASI75) response at Week 16.
• Patients achieving a score of Clear (0) or Almost Clear (1) and an at least 2-point improvement in Investigator Global Assessment (IGA) at Week 16.

Other secondary endpoints

- Patients achieving a score of Clear (0) or Almost Clear (1) and an at least 2-point improvement in IGA at Weeks 4, 8, 12, and 20.
• Patients achieving PASI75 response at Weeks 4, 8, 12, and 20.

- Patients achieving 50% reduction in PASI (PASI50) and 90% reduction in PASI (PASI90) response at Weeks 4, 8, 12, 16, and 20.
- Change from Baseline in PASI at Weeks 4, 8, 12, and 20.
- Change from Baseline in total Psoriasis Symptoms Scale (PSS) score at Weeks 4, 8, 12, 16, and 20.
- Change from Baseline in each individual item of the PSS at Weeks 4, 8, 12, 16, and 20.
- Change from Baseline in the affected body surface area (BSA) at Weeks 4, 8, 12, 16, and 20.
- Change from Baseline in Dermatology Life Quality Index (DLQI) score at Weeks 16 and 20.
- Patients experiencing psoriasis rebound by Week 20, defined as PASI $\geq 125\%$ of Baseline or new generalized pustular, erythrodermic, or more inflammatory psoriasis.

Safety endpoints:

- The occurrence, severity, and seriousness of treatment-emergent adverse events (TEAEs) reported over the 16-week Treatment Period and the 4-week Follow-up Period.
- Changes from Baseline in physical examination; vital sign measurements (body temperature, respiration rate, heart rate, and systolic and diastolic blood pressure measurements); and body weight over the 16-week Treatment Period and the 4-week Follow-up Period.
- Changes from Baseline in electrocardiogram (ECG) findings over the 16-week Treatment Period and the 4-week Follow-up Period.
- Changes from Baseline in safety laboratory values (haematology, serum chemistry, and urinalysis) over the 16-week Treatment Period and the 4-week Follow-up Period.
- Hospital Anxiety and Depression Scale at each visit except Week 2.
- Columbia-Suicide Severity Rating Scale (C-SSRS) at each visit except Weeks 1 and 2.

Exploratory endpoints:

- Change from Baseline in Physician's Global Assessment of Fingernails (PGA-F) at Week 16.

- Change in Scalp-Specific Investigator Global Assessment (ss-IGA) from Baseline at Week 16 in the subgroup of patients with Baseline score of at least 2 (mild scalp psoriasis).
- Change from Baseline of scalp itch Numeric Rating Scale (NRS) at Week 16 in the subgroup of patients with Baseline score of at least 4 on the 11-point NRS.
- 5 • Change from Baseline in joint pain NRS at Week 16 in patients with psoriatic arthritis (PsA) and a Baseline joint pain score of at least 4.
- Change in cardiovascular risk factors at Week 16. The following parameters will be collected: weight, body mass index, waist and hip circumferences, blood pressure, fasting serum glucose, triglycerides, cholesterol (total and high-density lipoprotein / low-density
- 10 lipoprotein fractions), and C-reactive protein.
- Change from Baseline in skin biomarkers at Week 16 collected via tape stripping and analysed using proteomic methods.
- Plasma levels of the drug and its metabolites at scheduled visits.

Study Design

- 15 **[00390]** A multicentre, randomized, double-blind, placebo-controlled, parallel group, Phase 2b dose-ranging study designed to assess the efficacy and safety of modified-release orismilast compared with placebo in adult patients with moderate-to-severe plaque-type psoriasis. Efficacy and safety outcomes will be evaluated to select an appropriate orismilast dose for subsequent Phase 3 studies.
- 20 **[00391]** After a Screening visit up to 28 days before Baseline, 202 patients were assigned randomly in a 1:1:1:1 ratio to receive 1 of the 3 orismilast doses (20 mg, 30 mg, or 40 mg) or placebo twice daily (BID) for 16 weeks, with a 4-week Follow-up visit. Administration will begin at Baseline with a dose titration period. The maximum duration of study participation was approximately 24 weeks.
- 25 **[00392]** Patients were seen at the site on Screening, Baseline (Day 1), and Weeks 1, 2, 4, 8, 12, 16 (End-of-Treatment visit), and 20 (Follow-up visit, 4 weeks after treatment completion or discontinuation). Visits at Weeks 1 and 2 could be conducted via a telemedicine procedure at Investigator's discretion.
- 30 **[00393]** At Baseline and each visit from Week 4 onwards, PASI, BSA, IGA, and PSS were assessed. Quality of life was assessed by administration of DLQI at Baseline and at Weeks 16 and 20 visits. Additional efficacy parameters include: an ss-IGA, a Physician Global Assessment of fingernail psoriasis (PGA-F), and patient's joint pain NRS for those with a diagnosis of PsA. These parameters were assessed at Baseline and Weeks 16 and 20.

Safety evaluations include adverse events (AEs), laboratory and vital sign assessments, physical examinations, as well as mood change evaluation by patient (Hospital Anxiety and Depression Scale) and suicidal ideation evaluation by Investigator (C-SSRS). A panel of cardiovascular risk factors were assessed at Baseline and Week 16.

- 5 **[00394]** Before administration of the study drug at Baseline and on Weeks 4, 8, and 16, blood was collected for orismilast concentration determination. In addition, non-invasive superficial skin sampling using tape stripping was conducted on a target lesion at Baseline and Week 16 in all patients proteomic analysis.

Inclusion Criteria

- 10 **[00395]** Patients are eligible to be included in the study only if all of the following criteria apply:

1. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the Informed Consent Form (ICF) and in the protocol.

2. Male and female patients ≥ 18 years of age at the time of signing the ICF.

- 15 3. Body weight of >40 kg at the time of signing the ICF.

4. Diagnosis of chronic, stable plaque-type psoriasis at least 2 months before the Screening visit. If the patient is diagnosed with psoriasis arthritis, the arthritis should be stable.

5. Moderate-to-severe plaque-type psoriasis as defined by PASI ≥ 12 , BSA $\geq 10\%$, and IGA ≥ 3 at the screening and baseline visits.

- 20 6. Candidate for systemic antipsoriatic treatment or phototherapy.

7. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at the Screening visit and a negative urine pregnancy test at the Baseline visit. In addition, sexually active WOCBP must agree to use a highly effective method of contraception until at least 4 weeks after the end of study treatment.

- 25 Exclusion Criteria

[00396] Patients are excluded from the study if any of the following criteria apply:

1. Therapy-resistant psoriasis defined as ≥ 2 treatment failures due to inadequate efficacy within the past 5 years of any biologic therapies (including but not limited to etanercept adalimumab, infliximab, certolizumab pegol, guselkumab, secukinumab, risankizumab,

- 30 ixekizumab, tildrakizumab, or ustekinumab) administered in adequate dose and duration according to the label or local/national guidelines (patients who stopped systemic treatment for reasons not related to lack of efficacy are not excluded).

2. Unstable psoriasis or PsA with acute deterioration within 4 weeks of the Screening visit.
3. History of allergy or hypersensitivity to any component of the study treatment.
4. Active infection (e.g., bacteria, viral, fungal) requiring treatment with systemic antibiotics within 4 weeks of the Screening visit.
5. 5. Malignancy or history of malignancy except for treated (i.e., cured) basal cell skin carcinomas.
6. Current diagnosis of predominant guttate, erythrodermic, exfoliative, or pustular psoriasis, or of drug-induced psoriasis, or other skin conditions that might confound the evaluation of psoriasis vulgaris, as judged by the Investigator (e.g. AD, lupus).
- 10 7. Any recurrent medical condition associated with serious GI diseases, such as inflammatory bowel disease.
8. Any medical or psychiatric condition (e.g., current major depression with a score for depressive symptoms ≥ 15 of HADS at Baseline, schizophrenia, suicidal behaviour, psychiatric hospitalization within the prior year) which, in the Investigator's opinion, would
15 preclude the patient from adhering to the protocol, completing the study per protocol, and/or would place the patient at unacceptable risk for receiving the investigational therapy.
9. Any therapies and systemic treatments which do not comply with the indicated washout interval.
10. Any previous treatment with orismilast or failure of treatment with apremilast or any other
20 systemic PDE4 inhibitor.
11. Any condition, including laboratory or ECG abnormalities, that places the patient at unacceptable risk to participate in the study or confounds the ability to interpret data from the study.
12. Severe hepatic impairment based upon medical history and laboratory abnormalities
25 (e.g., low albumin and abnormal bilirubin).
13. Any abnormalities in clinical laboratory tests at Screening, (low neutrophil count, low haemoglobin, low platelet count, low absolute lymphocyte count, high bilirubin, high alanine transferase or aspartate aminotransferase or high serum creatine.
14. History or evidence of hepatitis B virus (HBV) infection at Screening. Patients with
30 positive hepatitis B surface antigen (HBsAg) are excluded. For patients with isolated positive antihepatitis B core antibody (HBcAb), hepatitis B surface antibody (HBsAb) result must also be positive to be considered for this study.

15. History or positive test result for hepatitis C virus (HCV) antibody, indicating ongoing infection, at Screening. Confirmatory testing for HCV RNA will be conducted for patients who have a positive test result. Patients who have a negative result for HCV RNA will be eligible to participate in the study.

- 5 16. History of positive HIV, or have congenital or acquired immunodeficiency (e.g., common variable immunodeficiency disease). Patients who are positive for HIV antibodies (HIV-1 or HIV-2) at Screening are excluded from the study.

- 10 17. Suicidal ideation or behaviour in the past 12 months as indicated by a positive response (yes) to questions 4 or 5 on the C-SSRS completed at the Screening visit or the C-SSRS completed at the Baseline visit.

18. Pregnant or breastfeeding.

19. History of alcohol or substance abuse within 6 months before Baseline that, in the opinion of the Investigator, will preclude participation in the study.

20. Institutionalized by court order or by local authority.

15 Treatments

[00397] Tablets were taken in the morning and in the evening approximately every 12 hours. The minimum time interval between 2 consecutive doses is 6 hours. The first dose of the study drug was taken in the evening of Day 1. The dosing schedule used is shown in Table 10:

20 **Table 10**

ARM name:	Orismilast 20 mg BID	Orismilast 30 mg BID	Orismilast 40 mg BID	Placebo
Name:	Orismilast	Orismilast	Orismilast	Placebo
Type:	Drug			
Dose formulation:	10 mg and 30 mg tablet or matching placebo tablet			
Frequency:	BID (approximately every 12 hours)			
Administered tablets:	2 × 10 mg orismilast tablets BID	1 × 30 mg orismilast tablet and 1 × placebo tablet BID	1 × 10 mg and 1 × 30 mg orismilast tablets BID	2 × placebo tablets BID
Route:	Oral			
Use:	Experimental			Placebo
Sourcing:	Provided centrally by the Sponsor			
Packaging and labeling:	Investigational medicinal product will be provided in individually labeled wallet cards with blistered tablets. Each card will be labeled as required per country requirement			

Abbreviation: BID, twice daily.

Dose Titration

[00398] The orismilast doses were titrated over a period of a maximum of 2 weeks according to the schedule shown in Table 11:

Table 11

Arm	Day 1 (mg)	Day 2 (mg)		Day 3 (mg)		Day 4 (mg)		Day 5 (mg)		Day 6 (mg)		Day 7 (mg)		Day 8 (mg)	
	AM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
20 mg BID	10	10	10	10	10	10	10	10	20	10	20	10	20	20	20
30 mg BID	10	10	10	10	20	20	20	20	20	20	30	20	30	20	30
40 mg BID	10	10	10	10	20	20	20	20	20	20	30	20	30	20	30
Placebo	P	P	P	P	P	P	P	P	P	P	P	P	P	P	P
Arm		Day 9 (mg)		Day 10 (mg)		Day 11 (mg)		Day 12 (mg)		Day 13 (mg)		Day 14 (mg)		From Day 15 (mg)	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
20 mg BID		20	20	20	20	20	20	20	20	20	20	20	20	20	20
30 mg BID		30	30	30	30	30	30	30	30	30	30	30	30	30	30
40 mg BID		30	30	30	30	30	30	30	40	30	40	30	40	40	40
Placebo		P	P	P	P	P	P	P	P	P	P	P	P	P	P

5 Efficacy Assessments

[00399] **Psoriasis Area and Severity Index:** The PASI is a measure of psoriatic disease severity, taking into account qualitative lesion characteristics (erythema, induration, and desquamation) and percentage of affected skin surface area on defined anatomical regions. The PASI is a validated instrument that is the most widely used tool for measurement of severity of psoriasis. Psoriasis Area Severity Index scores range from 0 to 72, with higher scores reflecting greater disease severity (Fredriksson et al., Dermatologica. 1978; 157(4):238-244). Erythema, induration/thickness, and scaling are scored on a scale of 0 (none) to 4 (very severe) on 4 anatomic regions of the body: head, trunk, upper limbs, and lower limbs. Degree of involvement on each of the 4 anatomic regions is scored on a scale of 0 (no involvement) to 6 (90% to 100% involvement). The total qualitative score (sum of erythema, thickness, and scaling scores) is multiplied by the degree of involvement for each anatomic region and then multiplied by a constant. The scores for each anatomic region are combined to yield the final PASI.

[00400] **Investigator Global Assessment:** The IGA is a measure used by physicians to determine the patient's overall severity of disease. The static version (Langley et al., J Dermatolog Treat. 2015, Feb;26(1):23-31) is used in this trial for measurement at a single

point in time as indicated in the schedule of assessments. The Investigator will rate the severity of patient's psoriasis on a 5-point scale ranging from 0 (clear) to 4 (severe).

[00401] Scalp-specific Investigator Global Assessment: The ss-IGA assesses lesions on the scalp for degree of redness, thickness, and scaling on a 5- point scale, with 0 indicating absence of disease and 4 indicating severe disease.

[00402] Physician's Global Assessment of Fingernail Psoriasis: The PGA-F is used in this trial to evaluate abnormalities in the fingernails, and the severity of these, in patients with nail psoriasis. It is a simple and reliable clinician-rated scale, which is easy to use in clinical practice and research. The scale rates the overall condition of the fingernails and is based on a 5-point scale, with 0 indicating clear and 4 indicating severe.

[00403] Body Surface Area: The BSA assessment estimates the extent of disease or skin affected by psoriasis and is expressed as a percentage of total body surface. BSA will be determined by the Investigator or designee using the patient palm = 1% BSA rule.

Patient-Reported Outcomes

[00404] Psoriasis Symptom Scale: The PSS is a 4-item patient-completed questionnaire (Rentz et al., J Patient Rep Outcomes. 2017;1(1):4.). It is patient relevant, its domains are reliable and valid, and it takes few minutes to complete. The PSS assesses severity of pain, itching, redness, and burning during the past 24 hours using a 5-point severity scale from 0 = none to 4 = very severe.

[00405] Scalp Itch Scalp: itch will be assessed by requesting the patients to grade their worst scalp itch over the past 24 hours on a 11-point with an NRS with 0 corresponding to No itch and 10 to Worst imaginable itch.

[00406] Arthritis Pain: Patients with a PsA diagnosis at Screening will assess their joint pain due to arthritis over the past 24 hours on a 11-point with an NRS with 0 corresponding to No pain and 10 to Worst imaginable pain.

[00407] Dermatology Life Quality Index: The DLQI is a 10-item validated questionnaire completed by the patient used to assess the impact of skin disease on the patient's QoL during the previous week. The 10 questions cover the following topics: symptoms, embarrassment, shopping and home care, clothes, social and leisure, sport, work or study, close relationships, sex, and treatment. Each question is scored from 0 to 3 ("not at all," "a little," "a lot," and "very much," respectively), giving a total score ranging from 0 to 30. A high score is indicative of a poor QoL.

Summary of Results

[00408] 202 patients were randomized and treated for 16 weeks. The effects of treatment on a range of parameters are shown in Table 12 below.

Table 12

Mean change from baseline Week 16	Placebo (n-51)	20 mg BID (n-48)	30 mg BID (n-50)	40 mg BID (n-53)
Weight (kg)	-0.2	-2.6	-2.8	-3.1
BMI (kg/m ²)	-0.1	-0.9	-0.9	-1.0
Waist circumference (cm)	-1.5	-3.1	-1.0	-1.9
Hip circumference (cm)	-1.0	-0.9	-2.8	-3.4
Systolic blood pressure (mmHg)	-2.4	-1.1	2.1	1.5
Diastolic blood pressure (mmHg)	-1.6	-1.6	1.3	1.0
Fasting serum glucose (mmol/L)	-0.3	-0.2	-0.2	-0.1
Triglycerides (mmol/L)	-0.1	-0.2	-0.1	0.2
Cholesterol (mmol/L)	-0.1	-0.2	0.0	-0.1
LDL cholesterol (mmol/L)	0.2	-0.1	0.0	-0.2
HDL cholesterol (mmol/L)	-0.1	0.0	0.0	0.0
C Reactive Protein (mmol/L)	3.0	3.4	-33.1	-27.2

5 **Example 4: Effect of PDE4 inhibitor and GLP1R agonist on insulin secretion and cAMP levels in pancreatic cell line in vitro**

[00409] The rat islet cell line RIN-5F is employed for assessing the effect of a PDE4 inhibitor alone and in combination with a GLP1R agonist on insulin secretion and cAMP levels in vitro. The RIN-5F cell line is a clone derived from the RIN-m rat islet line (ATCC CRL-2057) and produces and secretes insulin.

[00410] RIN-5F cells are seeded in 96-well plate format and incubated in appropriate media for a specific time. Then, cells are incubated with glucose and serial dilutions of a PDE4 inhibitor or GLP1R agonist under appropriate conditions. Insulin levels are determined in the media following the manufacturer's instruction of the Ultrasensitive Rat Insulin ELISA Kit Protocol. Cells are lysed and intracellular concentration of cAMP analysed using a bioluminescence-based assay (cAMP-Glo™ Assay, Promega). The EC50 are calculated accordingly for each test item and efficacy readout.

[00411] The PDE4 inhibitor and GLP1R agonist are tested alone and in combination based on the below matrix in the above assay to assess the effects:

Table 13

	No GLP1R agonist	IC20 GLP1R agonist	IC50 GLP1R agonist	IC80 GLP1R agonist
No PDE4i	-	TEST	TEST	TEST
IC20 PDE4i	TEST	TEST	TEST	TEST
IC50 PDE4i	TEST	TEST	TEST	TEST
IC80 PDE4i	TEST	TEST	TEST	TEST

5 Example 5 - Effect of orismilast and semaglutide on insulin secretion in a pancreatic cell line in vitro.

[00412] As described herein, orismilast is a selective and potent PDE4B/D inhibitor in clinical development for psoriasis and atopic dermatitis. Semaglutide is a GLP-1 receptor agonist marketed for type 2 diabetes and obesity with a mode of action that signals through the GLP1-receptor/cAMP pathway in pancreatic cells. The inventors have investigated the impact of orismilast alone and in combination with semaglutide on insulin secretion in a pancreatic cell line.

5.1 Methods

[00413] The assay was performed according to Bruzzone et al.(2008) J Biol Chem. Nov 21; 283(47): 32188-97 doi: 10.1074/jbc.M802603200. Epub 2008 Sep 10 using a beta cell line which was isolated from a rat pancreas with insulinoma.

[00414] Briefly, Rin-m cells (ATCC, CRL-2057) were seeded in a 24 -well plate (0.5 million cells/well) for 48 hrs in appropriate RPMI culture medium (10% FBS, RPMI 1640 Medium). After 48 hrs, the culture medium was removed and replaced with Low Glucose media (5.6 mM Glucose, DMEM (D5546, Sigma-Aldrich) supplemented with 2 mM L-glutamine, 10 mM HEPES, 10% FBS, and 1% Penicillin/Streptomycin). Cells were incubated in Low Glucose media for 4 hrs to glucose-starve the cells. Thereafter, media was replaced and cells were incubated with high glucose media (16.7 mM Glucose, DMEM (D5546, Sigma-Aldrich) media supplemented with 2 mM L-glutamine, 10 mM HEPES, 10% FBS, and 1%

Penicillin/Streptomycin) or co-treated with orismilast alone, semaglutide alone or the combination of both (see Table 14 for concentrations/combinations used).

[00415] Following incubation for 1 hr, the supernatant was removed and insulin levels were quantified using an ultrasensitive ELISA, according to manufacturer's instruction

5 (CrystalChem, Ultra Sensitive Rat Insulin ELISA kit). Cell viability and an intact cell layer was confirmed using a standard microscope prior to removal of supernatant. Insulin levels of treated conditions were normalized to levels of the media control. Analysis and visualizations were carried out in GraphPad Prism version 10.0.2. The concentration of semaglutide to reach 50% of effect (EC₅₀) was estimated using linear regression with $Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{((\text{LogEC}_{50} - X) * \text{HillSlope}))}$. Statistical tests were carried out using ordinary
10 One-way ANOVA with Šídák's correction for multiple comparisons.

Table 14: Concentrations of orismilast and semaglutide tested alone and in combination.

	Media	Orismilast	Orismilast
Media	Control	100 nM	1000 nM
Semaglutide	0.04 nM	0.04 nM + 100 nM	0.04 nM + 1000 nM
Semaglutide	1 nM	1 nM + 100 nM	1 nM + 1000 nM
Semaglutide	9 nM	9 nM + 100 nM	9 nM + 1000 nM
Semaglutide	1000 nM	1000 nM + 100 nM	1000 nM + 1000 nM

5.2 Results

15 **[00416]** It was found that orismilast increases insulin secretion 61% to 79% at 100 and 1000 nM (**Figure 4A**), respectively, whereas semaglutide follows a dose response curve reaching an EC₅₀ of 26 nM (**Figure 4B**). The results show the ability of orismilast to increase insulin secretion without a co-stimulus such as native GLP-1 or a GLP1 receptor agonist.

[00417] An additive effect of insulin release was observed across doses from 1nM to
20 1000nM semaglutide in combination with 1000nM orismilast. It was found that the maximum additive effect is dose-dependent and reaches its maximum of 74% to 77% when 1000 nM are combined with 1 nM to 9 nM semaglutide (**Figure 4D**), meaning that the optimal window of opportunity for orismilat to add on to the effect of semaglutide is achieved when high orismilast concentrations are combined with sub-EC₅₀ concentrations of semaglutide.

25

Example 6 – A randomised placebo-controlled study to investigate the efficacy of orismilast administered orally twice daily (BID) separately or combined with open-label once weekly s.c. administered semaglutide in individuals with obesity during a 16-week treatment period.

5 [00418] The following clinical trial may be carried out.

Aims

[00419] The primary aim is to evaluate the effects of 30 mg orismilast modified release tablets BID with or without semaglutide 1.0 mg subcutaneously (s.c.) once weekly on percentual change from baseline in body weight.

10 [00420] Secondary and exploratory aims include evaluating the effects of treatment on:

- Lean body mass, fat mass, and visceral fat mass
- Systemic low-grade inflammation
- Patient-reported outcomes (PROs)
- Safety and tolerability

15 [00421] The study may assess the effect of treatment with orismilast 30 mg BID plus semaglutide 1.0 mg s.c once weekly for 16 weeks compared to: placebo treatment; monotherapy orismilast 30 mg BID treatment; and monotherapy semaglutide 1.0 mg s.c once-weekly treatment; for 16 weeks in reducing body weight relative to baseline. The study may also assess the effect of treatment with orismilast 30 mg BID plus semaglutide 1.0 mg
20 s.c once weekly compared to placebo in reducing systemic low-grade inflammation as assessed by circulating levels of high-sensitivity C-reactive protein (hs-CRP), interleukin 6 (IL-6), or tumour necrosis factor α (TNF- α) relative to baseline.

Study design

[00422] An investigator-initiated, proof-of-concept, randomised, parallel-group, single-centre
25 clinical trial investigating the body weight loss potential of open-label once-weekly s.c. semaglutide with- or without double-blind, placebo-controlled orismilast, an oral PDE4 inhibitor, administered twice daily.

[00423] Eligible individuals are randomised to one of four treatment arms as illustrated in Table 15 below:

Table 15 Overview of treatment arms, dose, usage, route- and frequency of investigational medicinal product (IMP) administration.

Treatment arm	IMPs	Dose	Pharmaceutical dosage form	Route of administration	Administration frequency
#1	Orismilast	30 mg	Orismilast-tablet (double-blinded)	Oral	Twice daily (BID)
#2	Orismilast, plus semaglutide (1 mg/0.5mL)	30 mg	Orismilast-tablet (double-blinded)	Oral	Twice daily (BID)
		1 mg	0.5 mL semaglutide solution for injection in prefixed pen (open-label)	Subcutaneous	Once weekly
#3	Placebo, plus semaglutide (1 mg/0.5mL)	-	Placebo-tablet (double-blinded)	Oral	Twice daily (BID)
		1 mg	0.5 mL semaglutide solution for injection in prefixed pen (open-label)	Subcutaneous	Once weekly
#4	Placebo	-	Placebo-tablet (double-blind)	Oral	Twice daily (BID)

[00424] In total, 80 participants with a BMI of ≥ 30 kg/m² are randomised to treatment with investigational medicinal product (IMP), being either 30 mg orismilast separately or combined with 1 mg semaglutide for 16 weeks in the randomisation sequence 1:1:1:1. Due to the lack of placebo material for semaglutide, this treatment modality is constructed as open-label, while the treatment modality of orismilast/placebo is double-blinded in all four treatment arms. Eligibility for trial participation is assessed during a 2-week screening period, including a screening visit (V1). Hereafter, the trial encompasses a randomisation visit (V2), two four-week up-titration periods with visits at week four (V3) and week eight (V4) followed by an eight-week steady-state treatment period with an end-of-treatment (EOT) visit (V5) and concluded with a four-week follow-up period (V6).

[00425] The semaglutide-IMP is subcutaneously administered abdominally once weekly from week 0 (V2) until week 16 (V5). Semaglutide administration is initiated at 0.25 mg once weekly and up-titrated every fourth week until a target dose of 1 mg is reached (see **Figure 5**). The orismilast-IMP is administered orally twice daily (in the morning and evening) from

week 0 (V2) until week 16 (V5). Orismilast administration (modified release tablet) is initiated at 20 mg once daily and up-titrated after four weeks to 20 mg twice daily, ultimately reaching the target dose of 30 mg twice daily from week 8 (V4) to week 16 (V5) (steady-state) (**Figure 5**). If the subjective tolerability of IMP administration is incompatible with trial participation, the investigator can postpone up-titration or reduce the IMP dose if judged necessary for participant retention or safety. In total, the trial schedule consists of six on-site visits, including screening (V1), randomisation (V2), two up-titration visits (V3 & V4), an EOT visit (V5), and a safety follow-up visit (V6), with additional frequent telephone consultations conducted during the entire trial period. Hence, the maximum trial duration is 22 weeks (including the screening period).

Study population

[00426] Eighty participants with obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$) are included in the study. Dropouts are not replaced unless the dropout rate surpasses 25% in one of the treatment arms.

Inclusion criteria

- Age 18–75 years
- $\text{BMI} \geq 30 \text{ kg/m}^2$
- History of at least one attempt to lose body weight

Exclusion criteria

- A self-reported change in body weight $\geq 5\%$ within the last three months prior to the screening visit
- Treatment with any therapy, including endoscopic procedures and/or medication (e.g. liraglutide, bupropion/naltrexone and orlistat), intended for weight management within three months prior to the screening visit
- Any type of bariatric surgery
- Previous, current or planned (during the trial period) obesity treatment with surgery or a weight loss device < 12 months prior to the screening visit
- Treatment with glucose-lowering agents within three months prior to the screening visit
- Use of GLP-1RAs, glucagon-like peptide 2 receptor agonists, dipeptidyl peptidase 4 (DPP) inhibitors, human growth hormone, somatostatin or analogues thereof, within three months prior to screening visit
- Treatment with antipsychotics known to modulate energy intake three months prior to screening visit

- Prolonged treatment (>1 week) with anti-inflammatory agents or any PDE4i within three months prior to the screening visit
- Glycated haemoglobin (HbA1c) ≥ 48 mmol/mol at the screening visit
- History of type 1 diabetes or type 2 diabetes
- 5 • Compromised kidney function (estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m²) at screening visit
- Known liver disease (except for MASLD) and/or elevated plasma alanine aminotransferase (ALT) > three times the upper limit of normal at screening visit
- History of acute or chronic pancreatitis
- 10 • History and/or family history of medullary carcinoma and/or multiple endocrine neoplasia syndrome
- History of any other cancers (except margin-free resected cutaneous basal or squamous cell carcinoma or adequately treated in situ cervical cancer) unless disease-free state for at least five years
- 15 • Uncontrolled thyroid disease as per the discretion of the investigators
- No history of major cardiovascular events three months prior to screening visit, including myocardial infarction, stroke, hospitalisation for angina and transient ischaemic attack
- Class IV heart failure, according to the New York Heart Association
- 20 • Any concomitant disease or treatment that, at the discretion of the investigators, might jeopardise the participant's safety during the trial
- Alcohol/drug abuse as per discretion of the investigators
- Known or suspected hypersensitivity to orismilast, semaglutide or related products
- Administration of any investigational drug within three months prior to the screening visit
- 25 • Simultaneous participation in any other clinical intervention trial until completion of follow-up visit (V6)
- Mental incapacity or language barriers that preclude adequate understanding or cooperation or unwillingness to comply with trial requirements
- 30 • Positive urine human chorionic gonadotropin (hCG) (for fertile women)
- Regarding fertile men and women:

- Women who are pregnant, intend to become pregnant, or are breastfeeding will not be included in the study
- Sterilised or postmenopausal women (> 12 months amenorrhoea or females ≥ 60 years of age) can be included without the hCG-testing during the trial period
- 5 ○ Female of childbearing potential: To exclude pregnancy, urine hCG tests are performed every fourth week after V2 (Week 4, 8, 12, 16 and 20). The following contraceptive methods are considered adequate for study enrolment for females if maintained throughout the study duration: an intrauterine device, hormonal contraception (birth control pills, implant, patch, vaginal ring or
10 injection), a monogamous relationship with a sterilized partner, or sexual abstinence.
- Men: The following contraceptive methods are considered adequate for study enrolment for male participants: surgically sterilised or willing to refrain from sexual intercourse from screening visit and until follow-up visit (V6), or, if
15 sexually active, condom usage or partner-practised contraception as described for females.

Endpoints

[00427] Endpoints are listed below.

Primary endpoint		
Endpoint title	Time frame	Unit
Change in body weight	From week 0 (baseline) to week 16 (EOT)	%-point

Secondary endpoints			
No.	Endpoint title	Time frame	Unit
#2	Body weight reduction ≥ 5%	At week 16 (EOT)	Yes/No
#3	Body weight reduction ≥ 10%	At week 16 (EOT)	Yes/No
#4	C-reactive protein (hs-CRP)	From week 0 (baseline) to week 16 (EOT)	%-point
#5	interleukin 6 (IL-6)	From week 0 (baseline) to week 16 (EOT)	%-point

#6	Tumour necrosis factor α (TNF- α)	From week 0 (baseline) to week 16 (EOT)	%-point
Exploratory endpoints			
#7	Body weight reduction $\geq 15\%$	At week 16 (EOT)	Yes/No
#8	Change in BMI (kg/m ²)	From week 0 (baseline) to week 16 (EOT)	kg/m ²
#9	Change in waist-hip ratio	From week 0 (baseline) to week 16 (EOT)	%-point
#10	Change in waist circumference (cm)	From week 0 (baseline) to week 16 (EOT)	cm
#11	Change in systolic blood pressure (mmHg)	From week 0 (baseline) to week 16 (EOT)	mmHg
#12	Change in diastolic blood pressure (mmHg)	From week 0 (baseline) to week 16 (EOT)	mmHg
#13	Change in heart rate (beats per minute)	From week 0 (baseline) to week 16 (EOT)	Beats per minute
#14	Change in fat-free mass as measured by bioimpedance	From week 0 (baseline) to week 16 (EOT)	%-point
#15	Change in total fat mass as measured by bioimpedance	From week 0 (baseline) to week 16 (EOT)	%-point
#16	Change in visceral fat mass rating as measured by bioimpedance	From week 0 (baseline) to week 16 (EOT)	%-point
#17	Change in bone mass as measured by bioimpedance	From week 0 (baseline) to week 16 (EOT)	%-point
#19	Change in fasting serum/plasma concentrations of inflammatory biomarkers • Fibrinogen • Serum amyloid A • Haptoglobin • Soluble cluster of differentiation 14 • Lactate dehydrogenase • IL-1 receptor antagonist, IL-1β, IL-2, IL-8, IL-10, IL-12, IL-17, IL-18, IL-22 • Interferon γ	From week 0 (baseline) to week 16 (EOT)	%-point

	• Resistin • Adiponectin • LPS-binding protein (LBP)		
#20	Change in fasting serum/plasma concentrations of leukocytes • Total leukocyte count • Neutrophil • Lymphocyte • Basophil • Eosinophil • Neutrophil:lymphocyte ratio	From week 0 (baseline) to week 16 (EOT)	%-point
#21	Change in fasting serum/plasma concentrations of lipid biomarkers • Low-density lipoprotein cholesterol • Very-low-density lipoprotein • High-density lipoprotein cholesterol • Triglycerides • Lipoprotein (a) • Apolipoprotein B • Apolipoprotein C3	From week 0 (baseline) to week 16 (EOT)	%-point
#22	Change in fasting serum/plasma concentrations of islet function and incretin biomarkers • Glucose • HbA1c • Insulin • C-peptide ◦ Insulin sensitivity as assessed by homeostasis model assessment 2 • Glucagon	From week 0 (baseline) to week 16 (EOT)	%-point
#23	Change in fasting serum/plasma concentrations of bone biomarkers • C-terminal telopeptides of type I collagen • Amino-terminal propeptide of type I procollagen • 25-hydroxy-vitamin D • Parathyroid hormone • Phosphate • Serum calcium • Sex hormone-binding globulin (SHBG) • Testosterone • Oestradiol	From week 0 (baseline) to week 16 (EOT)	%-point

#24	Change in fasting serum/plasma concentrations of coagulability as measured by thromboelastography (TEG) • R (min) • K (min) • Angle (degrees) • MA (mm) • LY30 (%)	From week 0 (baseline) to week 16 (EOT)	%-point
#24	Change in fasting serum/plasma concentrations of additional blood tests • Haemoglobin • Thrombocytes • Serum albumin • Potassium • Sodium • Creatinine • eGFR • ALT • Aspartate aminotransferase (AST) • Gamma-glutamyl transferase • Bilirubin • Amylase • Triacylglycerol lipase • Thyroid-stimulating hormone • Fibroblast growth factor 19 • Fibroblast growth factor 21 • α-hydroxy-4-cholesten-3-one (C4) • Leptin • Lipocalin 2	From week 0 (baseline) to week 16 (EOT)	%-point
#26	Change in FibroScan®-assessed hepatic fat content (dB/m)	From week 0 (baseline) to week 16 (EOT)	%-point
#27	Change in FibroScan®-assessed liver stiffness (kPa)	From week 0 (baseline) to week 16 (EOT)	%-point
#28	Change in fatty liver index score	From week 0 (baseline) to week 16 (EOT)	%-point
#29	Change in fibrosis 4 score (FIB-4)	From week 0 (baseline) to week 16 (EOT)	%-point
<i>Patient-reported outcomes</i>			
#30	Change in the 36-Item Short Form Survey (SF-36) • Physical functioning • Role-physical • Bodily pain	From week 0 (baseline) to week 16 (EOT)	Score points

	• General health • Vitality • Social functioning • Role-emotional • Mental health • Physical component summary • Mental component summary		
#31	Change in The Impact of Weight on Quality of Life-Lite Clinical Trials Version (IWQOL-Lite-CT) • Pain/discomfort domain score • Psychosocial domain score • Total score	From week 0 (baseline) to week 16 (EOT)	Score points
Safety endpoints			
#32	Number of treatment-emergent adverse events (TEAEs)	From signed consent form (week -2) to follow-up visit (week 20)	Counts of events
#33	Number of serious AEs (SAEs)	From signed consent form (week -2) to follow-up visit (week 20)	Counts of events

Rationale for study design and orismilast dose

[00428] In the Phase 2b trial of orismilast in patients with psoriasis described in Example 3, a dose-dependent body weight reduction was observed. The mean body weight loss was approximately -2.6 kg, -2.8 kg and -3.1 kg with 20, 30 and 40 mg orismilast BID; however, the 30 mg dose exhibited a more favourable tolerability profile with 10 TEAEs leading to trial discontinuation (20%) versus 20 (40%) in the 40 mg group. Thus, the 30 mg dose of orismilast is deemed to have a more optimal risk-benefit profile compared with 20 mg or 40 mg BID. The most common PDE4i-related AEs across all dose groups were gastrointestinal-related, with diarrhoea (48%) and nausea (38%) being the most frequent.

[00429] In order to reduce the number of AEs observed with the 30 mg dose in the trial in Example 3, an up-titration cycle every fourth week is employed in the present trial. Consequently, 20 mg orismilast is administered once daily for the first four weeks, 20 mg orismilast BID for the following four weeks, and, ultimately, 30 mg orismilast BID for the remainder of the treatment period (**Figure 5**).

Interactions and use of concomitant medicines

[00430] The use of concomitant medication not interfering with exclusion criteria and DDI considerations is allowed at time of enrolment. Participants are instructed not to initiate treatment with any medication that might significantly interfere with primary or secondary end points, hereunder the use of systemic glucocorticoids and non-steroid anti-inflammatory

drugs. Due to their frequent use, participants will be explicitly instructed to refrain from these specific drug classes. Initiation of any new medication will be evaluated and recorded at each visit.

Route of administration

- 5 **[00431]** Semaglutide is administered as an s.c. injection using the included standard manufacturer-produced injection device, while orismilast and placebo are administered orally.

Biological material

- 10 **[00432]** Blood and faecal samples are obtained at appropriate time points according to the protocol.

Claims

1. A method for the treatment or prevention of a disease or disorder, the method comprising administering a PDE4 inhibitor and a GLP1 receptor agonist to a subject, wherein the disease or disorder is selected from: an inflammatory disease, an autoimmune disease, fibrosis, a neurodegenerative disease, a musculoskeletal disorder, a metabolic disease or disorder, alcoholic liver disease (ALD), cardiovascular disease and a gastrointestinal disorder.
2. The method according to claim 1, wherein:
 - (i) the metabolic disease or disorder is selected from: obesity, hyperlipidaemia, diabetes (including pre-diabetes), diabetes-associated cardiac dysfunction, metabolic syndrome, non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD);
 - (ii) the inflammatory disease is an inflammatory pulmonary, dermatological or neurological disease or inflammatory myopathy (e.g. polymyositis);
 - (iii) the musculoskeletal disorder is muscular dystrophy (e.g. Duchenne muscular dystrophy), sarcopenia, or sporadic inclusion body myositis;
 - (iv) the fibrosis is hepatic fibrosis, renal fibrosis, biliary fibrosis, pancreatic fibrosis, or idiopathic pulmonary fibrosis.
 - (v) the autoimmune disease is ulcerative colitis, Crohn's disease, primary sclerosing cholangitis or primary biliary cholangitis,
 - (vi) the neurodegenerative disease is dementia, Alzheimer's disease, amyotrophic lateral sclerosis, Huntingdon's disease, neurodegeneration or Parkinson's disease; and
 - (vii) the gastrointestinal disorder is inflammatory bowel disease, short bowel syndrome, coeliac disease or intestinal toxicity.

3. The method according to claim 1 or claim 2, wherein the PDE4 inhibitor and the GLP1 receptor agonist are administered for a treatment period which is at least 4 weeks, optionally at least 8 weeks.
4. The method according to any preceding claim, wherein the PDE4 inhibitor and the GLP1 receptor agonist are administered simultaneously, separately or sequentially.
5. The method according to any preceding claim, wherein the PDE4 inhibitor is administered to the subject once daily or twice daily, optionally wherein the PDE4 inhibitor, or the pharmaceutically acceptable solvate thereof, is administered to the subject at a total daily dose of no more than 500 mg, optionally no more than 250 mg, no more than 120 mg, no more than 80 mg, no more than 60 mg or no more than 40 mg.
6. The method according to any preceding claim, wherein the PDE4 inhibitor is administered to the subject at a unit dose of from 0.01 mg to 250 mg, optionally from 1 to 100 mg or from 5 to 70 mg, e.g. 10, 15, 20, 30 or 40 mg.
7. The method according to any preceding claim, wherein the PDE4 inhibitor is administered to the subject orally.
8. The method according to any preceding claim, wherein the PDE4 inhibitor is selected from difamilast, crisaborole, apremilast, roflumilast, ibudilast, drotaverine (e.g. drotaverine hydrochloride), orismilast, mufemilast, tanimilast (tranimilast), ensifentrine, zatolmilast, BI-1015550, TQC-3721, ME-3183, PF-07038124 or a pharmaceutically acceptable salt, solvate or hydrate thereof.
9. The method according to claim 8, wherein the PDE4 inhibitor is orismilast, or a pharmaceutically acceptable salt, solvate or hydrate thereof.
10. The method according to any preceding claim, wherein the GLP1R agonist is administered to the subject once or twice daily, optionally wherein the total daily dose of the GLP1R agonist is from about 1 µg to about 100 mg, or wherein the GLP1R agonist is administered to the subject once or twice weekly, optionally wherein the total weekly dose of the GLP1R agonist is from about 0.05 mg to about 100 mg.

11. The method according to any preceding claim, wherein the GLP1R agonist is administered at a unit dose of from about 0.5 µg to about 500 mg, from about 1 µg to about 200 mg, from about 5 µg to about 100 mg, from about 10 µg to about 50 mg, from about 100 µg to about 10 mg, or from about 0.5 mg to about 4 mg.
12. The method according to any preceding claim, wherein the GLP1R agonist is administered to the subject orally or subcutaneously.
13. The method according to any preceding claim, wherein the GLP1 receptor agonist is exenatide (including exenatide extended release), lixisenatide, beinaglutide, dulaglutide, liraglutide, semaglutide, albiglutide, efpeglenatide, PEG-Ionexatide or tirzepatide, or a pharmaceutically acceptable salt, solvate or hydrate thereof, optionally wherein the GLP1 receptor agonist is semaglutide.
14. A PDE4 inhibitor for use in the treatment or prevention of an inflammatory disease, an autoimmune disease, fibrosis, a neurodegenerative disease, a musculoskeletal disorder, a metabolic disease or disorder, alcoholic liver disease (ALD), cardiovascular disease or a gastrointestinal disorder, said use comprising co-administration of the PDE4 inhibitor with a GLP1 receptor agonist.
15. A GLP1 receptor agonist for use in the treatment or prevention of an inflammatory disease, an autoimmune disease, fibrosis, a neurodegenerative disease, a musculoskeletal disorder, a metabolic disease or disorder, alcoholic liver disease (ALD), cardiovascular disease or a gastrointestinal disorder, said use comprising co-administration of the GLP1 receptor agonist with a PDE4 inhibitor.
16. Use of a PDE4 inhibitor in the manufacture of a medicament for the treatment or prevention of an inflammatory disease, an autoimmune disease, fibrosis, a neurodegenerative disease, a musculoskeletal disorder, a metabolic disease or disorder, alcoholic liver disease (ALD), cardiovascular disease or a gastrointestinal disorder in a subject in need thereof by co-administration with a GLP1 receptor agonist.
17. Use of a GLP1 receptor agonist in the manufacture of a medicament for the treatment or prevention of an inflammatory disease, an autoimmune disease, fibrosis, a neurodegenerative disease, a musculoskeletal disorder, a metabolic disease or disorder, alcoholic liver disease (ALD), cardiovascular disease or a gastrointestinal disorder in a subject in need thereof by co-administration with a PDE4 inhibitor.

18. A combination comprising a PDE4 inhibitor and a GLP1 receptor agonist.
19. A pharmaceutical composition comprising the combination of claim 18.
20. A kit comprising the combination of claim 18, or the composition of claim 19, and instructions for use.
21. A product comprising a PDE4 inhibitor and a GLP1 receptor agonist for simultaneous, separate or sequential use in the treatment or prevention of an inflammatory disease, an autoimmune disease, fibrosis, a neurodegenerative disease, a musculoskeletal disorder, a metabolic disease or disorder, alcoholic liver disease (ALD), cardiovascular disease or a gastrointestinal disorder.

Figure 1

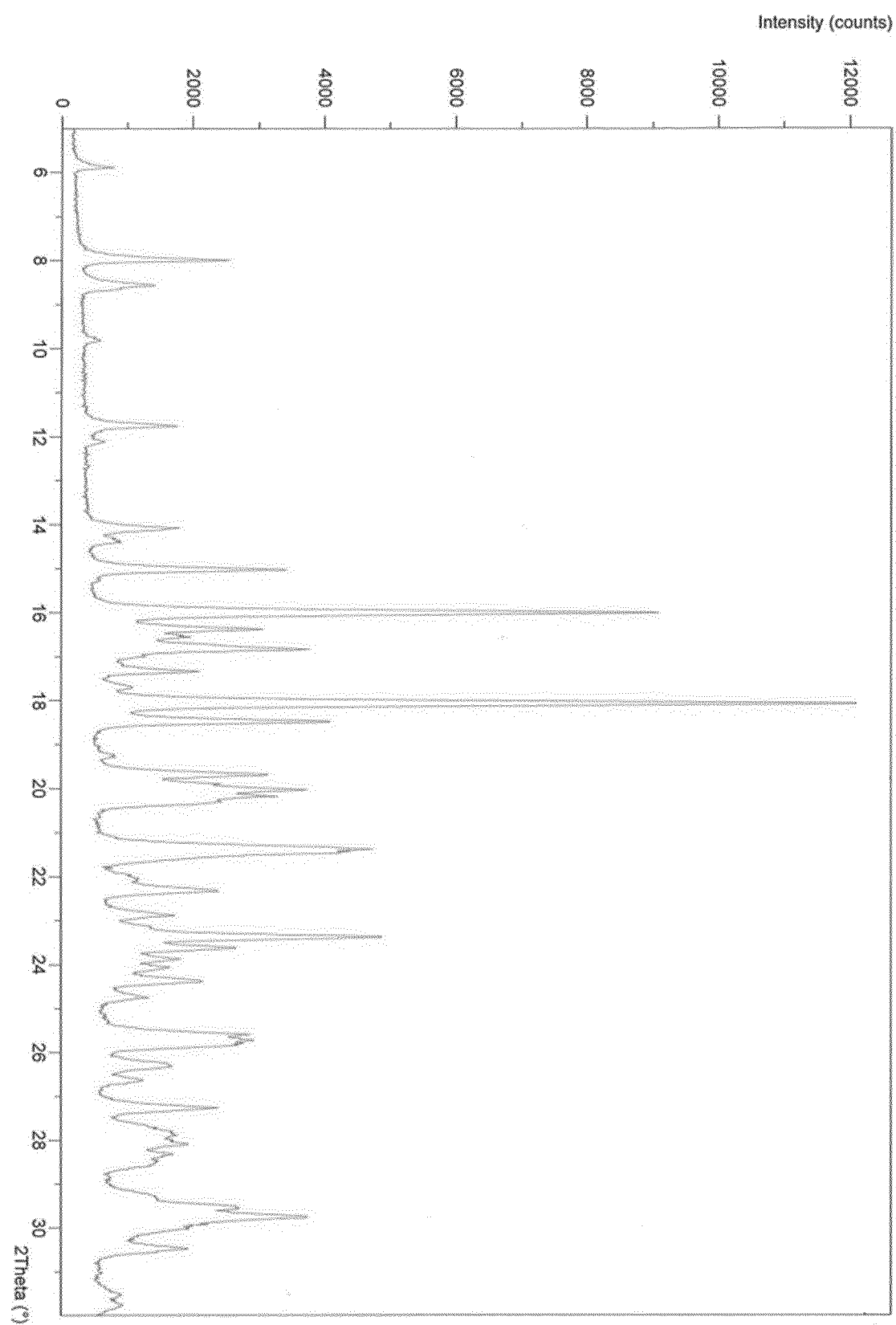


Figure 2

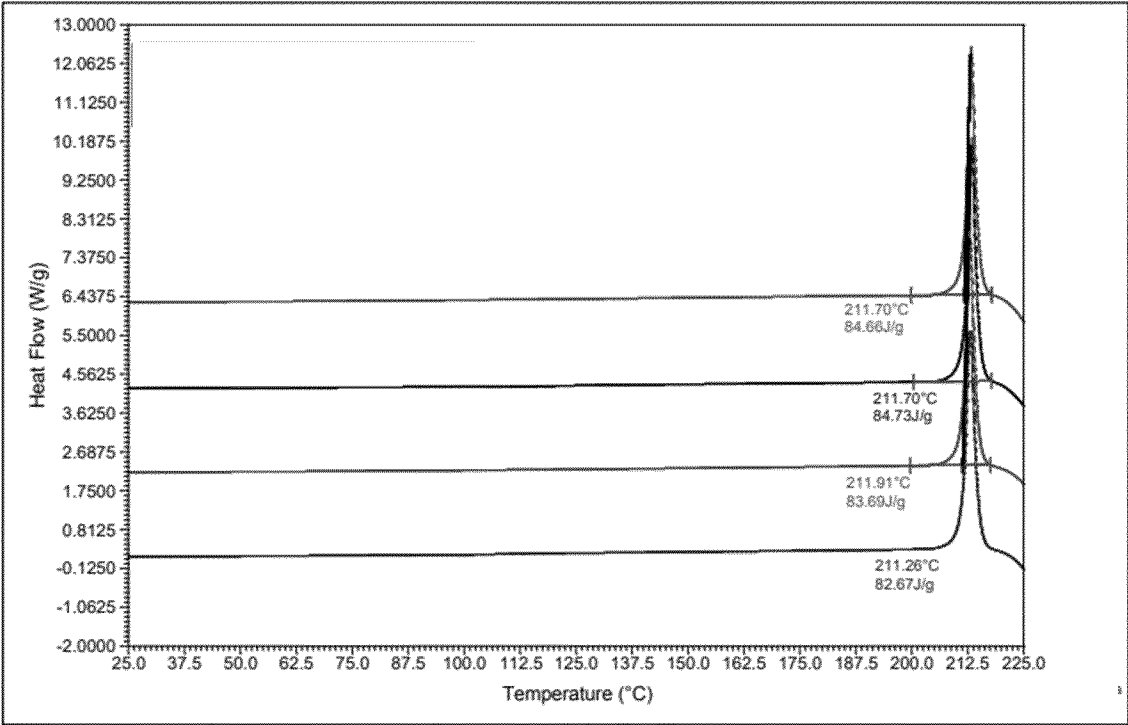


Figure 3

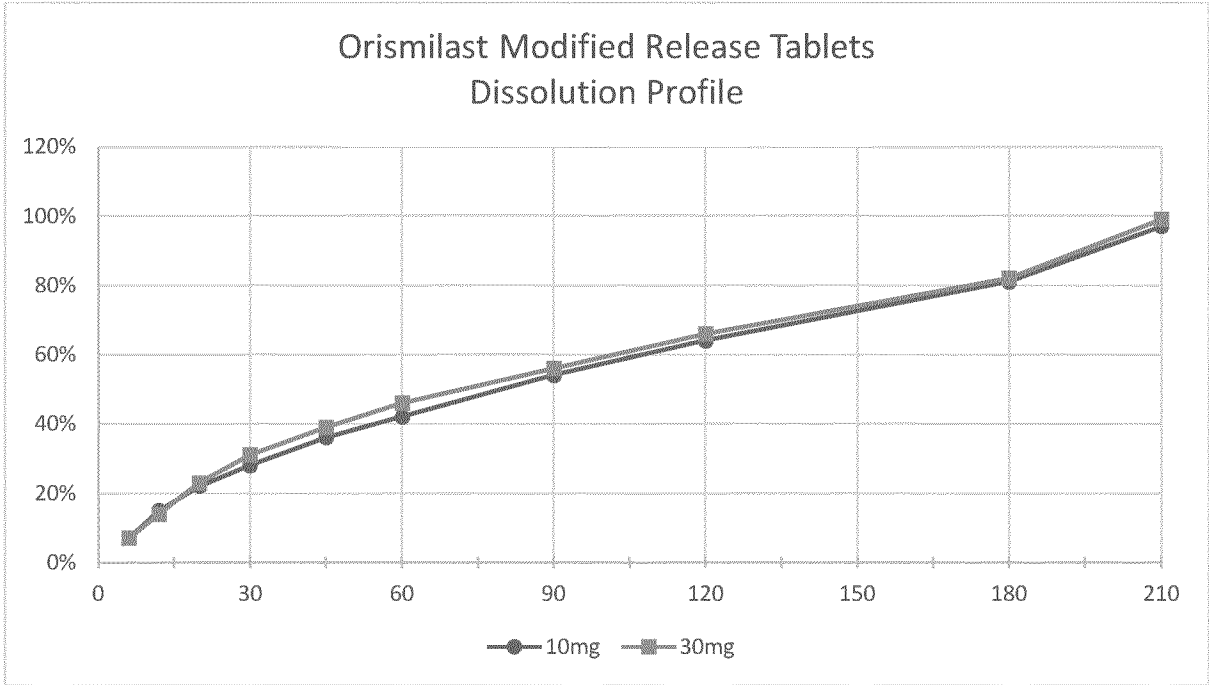


Figure 4

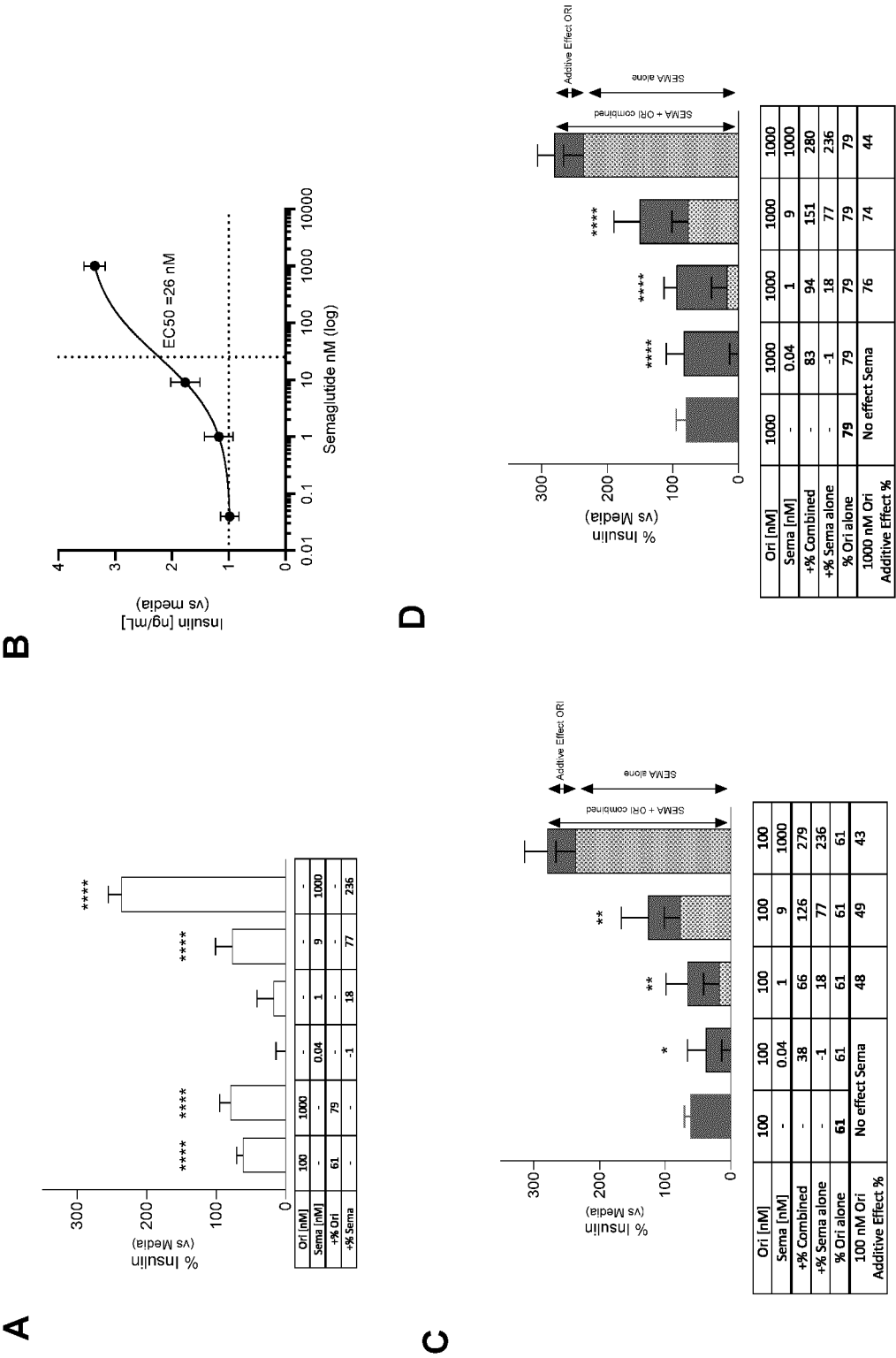


Figure 5

